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HARMACOLOGICAL REVIEWS
 Neuropharmacology of Quinolinic and Kynurenic Acids

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PHARMACOLOGICAL REVIEWS

I. Introduction
Although kynurenic acid was recognised long ago as a tryptophan metabolite in canine urine (Ellinger, 1904), (Be I. Introduction
Although kynurenic acid was recognised long ago as a
tryptophan metabolite in canine urine (Ellinger, 1904),
it was not until about 1947 that the kynurenine pathway I. Introduction was not until about 1947 that the kynurenine pathway is
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was recognised as a major route for the conversion of
tryptophan to nicotinamide and its nucleotide conjugates was recognised as a major route for the conversion of
tryptophan to nicotinamide and its nucleotide conjugates
(Beadle et al., 1947). It was some years later that quinowas recognised as a major route for the conversion
tryptophan to nicotinamide and its nucleotide conjugat
(Beadle et al., 1947). It was some years later that quin
linic acid was accepted as an intermediate (Gholson was recognised as a major route for the conversion of tryptophan to nicotinamide and its nucleotide conjugates (Beadle et al., 1947). It was some years later that quino-
linic acid was accepted as an intermediate (Gholson

PHARMACOLOGICAL REVIEWS

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al., 1964). Interest in the kynurenine pathway was long concentred around its importance as a source of nicotina-QUINOLINIC A
al., 1964). Interest in the kynurenine pathway was k
centred around its importance as a source of nicotina-
mide and as a major disturbed pathway in cases QUINOLINIC AND KYI
al., 1964). Interest in the kynurenine pathway was long co
centred around its importance as a source of nicotina-
mide and as a major disturbed pathway in cases of yer
pyridoxine deficiency, this vitamin al., 1964). Interest in the kynurenine pathway was long centred around its importance as a source of nicotinamide and as a major disturbed pathway in cases of pyridoxine deficiency, this vitamin being an essential cofactor al., 1964). Interest in the kynurenine pathway v
centred around its importance as a source of r
mide and as a major disturbed pathway in
pyridoxine deficiency, this vitamin being an cofactor for several of the kynurenine e mide and as a major disturbed pathway in cases of pyridoxine deficiency, this vitamin being an essential cofactor for several of the kynurenine enzymes.
With the discovery of neurones and other cells releasing 5HT as a neu

mide and as a major disturbed pathway in cases
pyridoxine deficiency, this vitamin being an essent
cofactor for several of the kynurenine enzymes.
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cofactor for several of the kynurenine enzymes.
With the discovery of neurones and other cells rele
ing 5HT as a neurotransmitter or local hormone, resp
tively, the inter cofactor for several of the kynurenine enzymes. 199
With the discovery of neurones and other cells releas-
ing 5HT as a neurotransmitter or local hormone, respec-
tively, the interest of most pharmacologists and neuros-
fo With the discovery of neurones and other cells releasing 5HT as a neurotransmitter or local hormone, respectively, the interest of most pharmacologists and neuroscientists in tryptophan then turned to its role as a precurs tively, the interest of most pharmacologists and neuros-

cientists in tryptophan then turned to its role as a

precursor of 5HT.* In retrospect, this was unfortunate

because, in peripheral tissues at least, only 1% of di tively, the interest of most pharmacologists and neuros
cientists in tryptophan then turned to its role as a
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because, in peripheral tissues at least, only 1% of dietar
 cientists in tryptophan then turned to its role as a precursor of 5HT.* In retrospect, this was unfortunate because, in peripheral tissues at least, only 1% of dietary tryptophan becomes converted to 5-hydroxytryptophan (P precursor of 5HT.* In retrospect, this was unfortunat
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tryptophan becomes converted to 5-hydroxytryptopha
(Peters, 1991), i.e., >95% is metabolised to kynurenine
(W because, in peripheral tissues at least, only 1% of dietary
tryptophan becomes converted to 5-hydroxytryptophan
(Peters, 1991), i.e., >95% is metabolised to kynurenine
(Wolf, 1974). It follows that alterations in tryptopha tryptophan becomes converted to 5-hydroxytryptophan (Peters, 1991), i.e., >95% is metabolised to kynurenines [Wolf, 1974). It follows that alterations in tryptophan, charged in terms of their effects species, which have be (Peters, 1991), i.e., $>95\%$ is metabolised to kynurenines per (Wolf, 1974). It follows that alterations in tryptophan, of tryptophan hydroxylase, and 5-hydroxytryptophan levels, which have been interpreted in terms of t (Wolf, 1974). It follows that alterations in tryptophan,
tryptophan hydroxylase, and 5-hydroxytryptophan lev-
els, which have been interpreted in terms of their effects
on 5HT (Price et al., 1990), may have had at least as pathway. It, which have been interpreted in terms of their effects \pm 5HT (Price et al., 1990), may have had at least as eat an impact, directly or indirectly, on the kynurenine thway.
This situation persisted until it was disco

on 5HT (Price et al., 1990), may have had at least as pyreat an impact, directly or indirectly, on the kynurenine ilipathway.

This situation persisted until it was discovered that requinolinic acid and kynurenic acid, tw great an impact, directly or indirectly, on the kynurenine ily
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tryptophan found in particularly high concentrations in met
the liver, al pathway.
This situation persisted until it was discovered the
quinolinic acid and kynurenic acid, two metabolites (
tryptophan found in particularly high concentrations is
the liver, also had pronounced effects on neuronal This situation persisted until it was discovered that
quinolinic acid and kynurenic acid, two metabolites of
tryptophan found in particularly high concentrations in
the liver, also had pronounced effects on neuronal activtryptophan found in particularly high concentrations in
the liver, also had pronounced effects on neuronal activ-
ity, showing activity at excitatory amino acid receptors
on central neurones (Stone and Perkins, 1981; Perki the liver, also had pronounced effects on neuronal activity, showing activity at excitatory amino acid receptors per on central neurones (Stone and Perkins, 1981; Perkins litter and Stone, 1982, 1983a,b). These same compou ity, showing activity at excitatory amino acid receptors
on central neurones (Stone and Perkins, 1981; Perkins
and Stone, 1982, 1983a,b). These same compounds had
been shown to have marked convulsant activity when
injected on central neurones (Stone and Perkins, 1981; Perkins
and Stone, 1982, 1983a,b). These same compounds had
been shown to have marked convulsant activity when
injected directly into the brains of rodents (Lapin,
1978a,b, 198 and Stone, 1982, 1983a,b). These same compounds had
been shown to have marked convulsant activity when
injected directly into the brains of rodents (Lapin,
1978a,b, 1981a,b), but the significance of this observation
had r been shown to have marked convulsant activity wh
injected directly into the brains of rodents (Lap
1978a,b, 1981a,b), but the significance of this observati
had remained unrealised. Since 1980, and in parallel wi
the subst injected directly into the brains of rodents (Lapin, date 1978a,b, 1981a,b), but the significance of this observation had remained unrealised. Since 1980, and in parallel with the substantial increase of interest in the r 1978a,b, 1981a,b), but the significance of this observation
had remained unrealised. Since 1980, and in parallel with
the substantial increase of interest in the role of excita-
tory amino acid receptors in neurotransmissi had remained unrealised. Since 1980, and in parallel with
the substantial increase of interest in the role of excita-
tory amino acid receptors in neurotransmission, learning
and memory, excitotoxicity, and neurodegenerati the substantial increase of interest in the role of excita-
tory amino acid receptors in neurotransmission, learning
and memory, excitotoxicity, and neurodegenerative dis-
eases (Choi, 1988; Stone and Burton, 1988; Colling tory amino acid receptors in neurotransmission, learning
and memory, excitotoxicity, and neurodegenerative dis-
eases (Choi, 1988; Stone and Burton, 1988; Collingridge
and Lester, 1989), there has been an accompanying exand memory, excitotoxicity, and neurodegenerative dis-
eases (Choi, 1988; Stone and Burton, 1988; Collingridge
and Lester, 1989), there has been an accompanying ex-
pansion of interest in the analysis and understanding of
 eases (Choi
and Lester
pansion of
function of
the CNS.
In this r d Lester, 1989), there has been an accompanying ex-
nsion of interest in the analysis and understanding of
nction of the kynurenine pathway from tryptophan in
e CNS.
In this review, information now available concerning
me pansion of interest in the analysis and understanding of function of the kynurenine pathway from tryptophan in the CNS.

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function of the kynurenine pathway from tryptophan in
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mamm

YNURENIC ACIDS

compilations and reviews provide a flavour of the large

volume of work conducted on other tissues in recent vnure acid compilations and reviews provide a flavour of the large
volume of work conducted on other tissues in recent
years (Schlossberger et al., 1984; Stone and Connick, 311

compilations and reviews provide a flavour of the large

volume of work conducted on other tissues in recent

years (Schlossberger et al., 1984; Stone and Connick,

1985; Badawy et al., 1987; Stone, 1989; Schwarcz et compilations and reviews provide a flavour of the large
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199 compilations and reviews provide a flavour of the laivolume of work conducted on other tissues in rece
years (Schlossberger et al., 1984; Stone and Connid
1985; Badawy et al., 1987; Stone, 1989; Schwarcz et a
1991). Throug volume of work conducted on other tissues in recent
years (Schlossberger et al., 1984; Stone and Connick,
1985; Badawy et al., 1987; Stone, 1989; Schwarcz et al.,
1991). Throughout the review the generic term "kynu-
renine years (Schlossberger et al., 1984; Stone and Connick, 1985; Badawy et al., 1987; Stone, 1989; Schwarcz et al., 1991). Throughout the review the generic term "kynurenine" will be used to refer to any component of the pathwa 1985; Badawy et al., 1987; Stone, 1989; Schwarcz et al., 1991). Throughout the review the generic term "kynurenine" will be used to refer to any component of the pathway, and the specific term L-kynurenine will be used
for the individual compound illustrated in figure 1. Literature is reviewed up to April 1993.
II. Kynurenine Bi **II. It is pecific term L-kynurenine**
 II. Kynurenine Biosynthesis
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quinolinic acid and kynurenic acid, two metabolites of induces the activity of tryptophan dioxygenase by a tryptophan found in particularly high concentrations in method not apparently dependent on protein or RNA the liver r the individual compound illustrated in figure 1. Lit-

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II. Kynurenine Biosynthesis

The kynurenine pathway is summarised in figure 1. In

ripheral tissues, most notably the liver, the erature is reviewed up to April 1993.
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peripheral tissues, most notably the liver, the indole ring

of tryptophan is oxidatively cleaved II. Kynurenine Biosynthesis
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peripheral tissues, most notably the liver, the indole ring
of tryptophan is oxidatively cleaved by the enzyme TDO,
sometimes referred to as I. Ny nureline Blosy lines is
The kynurenine pathway is summarised in figure 1. In
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of tryptophan is oxidatively cleaved by the enzyme TDO,
sometimes referred to a The kynurenine pathway is summarised in figure 1. In
peripheral tissues, most notably the liver, the indole ring
of tryptophan is oxidatively cleaved by the enzyme TDO,
sometimes referred to as tryptophan pyrrolase. The en peripheral tissues, most notably the liver, the indole rin
of tryptophan is oxidatively cleaved by the enzyme TDC
sometimes referred to as tryptophan pyrrolase. The en
zyme, which is haem dependent, has a half-life of ap
p of tryptophan is oxidatively cleaved by the enzyme TDO,
sometimes referred to as tryptophan pyrrolase. The en-
zyme, which is haem dependent, has a half-life of ap-
proximately 2 hours in mammals, its activity being read-
 sometimes referred to as tryptophan pyrrolase. The en-
zyme, which is haem dependent, has a half-life of ap-
proximately 2 hours in mammals, its activity being read-
ily and rapidly modified by substrate availability
(Ben zyme, which is haem dependent, has a half-life of ap-
proximately 2 hours in mammals, its activity being read-
ily and rapidly modified by substrate availability
(Bender, 1989b). The administration of tryptophan or
related proximately 2 hours in mammals, its activity being read-
ily and rapidly modified by substrate availability
(Bender, 1989b). The administration of tryptophan or
related compounds, such as α -methyl tryptophan, greatly
i ily and rapidly modified by substrate availability

(Bender, 1989b). The administration of tryptophan or

related compounds, such as α -methyl tryptophan, greatly

induces the activity of tryptophan dioxygenase by a

me related compounds, such as α -methyl tryptophan, greatly related compounds, such as α -methyl tryptophan, greatly
induces the activity of tryptophan dioxygenase by a
method not apparently dependent on protein or RNA
synthesis (Schimke et al., 1965) to a level at which most
pe induces the activity of tryptophan dioxygenase by
method not apparently dependent on protein or RN
synthesis (Schimke et al., 1965) to a level at which mo
peripheral tryptophan is metabolised by cleavage a
little is availa method not apparently dependent on protein or RNA
synthesis (Schimke et al., 1965) to a level at which most
peripheral tryptophan is metabolised by cleavage and
little is available for penetration to the CNS and subse-
que synthesis (Schimke et al., 1965) to a level at which most
peripheral tryptophan is metabolised by cleavage and
little is available for penetration to the CNS and subse-
quent metabolism to 5HT or kynurenines (Sourkes,
1971 peripheral tryptophan is metabolised
little is available for penetration to the
quent metabolism to 5HT or kynure
1971). The consequence is a profound de
derivatives of tryptophan in the CNS.
Tryptophan dioxygenase can als the is available for penetration to the CNS and subse-
ent metabolism to 5HT or kynurenines (Sourkes,
71). The consequence is a profound depletion of indole
rivatives of tryptophan in the CNS.
Tryptophan dioxygenase can al

quent metabolism to 5HT or kynurenines (Sourkes,
1971). The consequence is a profound depletion of indole
derivatives of tryptophan in the CNS.
Tryptophan dioxygenase can also be inducted by glu-
cocorticoids by a mechanis 1971). The consequence is a profound depletion of indole
derivatives of tryptophan in the CNS.
Tryptophan dioxygenase can also be induced by glu-
cocorticoids by a mechanism that involves the induction
of new mRNA and prot derivatives of tryptophan in the CNS.

Tryptophan dioxygenase can also be induced by glu-

cocorticoids by a mechanism that involves the induction

of new mRNA and protein synthesis (Schutz et al., 1973;

Joseph et al., 19 Tryptophan dioxygenase can also be induced by glu-
cocorticoids by a mechanism that involves the induction
of new mRNA and protein synthesis (Schutz et al., 1973;
Joseph et al., 1976; Danesch et al., 1983; Salter and
Pogso cocorticoids by a mechanism that involves the induction
of new mRNA and protein synthesis (Schutz et al., 1973;
Joseph et al., 1976; Danesch et al., 1983; Salter and
Pogson, 1985). Glucagon appears to have a permissive or
 of new mRNA and protein synthesis (Schutz et al., 1973;
Joseph et al., 1976; Danesch et al., 1983; Salter and
Pogson, 1985). Glucagon appears to have a permissive or
enhancing effect on glucocorticoid induction of this en-Joseph et al., 1976; Danesch et al., 1983; Salter and
Pogson, 1985). Glucagon appears to have a permissive or
enhancing effect on glucocorticoid induction of this en-
zyme, whereas insulin prevents induction (Nakamura et
a Pogson, 1985). Glucagon appears to have a permissive or
enhancing effect on glucocorticoid induction of this en-
zyme, whereas insulin prevents induction (Nakamura et
al., 1980). Tryptophan dioxygenase is also induced aft enhancing effect on glucocorticoid induction of this en
zyme, whereas insulin prevents induction (Nakamura e
al., 1980). Tryptophan dioxygenase is also induced afte
morphine, theophylline, or salicylate administration an
 zyme, whereas insulin prevent
al., 1980). Tryptophan dioxyge
morphine, theophylline, or sali
may be regulated by β -adrenoc
gan, 1982; El-Sewedy, 1989).
Whereas TDO is active only , 1980). Tryptophan dioxygenase is also induced after
orphine, theophylline, or salicylate administration and
ay be regulated by β -adrenoceptors (Badawy and Mor-
n, 1982; El-Sewedy, 1989).
Whereas TDO is active only on

morphine, theophylline, or salicylate administration and
may be regulated by β -adrenoceptors (Badawy and Morgan, 1982; El-Sewedy, 1989).
Whereas TDO is active only on the metabolism of L-
tryptophan, the administration may be regulated by β -adrenoceptors (Badawy and M
gan, 1982; El-Sewedy, 1989).
Whereas TDO is active only on the metabolism of
tryptophan, the administration of L-tryptophan res
in the production of L-kynurenine via Lgan, 1982; El-Sewedy, 1989).
Whereas TDO is active only on the metabolism of
tryptophan, the administration of L-tryptophan resu
in the production of L-kynurenine via L-formyl kynure
ine (Higuchi and Hayaishi, 1967). The e Whereas TDO is active only on the metabolism of L-
tryptophan, the administration of L-tryptophan results
in the production of L-kynurenine via L-formyl kynuren-
ine (Higuchi and Hayaishi, 1967). The enzyme respon-
sible f tryptophan, the administration of L-tryptophan results
in the production of L-kynurenine via L-formyl kynuren-
ine (Higuchi and Hayaishi, 1967). The enzyme respon-
sible for this is another haem dependent enzyme: IDO.
This in the production of L-kynurenine via L-formyl kynuren-
ine (Higuchi and Hayaishi, 1967). The enzyme respon-
sible for this is another haem dependent enzyme: IDO.
This is a superoxide-dependent enzyme because activity
is d ine (Higuchi and Hayaishi, 1967). The enzyme responsible for this is another haem dependent enzyme: IDO
This is a superoxide-dependent enzyme because activity
is dependent on the presence of free radical-generating
systems sible for this is another haem dependent enzyme: IDO.
This is a superoxide-dependent enzyme because activity
is dependent on the presence of free radical-generating
systems, such as ascorbate and methylene blue or xan-
thi This is a superoxide-dependent enzyme because activity
is dependent on the presence of free radical-generating
systems, such as ascorbate and methylene blue or xan-
thine and xanthine oxidase; activity is inhibited by su-
 is dependent on the presence of free radical-generating
systems, such as ascorbate and methylene blue or xan-
thine and xanthine oxidase; activity is inhibited by su-
peroxide dismutase (Hirata and Hayaishi, 1971). The
bre systems, such as ascorbate and methylene blue or xanthine and xanthine oxidase; activity is inhibited by superoxide dismutase (Hirata and Hayaishi, 1971). The breadth of activity implied by the name reflects the fact that thine and xanthine oxidase; activity is inhibited by superoxide dismutase (Hirata and Hayaishi, 1971). The breadth of activity implied by the name reflects the fact that IDO is also active in metabolising L- and L-5-hydrox peroxide dismutase (Hirata and Hayaishi, 1971). Th
breadth of activity implied by the name reflects the fact
that IDO is also active in metabolising L- and L-5
hydroxytryptophan, tryptamine, 5HT, and melatonii
(Hirata and breadth of activity implied by the name reflects the fact
that IDO is also active in metabolising L- and L-5-
hydroxytryptophan, tryptamine, 5HT, and melatonin
(Hirata and Hayaishi, 1971). Whereas tryptophan diox-
ygenase that IDO is also active in metabolising L- and L-5-
hydroxytryptophan, tryptamine, 5HT, and melatonin
(Hirata and Hayaishi, 1971). Whereas tryptophan diox-
ygenase is present in by far the highest activity in liver,
the ID (Hirata and Hayaishi, 1971). Whereas tryptophan diox-
ygenase is present in by far the highest activity in liver,
the IDO is absent from the liver of most mammals but
has an otherwise wide distribution in intestinal tissue

^{*} Abbreviations: 5HT, 5-hydroxytryptamine; CNS, central nervous system; IDO, indoleamine dioxygenase; TDO, tryptophan-2,3-dioxygenase; 3HAO, 3-hydroxyanthranilate oxygenase; QPRT, quinolinate phosphoribosyltransferase; C system; IDO, indoleamine dioxygenase; TDO, tryptophan-2,3-qenase; 3HAO, 3-hydroxyanthranilate oxygenase; QPRT, quinophosphoribosyltransferase; CSF, cerebrospinal fluid; NMDA methyl-D-aspartate; icv, intracerebroventricular genase; 3HAO, 3-hydroxyanthranilate oxygenase; QPRT, que phosphoribosyltransferase; CSF, cerebrospinal fluid; NM
methyl-D-aspartate; icv, intracerebroventricular; AMPA (α -hydroxy-5-methyl-4-isoxazole propionic acid); AC phosphoribosyltransferase; CSF, cerebrospinal fluid; NMDA, N-
methyl-D-aspartate; icv, intracerebroventricular; AMPA (α -amino-3-
hydroxy-5-methyl-4-isoxazole propionic acid; ACPD, *trans*-1-amino-
cyclopentane-1,3-dicar hydroxy-5-methyl-4-isoxazole propionic acid); ACPD, *trans*-1-amino-cyclopentane-1,3-dicarboxylic acid; 2AP5, 2-amino-5-phosphonopentanoic acid; 2AP7, 2-amino-7-phosphonoheptanoic acid; GABA, γ -aminobutyric acid; NMDLA, cyclopentane-1,3-dicarboxylic acid; 2AP5, 2-amino-5-phosphonopentanoic acid; 2AP7, 2-amino-7-phosphonoheptanoic acid; GABA, γ -
aminobutyric acid; NMDLA, N-methyl-DL-aspartate; epsp, excitatory
postsynaptic potential; PG tanoic acid; 2AP7, 2-amino-7-phosphonoheptanoic acid; GABA, γ aminobutyric acid; NMDLA, N-methyl-DL-aspartate; epsp, excitator
postsynaptic potential; PGCL, paragigantocellularis lateralis; NTS
nucleus tractus solitarius aminobutyric acid; NMDLA, N-methyl-DL-aspartate; epsp, excitatory postsynaptic potential; PGCL, paragigantocellularis lateralis; NTS, nucleus tractus solitarius; LTP, long-term potentiation; HA966, 1-hydroxy-3-amino-pyrrol postsynaptic potential; PGCL, paragigantocellularis latera
nucleus tractus solitarius; LTP, long-term potentiation; h
hydroxy-3-amino-pyrrolidone-2; NADPH, nicotinamide ader
cleotide phosphate; AIDS, acquired immunodeficie nucleus tractus solitarius; LTP, long-term potentiation; HA966
hydroxy-3-amino-pyrrolidone-2; NADPH, nicotinamide adenine c
cleotide phosphate; AIDS, acquired immunodeficiency syndrome; h
uman immunodeficiency virus; CNQX, piperazin-4-yl)propyl-i-phosphonic acid.

FIG. 1. Kynurenine pathway from tryptophan. The following enzymes are indicated: tryptophan pyrrolase (TDO, EC 1.13.11.11, or indolea-
mine-2,3-dioxygenase, EC 1.13.11.17); kynurenine formylase, EC 3.5.1.9; kynurenine hydr FIG. 1. Kynurenine pathway from tryptophan. The following enzymes are indicated: tryptophan pyrrolase (TDO, EC 1.13.11.11, or indolearmine-2,3-dioxygenase, EC 1.13.11.17); kynurenine formylase, EC 3.5.1.9; kynurenine hydro rio. 1. Kynutelline pathway from tryptophan. The following enzymes
mine-2,3-dioxygenase, EC 1.13.11.17); kynurenine formylase, EC 3.5.1.9
kynurenine aminotransferase, EC 2.6.1.7; 3-hydroxyanthranilic acid oxida
also known are indicated. dyplopian pyrrolase (1DO, EC 1.13.11.11, or indices-
9; kynurenine hydroxylase, EC 1.14.13.9; kynureninase, EC 3.7.1.3;
ase, EC 1.13.11.6; picolinate carboxylase, EC 4.1.1.45. *, kynuramines
largely cytosoli

kynurenine aminotransferase, EC 2.6.1.7; 3-hydroxyanthranilic acid oxialso known as kynurenamines.
lung, placenta, and brain. In rat brain, the enzyme shows
highest activity in the hypothalamus where it has about
twice the also known as kynurenamines.

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highest activity in the hypothalamus where it has about are

twice the activity of the colliculi and 15-fold more than

in

the lung, placenta, and brain. In rat brain, the
highest activity in the hypothalamus whe
twice the activity of the colliculi and 15-1
the neocortex (Gal and Sherman, 1980).
The detailed biochemistry of the kynure ng, placenta, and brain. In rat brain, the enzyme shows
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The detailed bioch

highest activity in the hypothalamus where it has about
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The detailed biochemistry of the kynurenine metabolic
pathway wil twice the activity of the colliculi and 15-fold more than
the neocortex (Gal and Sherman, 1980).
The detailed biochemistry of the kynurenine metabolic
pathway will not be treated further in this review because
it has been the neccortex (Gal and Sherman, 1980).
The detailed biochemistry of the kynurenine metab
pathway will not be treated further in this review beca
it has been extensively analysed and discussed by Ben
(1989a,b). One of the m The detailed biochemistry of the kynurenine metabolic humpathway will not be treated further in this review because tive it has been extensively analysed and discussed by Bender [1989a,b). One of the major questions, howev pathway will not be treated further in this review because
it has been extensively analysed and discussed by Bender
(1989a,b). One of the major questions, however, concern-
ing the physiological role of the kynurenine path it has been extensively analysed and discussed by Bender

(1989a,b). One of the major questions, however, concern-

ing the physiological role of the kynurenine pathway and

its pharmacological relevance is the extent to w (1989a,b). One of the major questions, however, concerning the physiological role of the kynurenine pathway and its pharmacological relevance is the extent to which metabolism down this pathway occurs within the brain as ing the physiological role of the kynurenine pathway and
its pharmacological relevance is the extent to which
metabolism down this pathway occurs within the brain
as well as peripherally. To this extent, the localisation
o its pharmacological relevance is the extent to whise metabolism down this pathway occurs within the brass well as peripherally. To this extent, the localisation of enzyme activities within the CNS, as well as the comparabi as well as peripherally. To this extent, the localisation
of enzyme activities within the CNS, as well as the
comparability between central enzymes and those occur-
ring peripherally, is of some importance.

A. Kynureninase and Kynurenine Hydroxylase

mparability between central enzymes and those occur-
ng peripherally, is of some importance.
kynureninase and Kynurenine Hydroxylase
Although kynureninase is present in large amounts in sub-
e liver, kidney and spleen, onl the peripherally, is of some importance. The liver of the liver, have the liver, kidney and spleen, only small amounts of this and spleen, only small amounts of this

ase, EC 1.13.11.6; picolinate carboxylase, EC 4.1.1.45. $*$, kynuramines
largely cytosolic, pyridoxal phosphate-dependent enzyme
are demonstrable in many other tissues, including brain;
in the rat this corresponds to $<0.$ largely cytosolic, pyridoxal phosphate-dependent enzyme
are demonstrable in many other tissues, including brain;
in the rat this corresponds to <0.2% of the activity found
in liver (Kawai et al., 1988; Okuno and Kido, 1991 largely cytosolic, pyridoxal phosphate-dependent enzyme
are demonstrable in many other tissues, including brain;
in the rat this corresponds to <0.2% of the activity found
in liver (Kawai et al., 1988; Okuno and Kido, 199 largely cytosolic, pyridoxal phosphate-dependent enzym-
are demonstrable in many other tissues, including brain
in the rat this corresponds to $<0.2\%$ of the activity found
in liver (Kawai et al., 1988; Okuno and Kido, 1 are demonstrable in many other tis
in the rat this corresponds to <0.2 ?
in liver (Kawai et al., 1988; Okuno
humans the cerebral enzyme is pre
tive activity (1% of that in liver).
Because kynurenine hydroxylase the rat this corresponds to $\langle 0.2\%$ of the activity found
liver (Kawai et al., 1988; Okuno and Kido, 1991). In
mans the cerebral enzyme is present at a higher rela-
ve activity (1% of that in liver).
Because kynurenine

in liver (Kawai et al., 1988; Okuno and Kido, 1991). In
humans the cerebral enzyme is present at a higher rela-
tive activity (1% of that in liver).
Because kynurenine hydroxylase activity also appears
to be present in bra humans the cerebral enzyme is present at a higher rela-
tive activity (1% of that in liver).
Because kynurenine hydroxylase activity also appears
to be present in brain at relatively low activity (Battie
and Verity, 1981; tive activity (1% of that in liver).
Because kynurenine hydroxylase activity also appears
to be present in brain at relatively low activity (Battie
and Verity, 1981; Gal and Sherman, 1978; Uemura and
Hirai, 1991), this rai Because kynurenine hydroxylase activity also appears
to be present in brain at relatively low activity (Battie
and Verity, 1981; Gal and Sherman, 1978; Uemura and
Hirai, 1991), this raises important questions about the
abi to be present in brain at relatively low activity (Battie and Verity, 1981; Gal and Sherman, 1978; Uemura and Hirai, 1991), this raises important questions about the ability of brain to metabolise its own kynurenines along and Verity, 1981; Gal and Sherman, 1978; Uemura an
Hirai, 1991), this raises important questions about the
ability of brain to metabolise its own kynurenines alor
the usually described pathway from L-kynurenine to ;
hydrox Hirai, 1991), this raises important questions about
ability of brain to metabolise its own kynurenines a
the usually described pathway from L-kynurenine t
hydroxy-kynurenine to 3-hydroxy-anthranilic acid. H
ever, although ability of brain to metabolise its own kynurenines along
the usually described pathway from L-kynurenine to 3-
hydroxykynurenine to 3-hydroxyanthranilic acid. How-
ever, although it shows greater activity for 3-hydroxy-
ky the usually described pathway from L-kynurenine to 3-hydroxykynurenine to 3-hydroxyanthranilic acid. However, although it shows greater activity for 3-hydroxy-
kynurenine as substrate, kynureninase is also able to
hydrolys hydroxykynurenine to 3-hydroxyanthranilic acid. How-
ever, although it shows greater activity for 3-hydroxy-
kynurenine as substrate, kynureninase is also able to
hydrolyse L-kynurenine to anthranilic acid (McDermot
et al. ever, although it shows greater activity for 3-hydre kynurenine as substrate, kynureninase is also able hydrolyse L-kynurenine to anthranilic acid (McDer et al., 1973; Bender and McCreanor, 1982), which subsequently underg hydrolyse L-kynurenine to anthranilic acid (McDermot et al., 1973; Bender and McCreanor, 1982), which can subsequently undergo hydroxylation to 5- or 3-hydroxy-anilic acid via nonspecific microsomal hydroxylating en-

QUINOLINIC AND KY
zymes (Bender, 1989b). This may explain the ability of where the ability of where the ability of the anquinolinic AND
brain to form 3-hydroxyanthrinilate directly from an-
thranilic acid (Baran and Schwarcz, 1990), and, in so far quinolinic and KY
zymes (Bender, 1989b). This may explain the ability of
brain to form 3-hydroxyanthrinilate directly from an-
thranilic acid (Baran and Schwarcz, 1990), and, in so far
as anthranilic acid from miscellaneou zymes (Bender, 1989b). This may explain the ability of was
brain to form 3-hydroxyanthrinilate directly from an-
thranilic acid (Baran and Schwarcz, 1990), and, in so far equ
as anthranilic acid from miscellaneous sources zymes (Bender, 1989b). This may explain the ability of was brain to form 3-hydroxyanthrinilate directly from an-
thranilic acid (Baran and Schwarcz, 1990), and, in so far equas anthranilic acid from miscellaneous sources m brain to form 3-hydroxyanthrinilate directly from anthranilic acid (Baran and Schwarcz, 1990), and, in so far
as anthranilic acid from miscellaneous sources may gain
access to the brain, this may provide an alternative ent tryptophan. as anthranilic acid from miscellaneous sources may gain
access to the brain, this may provide an alternative entry
into the kynurenine pathway independently of cerebral
tryptophan.
Some oestrogenic compounds are able to in access to the brain, this may provide an alternative en
into the kynurenine pathway independently of cereb
tryptophan.
Some oestrogenic compounds are able to inhibit k
ureninase and L-kynurenine hydroxylase in a comp
tive

into the kynurenine pathway independently of cerebral acid
tryptophan. T
Some oestrogenic compounds are able to inhibit kyn-
ureninase and L-kynurenine hydroxylase in a competi-
tive manner. This will result in a substanti tryptophan.
Some oestrogenic compounds are able to inhibit
ureninase and L-kynurenine hydroxylase in a com
tive manner. This will result in a substantial increa
plasma and urinary L-kynurenine, 3-hydroxykynure
and xanthure Some oestrogenic compounds are able to inhibit ky
ureninase and L-kynurenine hydroxylase in a compe
tive manner. This will result in a substantial increase
plasma and urinary L-kynurenine, 3-hydroxykynurenin
and xanthureni ureninase and L-kynurenine hydroxylase in a competitive manner. This will result in a substantial increase in plasma and urinary L-kynurenine, 3-hydroxykynurenine, and xanthurenic acid (Bender, 1989a,b) and, thus, potentia tive manner. This
plasma and urinary
and xanthurenic ac
tially modify the ce
and its metabolites
1. Inhibition of l

and xanthurenic acid (Bender, 1989a,b) and, thus, potentially modify the cerebral concentrations of L-kynurenine
and its metabolites.
1. Inhibition of kynureninase. Several compounds are
now known that can inhibit kynureni ially modify the cerebral concentrations of L-kynure
and its metabolites.
1. Inhibition of kynureninase. Several compound
now known that can inhibit kynureninase. One of t
synthesised by Whitten et al. (1989), is a difluor and its metabolites.

1. Inhibition of kynureninase. Several compounds and the synthesised by Whitten et al. (1989), is a difluoro-superituted desamino analogue of L-kynurenine; few biological data concerning this compound 1. Inhibition of kynureninase. Several compounds and now known that can inhibit kynureninase. One of the synthesised by Whitten et al. (1989), is a difluoro-sul stituted desamino analogue of L-kynurenine; few biological da synthesised by Whitten et al. (1989), is a difluoro-sub-
stituted desamino analogue of L-kynurenine; few biolog-
ical data concerning this compound are presently avail-
able.
a. NICOTINYLALANINE. Some success has been neu

stituted desamino analogue of L-kynurenine; few biolog-
ical data concerning this compound are presently avail-
able.
a. NICOTINYLALANINE. Some success has been ne
achieved in manipulating the kynurenine pathway using fin
 ical data concerning this compound are presently available.

a. NICOTINYLALANINE. Some success has been nucleosed in manipulating the kynurenine pathway using field an analogue of L-kynurenine: nicotinylalanine. This the c acksome success has been a
achieved in manipulating the kynurenine pathway using fi
an analogue of L-kynurenine: nicotinylalanine. This the
compound, originally reported as a potential inhibitor of h
kynureninase and kynur a. NICOTINYLALANINE. Some success has been a
achieved in manipulating the kynurenine pathway using f
an analogue of L-kynurenine: nicotinylalanine. This
compound, originally reported as a potential inhibitor of l
kynurenin an analogue of L-kynurenine: nicotinylalanine. This the compound, originally reported as a potential inhibitor of has kynureninase and kynurenine hydroxylase (Decker et as al., 1963), has been found to elevate the brain co compound, originally reported as a potential inhibitor of
kynureninase and kynurenine hydroxylase (Decker et
al., 1963), has been found to elevate the brain content of
kynurenic acid at the expense of quinolinic acid, whic kynureninase and kynurenine hydroxylase (Decker et al., 1963), has been found to elevate the brain content of kynurenic acid at the expense of quinolinic acid, which is decreased (Moroni et al., 1991a; Connick et al., 1992 al., 1963), has been found to elevate the brain content of syntynurenic acid at the expense of quinolinic acid, which ine is decreased (Moroni et al., 1991a; Connick et al., 1992). other this effect is seen especially whe kynurenic acid at the expense of quinolinic acid, which in
is decreased (Moroni et al., 1991a; Connick et al., 1992). ot
This effect is seen especially when nicotinylalanine ad-
is ministration is accompanied by a tryptop is decreased (Moroni et al., 1991a; Connick et al., 1992). otl
This effect is seen especially when nicotinylalanine adinglessive is accompanied by a tryptophan load, when has
brain kynurenate levels can increase almost 20 This effect is seen especially when nicotinylalanine aoministration is accompanied by a tryptophan load, whe brain kynurenate levels can increase almost 20-fol (Connick et al., 1992). It also is seen when the drug administ ministration is accompanied by a tryptophan load, when had brain kynurenate levels can increase almost 20-fold K_n (Connick et al., 1992). It also is seen when the drug is administered to animals pretreated with bacteria brain kynurenate levels can increase almost 20-fold
(Connick et al., 1992). It also is seen when the drug is
administered to animals pretreated with bacterial endo-
toxin (Moroni et al., 1991a). In mice with elevated brain (Connick et al., 1992). It also is seen when the dru
administered to animals pretreated with bacterial er
toxin (Moroni et al., 1991a). In mice with elevated bi
kynurenate levels, nicotinylalanine was able to supp
seizures administered to animals pretreated with bacterial endo-
toxin (Moroni et al., 1991a). In mice with elevated brain
kynurenate levels, nicotinylalanine was able to suppress
seizures induced either by pentylenetetrazol or ele toxin (Moroni et al., 1991a). In mice with elevated brain kynurenate levels, nicotinylalanine was able to suppress
seizures induced either by pentylenetetrazol or electrosh-
ock treatment (Connick et al., 1992). Although t kynurenate levels, nicotinylalanine was able to suppresseizures induced either by pentylenetetrazol or electrosh-
ock treatment (Connick et al., 1992). Although the doses
required were relatively high, there may be potenti seizures induced either by pentylenetetrazol or electrosh-

ock treatment (Connick et al., 1992). Although the doses

required were relatively high, there may be potential

metherapeutic value in developing other analogues ock treatment (Connick et al., 1992). Although the doses
required were relatively high, there may be potential
therapeutic value in developing other analogues of kyn-
urenines or nicotinylalanine with which to increase bra required were relatively high, there may be potential mother
appeutic value in developing other analogues of kyn-
urenines or nicotinylalanine with which to increase brain
but
kynurenate to quinolinate ratios. This may be therapeutic value in developing other analogues of kyn-
urenines or nicotinylalanine with which to increase brain
kynurenate to quinolinate ratios. This may be of special
regivalue, for example, in those cases in which a v urenines or nicotinylalanine with which to
kynurenate to quinolinate ratios. This may
value, for example, in those cases in whic
concentration of quinolinate is attained,
some viral infections (see section VI.E.8). *B. L-Kynurenine Aminotransferance Like Concentration* of quinolinate is
B. L-Kynurenine Aminotransfer
The convergion of Lumur

some viral infections (see section VI.E.8). and a transmission of L-kynurenine to kynurenate is transamination reaction which can be row brought about by several transaminase enzymes found following. B. L-Kynurenine Aminotransferase

The conversion of L-kynurenine to kynurenate is transamination reaction which can be rought about by several transaminase enzymes found fol

in visceral structures (Kido, 1984; Noguchi et B. L-Rynurenine Aminotransferase

The conversion of L-kynurenine to kynurenate is

achieved by a transamination reaction which can be

brought about by several transaminase enzymes found

in visceral structures (Kido, 1984 The conversion of L-kynurenine to kynurenate is trachieved by a transamination reaction which can be row brought about by several transaminase enzymes found for visceral structures (Kido, 1984; Noguchi et al., 1975; O Hara achieved by a transamination reaction which can
brought about by several transaminase enzymes fou
in visceral structures (Kido, 1984; Noguchi et al., 19
Harada et al., 1978; Okuno et al., 1991a). One of th
enzymes is ident brought about by several transaminase enzymes found fol
in visceral structures (Kido, 1984; Noguchi et al., 1975; Ok
Harada et al., 1978; Okuno et al., 1991a). One of these me
enzymes is identical biochemically, physicoche in visceral structures (Kido, 1984; Noguchi et al., 1975; Okunda et al., 1978; Okuno et al., 1991a). One of these met
enzymes is identical biochemically, physicochemically, kyn
and immunologically with an enzyme present in Harada et al., 1978; Okuno et al., 1991a). One of these metersymes is identical biochemically, physicochemically, kyn and immunologically with an enzyme present in rat brain (Sc (Minatogawa et al., 1974; Ishikawa et al., 1 enzymes is identical biochemically, physicochemically, land immunologically with an enzyme present in rat brain (Minatogawa et al., 1974; Ishikawa et al., 1991). This led of Ckuno et al. (1990) to postulate that it might p

YNURENIC ACIDS 313
was later confirmed that in the rat brain this activity
resided in a single protein that was able to function FINURENIC ACIDS 313
was later confirmed that in the rat brain this activity
resided in a single protein that was able to function
equally well using either pyruvate or 2-oxo-glutarate as SIMURENIC ACIDS 313
was later confirmed that in the rat brain this activity
resided in a single protein that was able to function
equally well using either pyruvate or 2-oxo-glutarate as
the amino group acceptor, although was later confirmed that in the rat brain this activity resided in a single protein that was able to function equally well using either pyruvate or 2 -oxo-glutarate as the amino group acceptor, although the K_m value fo was later confirmed that in the rat brain this activity resided in a single protein that was able to function equally well using either pyruvate or 2-oxo-glutarate as the amino group acceptor, although the K_m value for resided in a single protein that
equally well using either pyruvate
the amino group acceptor, althoug
kynurenine was substantially lowe
acid (17 compared with 910 μ M).
The enzyme was localised prima ually well using either pyruvate or 2-oxo-glutarate a mino group acceptor, although the K_m value for nurenine was substantially lower when using the laid (17 compared with 910 μ M). The enzyme was localised primarily the amino group acceptor, although the K_m value for L-
kynurenine was substantially lower when using the latter
acid (17 compared with 910 μ M).
The enzyme was localised primarily in the mitochon-
drial fraction of br

and xanthurenic acid (Bender, 1989a,b) and, thus, poten-
 ially modify the cerebral concentrations of L-kynurenine that in cerebellum (using pyruvate as amino acceptor).

and its metabolites.
 1. Inhibition of kynurenin kynurenine was substantially lower when using the latter
acid (17 compared with 910 μ M).
The enzyme was localised primarily in the mitochon-
drial fraction of brain homogenates, although significant
amounts were also d acid (17 compared with 910 μ M).
The enzyme was localised primarily in the mitochondrial fraction of brain homogenates, although significant amounts were also detected in the soluble fractions.
Evidence was also obtaine The enzyme was localised primarily in the mitochon-
drial fraction of brain homogenates, although significant
amounts were also detected in the soluble fractions.
Evidence was also obtained for a gradient of distribution
t drial fraction of brain homogenates, although significant
amounts were also detected in the soluble fractions.
Evidence was also obtained for a gradient of distribution
throughout the CNS with the greatest activity, in the amounts were also detected in the soluble fractions.
Evidence was also obtained for a gradient of distribution
throughout the CNS with the greatest activity, in the
olfactory bulb, being approximately 10-fold higher than
t Evidence was also obtained for a gradient of distribution
throughout the CNS with the greatest activity, in the
olfactory bulb, being approximately 10-fold higher than
that in cerebellum (using pyruvate as amino acceptor). olfactory bulb, being approximately 10-fold higher than olfactory bulb, being approximately 10
that in cerebellum (using pyruvate as
Activities in the frontal neocortex, hy
neostriatum were approximately one-ha
system activity (Okuno et al., 1991a).
In addition, an elevation of at in cerebellum (using pyruvate as amino acceptor).

tivities in the frontal neocortex, hypothalamus, and

costriatum were approximately one-half of the olfactory

stem activity (Okuno et al., 1991a).

In addition, an ele Activities in the frontal neocortex, hypothalamus, and
neostriatum were approximately one-half of the olfactory
system activity (Okuno et al., 1991a).
In addition, an elevation of enzyme activity, to about
180% of control,

achieved in manipulating the kynurenine pathway using finding was taken to indicate a preferential location of
an analogue of L-kynurenine: nicotinylalanine. This the enzyme in the glial compartment, a suggestion that
comp neostriatum were approximately one-half of the olfactory
system activity (Okuno et al., 1991a).
In addition, an elevation of enzyme activity, to about
180% of control, was noted in the striatum of animals
exhibiting profou system activity (Okuno et al., 1991a).

In addition, an elevation of enzyme activity, to about

180% of control, was noted in the striatum of animals

exhibiting profound neuronal loss and gliotic infiltration

several da In addition, an elevation of enzyme activity, to about 180% of control, was noted in the striatum of animals exhibiting profound neuronal loss and gliotic infiltration several days after the injection of quinolinic acid as 180% of control, was noted in the striatum of animals exhibiting profound neuronal loss and gliotic infiltration several days after the injection of quinolinic acid as a neurotoxin into the region (Okuno et al., 1991a). Th exhibiting profound neuronal loss and gliotic infiltration
several days after the injection of quinolinic acid as a
neurotoxin into the region (Okuno et al., 1991a). This
finding was taken to indicate a preferential locati several days after the injection of quinolinic acid as a neurotoxin into the region (Okuno et al., 1991a). This finding was taken to indicate a preferential location of the enzyme in the glial compartment, a suggestion tha neurotoxin into the region (Okuno et al., 1991a). This
finding was taken to indicate a preferential location of
the enzyme in the glial compartment, a suggestion that
has received direct support from the demonstration tha finding was taken to indicate a preferential locatio
the enzyme in the glial compartment, a suggestion
has received direct support from the demonstration
astrocytic cultures or human glioma tissue are abl
synthesise kynure the enzyme in the glial compartment, a suggestion that
has received direct support from the demonstration that
astrocytic cultures or human glioma tissue are able to
synthesise kynurenate and quinolinate from L-kynuren-
in has received direct support from the demonstration t
astrocytic cultures or human glioma tissue are able
synthesise kynurenate and quinolinate from L-kynur
ine (Vezzani et al., 1990, 1991a). Although at least
other enzyme astrocytic cultures or human glioma tissue are able to
synthesise kynurenate and quinolinate from L-kynuren-
ine (Vezzani et al., 1990, 1991a). Although at least one
other enzyme in the CNS, aspartate aminotransferase,
is synthesise kynurenate and quinolinate from L-kynuren-
ine (Vezzani et al., 1990, 1991a). Although at least one
other enzyme in the CNS, aspartate aminotransferase,
is capable of forming kynurenate from L-kynurenine and
ha ine (Vezzani et al., 1990, 1991a). Although at least on
other enzyme in the CNS, aspartate aminotransferas
is capable of forming kynurenate from L-kynurenine an
has a predominantly neuronal location, it has a very hig
 K_m her enzyme in the CNS, aspartate aminotransferase,
capable of forming kynurenate from L-kynurenine and
is a predominantly neuronal location, it has a very high
 $_n$ (>20 mM) for L-kynurenine (Okuno et al., 1991a).
The part is capable of forming kynurenate from L-kynurenine and
has a predominantly neuronal location, it has a very high
 K_m (>20 mM) for L-kynurenine (Okuno et al., 1991a).
The particular importance of the rat brain kynurenine

concentration of quinolinate is attained, as occurs in urenate (as reflected in the release of kynurenate follow-
some viral infections (see section VI.E.8).
B. L-Kynurenine Aminotransferase
There is also a good correlatio has a predominantly neuronal location, it has a very high K_m (>20 mM) for L-kynurenine (Okuno et al., 1991a).
The particular importance of the rat brain kynurenine aminotransferase for the metabolism of L-kynurenine was K_m (>20 mM) for L-kynurenine (Okuno et al., 1991a).
The particular importance of the rat brain kynurenine
aminotransferase for the metabolism of L-kynurenine
was emphasised by its remarkable selectivity for sub
strate. The particular importance of the rat brain kynurenine
aminotransferase for the metabolism of L-kynurenine
was emphasised by its remarkable selectivity for sub-
strate. Even at concentrations of 2 mM, L-tryptophan, L-
glut aminotransferase for the metabolism of L-kynurenine
was emphasised by its remarkable selectivity for sub-
strate. Even at concentrations of 2 mM, L-tryptophan, L-
glutamate, or L- α -aminoadipate competed poorly against
 was emphasised by its remarkable selectivity for sub-
strate. Even at concentrations of 2 mM, L-tryptophan, L-
glutamate, or L- α -aminoadipate competed poorly against
L-kynurenine and could reduce enzyme activity by no
 strate. Even at concentrations of 2 mM, L-tryptophan, glutamate, or L- α -aminoadipate competed poorly again L-kynurenine and could reduce enzyme activity by more than 50% with 2 μ M L-kynurenine as substra Furthermore glutamate, or L- α -aminoadipate competed poorly against
L-kynurenine and could reduce enzyme activity by no
more than 50% with 2 μ M L-kynurenine as substrate.
Furthermore, there is a clear parallel between the distri L-kynurenine and could reduce enzyme activity by no
more than 50% with 2 μ M L-kynurenine as substrate.
Furthermore, there is a clear parallel between the distri-
bution of kynurenine aminotransferase in different brain Furthermore, there is a clear parallel between the distribution of kynurenine aminotransferase in different brain regions and at different stages of development, and the ability of those regions to convert L-kynurenine to Furthermore, there is a clear parallel between the dist
bution of kynurenine aminotransferase in different bre
regions and at different stages of development, and t
ability of those regions to convert L-kynurenine to ky
u bution of kynurenine aminotransferase in different brain
regions and at different stages of development, and the
ability of those regions to convert L-kynurenine to kyn-
urenate (as reflected in the release of kynurenate f 1989). ility of those regions to convert L-kynurenine to kynamete (as reflected in the release of kynurenate follog preincubation with L-kynurenine) (Turski et 89).
There is also a good correlation between the aminometries also a

urenate (as reflected in the release of kynurenate following preincubation with L-kynurenine) (Turski et al. 1989).
There is also a good correlation between the amino-
transferase activity and kynurenate release from neu-
 ing preincubation with L-kynurenine) (Turski et al., 1989).

There is also a good correlation between the amino-

transferase activity and kynurenate release from neu-

rone-depleted, glial cell-enriched preparations of br 1989).
There is also a good correlation between the amino-
transferase activity and kynurenate release from neu-
rone-depleted, glial cell-enriched preparations of brain
following excitotoxin administration (Turski et al., There is also a good correlation between the am
transferase activity and kynurenate release from
rone-depleted, glial cell-enriched preparations of b
following excitotoxin administration (Turski et al., 1
Okuno et al., 199 transferase activity and kynurenate release from neu-
rone-depleted, glial cell-enriched preparations of brain
following excitotoxin administration (Turski et al., 1989;
Okuno et al., 1991a). The use of immunohistochemical rone-depleted, glial cell-enriched preparations of brain following excitotoxin administration (Turski et al., 1989; Okuno et al., 1991a). The use of immunohistochemical methods has allowed the direct visual localisation of following excitotoxin administration (Turski et al., 1989;
Okuno et al., 1991a). The use of immunohistochemical
methods has allowed the direct visual localisation of
kynurenine aminotransferase to the astrocyte population
 Okuno et al., 1991a). The use of immunohistochemical
methods has allowed the direct visual localisation of
kynurenine aminotransferase to the astrocyte population
(Schwarcz and Du, 1991). In more recent reports, Du et
al. methods has allowed the direct visual localisation of
kynurenine aminotransferase to the astrocyte population
(Schwarcz and Du, 1991). In more recent reports, Du et
al. (1991) and Fueral. (1992) detailed the distribution o kynurenine aminotransferase to the astrocyte population (Schwarcz and Du, 1991). In more recent reports, Du et al. (1991) and Fueral. (1992) detailed the distribution of kynurenine aminotransferase within different regions

ST
ferase-containing cells was in the stratum lacunosum-
moleculare, with a lower density in the granule cell layer STON
ferase-containing cells was in the stratum lacunosum-
moleculare, with a lower density in the granule cell layer
and stratum radiatum, predominantly in glial cells. Few STONE

ferase-containing cells was in the stratum lacunosum-

imoleculare, with a lower density in the granule cell layer

and stratum radiatum, predominantly in glial cells. Few

neurones showed any immunoreactivity, and ferase-containing cells was in the stratum lacunosum-
moleculare, with a lower density in the granule cell layer stand stratum radiatum, predominantly in glial cells. Few po
neurones showed any immunoreactivity, and all we ferase-containing cells was in the stratum lacunosum-
moleculare, with a lower density in the granule cell layer
and stratum radiatum, predominantly in glial cells. Few
neurones showed any immunoreactivity, and all were
no moleculare, with a lower density in the granule cell layer stomed stratum radiatum, predominantly in glial cells. Few posineurones showed any immunoreactivity, and all were animonpyramidal in appearance, although immunore and stratum radiatum, predominantly in glial cells. Few
neurones showed any immunoreactivity, and all were
nonpyramidal in appearance, although immunoreactive
neurones have been observed in other regions of the CNS
(Schwar neurones showed any immunoreactivity, and all wer
nonpyramidal in appearance, although immunoreactiv
neurones have been observed in other regions of the CN
(Schwarcz et al., 1992). In particular, Roberts et a
(1992) report neurones have been observed in other regions of the CNS (Schwarcz et al., 1992). In particular, Roberts et al. (1992) reported the light and electron microscopic localisation of kynurenine aminotransferase in rat striatum. neurones have been observed in other regions of the CNS
(Schwarcz et al., 1992). In particular, Roberts et al.
(1992) reported the light and electron microscopic local-
isation of kynurenine aminotransferase in rat striatu (Schwarcz et al., 1992). In particular, Roberts et al. (1992) reported the light and electron microscopic localisation of kynurenine aminotransferase in rat striatum. ol
Although present predominantly in glial cells, distr (1992) reported the light and electron microscopic localisation of kynurenine aminotransferase in rat striatum.
Although present predominantly in glial cells, distributed throughout the nucleus and cytoplasm, the enzyme wa isation of kynurenine aminotransferase in rat striatum.
Although present predominantly in glial cells, distributed
throughout the nucleus and cytoplasm, the enzyme was
also found in medium- and large-sized neurones. Here,
 Although present predominantly in glial cells, distributed of throughout the nucleus and cytoplasm, the enzyme was unalso found in medium- and large-sized neurones. Here, (Let the enzyme was localised to cytoplasmic organe also found in medium- and large-sized neurones. He
the enzyme was localised to cytoplasmic organelles,
sociated with cell membranes. Immunoreactivity v
also demonstrated in astrocytic processes making cle
contact with dend the enzyme was localised to cytoplasmic organelles, as-
sociated with cell membranes. Immunoreactivity was
also demonstrated in astrocytic processes making close
contact with dendritic synapses. This raises the tantal-
isi sociated with cell membranes. Immunoreactivity was
also demonstrated in astrocytic processes making close
contact with dendritic synapses. This raises the tantal-
ising possibility that kynurenate is secreted by glial cell also demonstrated in astrocytic processes making close contact with dendritic synapses. This raises the tantal-
ising possibility that kynurenate is secreted by glial cells The
into the immediate vicinity of specific synap contact with dendritic synapses. This raises the tantal-
ising possibility that kynurenate is secreted by glial cells T
into the immediate vicinity of specific synaptic contacts. 3
It will now be interesting to await a com QPRT. into the immediate vicinity of specific synaptic contacts.
It will now be interesting to await a comparative study
of the localisation of this enzyme with either 3HAO or
QPRT.
Despite the apparently poor ability of $L-\alpha$ -

It will now be interesting to await a comparative study
of the localisation of this enzyme with either 3HAO or
QPRT.
Despite the apparently poor ability of L- α -aminoadi-
pate to inhibit kynurenine aminotransferase acti of the localisation of this enzyme with either 3HAO or acid

QPRT. enzymently poor ability of $L-\alpha$ -aminoadi-

pate to inhibit kynurenine aminotransferase activity, it brain

appears that this same enzyme may be responsib QPRT.
Despite the apparently poor ability of L- α -aminoadi-
pate to inhibit kynurenine aminotransferase activity, it
appears that this same enzyme may be responsible in
vivo, at least in peripheral tissues, for the tran Despite the apparently poor ability of $L-\alpha$ -aminoadi-
pate to inhibit kynurenine aminotransferase activity, it brappears that this same enzyme may be responsible in fri
vivo, at least in peripheral tissues, for the trans appears that this same enzyme may be responsible in fractive, at least in peripheral tissues, for the transamination for α -aminoadipate to α -ketoadipate. Tobes and Mason selection (1975) claimed that the two enzymes vivo, at least in peripheral tissues, for the transamination for
of α -aminoadipate to α -ketoadipate. Tobes and Mason sele
(1975) claimed that the two enzymes, formerly believed try
to be distinct, could not be disti of α -aminoadipate to α -ketoadipate. Tobes and Mason sele (1975) claimed that the two enzymes, formerly believed try to be distinct, could not be distinguished either on the actions of cellular distribution or throug (1975) claimed that the two enzymes, formerly believed to be distinct, could not be distinguished either on the absis of cellular distribution or through inhibition by a veries of analogues. If true, this identity would m to be distinct, could not be distinguished either on the basis of cellular distribution or through inhibition by a series of analogues. If true, this identity would mean a potential competition between tryptophan and lysin basis of cellular distribution or through inhibition by a
series of analogues. If true, this identity would mean a
footential competition between tryptophan and lysine for
caminotransferase activity and could have importan series of analogues. If true, this identity would mean a potential competition between tryptophan and lysine for aminotransferase activity and could have important implications for conditions in which increased levels of e potential competition between tryptophan and lysine for
aminotransferase activity and could have important im-
plications for conditions in which increased levels of
either of these amino acids is a feature. More recent
ev aminotransferase activity and could have imporplications for conditions in which increased either of these amino acids is a feature. Morevidence, however, suggests that the enzymes mall, be distinct (Mawal and Deshmukh, 19 either of these amino acids is a feature. More recent evidence, however, suggests that the enzymes may, after all, be distinct (Mawal and Deshmukh, 1991).
Although the driving force for investigating these enzymes in rat b

either of these amino acids is a feature. More recent Sevidence, however, suggests that the enzymes may, after immall, be distinct (Mawal and Deshmukh, 1991). with Although the driving force for investigating these en-
Exy evidence, however, suggests that the enzymes may, after all, be distinct (Mawal and Deshmukh, 1991).
Although the driving force for investigating these enzymes in rat brain has been the potential relevance to an understand all, be distinct (Mawal and Deshmukh, 1991). w
Although the driving force for investigating these en-
zymes in rat brain has been the potential relevance to an
anderstanding of the regulation of amino acid receptors can
in Although the driving force for investigating these en-
zymes in rat brain has been the potential relevance to an
althounderstanding of the regulation of amino acid receptors cated t
in humans, the kynurenine aminotransfera zymes in rat brain has been the potential relevance to an $3H/A$
understanding of the regulation of amino acid receptors cate
in humans, the kynurenine aminotransferase activity of tire
human brain appears to be fundamenta understanding of the regulation of amino acid receptors
in humans, the kynurenine aminotransferase activity of
human brain appears to be fundamentally different from
that of the rat. No enzymic activity was detectable in
h in humans, the kynurenine aminotransferase activity of
human brain appears to be fundamentally different from
that of the rat. No enzymic activity was detectable in
human tissue by Okuno et al. (1991b) unless Tris buffers
 human brain appears to be fundamentally different from activation of the rat. No enzymic activity was detectable in polynoman tissue by Okuno et al. (1991b) unless Tris buffers survere used; two clearly distinct enzymes th that of the rat. No enzymic activity was detectable in human tissue by Okuno et al. (1991b) unless Tris buffers were used; two clearly distinct enzymes that were responsible for this activity were eventually isolated. The human tissue by Okuno et al. (1991b) unless Tris buffers
were used; two clearly distinct enzymes that were re-
sponsible for this activity were eventually isolated. The
properties of both of these proteins, which did not r were used; two clearly distinct enzymes that were re-
sponsible for this activity were eventually isolated. The im
properties of both of these proteins, which did not react bu
with antibodies to the rat enzyme, were signi sponsible for this activity were eventually isolated. The im
properties of both of these proteins, which did not react bu
with antibodies to the rat enzyme, were significantly fai
different from the rodent molecule. Most properties of both of these proteins, which did not react bull
with antibodies to the rat enzyme, were significantly fair
different from the rodent molecule. Most strikingly, the out
 K_m values for L-kynurenine were 8.3 with antibodies to the different from the rod K_m values for L-kynupyruvate as the aming H optimum of 9.6. There must, therefore fferent from the rodent molecule. Most strikingly, the $\frac{1}{n}$ values for L-kynurenine were 8.3 and 3.3 mM using ruvate as the amino acceptor, the former showing a I optimum of 9.6.
There must, therefore, be serious dou

 K_m values for L-kynurenine were 8.3 and 3.3 mM using degr
pyruvate as the amino acceptor, the former showing a nal
pH optimum of 9.6. tivel
There must, therefore, be serious doubts as to whether med
either of these enzy pyruvate as the amino acceptor, the former showing
pH optimum of 9.6.
There must, therefore, be serious doubts as to whet
either of these enzymes is of relevance to the metabolis
of kynurenines at physiological, or even re pH optimum of 9.6. tivels are to the serious doubts as to whether move ither of these enzymes is of relevance to the metabolism loof kynurenines at physiological, or even realistic pathoimorphical, levels and conditions. H There must, therefore, be serious doubts as to whether
either of these enzymes is of relevance to the metabolism
of kynurenines at physiological, or even realistic patho-
logical, levels and conditions. However, no details

STONE
n- technical factors, such as postmortem delay or early
er storage conditions. It would be of interest to compare STR EXECT EXECT STREAGHT CREAT ARREST MELT CONTROLLED STATE SURFERIST AND MORE POSTMORTED ASSEMBLED ASSEMBLED AND MORE POSTMORTED AND NOTELLA STATE OF OUR STATE AND MORE WE
technical factors, such as postmortem delay or early
storage conditions. It would be of interest to compare
postmortem enzyme activity in rats and activity in old
animals to determine whether such factors could account technical factors, such as postmortem delay or early storage conditions. It would be of interest to compare postmortem enzyme activity in rats and activity in old animals to determine whether such factors could account for technical factors, such as postmort
storage conditions. It would be of ir
postmortem enzyme activity in rats
animals to determine whether such factor
for the disappointing human results.
 $C²$ Hudsomanthanilia Acid Om **C.** *3-Hydroxyanthranilic Acid Oxygenase*

The conversion of 3-hydroxyanthranilic acid to quin-
olinate by hepatic 3HAO involves the initial production
of aminocarboxymuconic semialdehyde, which then olinate by hepatic 3HAO involves the initial production C. 3-Hydroxyanthranilic Acid Oxygenase
The conversion of 3-hydroxyanthranilic acid to quin-
olinate by hepatic 3HAO involves the initial production
of aminocarboxymuconic semialdehyde, which then
undergoes a nonenzymic cyc C. 3-Hydroxyanthranux Acta Oxygenase
The conversion of 3-hydroxyanthranilic acid to quin-
olinate by hepatic 3HAO involves the initial production
of aminocarboxymuconic semialdehyde, which then
undergoes a nonenzymic cycli The conversion of 3-hydroxyanthranilic acid to quin-
olinate by hepatic 3HAO involves the initial production
of aminocarboxymuconic semialdehyde, which then
undergoes a nonenzymic cyclisation to quinolinic acid
(Long et al olinate by hepatic 3HAO involves the initial production
of aminocarboxymuconic semialdehyde, which then
undergoes a nonenzymic cyclisation to quinolinic acid
(Long et al., 1954). There is also evidence for an enzyme,
inapp of aminocarboxymuconic semialdehyde, which tundergoes a nonenzymic cyclisation to quinolinic (Long et al., 1954). There is also evidence for an enzy inappropriately known as picolinic carboxylase, where dividends to aminom undergoes a nonenzymic cyclisation to quinolinic a
(Long et al., 1954). There is also evidence for an enzyr
inappropriately known as picolinic carboxylase, which
decarboxylates the unstable intermediate to aminon
conic sem (Long et al., 1954). There is also evidence for an enzyme,
inappropriately known as picolinic carboxylase, which
decarboxylates the unstable intermediate to aminomu-
conic semialdehyde. The latter can then undergo nonen-
z inappropriately known as picolinic carboxylase, which
decarboxylates the unstable intermediate to aminomu-
conic semialdehyde. The latter can then undergo nonen-
zymic cyclisation with the formation of picolinic acid.
The decarboxylates the unstable intermediate to aminomu-
conic semialdehyde. The latter can then undergo nonen-
zymic cyclisation with the formation of picolinic acid.
The latter sequence seems to occur especially when
3HAO is conic semialdehyde. The latter can then undergo no
zymic cyclisation with the formation of picolinic
The latter sequence seems to occur especially
3HAO is exposed to low concentrations of its subst
3HAO can be inhibited by zymic cyclisation with the formation of picolinic acid.
The latter sequence seems to occur especially when
3HAO is exposed to low concentrations of its substrate.
3HAO can be inhibited by 4-chloro-3-hydroxyanthranilic
acid The latter sequence seems to occur especially when
3HAO is exposed to low concentrations of its substrate.
3HAO can be inhibited by 4-chloro-3-hydroxyanthranilic
acid, which is effective against both liver and cerebral
enz IAO is exposed to low concentrations of its substrate.
IAO can be inhibited by 4-chloro-3-hydroxyanthranilic
id, which is effective against both liver and cerebral
zymes (Cook and Pogson, 1983; Heyes et al., 1988a).
It has

pate to inhibit kynurenine aminotransferase activity, it brain, where it is present in the soluble cytoplasmic
appears that this same enzyme may be responsible in fraction of rat brain tissue and exhibits a K_m of 3.6 $\$ 3HAO can be inhibited by 4-chloro-3-hydroxyanthranilic
acid, which is effective against both liver and cerebral
enzymes (Cook and Pogson, 1983; Heyes et al., 1988a).
It has been confirmed that 3HAO is also found in the
br acid, which is effective against both liver and cerebral
enzymes (Cook and Pogson, 1983; Heyes et al., 1988a).
It has been confirmed that 3HAO is also found in the
brain, where it is present in the soluble cytoplasmic
fra enzymes (Cook and Pogson, 1983; Heyes et al., 1988a).
It has been confirmed that 3HAO is also found in the
brain, where it is present in the soluble cytoplasmic
fraction of rat brain tissue and exhibits a K_m of 3.6 μ It has been confirmed that 3HAO is also found in the
brain, where it is present in the soluble cytoplasmic
fraction of rat brain tissue and exhibits a K_m of 3.6 μ M
for 3-hydroxyanthranilic acid with substantial subst brain, where it is present in the soluble cytoplasmic
fraction of rat brain tissue and exhibits a K_m of 3.6 μ M
for 3-hydroxyanthranilic acid with substantial substrate
selectivity; several excitatory amino acids toge fraction of rat brain tissue and exhibits a K_m of 3.6 μ M
for 3-hydroxyanthranilic acid with substantial substrate
selectivity; several excitatory amino acids together with
tryptophan and kynurenic acid did not influe for 3-hydroxyanthranilic acid with substantial substrate
selectivity; several excitatory amino acids together with
tryptophan and kynurenic acid did not influence enzyme
activity (Foster et al., 1986). There is only a mode selectivity; several excitatory amino acids together with
tryptophan and kynurenic acid did not influence enzyme
activity (Foster et al., 1986). There is only a moderate
variation of activity across the CNS with less than tryptophan and kynurenic acid did not influence enzyme
activity (Foster et al., 1986). There is only a moderate
variation of activity across the CNS with less than a 4-
fold difference in activity between olfactory bulb an variation of activity across the CNS with less than a 4-
fold difference in activity between olfactory bulb and
cerebellum. The enzyme appears to be bound to both
inner and outer surfaces of mitochondrial membranes (Kohler et a!., 1988a,b, 1989). dd difference in activity between olfactory bulb and
rebellum. The enzyme appears to be bound to both
ner and outer surfaces of mitochondrial membranes
fohler et al., 1988a,b, 1989).
Schwarcz and colleagues have now develo

cerebellum. The enzyme appears to be bound to both

inner and outer surfaces of mitochondrial membranes

(Kohler et al., 1988a,b, 1989).

Schwarcz and colleagues have now developed sensitive

immunohistochemical technique inner and outer surfaces of mitochondrial membranes

(Kohler et al., 1988a,b, 1989).

Schwarcz and colleagues have now developed sensitive

immunohistochemical techniques for localising 3HAO

within individual cells of the (Kohler et al., 1988a,b, 1989).
Schwarcz and colleagues have now developed sensitive
immunohistochemical techniques for localising 3HAO
within individual cells of the CNS (Okuno et al., 1987;
Kohler et al., 1988a,b, 1989). Schwarcz and colleagues have now developed sensitive
immunohistochemical techniques for localising 3HAC
within individual cells of the CNS (Okuno et al., 1987
Kohler et al., 1988a,b, 1989). Double labeling with the
3HAO an immunohistochemical techniques for localising 3HAO
within individual cells of the CNS (Okuno et al., 1987;
Kohler et al., 1988a,b, 1989). Double labeling with the
3HAO antibodies and glial fibrillary acidic protein indi-
c within individual cells of the CNS (Okuno et al., 1
Kohler et al., 1988a,b, 1989). Double labeling with
3HAO antibodies and glial fibrillary acidic protein i
cated the localisation of the former enzyme almost
tirely to gli Kohler et al., 1988a,b, 1989). Double labeling with the 3HAO antibodies and glial fibrillary acidic protein indicated the localisation of the former enzyme almost entirely to glial cells. The highest numbers of immunore-
a 3HAO antibodies and glial fibrillary acidic protein indicated the localisation of the former enzyme almost entirely to glial cells. The highest numbers of immunore-
active cells were found in the striatum, neocortex, hip-
 cated the localisation of the former enzyme almost entirely to glial cells. The highest numbers of immunore-
active cells were found in the striatum, neocortex, hip-
pocampus, and septal regions. Areas such as the
substant tirely to glial cells. The highest numbers of immunore-
active cells were found in the striatum, neocortex, hip-
pocampus, and septal regions. Areas such as the
substantia innominata and substantia nigra contained
fewer re active cells were found in the striatum, neocortex, hip-
pocampus, and septal regions. Areas such as the
substantia innominata and substantia nigra contained
fewer reactive glial cells. A moderately high density of
immunor pocampus, and septal regions. Areas such as the substantia innominata and substantia nigra contained fewer reactive glial cells. A moderately high density of immunoreactive cells was also noted in the olfactory bulb, altho substantia innominata and substantia nigra contai
fewer reactive glial cells. A moderately high density
immunoreactive cells was also noted in the olfact
bulb, although, whereas most brain regions exhibite
fairly homogeneo fewer reactive glial cells. A moderately high density of
immunoreactive cells was also noted in the olfactory
bulb, although, whereas most brain regions exhibited a
fairly homogeneous distribution of the enzyme through-
ou immunoreactive cells was also noted in the olfacto
bulb, although, whereas most brain regions exhibited
fairly homogeneous distribution of the enzyme throug
out the region, the olfactory bulb demonstrated a hig
degree of l bulb, although, whereas most brain regions exhibited a fairly homogeneous distribution of the enzyme through out the region, the olfactory bulb demonstrated a high degree of localisation of 3HAO in the internal and externa fairly homogeneous distribution of the enzyme througout the region, the olfactory bulb demonstrated a hidegree of localisation of 3HAO in the internal and ext
nal plexiform layers. Immunoreactivity was also retively intens out the region, the olfactory bulb demonstrated a high
degree of localisation of 3HAO in the internal and exter-
nal plexiform layers. Immunoreactivity was also rela-
tively intense in thalamic nuclei, especially the ventr degree of localisation of 3HAO in the internal and external plexiform layers. Immunoreactivity was also relatively intense in thalamic nuclei, especially the ventro-
medial and dorsomedial portions, with very little 3HAC
l nal plexiform layers. Immunoreactivity was also rel
tively intense in thalamic nuclei, especially the ventr
medial and dorsomedial portions, with very little 3HA
localised to hypothalamic regions. In the cerebellu
immunore tively intense in thalamic nuclei, especially the ventro-
medial and dorsomedial portions, with very little 3HAO
localised to hypothalamic regions. In the cerebellum,
immunoreactivity for 3HAO was localised almost exclu-
s medial and dorsomedial portions, with very little 3HAO localised to hypothalamic regions. In the cerebellum,
immunoreactivity for 3HAO was localised almost exclu-
sively to the granule cell layer. Despite the primary
local

QUINOLINIC AND KY

clearly identifiable as neurones, were also stained for

3HAO, especially in the olfactory bulb (Kohler et al., C QUINOLINIC AND K
21HAO, especially in the olfactory bulb (Kohler et al.,
1988a). 1988a). Exarly identifiable as neurones, were also stained
HAO, especially in the olfactory bulb (Kohler et a
88a).
Activity of 3HAO in vitro has been studied by admin-
tering 3-hydroxyanthranilic acid to striatal slices. T

clearly identifiable as neurones, were also stained for not 3HAO, especially in the olfactory bulb (Kohler et al., C
1988a).
Activity of 3HAO in vitro has been studied by admin-
istering 3-hydroxyanthranilic acid to striat 3HAO, especially in the olfactory bulb (Kohler et al., Gotal 1988a).

1988a).

Activity of 3HAO in vitro has been studied by adminitering 3-hydroxyanthranilic acid to striatal slices. This convessuited in the formation of 1988a).

Activity of 3HAO in vitro has been studied by admin-

istering 3-hydroxyanthranilic acid to striatal slices. This

convessulted in the formation of quinolinic acid, part of which

was retained intracellularly and Activity of 3HAO in vitro has been studied by administering 3-hydroxyanthranilic acid to striatal slices. This resulted in the formation of quinolinic acid, part of which was retained intracellularly and part released into istering 3-hydroxyanthranilic acid to striatal slices. This consider resulted in the formation of quinolinic acid, part of which was retained intracellularly and part released into the medium in a ratio of 4.6:1 (Speciale was retained intracellularly and part released into the medium in a ratio of 4.6:1 (Speciale and Schwarcz, 1991).
After the striatum was lesioned with ibotenic acid, slices were found to contain 6-fold more quinolinic acid was retained intracellularly and part released into the medium in a ratio of 4.6:1 (Speciale and Schwarcz, 1991). of After the striatum was lesioned with ibotenic acid, slices the were found to contain 6-fold more quinoli medium in a ratio of 4.6:1 (Speciale and Schwarcz, 1991).
After the striatum was lesioned with ibotenic acid, slices
were found to contain 6-fold more quinolinic acid intra-
cellularly but to yield a 10-fold greater amount After the striatum was lesioned with ibotenic acid, slices
were found to contain 6-fold more quinolinic acid intra-
cellularly but to yield a 10-fold greater amount than
control slices into the medium, with a progressive i were found to contain 6-fold more quinolinic acid intra-
cellularly but to yield a 10-fold greater amount than
control slices into the medium, with a progressive in-
crease of medium concentration during the 90-minute
meas cellularly but to yield a 10-fold greater amount than
control slices into the medium, with a progressive in-
crease of medium concentration during the 90-minute
measurement period. In view of the glial proliferation
that control slices into the medium, with a progressive in-
crease of medium concentration during the 90-minute are the
measurement period. In view of the glial proliferation has be
that occurs in response to excitotoxin lesio crease of medium concentration during the 90-minute
measurement period. In view of the glial proliferation
that occurs in response to excitotoxin lesions, this profile
is entirely consistent with a glial localisation of 3 measurement period. In view of the glial proliter
that occurs in response to excitotoxin lesions, this p
is entirely consistent with a glial localisation of 3
and is supported by a report that human glioma tis
also able to that occurs in response to excitotoxin lesions, this profile
is entirely consistent with a glial localisation of 3HAO
and is supported by a report that human glioma tissue is
also able to synthesise quinolinate from 3-hyd is entirely consistent with a glial localisation of 3HAO
and is supported by a report that human glioma tissue is
also able to synthesise quinolinate from 3-hydroxyan-
thranilate (Vezzani et al., 1991a). The latter compoun also able to synthesise quinolinate from 3-hydroxyan-
thranilate (Vezzani et al., 1991a). The latter compound
is a better precursor compound in this tissue than L-
kynurenine or tryptophan. The ability of 3-hydroxyan-
thra thranilate (Vezzani et al., 1991a). The latter compound
is a better precursor compound in this tissue than L-
kynurenine or tryptophan. The ability of 3-hydroxyan-
thranilic acid loading to induce such marked increases
of thranilate (Vezzani et al., 1991a). The latter compound
is a better precursor compound in this tissue than L-
kynurenine or tryptophan. The ability of 3-hydroxyan-
thranilic acid loading to induce such marked increases
of is a better precursor compound in this tissue than L
kynurenine or tryptophan. The ability of 3-hydroxyan
thranilic acid loading to induce such marked increase
of quinolinic acid concentrations would seem to confirm
that 3 kynurenine or tryptophan. The ability of 3-
thranilic acid loading to induce such marke
of quinolinic acid concentrations would seen
that 3HAO does not normally appear to b
limiting enzyme of the kynurenine pathway. of quinolinic acid concentrations would se

that 3HAO does not normally appear to

limiting enzyme of the kynurenine pathwa

D. Quinolinic Acid Phosphoribosyltransfere

QPRT catalyses the condensation of gra

limiting enzyme of the kynurenine pathway.

D. Quinolinic Acid Phosphoribosyltransferase

QPRT catalyses the condensation of quinolinate

phosphoribosyl-pyrophosphate as well as the decart

ylation of the intermediate conj D. Quinolinic Acid Phosphoribosyltransferase whose
QPRT catalyses the condensation of quinolinate and
phosphoribosyl-pyrophosphate as well as the decarbox-
ylation of the intermediate conjugate to nicotinic acid
mononucle D. Quintime Actu I hospion loosytruis jeruse
QPRT catalyses the condensation of quinolinate and
phosphoribosyl-pyrophosphate as well as the decarbox-
ylation of the intermediate conjugate to nicotinic acid
mononucleotide. GPRT catalyses the condensation of quinolinate and
phosphoribosyl-pyrophosphate as well as the decarbox-
ylation of the intermediate conjugate to nicotinic acid
fermononucleotide. GPRT appears to exist in several iso-
for ylation of the intermediate conjugate to nicotinic acid mononucleotide. QPRT appears to exist in several iso-
forms. The enzymes detected in liver, kidney, and brain
show different electrophoretic mobilities and molecular
 ylation of the intermediate conjugate to nicotinic acid mononucleotide. QPRT appears to exist in several iso-
forms. The enzymes detected in liver, kidney, and brain
show different electrophoretic mobilities and molecular
 mononucleotide. QPRT appears to exist in several iso-
forms. The enzymes detected in liver, kidney, and brain
show different electrophoretic mobilities and molecular
properties despite comparable reactivity with antibodie forms. The enzymes detected in liver, kidney, and brashow different electrophoretic mobilities and molecul properties despite comparable reactivity with antibod to rat liver enzyme (Okuno and Schwarcz, 1985). Tenzyme can b show different electrophoretic mobilities and molecular properties despite comparable reactivity with antibodies to rat liver enzyme (Okuno and Schwarcz, 1985). The enzyme can be inhibited by several analogues of quino-
l properties despite comparable reactivity with antibodies
to rat liver enzyme (Okuno and Schwarcz, 1985). The
enzyme can be inhibited by several analogues of quino
linate (Kalikin and Calvo, 1988). In the CNS, QPRT was
init to rat liver enzyme (Okuno and Schwarcz, 1985). The
enzyme can be inhibited by several analogues of quino-
linate (Kalikin and Calvo, 1988). In the CNS, QPRT was
initially localised to the nerve ending synaptosomal frac-
t enzyme can be inhibited by several analogues of quino-

linate (Kalikin and Calvo, 1988). In the CNS, QPRT was

initially localised to the nerve ending synaptosomal frac-

tion (Foster et al., 1985a,b) giving rise to spec linate (Kalikin and Calvo, 1988). In the CNS, QPRT was
initially localised to the nerve ending synaptosomal frac-
tion (Foster et al., 1985a,b) giving rise to speculation
that its function here is primarily concerned with initially localised to the nerve ending synaptosomal fraction (Foster et al., 1985a,b) giving rise to speculation
that its function here is primarily concerned with the
potential neuromodulatory role of quinolinic acid pre tion (Foster et al.,
that its function he
potential neuromodu
in the extracellular s
glutamate receptors.
Subsequent work, potential neuromodulatory role of quinolinic acid present
in the extracellular space and acting at NMDA-sensitive
glutamate receptors.
Subsequent work, using immunocytochemical methods
and antibodies to liver QPRT, reveale

potential neuromodulatory role of quinolinic acid presen
in the extracellular space and acting at NMDA-sensitiv
glutamate receptors.
Subsequent work, using immunocytochemical method
and antibodies to liver QPRT, revealed a in the extracellular space and acting at NMDA-sensitivelutamate receptors.

Subsequent work, using immunocytochemical method

and antibodies to liver QPRT, revealed a predominar

location in CNS glial cells and some ventri glutamate receptors. (Mc Subsequent work, using immunocytochemical methods pour and antibodies to liver QPRT, revealed a predominant location in CNS glial cells and some ventricular epen-
dymal cells, with a relatively sma Subsequent work, using immunocytochemical methods
and antibodies to liver QPRT, revealed a predominant
location in CNS glial cells and some ventricular epen-
dymal cells, with a relatively small portion occurring in
neuro and antibodies to liver QPRT, revealed a predomina
location in CNS glial cells and some ventricular eper
dymal cells, with a relatively small portion occurring
neurones. The relevant glial cells were generally sm
(<10 μ location in CNS glial cells and some ventricular ep
dymal cells, with a relatively small portion occurring
neurones. The relevant glial cells were generally sn
 $(<10 \ \mu m$ in diameter) and of variable shape, some exh
iting dymal cells, with a relatively small portion occurring
neurones. The relevant glial cells were generally sn
 $(<10 \mu m$ in diameter) and of variable shape, some ex-
iting a remarkably close and specific physical relati
ship neurones. The relevant glial cells were generally small $\langle 10 \mu m$ in diameter) and of variable shape, some exhibiting a remarkably close and specific physical relationship with neurones and suggesting a possible oligoden (\leq 10 μ m in diameter) and of variable shape, some exhibiting a remarkably close and specific physical relation-
ship with neurones and suggesting a possible oligoden-
droglial identity (Kohler et al., 1987). Stained iting a remarkably close and specific physical relationship with neurones and suggesting a possible oligoden-
droglial identity (Kohler et al., 1987). Stained neurones
were generally 15 to 20 μ m in diameter and were lo ship with neurones and suggesting a possible oligoden-
droglial identity (Kohler et al., 1987). Stained neurones Gal
were generally 15 to 20 μ m in diameter and were located repo
primarily in the thalamus, hypothalamus,

YNURENIC ACIDS
membrane-bound organelles distinct from mitochondri
Golgi vesicles, and lysosomes (Kohler et al., 1988c). YNURENIC ACIDS
membrane-bound organelles distinct from mitochond
Golgi vesicles, and lysosomes (Kohler et al., 1988c).
The identity of these organelles remains unknown,

GUINOLINIC AND KYNURENIC ACIDS
also stained for membrane-bound organelles distinct from mitochondria,
b (Kohler et al., Golgi vesicles, and lysosomes (Kohler et al., 1988c).
The identity of these organelles remains unknown membrane-bound organelles distinct from mitochondria,
Golgi vesicles, and lysosomes (Kohler et al., 1988c).
The identity of these organelles remains unknown, but
their existence might suggest a degree of subcellular
compar membrane-bound organelles distinct from mitochondri
Golgi vesicles, and lysosomes (Kohler et al., 1988c).
The identity of these organelles remains unknown, be
their existence might suggest a degree of subcellula
compartmen way. The identity of these organelles remains unknown, but
eir existence might suggest a degree of subcellular
mpartmentation for portions of the kynurenine path-
y.
It is interesting to note the comparative distribution
3HAO a

their existence might suggest a degree of subcellular
compartmentation for portions of the kynurenine path-
way.
It is interesting to note the comparative distribution
of 3HAO and QPRT in brain, because the ratio between
t compartmentation for portions of the kynurenine pathway.

It is interesting to note the comparative distribution

of 3HAO and QPRT in brain, because the ratio between

them varies throughout the neuraxis, being highest in
 way.
It is interesting to note the comparative distribution
of 3HAO and QPRT in brain, because the ratio between
them varies throughout the neuraxis, being highest in
the frontal neocortex, striatum, and hippocampus. The
c It is interesting to note the comparative distribution
of 3HAO and QPRT in brain, because the ratio between
them varies throughout the neuraxis, being highest in
the frontal neocortex, striatum, and hippocampus. The
corres of 3HAO and QPRT in brain, because the ratio between
them varies throughout the neuraxis, being highest in
the frontal neocortex, striatum, and hippocampus. The
correspondence between those areas showing the greatest
dispa them varies throughout the neuraxis, being highest in
the frontal neocortex, striatum, and hippocampus. The
correspondence between those areas showing the greatest
disparity between these enzymes and those areas that
are t the frontal neocortex, striatum, and hippocampus. The
correspondence between those areas showing the greatest
disparity between these enzymes and those areas that
are the most susceptible to neurodegenerative changes
has b correspondence between those areas showing the gread
disparity between these enzymes and those areas t
are the most susceptible to neurodegenerative chan
has been remarked upon (Foster et al., 1986). There
clear lack of co disparity between these enzymes and those areas that
are the most susceptible to neurodegenerative changes
has been remarked upon (Foster et al., 1986). There is a
clear lack of correspondence between glial cells contain-
 are the most susceptible to neurodegenerative changes
has been remarked upon (Foster et al., 1986). There is a
clear lack of correspondence between glial cells contain-
ing the synthetic enzyme 3HAO and the quinolinate
cat has been remarked upon (Foster et al., 1986). There is a clear lack of correspondence between glial cells containing the synthetic enzyme 3HAO and the quinolinate catabolic enzyme QPRT. This implies that quinolinic acid mu clear lack of correspondence between glial cells contain-
ing the synthetic enzyme 3HAO and the quinolinate
catabolic enzyme QPRT. This implies that quinolinic
acid must be catabolised in cells other than those re-
sponsib catabolic enzyme QPRT. This implies that quinolinic
acid must be catabolised in cells other than those re-
sponsible for its production and that, consequently, it
must enter the extracellular space in its migration be-
twe catabolic enzym
acid must be ca
sponsible for its
must enter the two.
The localisatic id must be catabolised in cells other than those r
onsible for its production and that, consequently,
ust enter the extracellular space in its migration b
veen the two.
The localisation of QPRT in glial cells, mainly astr

that 3HAO does not normally appear to be the rate-
limiting enzyme of the kynurenine pathway.
D. Quinolinic Acid Phosphoribosyltransferase
QPRT catalyses the condensation of quinolinate and
qPRT catalyses the condensation clear lack of correspondence between glial cells contain-
ing the synthetic enzyme GPRT. This implies that quinolinite
catabolic enzyme GPRT. This implies that quinolinic
acid must be catabolised in cells other than those must enter the extracellular space in its migration be-
tween the two.
The localisation of QPRT in glial cells, mainly astro-
cytes, and some neurones has also been claimed in human
striatum (Du et al., 1991). Here, the ne tween the two.
The localisation of QPRT in glial cells, mainly astro-
cytes, and some neurones has also been claimed in human
striatum (Du et al., 1991). Here, the neurones were of at
least three varieties, varying conside The localisation of QPRT in glial cells, mainly astrocytes, and some neurones has also been claimed in human
striatum (Du et al., 1991). Here, the neurones were of at
least three varieties, varying considerably in size but cytes, and some neurones has also been claimed in human
striatum (Du et al., 1991). Here, the neurones were of at
least three varieties, varying considerably in size but
appearing to include aspiny neurones. It is not clea striatum (Du et al., 1991). Here, the neurones were of at least three varieties, varying considerably in size but appearing to include aspiny neurones. It is not clear whether there is a significant degree of interspecies least three varieties, varying considerably in size but
appearing to include aspiny neurones. It is not clear
whether there is a significant degree of interspecies var-
iation in the location of these enzymes, although a d appearing to include aspiny neurones. It is not clear
whether there is a significant degree of interspecies var-
iation in the location of these enzymes, although a de-
tailed comparison of the distribution of 3HAO and
QPR whether there is a significant degree of interspecies variation in the location of these enzymes, although a detailed comparison of the distribution of 3HAO and QPRT in hippocampal tissue has revealed marked differences be iation in the location of these enzymes, although a detailed comparison of the distribution of 3HAO and QPRT in hippocampal tissue has revealed marked differences between rat and human tissue (Kohler et al., 1988b). Simila tailed comparison of the distribution of 3HAO and QPRT in hippocampal tissue has revealed marked differences between rat and human tissue (Kohler et al., 1988b). Similarly, relatively little information has been published ferences between rat and human tissue (Kohler et al., 1988b). Similarly, relatively little information has been published concerning species or strain differences in other enzymes of the kynurenine pathway. Small, but occa ferences between rat and human tissue (Kohler et al., 1988b). Similarly, relatively little information has been published concerning species or strain differences in other enzymes of the kynurenine pathway. Small, but occa 1988b). Similarly, relatively little information has been
published concerning species or strain differences in
other enzymes of the kynurenine pathway. Small, but
occasionally significant, differences have been claimed
fo published concerning species or strain differences in
other enzymes of the kynurenine pathway. Small, but
occasionally significant, differences have been claimed
for some rat strains (Shibata et al., 1986; Costa et al.,
19 other enzymes of the kynurenine pathway. Small, bu
occasionally significant, differences have been claimed
for some rat strains (Shibata et al., 1986; Costa et al.
1982), but to date, no meaningful correlations have been
e occasionally significant, differences have
for some rat strains (Shibata et al., 19
1982), but to date, no meaningful correla
established with other neuropharmacolo,
physiological, or behavioural parameters
The pharmacolog for some rat strains (Shibata et al., 1986; Costa et al., 1982), but to date, no meaningful correlations have been established with other neuropharmacological, functional, physiological, or behavioural parameters.
The phar

established with other neuropharmacological, functional,
physiological, or behavioural parameters.
The pharmacology of kynurenine-metabolising en-
zymes has not been studied in great depth, but several of
the enzymes are k physiological, or behavioural parameters.
The pharmacology of kynurenine-metabolising en-
zymes has not been studied in great depth, but several of
the enzymes are known to be affected by a number of
antibiotic, anti-schis The pharmacology of kynurenine-metabolising en
zymes has not been studied in great depth, but several c
the enzymes are known to be affected by a number c
antibiotic, anti-schistosomal, and psychotropic agent
(Mostafa et a zymes has not been studied in great depth, but several of
the enzymes are known to be affected by a number of
antibiotic, anti-schistosomal, and psychotropic agents
(Mostafa et al., 1982), as well as by oestrogenic com-
p the enzymes are known to be affected by a number of antibiotic, anti-schistosomal, and psychotropic agents (Mostafa et al., 1982), as well as by oestrogenic compounds, although emphasis has usually been placed on the perip antibiotic, anti-schistosomal, a
(Mostafa et al., 1982), as well
pounds, although emphasis has
the peripherally located enzym
reviewed by El-Sewedy (1989). (Mostafa et al., 1982), as well as by oestrogenic compounds, although emphasis has usually been placed on the peripherally located enzymes. These aspects were reviewed by El-Sewedy (1989).
 III. Kynurenines in Brain

Ear

concerned primarily with metabolism in peripheral tissues. Although TDO activity was reported in brain by III. Kynurenines in Brain
Early studies of the biochemistry of kynurenines were
concerned primarily with metabolism in peripheral tis-
sues. Although TDO activity was reported in brain by
Gal et al. (1966), it was not unti Early studies of the biochemistry of kynurenines were
concerned primarily with metabolism in peripheral tis-
sues. Although TDO activity was reported in brain by
Gal et al. (1966), it was not until 1977 that the first
repo Early studies of the biochemistry of kynurenines we
concerned primarily with metabolism in peripheral tis
sues. Although TDO activity was reported in brain b
Gal et al. (1966), it was not until 1977 that the fir-
reports a concerned primarily with metabolism in peripheral tis-
sues. Although TDO activity was reported in brain by
Gal et al. (1966), it was not until 1977 that the first
reports appeared of the definitive presence of any prod-
u sues. Although TDO activity was reported in brain by
Gal et al. (1966), it was not until 1977 that the first
reports appeared of the definitive presence of any prod-
ucts of this pathway in the CNS. Joseph et al (1978) and

identification of L-kynurenine in brain tissue. The latter STONE
identification of L-kynurenine in brain tissue. The latter
authors also reported significant concentrations of 3-
hydroxykynurenine and kynuramine in brain (Gal and e: STONE
identification of L-kynurenine in brain tissue. The latter
authors also reported significant concentrations of 3-
hydroxykynurenine and kynuramine in brain (Gal and exh
Sherman, 1980), although recent work has called identification of L-kynurenine in brain tissue. The latter rap
authors also reported significant concentrations of 3- des
hydroxykynurenine and kynuramine in brain (Gal and exh
Sherman, 1980), although recent work has call identification of L-kynurenine in brain tissue. The latter rap
authors also reported significant concentrations of 3-
hydroxykynurenine and kynuramine in brain (Gal and exl
Sherman, 1980), although recent work has called i authors also rep
hydroxykynureni
Sherman, 1980),
question the val
(Joseph, 1989).
Approximately droxykynurenine and kynuramine in brain (Gal and exerman, 1980), although recent work has called into lot estion the validity of some of the techniques used coseph, 1989).
Approximately 40% of the L-kynurenine detected A

Sherman, 1980), although recent work has called into
question the validity of some of the techniques used
(Joseph, 1989).
Approximately 40% of the L-kynurenine detected
within the CNS is synthesised in that tissue. This ca question the validity of some of the techniques used
(Joseph, 1989).
Approximately 40% of the L-kynurenine detected
within the CNS is synthesised in that tissue. This cal-
culation is based on the use of radiolabeled trypt (Joseph, 1989).

Approximately 40% of the L-kynurenine detected A .

within the CNS is synthesised in that tissue. This calculation is based on the use of radiolabeled tryptophan

and implies that the other 60% of brain Approximately 40% of the L-kynurenine detected within the CNS is synthesised in that tissue. This calculation is based on the use of radiolabeled tryptophan and implies that the other 60% of brain L-kynurenine is derived within the CNS is synthesised in that tissue. This calculation is based on the use of radiolabeled tryptophan b
and implies that the other 60% of brain L-kynurenine is 1:
derived by uptake from plasma kynurenines synthesis culation is based on the use of radiolabeled tryptop
and implies that the other 60% of brain L-kynurenin
derived by uptake from plasma kynurenines synthes
in peripheral tissues. Other work in support of
interpretation was and implies that the other 60% of brain L-kynurenine is
derived by uptake from plasma kynurenines synthesised
in peripheral tissues. Other work in support of this
interpretation was performed by Joseph and Hall-Tip-
ping (derived by uptake from plasma kynurenines synthesised
in peripheral tissues. Other work in support of this
interpretation was performed by Joseph and Hall-Tip-
ping (1978), who inhibited tryptophan dioxygenase pe-
ripheral in peripheral tissues. Other work in support of this
interpretation was performed by Joseph and Hall-Tip-
ping (1978), who inhibited tryptophan dioxygenase pe-
ripherally and observed that a subsequent tryptophan
load caus interpretation was performed by Joseph and Hall-Tip-

ping (1978), who inhibited tryptophan dioxygenase pe-

ripherally and observed that a subsequent tryptophan

of load caused the expected reduced elevation of plasma Lping (1978), who inhibited tryptophan dioxygenase peripherally and observed that a subsequent tryptophan load caused the expected reduced elevation of plasma L-kynurenine concentration but that the increase of brain L-kynu ripherally and observed that a subsequent tryptophan of load caused the expected reduced elevation of plasma L -
kynurenine concentration but that the increase of brain try
L-kynurenine concentrations was greater than in load caused the expected reduced elevation of plasma L-kynurenine concentration but that the increase of brain
L-kynurenine concentrations was greater than in control
animals. A similar dissociation between plasma and brai kynurenine concentration but that the increase of brain
L-kynurenine concentrations was greater than in control
ue
animals. A similar dissociation between plasma and brain
male. A similar dissociation between plasma and br L-kynurenine concentrations was greater than in control
animals. A similar dissociation between plasma and brain
L-kynurenine concentrations was also detected after sub-
jecting animals to stress and administering valine, animals. A similar dissociation between plasma and brain
L-kynurenine concentrations was also detected after sub-
jecting animals to stress and administering valine, which
reduces tryptophan uptake into brain (Kennett and kynurenine concentrations was also detected after sub-
ting animals to stress and administering valine, which
duces tryptophan uptake into brain (Kennett and Jo-
ph, 1981).
Young et al. (1983) also argued that much of the

jecting animals to stress and administering valine, which
reduces tryptophan uptake into brain (Kennett and Jo-
seph, 1981).
Young et al. (1983) also argued that much of the L-
kynurenine found in the CSF is of peripheral reduces tryptophan uptake into brain (Kennett and Jo-
seph, 1981).
Voung et al. (1983) also argued that much of the L-
kynurenine found in the CSF is of peripheral origin. the
Their conclusion was based partly on their fai seph, 1981).

Young et al. (1983) also argued that much of the L-kynurenine found in the CSF is of peripheral origin.

Their conclusion was based partly on their failure to

detect any gradient of L-kynurenine concentratio Young et al. (1983) also argued that much of the L-
kynurenine found in the CSF is of peripheral origin. the
Their conclusion was based partly on their failure to
the
detect any gradient of L-kynurenine concentration me
th kynurenine found in the CSF is of peripheral origin. the Their conclusion was based partly on their failure to the detect any gradient of L-kynurenine concentration methroughout the CSF and partly on the fact that the of p Their conclusion was based partly on their failure to that detect any gradient of L-kynurenine concentration met throughout the CSF and partly on the fact that the of plasma to CSF ratio of L-kynurenine was higher than tox detect any gradient of L-kynurenine concentration
throughout the CSF and partly on the fact that the
plasma to CSF ratio of L-kynurenine was higher the
that of tryptophan and other amino acids transported if
the neutral am plasma to CSF ratio of L-kynurenine was higher than
that of tryptophan and other amino acids transported by
the neutral amino acid carrier. There was also no corre-
lation between CSF tryptophan and L-kynurenine levels.

that of tryptophan and other amino acids transported by
the neutral amino acid carrier. There was also no corre-
lation between CSF tryptophan and L-kynurenine levels.
There continues to be argument as to whether the
effec the neutral amino acid carrier. There was also no corre-
lation between CSF tryptophan and L-kynurenine levels.
There continues to be argument as to whether the
effects of peripherally administered L-kynurenine can
growing lation between CSF tryptophan and L-kynurenine levels.
There continues to be argument as to whether the
effects of peripherally administered L-kynurenine can
modify CNS activity by competition with the uptake of
tryptophan There continues to be argument as to whether the
effects of peripherally administered L-kynurenine can
modify CNS activity by competition with the uptake of
tryptophan by the large neutral amino acid carrier
(Green and Cur effects of peripherally administered L-kynurenine can
modify CNS activity by competition with the uptake of
tryptophan by the large neutral amino acid carrier
(Green and Curzon, 1970). It has been pointed out,
however, tha modify CNS activity by competition with the uptake of mitryptophan by the large neutral amino acid carrier bri
(Green and Curzon, 1970). It has been pointed out, gen
however, that the normal plasma L-kynurenine levels, str tryptophan by the large neutral amino acid carrier (Green and Curzon, 1970). It has been pointed out, however, that the normal plasma L-kynurenine levels, even after loading with tryptophan or L-kynurenine, are in the low (Green and Curzon, 1970). It has been pointed out,
however, that the normal plasma L-kynurenine levels,
even after loading with tryptophan or L-kynurenine, are
in the low nanomolar range (Naito et al., 1987; Joseph,
1989), however, that the normal plasma L-kynurenine levels, st
even after loading with tryptophan or L-kynurenine, are
in the low nanomolar range (Naito et al., 1987; Joseph,
1989), whereas concentrations at least 1000-fold highe even after loading with tryptop
in the low nanomolar range (N
1989), whereas concentrations
are required to produce a barel
tryptophan uptake into brain.
It should be emphasised the the low nanomolar range (Naito et al., 1987; Joseph,
89), whereas concentrations at least 1000-fold higher the
e required to produce a barely detectable reduction of do
ptophan uptake into brain. a 1
It should be emphasise

1989), whereas concentrations at least 1000-fold higher equired to produce a barely detectable reduction tryptophan uptake into brain.
It should be emphasised that, as anticipated by discussion of enzyme distributions, the are required to produce a barely detectable reduction of do
tryptophan uptake into brain. a 1
It should be emphasised that, as anticipated by the al.
discussion of enzyme distributions, there is no relation-
ship between t tryptophan uptake into brain.
It should be emphasised that, as anticipated by the
discussion of enzyme distributions, there is no relation-
ship between the presence of kynurenines in the brain
and the existence of 5HT-rel It should be emphasised that, as anticipated by the
discussion of enzyme distributions, there is no relation-
ship between the presence of kynurenines in the brain-
and the existence of 5HT-releasing neurones. Indeed
reser discussion of enzyme distributions, there is no relation-
ship between the presence of kynurenines in the brain
and the existence of 5HT-releasing neurones. Indeed,
reserpine- or toxin-mediated destruction of 5HT neu-
rone ship between the presence of kynurenines in the brand the existence of 5HT-releasing neurones. Indereserpine- or toxin-mediated destruction of 5HT narones results in the elevation of cerebral L-kynureniconcentrations, poss reserpine- or toxin-mediated destruction of 5HT neurones results in the elevation of cerebral L-kynurenine concentrations, possibly due to the diversion of trypto-
phan along the kynurenine pathway (Joseph, 1989).
L-Kynure

rones results in the elevation of cerebral L-kynurenine
concentrations, possibly due to the diversion of trypto-
phan along the kynurenine pathway (Joseph, 1989).
L-Kynurenine has been demonstrated in human brain
tissue po concentrations, possibly due to the diversion of trypto-charaboral phan along the kynurenine pathway (Joseph, 1989). work L-Kynurenine has been demonstrated in human brain star tissue post mortem (Joseph et al., 1978; Ried phan along the kynurenine pathway (Joseph, 1989).

L-Kynurenine has been demonstrated in human brain

tissue post mortem (Joseph et al., 1978; Riederer et al.,

1981), and although no difference has been reported in

brain L-Kynurenine has been demonstrated in human brain statissue post mortem (Joseph et al., 1978; Riederer et al., gro
1981), and although no difference has been reported in Eve
brain samples from schizophrenic and normal subj

rapid increase of brain L-kynurenine concentration after NE
rapid increase of brain L-kynurenine concentration after
death. Despite this difficulty, it was noted that patients
exhibiting partial complex seizures had significantly WE
rapid increase of brain L-kynurenine concentration after
death. Despite this difficulty, it was noted that patients
exhibiting partial complex seizures had significantly
lower concentrations of L-kynurenine in CSF than rapid increase of brain L-kynurenine concentration after
death. Despite this difficulty, it was noted that patients
exhibiting partial complex seizures had significantly
lower concentrations of L-kynurenine in CSF than did rapid increase of brain L-kynurenine codeath. Despite this difficulty, it was nexhibiting partial complex seizures
lower concentrations of L-kynurenine
control patients (Young et al., 1983). **Exhibiting partial com

lower concentrations of

control patients (Young
** *A. Quinolinic Acid***

The first reports of the** Iower concentrations of L-kynurenine in CSF than did
control patients (Young et al., 1983).
A. Quinolinic Acid
The first reports of the presence of quinolinic acid in

control patients (Young et al., 1983).

A. Quinolinic Acid

The first reports of the presence of quinolinic acid in

brain (Lombardi et al., 1983a,b; Wolfensberger et al.,

1984) followed the development of a technique wit 4. Quinolinic Acid

The first reports of the presence of quinolinic acid in

brain (Lombardi et al., 1983a,b; Wolfensberger et al.,

1984) followed the development of a technique with

substantially increased sensitivity c substantially increased sensitivity compared to the presence of quinolinic acid brain (Lombardi et al., 1983a,b; Wolfensberger et a 1984) followed the development of a technique with substantially increased sensitivity com The first reports of the presence of quinolinic acid in
brain (Lombardi et al., 1983a,b; Wolfensberger et al.,
1984) followed the development of a technique with
substantially increased sensitivity compared with previ-
ous brain (Lombardi et al., 1983a,b; Wolfensberger et al., 1984) followed the development of a technique with substantially increased sensitivity compared with previously available methods (Moroni et al., 1989a; table 1). A ma 1984) followed the development of a technique with
substantially increased sensitivity compared with previ-
ously available methods (Moroni et al., 1989a; table 1).
A mass spectrometric method was described that yielded
va substantially increased sensitivity compared with previously available methods (Moroni et al., 1989a; table 1).
A mass spectrometric method was described that yielded
values of up to 12 pmol/mg protein or 2.1 nmol/g tissue ously available methods (Moroni et al., 1989a; table 1).
A mass spectrometric method was described that yielded
values of up to 12 pmol/mg protein or 2.1 nmol/g tissue
of quinolinate in rat brain (Lombardi et al., 1983a) A mass spectrometric method was described that yielded
values of up to 12 pmol/mg protein or 2.1 nmol/g tissue
of quinolinate in rat brain (Lombardi et al., 1983a) and
a 150% increase in those concentrations in response to values of up to 12 pmol/mg protein or 2.1 nmol/g tis
of quinolinate in rat brain (Lombardi et al., 1983a) a
a 150% increase in those concentrations in response
tryptophan loading (Lombardi et al., 1983b). These v
ues repr a 150% increase in those concentrations in response to tryptophan loading (Lombardi et al., 1983b). These values represent whole brain concentrations of approximately 2 μ M and, although a measurable degree of heterogen a 150% increase in those concentrations in response tryptophan loading (Lombardi et al., 1983b). These values represent whole brain concentrations of approximately 2 μ M and, although a measurable degree of heterogeneit tryptophan loading (Lombardi et al., 1983b). These values represent whole brain concentrations of approximately 2 μ M and, although a measurable degree of heterogeneity throughout the brain was reported, with highest le ues represent whole brain concentrations of approxi-
mately 2 μ M and, although a measurable degree of het-
erogeneity throughout the brain was reported, with high-
est levels being recorded in neocortex (2.1 nmol/g) an mately 2 μ M and, although a measurable degree of herogeneity throughout the brain was reported, with higest levels being recorded in neocortex (2.1 nmol/g) a lowest in the striatum (0.6 nmol/g), it has proved diffice t erogeneity throughout the brain was reported, with highest levels being recorded in neocortex (2.1 nmol/g) and
lowest in the striatum (0.6 nmol/g) , it has proved difficult
to replicate these results. There is no apparen est levels being recorded in neocortex (2.1 nmol/g) and
lowest in the striatum (0.6 nmol/g) , it has proved difficult
to replicate these results. There is no apparent correla-
tion between the distribution of quinolinate lowest in the striatum (0.6 nmol/g) , it has proved difficult
to replicate these results. There is no apparent correla-
tion between the distribution of quinolinate and 5HT in
the brain areas studied (Moroni et al., 1984a to replicate these results. There is no apparent correlation between the distribution of quinolinate and 5HT in the brain areas studied (Moroni et al., 1984a), a finding that implies a separate compartmentation of the rele tion between the distribution of quinolinate and 5HT in
the brain areas studied (Moroni et al., 1984a), a finding
that implies a separate compartmentation of the relevant
metabolic pathways and that is supported by the fai the brain areas studied (Moroni et a
that implies a separate compartment
metabolic pathways and that is supp
of 5,7-dihydroxytryptamine, a ser
toxin, to modify quinolinate levels.
Quinolinate was also shown to be at implies a separate compartmentation of the relevant
etabolic pathways and that is supported by the failure
5,7-dihydroxytryptamine, a serotonergic neuronal
xin, to modify quinolinate levels.
Quinolinate was also shown t of quinolinate in rat brain (Lombardi et al., 1983a) and
a 150% increase in those concentrations in response to
tryptophan loading (Lombardi et al., 1983b). These values
represent whole brain concentrations of approximate

asma to CSF ratio of L-kynurenine was higher than
at of tryptophan and other amino acids transported by Quinolinate was also shown to be present in normal
e neutral amino acid carrier. There was also no corre-
bostmortem h metabolic pathways and that is supported by the failure

of 5,7-dihydroxytryptamine, a serotonergic neuronal

toxin, to modify quinolinate levels.

Quinolinate was also shown to be present in normal

postmortem human brai of 5,7-dihydroxytryptamine, a serotonergic neuronal
toxin, to modify quinolinate levels.
Quinolinate was also shown to be present in normal
postmortem human brain at levels remarkably similar to
those of rat and other spec toxin, to modify quinolinate levels.

Quinolinate was also shown to be present in normal

postmortem human brain at levels remarkably similar to

those of rat and other species (Wolfensberger et al.,

1984). The concentrat Quinolinate was also shown to be present in normal
postmortem human brain at levels remarkably similar to
those of rat and other species (Wolfensberger et al.,
1984). The concentrations of quinolinic acid did not vary
grea postmortem human brain at levels remarkably similar t
those of rat and other species (Wolfensberger et al
1984). The concentrations of quinolinic acid did not var
greatly among different brain regions and all were in th
mi those of rat and other species (Wolfensberger et al., 1984). The concentrations of quinolinic acid did not vary greatly among different brain regions and all were in the micromolar concentration range. Nonetheless, the cer bral cortex (with approximately 2 nmol/g wet weight) 1984). al cortex (with approximately 2 nmol/g wet weight)
nerally had levels 2- to 4-fold those present in the
riatum (Moroni et al., 1984a; Wolfensberger et al.,
84).
The administration of tryptophan to rats can increase
e brain

rones results in the elevation of cerebral L-kynurenine droxyindoleacetic acid (all approximately 2-fold concentrations, possibly due to the diversion of trypto-

changes). However, the basal levels recorded by these

phan generally had levels 2- to 4-fold those present in the
striatum (Moroni et al., 1984a; Wolfensberger et al.,
1984).
The administration of tryptophan to rats can increase
the brain content of both 5HT and quinolinic acid i striatum (Moroni et al., 1984a; Wolfensberger et al., $\frac{9}{5}$
1984).
The administration of tryptophan to rats can increase
the brain content of both 5HT and quinolinic acid in a
dose-dependent manner; injection of 400 m 1984).
The administration of tryptophan to rats can increase
the brain content of both 5HT and quinolinic acid in a
dose-dependent manner; injection of 400 mg/kg leads to
a 10-fold elevation of quinolinate in the brain The administration of tryptophan to rats can increase
the brain content of both 5HT and quinolinic acid in a
dose-dependent manner; injection of 400 mg/kg leads to
a 10-fold elevation of quinolinate in the brain (Russi et
 the brain content of both 5HT and quinolinic acid in a
dose-dependent manner; injection of 400 mg/kg leads to
a 10-fold elevation of quinolinate in the brain (Russi et
al., 1991). Comparable changes were reported by Heyes
 dose-dependent manner; injection of 400 mg/kg leads to
a 10-fold elevation of quinolinate in the brain (Russi et
al., 1991). Comparable changes were reported by Heyes
and Markey (1988) who injected between 77 and 208 mg/
k al., 1991). Comparable changes were reported by Heyes and Markey (1988) who injected between 77 and 208 mg/ kg tryptophan intraperitoneally and observed up to a 23and Markey (1988) who injected between 77 and 208 mg/
kg tryptophan intraperitoneally and observed up to a 23-fold increase of quinolinate in rat frontal cortex, a change
far exceeding that of tryptophan itself, 5HT, or 5kg tryptophan intraperitoneally and observed up to a 23-
fold increase of quinolinate in rat frontal cortex, a change
far exceeding that of tryptophan itself, 5HT, or 5-hy-
droxyindoleacetic acid (all approximately 2-fold
 far exceeding that of tryptophan itself, 5HT, or 5-hyfar exceeding that of tryptophan itself, 5HT, or 5-hy-
droxyindoleacetic acid (all approximately 2-fold
changes). However, the basal levels recorded by these
workers, approximately 100 fmol/mg tissue, were sub-
stantially droxyindoleacetic acid (all approximately 2-fold
changes). However, the basal levels recorded by these
workers, approximately 100 fmol/mg tissue, were sub-
stantially lower than those determined by the previous
groups (Mor changes). However, the basal levels recorded by these
workers, approximately 100 fmol/mg tissue, were sub-
stantially lower than those determined by the previous
groups (Moroni et al., 1984a; Wolfensberger et al., 1984).
E workers, approximately 100 fmol/mg tissue, were sultantially lower than those determined by the previous groups (Moroni et al., 1984a; Wolfensberger et al., 1984
Even more dramatic results were obtained when the extracellu stantially lower than those determined by the previous groups (Moroni et al., 1984a; Wolfensberger et al., 1984).
Even more dramatic results were obtained when the extracellular concentrations of quinolinate were measured

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TABLE 1

QUINOLINIC AND KYNURENIC ACIDS
TABLE 1
*Concentrations of quinolinic acid in brain and blood**

in places according to estimation from figures. Many authors quote values in other brain regions or after **treatments not summarized** here.

Human serum

* This table is not meant to be exhaustive, only to convey an indication

in places according to estimation from figures. Many authors quote value

al., 1989). Whereas intravenous infusion of quinolinate

itse * This table is not meant to be exhaustive, only to convey an indication places according to estimation from figures. Many authors quote value al., 1989). Whereas intravenous infusion of quinolinate itself induced less tha in places according to estimation from figures. Many authors quote v
al., 1989). Whereas intravenous infusion of quinolinat
itself induced less than a 10-fold increase of striat
extracellular quinolinate, a single intraper al., 1989). Whereas intravenous infusion of quinolinate different different induced less than a 10-fold increase of striatal questinacellular quinolinate, a single intraperitoneal injection of tryptophan 250 mg/kg resulted al., 1989). Whereas intravenous infusion of quinolinitself induced less than a 10-fold increase of strie extracellular quinolinate, a single intraperitoneal injution of tryptophan 250 mg/kg resulted in a 230-f increase of itself induced less than a 10-fold increase of striatal extracellular quinolinate, a single intraperitoneal injection of tryptophan 250 mg/kg resulted in a 230-fold increase of quinolinate from basal levels of approximate extracellular quinolinate, a single intraperitoneal injection of tryptophan 250 mg/kg resulted in a 230-fold increase of quinolinate from basal levels of approximately 5.5 nM up to 1.4 μ M. The latter are approaching co tion of tryptophan 250 mg/kg resulted in a 230-fold
increase of quinolinate from basal levels of approximately 5.5 nM up to 1.4 μ M. The latter are approaching
concentrations that can be neurotoxic if maintained, at
lea 1989). mately 5.5 nM up to 1.4 μ M. The latter are approaching concentrations that can be neurotoxic if maintained, at least in cultured neurones (Whetsell, and Schwarcz 1989).
Paradoxically, administration of a tryptophan-fre

416 nM Halperin and Heyes (1992)

n of the range of values reported. Approximate values have been given

in other brain regions or after treatments not summarized here.

diet to rats for 15 days also resulted in a doubling n of the range of values reported. Approximate values have been given
in the concentrations or after treatments not summarized here.
diet to rats for 15 days also resulted in a doubling of
quinolinic acid concentrations in s in other brain regions or after treatments not summarized here.
diet to rats for 15 days also resulted in a doubling quinolinic acid concentrations in the cortex, despite
substantial reduction of 5HT and 5-hydroxyindolea diet to rats for 15 days also resulted in a doubling
quinolinic acid concentrations in the cortex, despite
substantial reduction of 5HT and 5-hydroxyindoleacet
acid levels (Moroni et al., 1989a). One suggested expl
nation diet to rats for 15 days also resulted in a doubling of
quinolinic acid concentrations in the cortex, despite a
substantial reduction of 5HT and 5-hydroxyindoleacetic
acid levels (Moroni et al., 1989a). One suggested expla quinolinic acid concentrations in the cortex, despite a substantial reduction of 5HT and 5-hydroxyindoleacetic acid levels (Moroni et al., 1989a). One suggested explanation for this may be that quinolinic acid can also be substantial reduction of 5HT and 5-hydroxyindoleacetic
acid levels (Moroni et al., 1989a). One suggested expla-
nation for this may be that quinolinic acid can also be
synthesised by a pathway distinct from the kynurenine
 acid levels (Moroni et al., 1989a). One suggested explanation for this may be that quinolinic acid can also be synthesised by a pathway distinct from the kynurenine pathway, particularly as some bacteria and plants are abl nation for this may be that quinolinic acid can also be synthesised by a pathway distinct from the kynurenine pathway, particularly as some bacteria and plants are able to synthesise quinolinic acid from the condensation o pathway, particularly as some bacteria and plants are

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seen in patients following tryptophan-deficient diets, is loc
accompanied by CNS symptoms including hallucinations ho sr
accompanied by CNS symptophan-deficient diets, is
accompanied by CNS symptoms including hallucinations
and signs of confusion and dementia, signs that could be STONE

seen in patients following tryptophan-deficient diets, is

accompanied by CNS symptoms including hallucinations

and signs of confusion and dementia, signs that could be

the related to the increased activation of N seen in patients following tryptophan-deficient diets, is
accompanied by CNS symptoms including hallucinations
and signs of confusion and dementia, signs that could be
related to the increased activation of NMDA receptors
 seen in patients following tryptoph
accompanied by CNS symptoms inc
and signs of confusion and dementi
related to the increased activation
by elevated quinolinic acid levels.
Quinolinic acid concentrations

and signs of confusion and dementia, signs that could be related to the increased activation of NMDA receptors
by elevated quinolinic acid levels.
Quinolinic acid concentrations increase several-fold
during the ageing proc related to the increased activation of NMDA receptors
by elevated quinolinic acid levels.
Quinolinic acid concentrations increase several-fold
during the ageing process in rats, varying in animals
from 3 days to 30 months by elevated quinolinic acid levels.

Quinolinic acid concentrations increase several-fold

during the ageing process in rats, varying in animals

from 3 days to 30 months in age (Moroni et al., 1984b).

About half of the Quinolinic acid concentrations increase several-fold the during the ageing process in rats, varying in animals in from 3 days to 30 months in age (Moroni et al., 1984b). In About half of the oldest group of rats had conce during the ageing process in rats, varying in animals if from 3 days to 30 months in age (Moroni et al., 1984b). I
About half of the oldest group of rats had concentrations of quinolinic acid in the brain approaching 10 from 3 days to 30 months in age (Moroni et al., 1984b). leads
hout half of the oldest group of rats had concentrations of
of quinolinic acid in the brain approaching 10 μ M, levels
that produce signs of neurotoxicity if About half of the oldest group of rats had concentrations
of quinolinic acid in the brain approaching 10μ M, levels
that produce signs of neurotoxicity if maintained over
several weeks (see section VI). As an extension of quinolinic acid in the brain approaching 10μ M, levels
that produce signs of neurotoxicity if maintained over
several weeks (see section VI). As an extension of this
in
study, the same group analysed the quinolinic a that produce signs of neurotoxicity if maintained over
several weeks (see section VI). As an extension of this
study, the same group analysed the quinolinic acid con-
tent of brain samples taken from patients with senile
d several weeks (see section VI). As an extension of the study, the same group analysed the quinolinic acid covert tends to the Alzheimer type (Moroni et al., 1986; Despite clear evidence for substantial neuronal degeneratio study, the same group analysed the quinolinic acid contract of brain samples taken from patients with senile potentia of the Alzheimer type (Moroni et al., 1986a). The Despite clear evidence for substantial neuronal degene tent of brain samples taken from patients with senile
dementia of the Alzheimer type (Moroni et al., 1986a).
Despite clear evidence for substantial neuronal degen-
eration in these brains, no evidence for a change of
quino Despite clear evidence for substantial neuronal degeneration in these brains, no evidence for a change of quinolinic acid content in the cerebral cortex was obtained in comparison with control subjects.

quinolinic acid content in the cerebral cortex was obtained in comparison with control subjects.
In patients dying in a coma resulting from severe liver damage the concentrations of quinolinic acid in the fron-
tal cortex quinolinic acid content in the cerebral cortex was ob-
tained in comparison with control subjects. dese
In patients dying in a coma resulting from severe liver
damage the concentrations of quinolinic acid in the fron-
ity tained in comparison with control subjects.
In patients dying in a coma resulting from severe live
damage the concentrations of quinolinic acid in the fron
tal cortex were found to be 2- to 3-fold greater than i
samples ta In patients dying in a coma resulting from severe liver
damage the concentrations of quinolinic acid in the fron-
tal cortex were found to be 2- to 3-fold greater than in
samples taken from control subjects. The levels of damage the concentrations of quinolinic acid in the frontal cortex were found to be 2- to 3-fold greater than in samples taken from control subjects. The levels of quinolinic acid in the CSF were found to be 5- to 6-fold h tal cortex were found to be 2- to 3-fold greater than in assumples taken from control subjects. The levels of quin-
polinic acid in the CSF were found to be 5- to 6-fold higher pothan those of control subjects (Moroni et a samples taken from control subjects. The levels of quin-
olinic acid in the CSF were found to be 5- to 6-fold higher
than those of control subjects (Moroni et al., 1989a).
Similarly, reduction of the peripheral metabolism olinic acid in the CSF were found to be 5- to 6-fold higher pather
than those of control subjects (Moroni et al., 1989a). and
Similarly, reduction of the peripheral metabolism of esse
tryptophan seen in rats with a portaca than those of control subjects (Moroni et al., 1989a).
Similarly, reduction of the peripheral metabolism of
tryptophan seen in rats with a portacaval anastomosis
results in a doubling of quinolinic acid concentration in
th tryptophan seen in rats with a portacaval anastomosis results in a doubling of quinolinic acid concentration in the cerebral cortex and other parts of the CNS (Moroni et al., 1986b). These pathological changes of kynurenin results in a doubling of quinolinic acid concentration in
the cerebral cortex and other parts of the CNS (Moroni
et al., 1986b). These pathological changes of kynurenine
concentration are discussed in section VI.E.7.
1. Fo Figure 3. Formation in the external cortex and other parts of the CNS (Moronic logical, 1986b). These pathological changes of kynurenine the metration are discussed in section VI.E.7.
1. Formation and removal of quinolinat

the cerebral cortex and other parts of the CNS (Moroni logical changes of kynurenine the concentration are discussed in section VI.E.7. the *1. Formation and removal of quinolinate*. A detailed the analysis of the propert et al., 1986b). These pathological changes of kynurenine the que concentration are discussed in section VI.E.7. the cat

1. Formation and removal of quinolinate. A detailed thesis analysis of the properties of 3HAO and QP concentration are discussed in section VI.E.7. the 1. Formation and removal of quinolinate. A detailed the analysis of the properties of 3HAO and QPRT derived has from mammalian forebrain indicates that both have K_m mea 1. Formation and removal of quinolinate. A detailed the analysis of the properties of 3HAO and QPRT derived has from mammalian forebrain indicates that both have K_m movalues of approximately 3.5 μ M, although values f analysis of the properties of 3HAO and QPRT derived
from mammalian forebrain indicates that both have K_m
values of approximately 3.5 μ M, although values for the
maximum reaction velocity were approximately 80-fold
hi from mammalian forebrain indicates that both have K_m ment for values of approximately 3.5 μ M, although values for the cofacto maximum reaction velocity were approximately 80-fold and QI higher for 3HAO than for QPRT values of approximately 3.5 μ M, although values for the constitution reaction velocity were approximately 80-fold a higher for 3HAO than for QPRT (Okuno and Schwarcz, r 1985; Foster et al., 1986; Okuno et al., 1987). S maximum reaction velocity were approximately 80-fold an higher for 3HAO than for QPRT (Okuno and Schwarcz, rat 1985; Foster et al., 1986; Okuno et al., 1987). Similar K_m values have been demonstrated for the enzyme extr higher for 3HAO than for QPRT (Okuno and Schwarcz, 1985; Foster et al., 1986; Okuno et al., 1987). Similar K_m values have been demonstrated for the enzyme extracted from human brain. This may have implications for the a values have been demonstrated for the enzyme extracted
from human brain. This may have implications for the
accumulation of quinolinic acid in the brain under cer-
tain pathological conditions or in the presence of abnorvalues have been demonstrated for the enzyme extracted
from human brain. This may have implications for the
accumulation of quinolinic acid in the brain under cer-
tain pathological conditions or in the presence of abnor-
 from human brain. This may have implications for the accumulation of quinolinic acid in the brain under certain pathological conditions or in the presence of abnormal enzyme activities. However, to date it is not clear whe accumulation of quinolinic acid in the brain under cer-
tain pathological conditions or in the presence of abnor-
rep
mal enzyme activities. However, to date it is not clear 3H
whether these enzyme activities are indeed cr tain pathological conditions or in the
mal enzyme activities. However, to
whether these enzyme activities are
tors in determining the concentration
and other kynurenines in the CNS.
Any attempt at a simplistic interpr whether these enzyme activities are indeed critical factors in determining the concentrations of quinolinic acid
and other kynurenines in the CNS.
Any attempt at a simplistic interpretation of the rela-
tionship between 3H

whether these enzyme activities are indeed critical fac-
tors in determining the concentrations of quinolinic acid
and other kynurenines in the CNS.
Any attempt at a simplistic interpretation of the rela-
quinoship between tors in determining the concentrations of quinolinic acid
and other kynurenines in the CNS.
Any attempt at a simplistic interpretation of the rela-
tionship between 3HAO and QPRT in relation to the
synthesis of quinolinic and other kynurenines in the CNS.
Any attempt at a simplistic interpretation of the rela-
tionship between 3HAO and QPRT in relation to the
synthesis of quinolinic acid is confounded by the distinct
regional distributions Any attempt at a simplistic interpretation of the relationship between 3HAO and QPRT in relation to the synthesis of quinolinic acid is confounded by the distinct regional distributions within the CNS described above. 3HAO tionship between 3HAO and QPRT in relation to synthesis of quinolinic acid is confounded by the distinguional distributions within the CNS described abore 3HAO is localised primarily in areas of the frontal cort striatum, synthesis of quinolinic acid is confounded by the distinct
regional distributions within the CNS described above. co
3HAO is localised primarily in areas of the frontal cortex, do
striatum, and hippocampus which possess li regional distributions within the CNS described above. compared activities of the frontal cortex, do striatum, and hippocampus which possess little detectable QPRT. The only brain region that appears to have approximately 3HAO is localised primarily in areas of the frontal cortex, do
striatum, and hippocampus which possess little detecta-
ble QPRT. The only brain region that appears to have
approximately equal activities of the two enzymes striatum, and hippocampus which possess little detecta-
ble QPRT. The only brain region that appears to have 7
approximately equal activities of the two enzymes is the the
olfactory bulb, an area that, interestingly, has a

accompanied by CNS symptoms including hallucinations homogenates, whereas QPRT is localised essentially to
and signs of confusion and dementia, signs that could be the particulate component of P2 synaptosomal fractions.
re NE
localised almost entirely in the soluble fraction of brain
homogenates, whereas QPRT is localised essentially to ^{IE}
localised almost entirely in the soluble fraction of brain
homogenates, whereas QPRT is localised essentially to
the particulate component of P2 synaptosomal fractions. The particulated almost entirely in the soluble fraction of brain
homogenates, whereas QPRT is localised essentially to
the particulate component of P2 synaptosomal fractions.
There is also a similar disparity between the localised almost entirely in the soluble fraction of brain
homogenates, whereas QPRT is localised essentially to
the particulate component of P2 synaptosomal fractions.
There is also a similar disparity between the localis localised almost entirely in the soluble fraction of brain
homogenates, whereas QPRT is localised essentially to
the particulate component of P2 synaptosomal fractions.
There is also a similar disparity between the localis homogenates, whereas QPRT is localised essentially to
the particulate component of P2 synaptosomal fractions.
There is also a similar disparity between the localisation
of 3HAO and of QPRT in the human brain, although
ther the particulate component of P2 synaptosomal fractions.
There is also a similar disparity between the localisation
of 3HAO and of QPRT in the human brain, although
there is some evidence that the relative activities are th There is also a similar disparity between the localisation
of 3HAO and of QPRT in the human brain, although
there is some evidence that the relative activities are the
inverse of those demonstrated in rat, with relatively of 3HAO and of QPRT
there is some evidence th
inverse of those demonst
levels of 3HAO in the nec
of QPRT in this region.
In view of this differen ere is some evidence that the relative activities are the
verse of those demonstrated in rat, with relatively high
vels of 3HAO in the neocortex and high concentrations
QPRT in this region.
In view of this differential loc

eration in these brains, no evidence for a change of circumstances, may accumulate sufficiently to activate
quinolinic acid content in the cerebral cortex was ob-
tained in comparison with control subjects.
In patients dyi inverse of those demonstrated in rat, with relatively high
levels of 3HAO in the neocortex and high concentrations
of QPRT in this region.
In view of this differential localisation, the conclusion
seems inescapable that qu levels of 3HAO in the neocortex and high concentrations
of QPRT in this region.
In view of this differential localisation, the conclusion
seems inescapable that quinolinate must be synthesised
in one population of glial ce of QPRT in this region.
In view of this differential localisation, the conclusion
seems inescapable that quinolinate must be synthesised
in one population of glial cells and must presumably exit
those cells to be metabolis In view of this differential localisation, the conclusion
seems inescapable that quinolinate must be synthesised
in one population of glial cells and must presumably exit
those cells to be metabolised by QPRT in a separate seems inescapable that quinolinate must be synthesised
in one population of glial cells and must presumably exit
those cells to be metabolised by QPRT in a separate
population of QPRT-containing glial cells and neurones.
T in one population of glial cells and must presumably exit
those cells to be metabolised by QPRT in a separate
population of QPRT-containing glial cells and neurones.
This raises the interesting possibility that quinolinic those cells to be metabolised by QPRT in a separate
population of QPRT-containing glial cells and neurones.
This raises the interesting possibility that quinolinic acid
must exist in the extracellular fluid and, under some population of QPRT-containing glial cells and neurones.
This raises the interesting possibility that quinolinic acid
must exist in the extracellular fluid and, under some
circumstances, may accumulate sufficiently to activ must exist in the extracellular fluid and, under some must exist in the extracellular fluid and, under so
circumstances, may accumulate sufficiently to activ
or otherwise modify, for example, by potentiation
desensitisation, the NMDA-sensitive population of g
tamate receptors circumstances, may accumulate sufficiently to activate
or otherwise modify, for example, by potentiation or
desensitisation, the NMDA-sensitive population of glu-
tamate receptors. Although this is an intriguing possibil-
 or otherwise modify, for example, by potentiation or
desensitisation, the NMDA-sensitive population of glu-
tamate receptors. Although this is an intriguing possibil-
ity in relation to much of the pharmacology of quinolin desensitisation, the NMDA-sensitive population of glu-
tamate receptors. Although this is an intriguing possibil-
ity in relation to much of the pharmacology of quinolinic
acid and other kynurenine metabolites, it should a tamate receptors. Although this is an intriguing possibility in relation to much of the pharmacology of quinolinic acid and other kynurenine metabolites, it should also be remembered that an important feature of the kynure ity in relation to much of the pharmacology of quinolinic
acid and other kynurenine metabolites, it should also be
remembered that an important feature of the kynurenine
pathway is that it leads to the formation of nicotin acid and other kynurenine metabolites, it should also be
remembered that an important feature of the kynurenine
pathway is that it leads to the formation of nicotinamide
and nicotinamide nucleotides (Bender, 1989b), which remembered that an important feature of the kynurenine
pathway is that it leads to the formation of nicotinamide
and nicotinamide nucleotides (Bender, 1989b), which are
essential cofactors in many metabolic processes. Al-
 pathway is that it leads to the formation of nicotinam
and nicotinamide nucleotides (Bender, 1989b), which
essential cofactors in many metabolic processes.
though this does not immediately answer the question
to why 3HAO a and nicotinamide nucleotides (Bender, 1989b), which are
essential cofactors in many metabolic processes. Al-
though this does not immediately answer the question as
to why 3HAO and QPRT should be located in morpho-
logical essential cofactors in many metabolic processes. Although this does not immediately answer the question as
to why 3HAO and QPRT should be located in morpho-
logically distinct compartments in the brain, it does raise
the q though this does not immediately answer the question as
to why 3HAO and QPRT should be located in morpho-
logically distinct compartments in the brain, it does raise
the question of whether QPRT has as its function not
the to why 3HAO and QPRT should be located in morpho-
logically distinct compartments in the brain, it does raise
the question of whether QPRT has as its function not
the catabolism of quinolinic acid but rather the biosyn-
th logically distinct compartments in the brain, it does rathe question of whether QPRT has as its function if the catabolism of quinolinic acid but rather the biosy thesis of nicotinamide and its nucleotides in cells thave, the question of whether QPRT has as its function not
the catabolism of quinolinic acid but rather the biosyn-
thesis of nicotinamide and its nucleotides in cells that
have, at the particular time of analysis, a high requir the catabolism of quinolinic acid but rather the biosynthesis of nicotinamide and its nucleotides in cells that
have, at the particular time of analysis, a high requirement for specific enzymes requiring these nucleotides thesis of nicotinamide and its nucleotides in cells that
have, at the particular time of analysis, a high require-
ment for specific enzymes requiring these nucleotides as
cofactors. This may explain the high activity of 3 have, at the particular time of analysis, a high rement for specific enzymes requiring these nucleoticofactors. This may explain the high activity of and QPRT in areas, such as olfactory bulb, with rate of neuronal turnove ent for specific enzymes requiring these nucleotides as
factors. This may explain the high activity of 3HAO
d QPRT in areas, such as olfactory bulb, with a high
te of neuronal turnover, requiring glial support.
Heyes et al

cofactors. This may explain the high activity of 3HAO and QPRT in areas, such as olfactory bulb, with a high rate of neuronal turnover, requiring glial support.
Heyes et al. (1988a) noted that administration of 3-hydroxyan and QPRT in areas, such as olfactory bulb, with a high rate of neuronal turnover, requiring glial support.
Heyes et al. (1988a) noted that administration of 3-hydroxyanthranilic acid into rat brain promotes the formation o rate of neuronal turnover, requiring glial support.
Heyes et al. (1988a) noted that administration of 3-
hydroxyanthranilic acid into rat brain promotes the for-
mation of quinolinic acid, indicating that 3HAO is not
satur Heyes et al. (1988a) noted that administration of 3-hydroxyanthranilic acid into rat brain promotes the formation of quinolinic acid, indicating that 3HAO is not saturated with substrate. In addition, the same group report hydroxyanthranilic acid into rat brain promotes the for-
mation of quinolinic acid, indicating that 3HAO is not
saturated with substrate. In addition, the same group
reported that 4-chloro-3-hydroxyanthranilate can inhibit mation of quinolinic acid, indicating that 3HAO is not saturated with substrate. In addition, the same group reported that 4-chloro-3-hydroxyanthranilate can inhibit 3HAO in liver and is also able to depress the conversion saturated with substrate. In addition, the same group
reported that 4-chloro-3-hydroxyanthranilate can inhibit
3HAO in liver and is also able to depress the conversion
of 3-hydroxyanthranilate into quinolinate in the CNS, reported that 4-chloro-3-hydroxyanthranilate can inhibit
3HAO in liver and is also able to depress the conversion
of 3-hydroxyanthranilate into quinolinate in the CNS,
an effect that was ascribed to inhibition of 3HAO in
b of 3-hydroxyanthranilate into quinolinate in the CNS,
an effect that was ascribed to inhibition of 3HAO in
brain and the need for this enzyme in the synthesis of
quinolinate. Brain slices prepared from excitotoxin-leof 3-hydroxyanthranilate into quinolinate in the CNS,
an effect that was ascribed to inhibition of 3HAO in
brain and the need for this enzyme in the synthesis of
quinolinate. Brain slices prepared from excitotoxin-le-
sion an effect that was ascribed to inhibition of 3HAO in
brain and the need for this enzyme in the synthesis of
quinolinate. Brain slices prepared from excitotoxin-le-
sioned animals exhibit a substantially higher capacity to
 brain and the need for this enzyme in the synthesis of quinolinate. Brain slices prepared from excitotoxin-le-
sioned animals exhibit a substantially higher capacity to
produce quinolinate from 3-hydroxyanthranilate than
c quinolinate. Brain slices prepared from excitotoxin-le-
sioned animals exhibit a substantially higher capacity to
produce quinolinate from 3-hydroxyanthranilate than
control preparations, a finding consistent with the preproduce quinolinate from 3-hydroxyanthranilate than
control preparations, a finding consistent with the pre-
dominantly glial localisation of 3HAO (Speciale and
Schwarcz, 1993).

The magnitude of the stimulation of quinolinate syncontrol preparations, a finding consistent with the pre-
dominantly glial localisation of 3HAO (Speciale and
Schwarcz, 1993).
The magnitude of the stimulation of quinolinate syn-
thesis by 3-hydroxyanthranilate was strikin dominantly glial localisation of 3HAO (Speciale and
Schwarcz, 1993).
The magnitude of the stimulation of quinolinate syn-
thesis by 3-hydroxyanthranilate was striking; although
some regional variability was observed in dif Schwarcz, 1993).
The magnitude of the stimulation of quinolinate syn-
thesis by 3-hydroxyanthranilate was striking; although
some regional variability was observed in different brain
regions, elevations of quinolinate conc

QUINOLINIC AND KYN
to 50-fold were recorded in the hippocampus. This would col
be consistent with the conclusion that the activity of kin QUINOLINIC AND KYI
to 50-fold were recorded in the hippocampus. This would
be consistent with the conclusion that the activity of ki
3HAO was approximately 80 times greater than that of If QUINOLINIC AND KYI
3HAO was approximately 80 times greater than that of If
3HAO was approximately 80 times greater than that of If
QPRT (Foster et al., 1985a,b) and emphasises the conto 50-fold were recorded in the hippocampus. This would
be consistent with the conclusion that the activity of
3HAO was approximately 80 times greater than that of
QPRT (Foster et al., 1985a,b) and emphasises the con-
tent be consistent with the conclusion that the activity of 3HAO was approximately 80 times greater than that of QPRT (Foster et al., 1985a,b) and emphasises the contention of Foster et al. (1986) that 3HAO activity may normal 3HAO was approximately 80 times greater than that of If t
QPRT (Foster et al., 1985a,b) and emphasises the con-
tention of Foster et al. (1986) that 3HAO activity may tion
normally be restrained by factors such as product QPRT (Foster et al., 1985a,b) and emphasises the contraction of Foster et al. (1986) that 3HAO activity may tion normally be restrained by factors such as product inhitial bition or the availability of Fe^{2+} ions. It sh tention of Foster et al. (1986) that 3HAO activity r
normally be restrained by factors such as product in
bition or the availability of Fe^{2+} ions. It should also
recalled that picolinic acid carboxylase may play a i
in normally be restrained by factors such
bition or the availability of Fe^{2+} ions.
recalled that picolinic acid carboxylass
in diverting some of the aminocarboxyn
hyde away from quinolinate formation.
These findings raise

recalled that picolinic acid carboxylase may play a role
in diverting some of the aminocarboxymuconic semialde-
hyde away from quinolinate formation.
These findings raise interest in the report that the
activity of 3HAO is in diverting some of the aminocarboxymuconic semialde-
hyde away from quinolinate formation. d
These findings raise interest in the report that the
ractivity of 3HAO is significantly increased in the brains
of patients suf hyde away from quinolinate formation. dance that the result of 3HAO is significantly increased in the brains central activity of 3HAO is significantly increased in the brains central of patients suffering from Huntington's These findings raise interest in the report that the reactivity of 3HAO is significantly increased in the brains cof patients suffering from Huntington's disease is (Schwarcz et al., 1988a). Unfortunately, a clear link to activity of 3HAO is significantly increased in the brains
of patients suffering from Huntington's disease
(Schwarcz et al., 1988a). Unfortunately, a clear link to
quinolinic acid could not be made because levels of this
ag (Schwarcz et al., 1988a). Unfortunately, a clear link to quinolinic acid could not be made because levels of this agent were normal in brain and CSF (Reynolds et al., 1988; Schwarcz et al., 1988b). The ability of 3-hydroxy

quinolinic acid could not be made because levels of this in t
agent were normal in brain and CSF (Reynolds et al., quin
1988; Schwarcz et al., 1988b). QP!
The ability of 3-hydroxyanthranilic acid to promote acid
the forma agent were normal in brain and CSF (Reynolds et 1988; Schwarcz et al., 1988b).

The ability of 3-hydroxyanthranilic acid to prom

the formation of quinolinate in brain was confirme

microdialysis experiments in which $10 \$ 1988; Schwarcz et al., 1988b).
The ability of 3-hydroxyanthranilic acid to promote
the formation of quinolinate in brain was confirmed by
microdialysis experiments in which 10 μ M 3-hydroxyan-
thranilate perfused throug The ability of 3-hydroxyanthranilic acid to promote acid
the formation of quinolinate in brain was confirmed by the
microdialysis experiments in which $10 \mu M$ 3-hydroxyan-
thranilate perfused through the dialysis probe wa the formation of quinolinate in brain was confirmed by
microdialysis experiments in which 10μ M 3-hydroxyan-
thranilate perfused through the dialysis probe was suf-
ficient to induce measurable amounts of quinolinate in microdialysis experiments in which 10 μ M 3-hydroxyan-
thranilate perfused through the dialysis probe was suf-
ficient to induce measurable amounts of quinolinate in
the striatum (Speciale et al., 1989a). Because only a thranilate perfused through the dialysis probe was suf-
ficient to induce measurable amounts of quinolinate in C
the striatum (Speciale et al., 1989a). Because only ap-
proximately 10 to 20% of most compounds pass across q ficient to induce measurable amounts of quinoli
the striatum (Speciale et al., 1989a). Because of
proximately 10 to 20% of most compounds pass
the dialysis membrane, it is likely that this efficachieved at low micromolar l the striatum (Speciale et al., 1989a). Because only approximately 10 to 20% of most compounds pass across
the dialysis membrane, it is likely that this effect was
achieved at low micromolar levels of 3-hydroxyanthran-
ilat proximately 10 to 20% of most compounds pass across
the dialysis membrane, it is likely that this effect was
achieved at low micromolar levels of 3-hydroxyanthran-
ilate in the brain, implying that this compound is sub-
st the dialysis membrane, it is likely that this effect was co
achieved at low micromolar levels of 3-hydroxyanthran-
ilate in the brain, implying that this compound is sub-
stantially more effective as a precursor of quinol achieved at low micromolar levels of 3-hydroxyanthran-
intitude in the brain, implying that this compound is sub-
stantially more effective as a precursor of quinolinate
than either tryptophan or L-kynurenine, either of w ilate in the brain, implying that this compound is substantially more effective as a precursor of quinolinate than either tryptophan or L-kynurenine, either of which is required at approximately 100 to 500 μ M to yield pathway. an either tryptophan or L-kynurenine, either of whice
required at approximately 100 to 500 μ M to yiel
gnificantly enhanced flux through the kynurenin
thway.
Although the modulation of quinolinate levels in path-
ogical

is required at approximately 100 to 500 μ M to yield the significantly enhanced flux through the kynurenine where pathway.

he discussed in section VI, it is hot objected conditions will be discussed in section VI, it i significantly enhanced flux through the kynurenine where the pathway.

he hological conditions will be discussed in section VI, it is hological conditions will be discussed in section VI, it is holoteworthy that a number o pathway.
Although the modulation of quinolinate levels in path-
ological conditions will be discussed in section VI, it is
noteworthy that a number of procedures, such as the
administration of endotoxin (as a mixture of ba Although the modulation of quinolinate levels in path-
ological conditions will be discussed in section VI, it is
noteworthy that a number of procedures, such as the
administration of endotoxin (as a mixture of bacterial a ological conditions will be discussed in section VI, it is
noteworthy that a number of procedures, such as the
administration of endotoxin (as a mixture of bacterial
lipopolysaccharides), can induce a significant increase noteworthy that a number of procedures, such as the hadministration of endotoxin (as a mixture of bacterial alipopolysaccharides), can induce a significant increase of nerebral quinolinate concentrations. Both Heyes et al. administration of endotoxin (as a mixture of bacterial at lipopolysaccharides), can induce a significant increase of nicerebral quinolinate concentrations. Both Heyes et al. its (1988b) and Moroni et al. (1991a) reported i lipopolysaccharides), can induce a significant increase of
cerebral quinolinate concentrations. Both Heyes et al.
(1988b) and Moroni et al. (1991a) reported increases of
brain quinolinate up to 81%, probably due to the abi cerebral quinolinate concentrations. Both Heyes et al. (1988b) and Moroni et al. (1991a) reported increases of brain quinolinate up to 81%, probably due to the ability of endotoxin to induce IDO (Yoshida and Hayaishi, 1978 (1988b) and Moroni et al. (1991a) reported increases of sight brain quinolinate up to 81%, probably due to the ability that of endotoxin to induce IDO (Yoshida and Hayaishi, ob 1978). Since only the peripheral, not icv, a brain quinolinate up to 81%, probably due to the ability tal
of endotoxin to induce IDO (Yoshida and Hayaishi, ob
1978). Since only the peripheral, not icv, administration hip
of lipopolysaccharides was effective, it is li of endotoxin to induce IDO (Yoshida and Hayais
1978). Since only the peripheral, not icv, administratiof
ipopolysaccharides was effective, it is likely that
thange of brain concentration was secondary to
production of incr 1978). Since only the peripheral, not icv, administration hipp of lipopolysaccharides was effective, it is likely that the any change of brain concentration was secondary to the T production of increased amounts of L-kynur of lipopolysaccharides was effective, it is likely that the and change of brain concentration was secondary to the production of increased amounts of L-kynurenine peripherally, which then crossed the blood-brain barrier to change of brain concentration was secondary to
production of increased amounts of L-kynurenine peri
erally, which then crossed the blood-brain barrier
enhance quinolinate formation. The administratior
nicotinylalanine, not production of increased amounts of L-kynurenine peripherally, which then crossed the blood-brain barrier to enhance quinolinate formation. The administration of nicotinylalanine, noted above as an inhibitor of kynureninase erally, which then crossed the blood-brain barrier to
enhance quinolinate formation. The administration of
nicotinylalanine, noted above as an inhibitor of kynuren-
inase and kynurenine hydroxylase, was able to prevent
the 1991a). cotinylalanine, noted above as an inhibitor of kynuren-
ase and kynurenine hydroxylase, was able to prevent (
e increase of quinolinate concentration (Moroni et al., metal)
91a).
What remains to be established is whether t inase and kynurenine hydroxylase, was able to prevent
the increase of quinolinate concentration (Moroni et al.,
1991a).
What remains to be established is whether there is any
high degree of localised compartmentation of qu

the increase of quinolinate concentration (Moroni et al., met
1991a).
What remains to be established is whether there is any it is
high degree of localised compartmentation of quinolinic neg
acid within cells. It is known ective inhibitor of human monoamine original series in the human monoamine of quinolinic education of quinolinic education of quinolinic education and within cells. It is known that quinolinic acid is an feature effective What remains to be established is whether there is any
high degree of localised compartmentation of quinolinic
acid within cells. It is known that quinolinic acid is an
effective inhibitor of human monoamine oxidase type B

be consistent with the conclusion that the activity of kinase (Endou et al., 1975; Macdonald and Grewe, 1981).
3HAO was approximately 80 times greater than that of If this indicates that quinolinic acid needs to be concenrecalled that picolinic acid carboxylase may play a role known to be neurotoxic. This in turn raises the possibil-
in diverting some of the aminocarboxymuconic semialde-
hyde away from quinolinate formation.
the damage or YNURENIC ACIDS
colytic enzymes, such as phosphoenolpyruvate carbo
kinase (Endou et al., 1975; Macdonald and Grewe, 198 XNURENIC ACIDS

stription and the subset of al., 1975; Macdonald and Grewe, 1981).

If this indicates that quinolinic acid needs to be concen-IMURENIC ACIDS

INSURENIC ACIDS
colytic enzymes, such as phosphoenolpyruvate carbol

kinase (Endou et al., 1975; Macdonald and Grewe, 198

If this indicates that quinolinic acid needs to be concent

trated in subcellular c colytic enzymes, such as phosphoenolpyruvate carb
kinase (Endou et al., 1975; Macdonald and Grewe, 19
If this indicates that quinolinic acid needs to be con
trated in subcellular compartments, then the concer
tion within t kinase (Endou et al., 1975; Macdonald and Grewe, 1981). kinase (Endou et al., 1975; Macdonald and Grewe, 1981).
If this indicates that quinolinic acid needs to be concentrated in subcellular compartments, then the concentration within those compartments will clearly be substant If this indicates that quinolinic acid needs to be concentrated in subcellular compartments, then the concentration within those compartments will clearly be substantially higher than the mean tissue content and could reac tially higher than the mean tissue content and could tion within those compartments will clearly be substantially higher than the mean tissue content and could reach the range at which exogenous quinolinic acid is known to be neurotoxic. This in turn raises the possibility t tially higher than the mean tissue content and could
reach the range at which exogenous quinolinic acid is
known to be neurotoxic. This in turn raises the possibil-
ity that any insult to CNS neurones that results in the
d reach the range at which exogenous quinolinic acid is
known to be neurotoxic. This in turn raises the possibil-
ity that any insult to CNS neurones that results in the
damage or lysis of cells containing quinolinic acid co known to be neurotoxic. This in turn raises the possity that any insult to CNS neurones that results in damage or lysis of cells containing quinolinic acid corresult in a positive feedback in which locally high contrations icity.

quinolinic acid could not be made because levels of this in the localisation of the primary synthetic enzyme of
agent were normal in brain and CSF (Reynolds et al., quinolinic acid, 3HAO, and its metabolising enzyme
1988; *2. Transport of quinolinic acid.* In view of the disparity result in a positive feedback in which locally high concentrations of quinolinic acid promote further excitotox-
icity.
2. Transport of quinolinic acid. In view of the disparity
in the localisation of the primary synthetic centrations of quinolinic acid promote further excitotox-
icity.
2. Transport of quinolinic acid. In view of the disparity
in the localisation of the primary synthetic enzyme of
quinolinic acid, 3HAO, and its metabolising icity.

2. Transport of quinolinic acid. In view of the disparity

in the localisation of the primary synthetic enzyme of

quinolinic acid, 3HAO, and its metabolising enzyme

QPRT, it is important to establish whether quin 2. Transport of quinolinic acid. In view of the disparity
in the localisation of the primary synthetic enzyme of
quinolinic acid, 3HAO, and its metabolising enzyme
QPRT, it is important to establish whether quinolinic
acid in the localisation of the primary synthetic enzyme of
quinolinic acid, 3HAO, and its metabolising enzyme
QPRT, it is important to establish whether quinolinic
acid is released from, and can be taken up by, cells within
th QPRT, it is important to establish whether quinolinic
acid is released from, and can be taken up by, cells within
the CNS. This information is also valuable in assessing
the possible physiological role of quinolinic acid a acid is released from, and can be taken up by, cells within
the CNS. This information is also valuable in assessing
the possible physiological role of quinolinic acid as an
endogenous neurotransmitter or neuromodulator in the CNS. This information is also valuable in assessing
the possible physiological role of quinolinic acid as an
endogenous neurotransmitter or neuromodulator in the
CNS in view of the selectivity of its action at the NMD the possible physiological role of quinolinic acid as an endogenous neurotransmitter or neuromodulator in the CNS in view of the selectivity of its action at the NMDA population of glutamate receptors. The use of tritiate endogenous neurotransmitter or neuromodulator in the

CNS in view of the selectivity of its action at the NMDA

population of glutamate receptors. The use of tritiated

quinolinic acid at either low (40 nM) or high (500 CNS in view of the selectivity of its action at the NMDA population of glutamate receptors. The use of tritiated quinolinic acid at either low (40 nM) or high (500 μ M) concentrations has indicated no efficient uptake s population of glutamate receptors.
quinolinic acid at either low (40 n
concentrations has indicated no ef
into slices of rat cerebral cortex at
1985; Connick and Stone, 1989a).
Foster et al. (1984a) attempted t inolinic acid at either low (40 nM) or high $(500 \mu\text{N})$
ncentrations has indicated no efficient uptake system
to slices of rat cerebral cortex at 34°C (Collins et al
85; Connick and Stone, 1989a).
Foster et

in the localisation of the primary synthetic enzyme of quinolinic acid, 3HAO, and its metabolising enzyme

QPRT, it is important to establish whether quinolinic acid is released from, and can be taken up by, cells within
 concentrations has indicated no efficient uptake system
into slices of rat cerebral cortex at 34°C (Collins et al.,
1985; Connick and Stone, 1989a).
Foster et al. (1984a) attempted to approach this prob-
lem by instilling into slices of rat cerebral cortex at 34°C (Collins et al., 1985; Connick and Stone, 1989a).
Foster et al. (1984a) attempted to approach this problem by instilling radiolabeled quinolinate directly into the rat striatum. D 1985; Connick and Stone, 1989a).
Foster et al. (1984a) attempted to approach this problem
by instilling radiolabeled quinolinate directly into
the rat striatum. Despite an initially rapid rate of loss,
which was also seen Foster et al. (1984a) attempted to approach this prob-
lem by instilling radiolabeled quinolinate directly into
the rat striatum. Despite an initially rapid rate of loss,
which was also seen using tritiated kainic acid, th lem by instilling radiolabeled quinolinate directly into
the rat striatum. Despite an initially rapid rate of loss,
which was also seen using tritiated kainic acid, the la-
beled compound was cleared from brain with a hal the rat striatum. Despite an initially rapid rate of loss,
which was also seen using tritiated kainic acid, the labeled compound was cleared from brain with a half-life
of 22 minutes, all residual radioactivity recovered which was also seen using tritiated kainic acid, the labeled compound was cleared from brain with a half-life of 22 minutes, all residual radioactivity recovered after 2 hours still being present as quinolinic acid, assay beled compound was cleared from brain with a half-lof 22 minutes, all residual radioactivity recovered after hours still being present as quinolinic acid, assayed high-performance liquid chromatography. The striate at leas hours still being present as quinolinic acid, assayed by high-performance liquid chromatography. The striatum at least does not, therefore, appear to possess mechanisms either for the rapid removal of quinolinate or for it hours still being present as quinolinic acid, assayed by
high-performance liquid chromatography. The striatum
at least does not, therefore, appear to possess mecha-
nisms either for the rapid removal of quinolinate or for high-performance liquid chromatography. The striatum
at least does not, therefore, appear to possess mecha-
nisms either for the rapid removal of quinolinate or for
its metabolic degradation in the extracellular space by
s at least does not, therefore, appear to possess mechanisms either for the rapid removal of quinolinate or for
its metabolic degradation in the extracellular space by
significant amounts of extracellular QPRT or other me-
 nisms either for the rapid removal of quinolinate or for
its metabolic degradation in the extracellular space by
significant amounts of extracellular QPRT or other me-
tabolising enzymes. This conclusion was supported by
 its metabolic degradation in the extracellular space by
significant amounts of extracellular QPRT or other me-
tabolising enzymes. This conclusion was supported by
observations that neither 400- μ m slices of striatum or
 significant amounts of extracellular QPF
tabolising enzymes. This conclusion was
observations that neither $400-\mu m$ slices
hippocampus nor crude synaptosomal frae
any ability to take up labeled quinolinate
The fundamental bolising enzymes. This conclusion was supported by
servations that neither $400-\mu m$ slices of striatum or
ppocampus nor crude synaptosomal fractions exhibited
y ability to take up labeled quinolinate.
The fundamental abse observations that neither $400-\mu m$ slices of striatum or hippocampus nor crude synaptosomal fractions exhibited any ability to take up labeled quinolinate.
The fundamental absence of any concentrative removal of quinolina

hippocampus nor crude synaptosomal fractions exhibited
any ability to take up labeled quinolinate.
The fundamental absence of any concentrative re-
moval of quinolinate by either brain or choroid plexus
was confirmed by Ki any ability to take up labeled quinolinate.
The fundamental absence of any concentrative re-
moval of quinolinate by either brain or choroid plexus
was confirmed by Kitt and Spector (1987) using rat and
rabbit preparations The fundamental absence of any concentrative
moval of quinolinate by either brain or choroid ple
was confirmed by Kitt and Spector (1987) using rat a
rabbit preparations. The data were consistent with
movement of quinolina oval of quinolinate by either brain or choroid plexus
is confirmed by Kitt and Spector (1987) using rat and
bbit preparations. The data were consistent with the
ovement of quinolinate by passive diffusion only.
On the basi

was confirmed by Kitt and Spector (1987) using rat and
rabbit preparations. The data were consistent with the
movement of quinolinate by passive diffusion only.
On the basis of this lack of uptake and extracellular
metabol rabbit preparations. The data were consistent with the movement of quinolinate by passive diffusion only.
On the basis of this lack of uptake and extracellular metabolism, it therefore seems unlikely that quinolinic acid i movement of quinolinate by passive diffusion only.

On the basis of this lack of uptake and extracellular

metabolism, it therefore seems unlikely that quinolinic

acid is a neurotransmitter in the classical sense, althoug On the basis of this lack of uptake and extracellular
metabolism, it therefore seems unlikely that quinolinic
acid is a neurotransmitter in the classical sense, although
it is important to consider the possibility that suc metabolism, it therefore seems unlikely that quinoline acid is a neurotransmitter in the classical sense, althou
it is important to consider the possibility that su
negative results simply reflect an ignorance of the tr
fe acid is a neurotransmitter in the classical sense, although
it is important to consider the possibility that such
negative results simply reflect an ignorance of the true
features of synaptic physiology. It is possible, fo it is important to consider the possibility that such negative results simply reflect an ignorance of the true features of synaptic physiology. It is possible, for example, that the usually accepted relationship between ne

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ST
anisms is more of a relevant correlation than a mecha-
nistic necessity. It could be that uptake mechanisms are 320

anisms is more of a relevant correlation than a mecha-

nistic necessity. It could be that uptake mechanisms are

required for the removal of substances that are not the strom

anisms is more of a relevant correlation than a mecha-

mistic necessity. It could be that uptake mechanisms are

required for the removal of substances that are not

primary neurotransmitters and, conversely, that anisms is more of a relevant correlation than a mecha-
nistic necessity. It could be that uptake mechanisms are
prequired for the removal of substances that are not the
primary neurotransmitters and, conversely, that some anisms is more of a relevant correlation than a mechanistic necessity. It could be that uptake mechanisms are required for the removal of substances that are not primary neurotransmitters and, conversely, that some substan mistic necessity. It could be that uptake mechanisms are required for the removal of substances that are not primary neurotransmitters and, conversely, that some substances such as quinolinic acid might fulfill a longer te required for the removal of substances that are not the primary neurotransmitters and, conversely, that some jectual
substances such as quinolinic acid might fulfill a longer moterm role in the maintenance and regulation o primary neurotransmitters and, conversely, that some justs in substances such as quinolinic acid might fulfill a longer nerm role in the maintenance and regulation of cerebral uptake excitability or cellular viability. The term role in the maintenance and regulation of cerebral urenate in rat brain (Moroni et al., 1988b).
excitability or cellular viability. The latter action would The concentration of kynurenate in rat brain was
not necessit term role in the maintenance and regulation of cerebral ure
excitability or cellular viability. The latter action would
not necessitate any specific uptake system. The uptake shows
tems for compounds acting at similar popu excitability or cellular viability. The latter action would
not necessitate any specific uptake system. The uptake
systems for compounds acting at similar populations of
receptors, including glutamate and aspartate, might not necessitate any specific uptake system. The uptake systems for compounds acting at similar populations creceptors, including glutamate and aspartate, might b viewed as a largely protective mechanism, maintainin
the ext receptors, including glutamate and aspartate, might be viewed as a largely protective mechanism, maintaining the extracellular levels of these amino acids at a sufficiently low level that at least a proportion of the physreceptors, including glutamate and aspartate, might be viewed as a largely protective mechanism, maintaining the extracellular levels of these amino acids at a sufficiently low level that at least a proportion of the physi viewed as a largely protective mechanism, maintaining the s
the extracellular levels of these amino acids at a suffi-
mark
ciently low level that at least a proportion of the phys-
conce
iologically relevant receptors for the extracellular level
ciently low level that
iologically relevant re
lated materials are th
unimpeded efficiency.
3. Blood-brain barri barrier. The physiograph barrier and the physiography relevant receptors for quinolinic acid and re-
ted materials are then able to operate with maximum
impeded efficiency.
3. *Blood-brain barrier*. Using radiolabeled qui

iologically relevant receptors for quinolinic acid and related materials are then able to operate with maximum
unimpeded efficiency.
3. Blood-brain barrier. Using radiolabeled quinolinate
administered intra-arterially at lated materials are then able to operate with maximum
unimpeded efficiency.
3. Blood-brain barrier. Using radiolabeled quinolinate
administered intra-arterially at a concentration of 2 μ M,
Foster et al. (1984a) calcula unimpeded efficiency. names and interpretent of 2 μ M, and initiate padministered intra-arterially at a concentration of 2 μ M, and Foster et al. (1984a) calculated that only 0.3% penetrated represent the blood-brain 3. Blood-brain barrier. Using radiolabeled quinolinate to administered intra-arterially at a concentration of 2μ M, n Foster et al. (1984a) calculated that only 0.3% penetrated represent the blood-brain barrier in a sin administered intra-arterially at a concentration of 2μ M, r
Foster et al. (1984a) calculated that only 0.3% penetrated
the blood-brain barrier in a single passage. Although
limited electroencephalographic changes were o Foster et al. (1984a) calculated that only 0.3% penetrated reference bood-brain barrier in a single passage. Although limited electroence phalographic changes were observed has to follow the intra-arterial injection of qui the blood-brain barrier in a single passage. Althou
limited electroencephalographic changes were observed to follow the intra-arterial injection of quinolinate,
was unclear whether this was due to the passage
material into limited electroencephalographic changes were observed
to follow the intra-arterial injection of quinolinate, it
was unclear whether this was due to the passage of
material into the brain. The seizures produced by periph-
e to follow the intra-arterial injection of quinolinate, it was unclear whether this was due to the passage of material into the brain. The seizures produced by peripheral injections of quinolinate are not prevented by admin was unclear whether this was due to the passage of the material into the brain. The seizures produced by periph-
eral injections of quinolinate are not prevented by ad-
trit ministration of the NMDA antagonist 2AP7 (Czuczw material into the brain. The seizures produced by periperal injections of quinolinate are not prevented by a ministration of the NMDA antagonist 2AP7 (Czuczy and Meldrum, 1982), implying that these seizures mot be centrall eral injections of quinolinate are not prevented by ad-
ministration of the NMDA antagonist 2AP7 (Czuczwar zyn
and Meldrum, 1982), implying that these seizures may oth
not be centrally mediated. On the other hand, unpub-
r and Meldrum, 1982), implying that these seizures may
not be centrally mediated. On the other hand, unpub-
lished results from Boni et al. (quoted by Heyes and
Lackner, 1990) indicate that significant amounts of ra-
diolabe and Meldrum, 1982), implying that these seizures may oth not be centrally mediated. On the other hand, unpub-
lished results from Boni et al. (quoted by Heyes and and
Lackner, 1990) indicate that significant amounts of ranot be centrally mediated. On the other hand, unpub-
lished results from Boni et al. (quoted by Heyes and a
Lackner, 1990) indicate that significant amounts of ra-
diolabeled quinolinate can indeed pass from blood into
che lished results from Boni et al. (quoted by Heyes and ideals. Lackner, 1990) indicate that significant amounts of radiolabeled quinolinate can indeed pass from blood into the CSF, and During et al. (1989) recorded almost a Lackner, 1990) indicate that signidiolabeled quinolinate can indeed
the CSF, and During et al. (1989)
fold increase of striatal quinolina
intravenous quinolinate injection.
Interestingly, quinolinate has re

the CSF, and During et al. (1989) recorded almost a 1 fold increase of striatal quinolinate concentration aft intravenous quinolinate injection.
Interestingly, quinolinate has recently been shown increase permeability of t fold increase of striatal quinolinate concentration after
intravenous quinolinate injection.
Interestingly, quinolinate has recently been shown to
increase permeability of the blood-brain barrier. Intra-
cerebroventricular intravenous quinolinate injection. Interestingly, quinolinate has recently been shown to wincrease permeability of the blood-brain barrier. Intra-
cerebroventricular injections of quinolinate or kainate fincreased the pene Interestingly, quinolinate has recently been shown to increase permeability of the blood-brain barrier. Intra-
cerebroventricular injections of quinolinate or kainate
increased the penetration of magnesium from plasma
into increase permeability of the blood-brain barrier. Intra-
cerebroventricular injections of quinolinate or kainate
increased the penetration of magnesium from plasma age
into brain (Rothe et al., 1993). It is not clear wheth increased the penetration of magnesium from plasma
into brain (Rothe et al., 1993). It is not clear whether
this effect involved activation of NMDA receptors, a
secondary change of extracellular osmolarity, or pH effects. *B. L-Kynurenine and Kynurenic Acid*
B. L-Kynurenine and Kynurenic Acid
B. L-Kynurenine and Kynurenic Acid

Kynurenic acid was one of the first of the kynurenines
to be demonstrated in mammalian tissues (Ellinger, fects.
B. L-Kynurenine and Kynurenic Acid
Kynurenic acid was one of the first of the kynurenines
to be demonstrated in mammalian tissues (Ellinger,
1904). Confirmation of the presence of kynurenic acid in B. L-Kynurenine and Kynurenic Acid atio atio atio atio atio Kynurenic acid was one of the first of the kynurenines geth to be demonstrated in mammalian tissues (Ellinger, associd 1904). Confirmation of the presence of kynu Brain Hastania and Kyndrend Acid
Kynurenic acid was one of the first of the kynurenines
to be demonstrated in mammalian tissues (Ellinger,
1904). Confirmation of the presence of kynurenic acid in
brain has appeared relativ Kynurenic acid was one of the first of the kynurenines
to be demonstrated in mammalian tissues (Ellinger,
1904). Confirmation of the presence of kynurenic acid in
brain has appeared relatively recently (Carla et al., 1988; to be demonstrated in mammalian tissues (Ellinger, assoticed 1904). Confirmation of the presence of kynurenic acid in urer
brain has appeared relatively recently (Carla et al., 1988; acid
Moroni et al., 1988a,b; Turski et 1904). Confirmation of the presence of kynurenic acid in
brain has appeared relatively recently (Carla et al., 1988;
Moroni et al., 1988a,b; Turski et al., 1988). Moroni et al.
(1988b) estimated the content of whole rat br brain has appeared relatively recently (Carla et al., 1988; acid Moroni et al., 1988a,b; Turski et al., 1988). Moroni et al. cognecies (1988b) estimated the content of whole rat brain as 24 T pmol/g with less than a 2-fold Moroni et al., 1988a,b; Turski et al., 1988). Moroni et al. (1988b) estimated the content of whole rat brain as 24 pmol/g with less than a 2-fold variation being apparent between brain regions; the brain stem contained 29 (1988b) estimated the content of whole rat brain as 24 pmol/g with less than a 2-fold variation being apparent leftween brain regions; the brain stem contained 29 ipmol/g and cerebellum 15 pmol/g, with hippocampus and str pmol/g with less than a 2-fold variation being apparent between brain regions; the brain stem contained 29 pmol/g and cerebellum 15 pmol/g, with hippocampus and striatum exhibiting intermediate amounts (table 2. Other spe between brain regions; the brain stem contained 29 pmol/g and cerebellum 15 pmol/g, with hippocampus and striatum exhibiting intermediate amounts (table 2. Other species, including mice, guinea pigs, and rabbits, were also

we
ranging from 5.8 pmol/g wet weight in mouse to 150
pmol/g in human neocortex. It may prove to be relevant NE
ranging from 5.8 pmol/g wet weight in mouse to 150
pmol/g in human neocortex. It may prove to be relevant
that the human tissue samples were obtained from sub-That the human tissue samples were veight in mouse to 150 pmol/g in human neocortex. It may prove to be relevant that the human tissue samples were obtained from sub-jects 70 to 80 years of age. Tests revealed that a postranging from 5.8 pmol/g wet weight in mouse to 15 pmol/g in human neocortex. It may prove to be relevant that the human tissue samples were obtained from subjects 70 to 80 years of age. Tests revealed that a post mortem d ranging from 5.8 pmol/g wet weight in mouse to 15 pmol/g in human neocortex. It may prove to be relevant that the human tissue samples were obtained from subjects 70 to 80 years of age. Tests revealed that a post mortem d pmol/g in human neocortex. It may prove to
that the human tissue samples were obtaine
jects 70 to 80 years of age. Tests revealed
mortem delay of 4 hours caused a 30% incr
urenate in rat brain (Moroni et al., 1988b).
The c jects 70 to 80 years of age. Tests revealed that a post-
mortem delay of 4 hours caused a 30% increase of kyn-
urenate in rat brain (Moroni et al., 1988b).
The concentration of kynurenate in rat brain was

jects 70 to 80 years of age. Tests revealed that a post-
mortem delay of 4 hours caused a 30% increase of kyn-
urenate in rat brain (Moroni et al., 1988b).
The concentration of kynurenate in rat brain was
shown to increase mortem delay of 4 hours caused a 30% increase of kyn-
urenate in rat brain (Moroni et al., 1988b).
The concentration of kynurenate in rat brain was
shown to increase about 18-fold from animals 7 days to
2 months of age (Mo urenate in rat brain (Moroni et al., 1988b).

The concentration of kynurenate in rat brain was

shown to increase about 18-fold from animals 7 days to

2 months of age (Moroni et al., 1988a). There is a further

3-fold inc The concentration of kynurenate in rat brain was
shown to increase about 18-fold from animals 7 days to
2 months of age (Moroni et al., 1988a). There is a further
3-fold increase from 2 to 18 months of age, and, although
t shown to increase about 18-fold from animals 7 days to 2 months of age (Moroni et al., 1988a). There is a further 3-fold increase from 2 to 18 months of age, and, although the significance of this finding is unknown, it st 2 months of age (Moroni et al., 1988a). There is a further 3-fold increase from 2 to 18 months of age, and, although the significance of this finding is unknown, it stands in marked contrast to the relative stability of ky 3-fold increase from 2 to 18 months of age, and, although
the significance of this finding is unknown, it stands in
marked contrast to the relative stability of kynurenate
concentrations in visceral structures (Moroni et a the significance of this finding is unknown, it stands in marked contrast to the relative stability of kynurenate concentrations in visceral structures (Moroni et al., 1988a). There is, however, an approximately parallel c marked contrast to the relative stability of kynurenate
concentrations in visceral structures (Moroni et al.,
1988a). There is, however, an approximately parallel
change in plasma kynurenate levels; this parallelism is
not concentrations in visceral structures (Moroni et al., 1988a). There is, however, an approximately parallel change in plasma kynurenate levels; this parallelism is not the result of a continuing increase of plasma tryptopha change in plasma kynurenate levels; this parallelism is
not the result of a continuing increase of plasma tryp-
tophan because no correlation was apparent between
neocortical concentrations of this amino acid and kynu-
ren change in plasma kynurenate
not the result of a continuing
tophan because no correlatio
neocortical concentrations of t
renate (Moroni et al., 1988a).
This progressive elevation o

diolabeled quinolinate can indeed pass from blood into complex, showing a peak shortly before birth, after which
the CSF, and During et al. (1989) recorded almost a 10-
fold increase of striatal quinolinate concentration a This progressive elevation of brain kynurenate level tophan because no correlation was apparent betw
neocortical concentrations of this amino acid and ky
renate (Moroni et al., 1988a).
This progressive elevation of brain kynurenate le
has been amply corroborated by evidence change in plasma kynurenate levels; this parallelism is
not the result of a continuing increase of plasma tryp-
actophan because no correlation was apparent between
neocortical concentrations of this amino acid and kynu-
 renate (Moroni et al., 1988a).
This progressive elevation of brain kynurenate level
has been amply corroborated by evidence that kynuren-
ine aminotransferase activity shows a similar increase in
the cortex and striatum in This progressive elevation of brain kynurenate level
has been amply corroborated by evidence that kynuren-
ine aminotransferase activity shows a similar increase in
the cortex and striatum in rats between 3 and 24 months
o has been amply corroborated by evidence that kynuren-
ine aminotransferase activity shows a similar increase in
the cortex and striatum in rats between 3 and 24 months
of age (Gramsbergen et al., 1992). This is probably at ine aminotransferase activity shows a similar increase in
the cortex and striatum in rats between 3 and 24 months
of age (Gramsbergen et al., 1992). This is probably at-
tributable to an increased astrocytic content of the the cortex and striatum in rats between 3 and 24 montl
of age (Gramsbergen et al., 1992). This is probably a
tributable to an increased astrocytic content of the er
zyme rather than to astrocytic proliferation becaus
other of age (Gramsbergen et al., 1992). This is probably at-
tributable to an increased astrocytic content of the en-
zyme rather than to astrocytic proliferation because
other markers were unchanged. Correspondingly, kynu-
ren tributable to an increased astrocytic content of the en-
zyme rather than to astrocytic proliferation because
other markers were unchanged. Correspondingly, kynu-
renate production from L-kynurenine in slices of cortex
and zyme rather than to astrocytic proliferation because
other markers were unchanged. Correspondingly, kynu-
renate production from L-kynurenine in slices of cortex
and hippocampus was also elevated in tissues from older
anim other markers were unchanged. Correspondingly, kynu-
renate production from L-kynurenine in slices of cortex
and hippocampus was also elevated in tissues from older
animals. Changes in kynurenate levels in utero are more
c renate production from L-kynurenine in slices of cortex
and hippocampus was also elevated in tissues from older
animals. Changes in kynurenate levels in utero are more
complex, showing a peak shortly before birth, after wh and hippocampus was also elevated in tissues from olde
animals. Changes in kynurenate levels in utero are mor
complex, showing a peak shortly before birth, after whicl
levels decrease within 24 hours before increasing agai animals. Changes in kynurenate levels in utero are more complex, showing a peak shortly before birth, after which levels decrease within 24 hours before increasing again postnatally (Beal et al., 1992a). There is a discrep complex, showing a peak shortly before birth, after which
levels decrease within 24 hours before increasing again
postnatally (Beal et al., 1992a). There is a discrepancy,
however, between this latter study, in which adult levels decrease within 24 hours before increasing again
postnatally (Beal et al., 1992a). There is a discrepancy,
however, between this latter study, in which adult levels
were said to be reached by 7 days postnatally, and postnatally (Beal et al., 1992a). There is a discrepancy, however, between this latter study, in which adult levels were said to be reached by 7 days postnatally, and the work of Moroni et al. (1988a), who observed a subst age. ere said to be reached by 7 days postnatally, and the ork of Moroni et al. (1988a), who observed a substantial rther increase (18-fold) from 7 days to 2 months of e.
The biological significance of these changes has at-acte

work of Moroni et al. (1988a), who observed a substantial
further increase (18-fold) from 7 days to 2 months of
age.
The biological significance of these changes has at-
tracted much speculation. In view of the role of NM further increase (18-fold) from 7 days to 2 months of
age.
The biological significance of these changes has at-
tracted much speculation. In view of the role of NMDA
receptors in neuronal growth and synapse formation, one
 age.

The biological significance of these changes has at-

tracted much speculation. In view of the role of NMDA

receptors in neuronal growth and synapse formation, one

possibility is that the dramatic perinatal decreas The biological significance of these changes has at
tracted much speculation. In view of the role of NMDA
receptors in neuronal growth and synapse formation, on
possibility is that the dramatic perinatal decrease in
rodent tracted much speculation. In view of the role of NMDA receptors in neuronal growth and synapse formation, one possibility is that the dramatic perinatal decrease in rodent kynurenate concentration is related to the initiat receptors in neuronal growth and synapse formation,
possibility is that the dramatic perinatal decrease
rodent kynurenate concentration is related to the in
ation of accelerated plasticity. Alternatively, taken
gether with possibility is that the dramatic perinatal decrease in
rodent kynurenate concentration is related to the initi-
ation of accelerated plasticity. Alternatively, taken to-
gether with the reports of decreased NMDA receptor-
 rodent kynurenate concentration is related to the initiation of accelerated plasticity. Alternatively, taken together with the reports of decreased NMDA receptor-
associated glycine binding with age, the increase of kynure ation of accelerated plasticity. Alternatively, taken to-
gether with the reports of decreased NMDA receptor-
associated glycine binding with age, the increase of kyn-
urenate levels may reflect a progressive loss of amino gether with the reports of decreased NMDA receptor-
associated glycine binding with age, the increase of kyn-
urenate levels may reflect a progressive loss of amino
acid receptor function, which may, in turn, underlie
cogn sociated glycine binding with age, the increase of kynemate levels may reflect a progressive loss of amino
id receptor function, which may, in turn, underlie
gnitive deficits with ageing (Gramsbergen et al., 1992).
The adm

urenate levels may reflect a progressive loss of amino
acid receptor function, which may, in turn, underlie
cognitive deficits with ageing (Gramsbergen et al., 1992).
The administration of L-kynurenine to rats increased
ky acid receptor function, which may, in turn, underlie cognitive deficits with ageing (Gramsbergen et al., 1992).
The administration of L-kynurenine to rats increased kynurenate concentrations in both plasma and CNS, increas cognitive deficits with ageing (Gramsbergen et al., 1992).
The administration of L-kynurenine to rats increased
kynurenate concentrations in both plasma and CNS,
increases of approximately 40-fold being achieved in both
co The administration of L-kynurenine to rats increa
kynurenate concentrations in both plasma and Cl
increases of approximately 40-fold being achieved in b
compartments after 600 mg/kg (Vecsei et al., 19922
Swartz et al., 199 kynurenate concentrations in both plasma and CNS,
increases of approximately 40-fold being achieved in both
compartments after 600 mg/kg (Vecsei et al., 1992a,b;
Swartz et al., 1990a). Such changes would yield microm-
olar compartments after 600 mg/kg (Vecsei et al., 1992a,b;
Swartz et al., 1990a). Such changes would yield microm-
olar concentrations in brain, values that would certainly
be expected to interfere with the glycine site on NMDA

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QUINOLINIC AND KYNURENIC ACIDS 321

322
receptors for which the IC_{50} of kynurenate is approxidely 15 μ M (Birch, et al., 1988a,b; Kessler et al., 19 322
receptors for which the IC_{60} of kynurenate is approxi-
mately 15 μ M (Birch, et al., 1988a,b; Kessler et al., 1989;
Danysz et al., 1989a). 322
receptors for which the
mately 15μ M (Birch, e
Danysz et al., 1989a).
The changes of kynu ceptors for which the IC_{50} of kynurenate is approxiately 15 μ M (Birch, et al., 1988a,b; Kessler et al., 1989; anysz et al., 1989a).
The changes of kynurenate were paralleled by changes 3-hydroxykynurenine concentrat

receptors for which the IC_{50} of kynurenate is approximately 15 μ M (Birch, et al., 1988a,b; Kessler et al., 1989;
Danysz et al., 1989a).
The changes of kynurenate were paralleled by changes
in 3-hydroxykynurenine con mately 15 μ M (Birch, et al., 1988a,b; Kessler et al., 1989; dep
Danysz et al., 1989a). int
The changes of kynurenate were paralleled by changes
in 3-hydroxykynurenine concentrations, which implies
that the main kynuren Danysz et al., 1989a).
The changes of kynurenate were paralleled by changes
in 3-hydroxykynurenine concentrations, which implies
that the main kynurenine pathway to quinolinic acid
would also be enhanced. However, no 3-hyd The changes of kynurenate were paralleled by changes
in 3-hydroxykynurenine concentrations, which implies
that the main kynurenine pathway to quinolinic acid
would also be enhanced. However, no 3-hydroxyanthran-
ilate coul in 3-hydroxykynurenine concentrations, which implies
that the main kynurenine pathway to quinolinic acid to
would also be enhanced. However, no 3-hydroxyanthran-
ilate could be detected in this work, although peripherally that the main kynurenine pathway to quinolinic acid
would also be enhanced. However, no 3-hydroxyanthran-
ilate could be detected in this work, although peripherally
administered anthranilic acid does lead to increased
amo would also be enhanced. However, no 3-hydroxyanthranilate could be detected in this work, although peripherand administered anthranilic acid does lead to increase amounts of the 3-hydroxy compound. This was though to suppo ilate could be detected in this work, although peripherally of induction administered anthranilic acid does lead to increased foll amounts of the 3-hydroxy compound. This was thought acid to support the proposal that most administered anthranilic acid does lead to increased
amounts of the 3-hydroxy compound. This was thought
to support the proposal that most 3-hydroxyanthranilate
in the CNS is derived from anthranilic acid (Baran and
Schwar amounts of the 3-hydroxy compound. This was thou
to support the proposal that most 3-hydroxyanthranil
in the CNS is derived from anthranilic acid (Baran a
Schwarcz, 1990), a route somewhat different from t
envisaged in cla to support the proposal that most 3-hydroxyanthranilate take in the CNS is derived from anthranilic acid (Baran and por Schwarcz, 1990), a route somewhat different from that pro
envisaged in classical schemes of kynurenine in the CNS is derived from anthranilic acid (Baran Schwarcz, 1990), a route somewhat different from tenvisaged in classical schemes of kynurenine metalism. Although probenecid was itself able to production significant, alt Schwarcz, 1990), a route somewhat different from that
envisaged in classical schemes of kynurenine metabo-
lism. Although probenecid was itself able to produce a
significant, although limited, increase of brain kynuren-
at envisaged in classical schemes of kynurenine met
lism. Although probenecid was itself able to produ
significant, although limited, increase of brain kynu
ate, the combined administration of this acidic trans
blocker with e lism. Although probenecid was itself able to produce a of osignificant, although limited, increase of brain kynuren-beinedec, the combined administration of this acidic transport uptublocker with even a low dose $(150 \text{ mg$ significant, although limited, increase of brain kynuren-beinding that the combined administration of this acidic transport uptublocker with even a low dose (150 mg/kg) of L-kynuren-Nevel in take the induced up to a 62-fol ate, the combined administration of this acidic transport
blocker with even a low dose (150 mg/kg) of L-kynuren-
ine induced up to a 62-fold increase of kynurenate in
striatum (Vecsei et al., 1992a,b). These results serv blocker with even a low dose (150 mg/kg) of L-kynum
ine induced up to a 62-fold increase of kynurenate
striatum (Vecsei et al., 1992a,b). These results serve
underline the extent to which central levels of kynur
ate may be ine induced up to a 62-fold increase of kynurenate in striatum (Vecsei et al., 1992a,b). These results serve to underline the extent to which central levels of kynurenate may be subject to variation with the plasma kynuren underline the extent to which central levels of kynurenate may be subject to variation with the plasma kynurenine levels and, thus, with liver function and peripheral tryptophan status. derline the extent to which central levels of kynuren-

e may be subject to variation with the plasma kynuren-

e levels and, thus, with liver function and peripheral p

ptophan status.

Even greater changes of up to 1300-

ate may be subject to variation with the plasma kynuren-
ine levels and, thus, with liver function and peripheral
tryptophan status.
Even greater changes of up to 1300-fold were reported
at to result from the combined admi ine levels and, thus, with liver function and periphtryptophan status.

Even greater changes of up to 1300-fold were repo

to result from the combined administration of the ac

transport inhibitor probenecid together with tryptophan status. mer

Even greater changes of up to 1300-fold were reported able

to result from the combined administration of the acidic Sch

transport inhibitor probenecid together with L-kynuren-

on ine in rats. St Even greater changes of up to 1300-fold were reported alto result from the combined administration of the acidic Stransport inhibitor probenecid together with L-kynurencies in rats. Striatal kynurenate increased from 1.6 to result from the combined administration of the acidic
transport inhibitor probenecid together with L-kynuren-
ine in rats. Striatal kynurenate increased from 1.6 nM to
2.1 μ M (Miller et al., 1992). Substantial incre transport inhibitor probenecid together with L-kynuren-
ine in rats. Striatal kynurenate increased from 1.6 nM to
2.1 μ M (Miller et al., 1992). Substantial increases of ir
approximately 50-fold (an increase from 6 to 3 ine in rats. Striatal kynurenate increased from 1.6 nM to
2.1 μ M (Miller et al., 1992). Substantial increases of increasers of increase from 6 to 300 nM) ure
were also described in the kynurenate content of CSF of rele 2.1 μ M (Miller et al., 1992). Substantial approximately 50-fold (an increase from were also described in the kynurenate contrhesus monkeys following intravenous injourg/kg L-kynurenine (Jauch et al., 1993). L-Kynurenin proximately 50-fold (an increase from 6 to 300 nM) uren
tre also described in the kynurenate content of CSF of releasus monkeys following intravenous injections of 200 main g/kg L-kynurenine (Jauch et al., 1993).
L-Kynure

were also described in the kynurenate content of CSF of
rhesus monkeys following intravenous injections of 200
mg/kg L-kynurenine (Jauch et al., 1993).
L-Kynurenine itself can be taken up by brain slices 7
to 8 times more rhesus monkeys following intravenous injections of 200 ma
mg/kg L-kynurenine (Jauch et al., 1993). fou
L-Kynurenine itself can be taken up by brain slices 7 wit
to 8 times more effectively than by slices of several ate
per mg/kg L-kynurenine (Jauch et al., 1993). fou
L-Kynurenine itself can be taken up by brain slices 7 wit
to 8 times more effectively than by slices of several ate
peripheral tissues, including spleen, liver, heart, and nat
k L-Kynurenine itself can be taken up by brain slices ⁷
to 8 times more effectively than by slices of severa
peripheral tissues, including spleen, liver, heart, and
kidney (Speciale and Schwarcz, 1990). The uptake into
bra to 8 times more effectively than by slices of severa-
peripheral tissues, including spleen, liver, heart, an
kidney (Speciale and Schwarcz, 1990). The uptake int
brain is partly (approximately 60%) sodium dependen-
whereas peripheral tissues, including spleen, liver, heart, and
kidney (Speciale and Schwarcz, 1990). The uptake into
brain is partly (approximately 60%) sodium dependent,
whereas that into visceral structures is not. Interestingl kidney (Speciale and Schwarcz, 1990). The uptake into
brain is partly (approximately 60%) sodium dependent,
whereas that into visceral structures is not. Interestingly,
although total L-kynurenine uptake was comparable
acr brain is partly (approximately 60%) sodium dependent, kynurenine aminotransferase.
whereas that into visceral structures is not. Interestingly, The overall conclusion from this work was that most
although total L-kynurenin whereas that into visceral structures is not. Interestingly,
although total L-kynurenine uptake was comparable of
across several brain regions, there were clear differences al
in the relative proportions of sodium-dependen although total L-kynurenine uptake was compara
across several brain regions, there were clear differen
in the relative proportions of sodium-dependent a
sodium-independent transport; the ratio between th
varied >10-fold fr across several brain regions, there were clear differen
in the relative proportions of sodium-dependent a
sodium-independent transport; the ratio between th
varied >10-fold from 2.3 in striatum to 0.24 in cereb
lum. The ex in the relative proportions of sodium-dependent and exodium-independent transport; the ratio between these carried >10 -fold from 2.3 in striatum to 0.24 in cerebel-
lum. The existence of a significant fraction of sodium sodium-independent transport; the ratio between th
varied >10-fold from 2.3 in striatum to 0.24 in cereb
lum. The existence of a significant fraction of sodiu
dependent transport may imply that brain uptake is
some physiol varied >10-fold from 2.3 in striatum to 0.24 in cerebel-
lum. The existence of a significant fraction of sodium-
dependent transport may imply that brain uptake is of
some physiological importance because sodium depend-
e lum. The existence of a significant fraction of sodium-
dependent transport may imply that brain uptake is of
some physiological importance because sodium depend-
ence is a characteristic of many reuptake processes for
neu dependent transport may imply that brain uptake is of cosome physiological importance because sodium depend-
ence is a characteristic of many reuptake processes for μ
neuronally important transmitters and modulatory (S some physiological importance because sodium dependence is a characteristic of many reuptake processes for neuronally important transmitters and modulatory (agents. The involvement of active uptake processes was toonfirmed ence is a characteristic of many reuptake processes for
neuronally important transmitters and modulatory
agents. The involvement of active uptake processes was
confirmed by the ability of low-temperature incubation
and sev neuronally important transmitters and modula-
agents. The involvement of active uptake processes
confirmed by the ability of low-temperature incuba-
and several metabolic inhibitors, including cyanide, o
bain, and 2,4-dini agents. The involvement of active uptake processes was to confirmed by the ability of low-temperature incubation sy
and several metabolic inhibitors, including cyanide, oua-
bain, and 2,4-dinitrophenol, to suppress the acc confirmed by the ability of low-temperature incubation
and several metabolic inhibitors, including cyanide, oua-
bain, and 2,4-dinitrophenol, to suppress the accumula-
tion of L-kynurenine. There was also no apparent bindi and several metabolic inhibitors
bain, and 2,4-dinitrophenol, to
tion of L-kynurenine. There was
of L-kynurenine to broken cell
for its removal for the medium.

The distinction between sodium-dependent and -in-
dependent processes probably corresponds to movement NE
The distinction between sodium-dependent and -in-
dependent processes probably corresponds to movement
into neurones and glial cells, respectively. This conclu-Interpretent and the distinction between sodium-dependent and -
dependent processes probably corresponds to movement
into neurones and glial cells, respectively. This conc
sion is based partly on the fact that relatively p sion is based partly on the fact that relatively pure astroglial cultures exhibited a highly efficient and active The distinction between sodium-dependent and -in-
dependent processes probably corresponds to movement
into neurones and glial cells, respectively. This conclu-
sion is based partly on the fact that relatively pure
astrogl dependent processes probably corresponds to moven
into neurones and glial cells, respectively. This con
sion is based partly on the fact that relatively p
astroglial cultures exhibited a highly efficient and ac
transport m into neurones and glial cells, respectively. This conclusion is based partly on the fact that relatively pure astroglial cultures exhibited a highly efficient and active transport mechanism for kynurenine that was independ sion is based partly on the fact that relatively pure
astroglial cultures exhibited a highly efficient and active
transport mechanism for kynurenine that was independ-
ent of sodium (Speciale et al., 1989b). In addition, u astroglial cultures exhibited a highly efficient and active
transport mechanism for kynurenine that was independ-
ent of sodium (Speciale et al., 1989b). In addition, uptake
of L-kynurenine into striatal slices prepared se transport mechanism for kynurenine that was independent of sodium (Speciale et al., 1989b). In addition, uptakent of L-kynurenine into striatal slices prepared several day following injections of the excitotoxic agent, ibo ent of sodium (Speciale et al., 1989b). In addition, upts
of L-kynurenine into striatal slices prepared several da
following injections of the excitotoxic agent, ibote
acid, revealed a 62% decrease of sodium-dependent tran of L-kynurenine into striatal slices prepared several days
following injections of the excitotoxic agent, ibotenic
acid, revealed a 62% decrease of sodium-dependent up-
take but a 61% increase of sodium-independent trans-
 following injections of the excitotoxic agent, ibotenic acid, revealed a 62% decrease of sodium-dependent uptake but a 61% increase of sodium-independent transport, presumably reflecting the neuronal loss and glial prolife acid, revealed a 62% decrease of sodium-dependent up-
take but a 61% increase of sodium-independent trans-
port, presumably reflecting the neuronal loss and glial
proliferation, respectively (Speciale and Schwarcz, 1990).
 take but a 61% increase of sodium-independent trans-
port, presumably reflecting the neuronal loss and glial
proliferation, respectively (Speciale and Schwarcz, 1990).
The neuronal uptake was not greatly affected by a rang port, presumably reflecting the neuronal loss and glial
proliferation, respectively (Speciale and Schwarcz, 1990).
The neuronal uptake was not greatly affected by a range
of other kynurenines or amino acids, the greatest e proliferation, respectively (Speciale and Schwarcz, 1990).
The neuronal uptake was not greatly affected by a range
of other kynurenines or amino acids, the greatest effect
being shown by 3-hydroxykynurenine which inhibited The neuronal uptake was not greatly affected by a range
of other kynurenines or amino acids, the greatest effect
being shown by 3-hydroxykynurenine which inhibited
uptake by about 70% at a concentration of 10 mM.
Never being shown by 3-hydroxykynurenine which inhibited
uptake by about 70% at a concentration of 10 mM. amino acid carrier (Speciale et al., 1988, 1989b).
After L-kynurenine is inside cells, there is some evi-Nevertheless, evidence suggests that L-kynurenine uptake into glial cells is likely to be mediated by a neutral amino acid carrier (Speciale et al., 1988, 1989b).
After L-kynurenine is inside cells, there is some evi-
denc

of other kynurenines or amino acids, the greatest effect
being shown by 3-hydroxykynurenine which inhibited
uptake by about 70% at a concentration of 10 mM.
Nevertheless, evidence suggests that L-kynurenine up-
take into take into glial cells is likely to be mediated by a neut
amino acid carrier (Speciale et al., 1988, 1989b).
After L-kynurenine is inside cells, there is some e
dence that it can be converted to kynurenic acid
peripheral t amino acid carrier (Speciale et al., 1988, 1989b).
After L-kynurenine is inside cells, there is some e
dence that it can be converted to kynurenic acid
peripheral tissues. However, in the brain slice expe
ments, <5% of the After L-kynurenine is inside cells, there is some evidence that it can be converted to kynurenic acid in peripheral tissues. However, in the brain slice experiments, $\leq 5\%$ of the transported L-kynurenine was detectabl dence that it can be converted to kynurenic acid in
peripheral tissues. However, in the brain slice experi-
ments, <5% of the transported L-kynurenine was detect-
able as metabolites after 60 minutes (Speciale and
Schwarcz peripheral tissues. However, in the brain slice experiments, <5% of the transported L-kynurenine was detectable as metabolites after 60 minutes (Speciale and Schwarcz, 1990). In a further analysis of the specific conversio ments, <5% of the transported L-kynurenine was detectable as metabolites after 60 minutes (Speciale and Schwarcz, 1990). In a further analysis of the specific conversion of L-kynurenine to kynurenic acid, Turski et al. (19 able as metabolites after 60 minutes (Speciale and Schwarcz, 1990). In a further analysis of the specific conversion of L-kynurenine to kynurenic acid, Turski e al. (1989) made the important observation that when incubate Schwarcz, 1990). In a further analysis of the specific
conversion of L-kynurenine to kynurenic acid, Turski et
al. (1989) made the important observation that when
incubated with L-kynurenine the small amounts of kyn-
uren conversion of L-kynurenine to kynurenic acid, Turski et al. (1989) made the important observation that when incubated with L-kynurenine the small amounts of kynurenic acid produced ($\leq 1\%$ of the L-kynurenine) were rel al. (1989) made the important observation that when
incubated with L-kynurenine the small amounts of kyn-
urenic acid produced $\langle 1\%$ of the L-kynurenine) were
released into the extracellular medium with $\langle 5\%$ re-
ma incubated with L-kynurenine the small amounts of kyn-
urenic acid produced $\langle 1\%$ of the L-kynurenine) were
released into the extracellular medium with $\langle 5\%$ re-
maining intracellularly. Most kynurenate production wa urenic acid produced $\langle 1\%$ of the L-kynurenine) were
released into the extracellular medium with $\langle 5\%$ re-
maining intracellularly. Most kynurenate production was
found using slices from hippocampus and pyriform cor released into the extracellular medium with <5%
maining intracellularly. Most kynurenate production with the least in cerebellar slices. An increased kynure
ate efflux from ibotenate-lesioned striatum or quino
nate-lesione maining intracellularly. Most kynurenate production was
found using slices from hippocampus and pyriform cortex
with the least in cerebellar slices. An increased kynuren-
ate efflux from ibotenate-lesioned striatum or quin found using slices from hippocampus and pyriform cortex
with the least in cerebellar slices. An increased kynuren-
ate efflux from ibotenate-lesioned striatum or quinoli-
nate-lesioned hippocampus (Wu et al., 1992b) suppor with the least in cerebellar
ate efflux from ibotenate-
nate-lesioned hippocampus
the histochemical evidence
kynurenine aminotransferre
The overall conclusion f e efflux from ibotenate-lesioned striatum or quinoli-
te-lesioned hippocampus (Wu et al., 1992b) supported
e histochemical evidence for a glial localisation of
nurenine aminotransferase.
The overall conclusion from this wo

nate-lesioned hippocampus (Wu et al., 1992b) supporte
the histochemical evidence for a glial localisation (
kynurenine aminotransferase.
The overall conclusion from this work was that most
of the normal extracellular kynur the histochemical evidence for a glial localisation of kynurenine aminotransferase.
The overall conclusion from this work was that most
of the normal extracellular kynurenate in brain is prob-
ably of glial origin. Since r kynurenine aminotransferase.
The overall conclusion from this work was that most
of the normal extracellular kynurenate in brain is prob-
ably of glial origin. Since release of kynurenate into the
extracellular medium pers The overall conclusion from this work was that most
of the normal extracellular kynurenate in brain is prob-
ably of glial origin. Since release of kynurenate into the
extracellular medium persisted in the absence of exter of the normal extracellular kynurenate in brain is
ably of glial origin. Since release of kynurenate in
extracellular medium persisted in the absence of ex
calcium, that release is probably the result of diffu
efflux rathe ly of glial origin. Since release of kynurenate into the tracellular medium persisted in the absence of external
lcium, that release is probably the result of diffusional
flux rather than an active exocytotic mechanism.
In

extracellular medium persisted in the absence of externacalcium, that release is probably the result of diffusions efflux rather than an active exocytotic mechanism.
In the striatum of freely moving rats, the extracellula calcium, that release is probably the result of diffusional
efflux rather than an active exocytotic mechanism.
In the striatum of freely moving rats, the extracellular
concentration of kynurenate, measured by microdialysi efflux rather than an active exocytotic mechanism.
In the striatum of freely moving rats, the extracellular
concentration of kynurenate, measured by microdialysis,
was increased from undetectable levels (≤ 250 nM) to In the striatum of freely moving rats, the extracellular concentration of kynurenate, measured by microdialysis, was increased from undetectable levels $(<250 \text{ nm})$ to >10 μ M after 2 hours perfusion with 2 mM L-kynure concentration of kynurenate, measured by microdialysis
was increased from undetectable levels $(<250 \text{ nm})$ to >1
 μ M after 2 hours perfusion with 2 mM L-kynurenin
(Speciale et al., 1990). Swartz et al. (1990a,b) were a was increased from undetectable levels $(<250 \text{ nm})$ to >10 μ M after 2 hours perfusion with 2 mM L-kynurenine (Speciale et al., 1990). Swartz et al. (1990a,b) were able to measure basal levels of 17 nM in the same expe (Speciale et al., 1990). Swartz et al. (1990a,b) were able
to measure basal levels of 17 nM in the same experimental
system and recorded a 37-fold increase after an injection
of $100 \text{ mg/kg L-kynurenine}$, to 630 nM . The (Speciale et al., 1990). Swartz et al. (1990a,b) were a
to measure basal levels of 17 nM in the same experimen
system and recorded a 37-fold increase after an injecti
of 100 mg/kg L-kynurenine, to 630 nM. The importan
of to measure basal levels of 17 nM in the same experimen
system and recorded a 37-fold increase after an inject
of 100 mg/kg L-kynurenine, to 630 nM. The importan
of an aminotransferase enzyme in catalysing the conv
sion of of 100 mg/kg L-kynurenine, to 630 nM. The importance
of an aminotransferase enzyme in catalysing the conver-
sion of the L-kynurenine load to kynurenate was empha-
sised by the decrease of kynurenate production and efflux
 sion of the L-kynurenine load to kynurenate was empha-

QUINOLINIC ANI
pound that shows inhibitory activity toward several ami-
notransferases, including kynurenine aminotransferase quinotinic and
pound that shows inhibitory activity toward several ami-
notransferases, including kynurenine aminotransferase
(K_i approximately 25 μ M) (Turski et al., 1989; Swartz et ² (*K1* approach that shows inhibitory activity toward several ami-
 (K₁ approximately 25 *μM*) (Turski et al., 1989; Swartz et al., 1990a; Wu et al., 1992a). pound that shows inhibitory a
notransferases, including kyr
 $(K_i$ approximately $25 \mu M$) (Tu
al., 1990a; Wu et al., 1992a).
Increased neuronal activity und that shows inhibitory activity toward several ami-
transferases, including kynurenine aminotransferase
 X_i approximately 25 μ M) (Turski et al., 1989; Swartz et
, 1990a; Wu et al., 1992a).
Increased neuronal activi

notransferases, including kynurenine aminotransferase sujetting $(K_i$ approximately $25 \mu M$ (Turski et al., 1989; Swartz et al., 1990a; Wu et al., 1992a). depolarisation (e.g., agentical metallical diminish the production $(K_i$ approximately 25 μ M) (Turski et al., 1989; Swartz
al., 1990a; Wu et al., 1992a).
Increased neuronal activity and depolarisation (e
induced by veratridine or potassium) can diminish
production of kynurenic acid, as al., 1990a; Wu et al., 1992a).

Increased neuronal activity and depolarisation (e.g.,

induced by veratridine or potassium) can diminish the

production of kynurenic acid, as reflected in its extracel-

lular concentration Increased neuronal activity and depolarisation (e.g., agent (Gramsbergen et al., 1991).

induced by veratridine or potassium) can diminish the Wu et al. (1992a,b) proposed that glutamate or a

production of kynurenic acid, induced by veratridine or potassium) can diminish the
production of kynurenic acid, as reflected in its extracel-
lular concentration after incubating brain slices with L-
kynurenine (Turski et al., 1989; Wu et al., 1992b) production of kynurenic acid, as reflected in its extracel-
lular concentration after incubating brain slices with L-
kynurenine (Turski et al., 1989; Wu et al., 1992b). If this
relationship extends to all methods of incre lular concentration after incubating brain slices with L-
kynurenine (Turski et al., 1989; Wu et al., 1992b). If this
relationship extends to all methods of increasing neu-
ronal activity, the hyperexcitability and behavio kynurenine (Turski et al., 1989; Wu et al., 1992b). If the relationship extends to all methods of increasing net ronal activity, the hyperexcitability and behavioural sequence seen after injections of kainate or NMDA agoni relationship extends to all methods of increasing ne
ronal activity, the hyperexcitability and behavioural s
zures seen after injections of kainate or NMDA agonis
could partly result from a decline of extracellular kyn
ren ronal activity, the hyperexcitability and behavioural seisonum activity, the hyperexcitability and behavioural seisonum accould partly result from a decline of extracellular kynumic renate levels. However, in experiments i zures seen after injections of kainate or NMDA agonists
could partly result from a decline of extracellular kynu-
renate levels. However, in experiments in which L-kyn-
urenine was preloaded into the tissue, brain slices t could partly result from a decline of extracellular kynu-
renate levels. However, in experiments in which L-kyn-
urenine was preloaded into the tissue, brain slices taken
from rats treated with kainate at a time when seizu renate levels. However, in experiments in which L-kyn-
urenine was preloaded into the tissue, brain slices taken
from rats treated with kainate at a time when seizures
were fully developed showed no decrease in kynurenate
 urenine was preloaded into the tissue, brain slices taken nefrom rats treated with kainate at a time when seizures wi
were fully developed showed no decrease in kynurenate ree
production compared with controls (Wu et al., from rats treated with kainate at a time when seizures
were fully developed showed no decrease in kynurenate
production compared with controls (Wu et al., 1991).
Similarly, microdialysis perfusion of the pyriform cortex
in were fully developed showed no decrease in kynurenate rece
production compared with controls (Wu et al., 1991). rece
Similarly, microdialysis perfusion of the pyriform cortex som
in unanaesthetised rats showed no decline o production compared with controls (Wu et al., 1991).

Similarly, microdialysis perfusion of the pyriform cortex

in unanaesthetised rats showed no decline of kynurenate

levels following kainate injections (Wu et al., 1991 Similarly, microdialysis perfusion of the pyriform cortex
in unanaesthetised rats showed no decline of kynurenate 199
levels following kainate injections (Wu et al., 1991). In but
contrast, kynurenate levels were elevated levels following kainate injections (Wu et al., 1991). In contrast, kynurenate levels were elevated 4 weeks after kainate administration, whether measured by in vivo microdialysis or using slices of pyriform cortex or hiplevels following kainate injections (Wu et al., 1991). In contrast, kynurenate levels were elevated 4 weeks after kainate administration, whether measured by in vivo microdialysis or using slices of pyriform cortex or hipp ntrast, kynurenate levels were elevated 4 weeks aft
inate administration, whether measured by in vi
icrodialysis or using slices of pyriform cortex or hi
campus. No changes were detected using striatal slice
These findings

kainate administration, whether measured by in vivo accordialysis or using slices of pyriform cortex or hip-
pocampus. No changes were detected using striatal slices.
These findings are consistent with the relative resistmicrodialysis or using slices of pyriform cortex or h
pocampus. No changes were detected using striatal slic
These findings are consistent with the relative resi
ance of striatum to systemic kainate damage as well
with the pocampus. No changes were detected using striatal slices.
These findings are consistent with the relative resisting
ance of striatum to systemic kainate damage as well as
with the apparent localisation of kynurenine amino-These findings are consistent with the relative resistance of striatum to systemic kainate damage as well as with the apparent localisation of kynurenine amino-
transferase to astrocytes. When veratridine was applied
via t ance of striatum to systemic kainate damage as well as
with the apparent localisation of kynurenine amino-
transferase to astrocytes. When veratridine was applied
via the microdialysis probe, a decrease of kynurenate with the apparent localisation of kynurenine amino-
transferase to astrocytes. When veratridine was applied
via the microdialysis probe, a decrease of kynurenate
levels was observed in normal, but not excitotoxin-le-
sione transferase to astrocytes. When veratridine was applied glu
via the microdialysis probe, a decrease of kynurenate pro
levels was observed in normal, but not excitotoxin-le-
vasioned, rats (Speciale et al., 1990; Wu et al., levels was observed in normal, but not excitotoxin-le-
sioned, rats (Speciale et al., 1990; Wu et al., 1992a,b).
This supports the in vitro data mentioned above but may
indicate important differences in the relationship of levels was observed in normal, but not excitotoxin-le-
sioned, rats (Speciale et al., 1990; Wu et al., 1992a,b). intr
This supports the in vitro data mentioned above but may indi
indicate important differences in the relat sioned, rats (Speciale et al., 1990; Wu et al., 1992a,b
This supports the in vitro data mentioned above but me
indicate important differences in the relationship of net
ronal depolarisation and kynurenate release induced t This supports the in vitro data mentioned above but may inconducte important differences in the relationship of neuronal depolarisation and kynurenate release induced by a the direct activation of voltage-dependent sodium indicate important differences in the relationship of neu-
ronal depolarisation and kynurenate release induced by
the direct activation of voltage-dependent sodium chan-
imples and by the activation of amino acid receptors ronal depolarisation and kynurenate release induced by
the direct activation of voltage-dependent sodium chan-
inels and by the activation of amino acid receptors. This
increase kynurenate synthesis and release in brain sl the direct activation of volta;
nels and by the activation of
idea is further borne out by
increase kynurenate synthesi
(Gramsbergen et al., 1989).
Although the mechanism b Is and by the activation of amino acid receptors. This
ea is further borne out by the failure of kainic acid to
crease kynurenate synthesis and release in brain slices
ramsbergen et al., 1989).
Although the mechanism by wh idea is further borne out by the failure of kainic acid to
increase kynurenate synthesis and release in brain slices
(Gramsbergen et al., 1989).
Although the mechanism by which depolarising agents
affect kynurenate product

increase kynurenate synthesis and release in brain slices
(Gramsbergen et al., 1989).
Although the mechanism by which depolarising agents
affect kynurenate production is obscure, it merits further
analysis. Apparently, ver (Gramsbergen et al., 1989).
Although the mechanism by which depolarising agents
affect kynurenate production is obscure, it merits further
analysis. Apparently, veratridine does not directly inhibit
kynurenine aminotransfe Although the mechanism by which depolarising agents
affect kynurenate production is obscure, it merits further
analysis. Apparently, veratridine does not directly inhibit
kynurenine aminotransferase in rat brain (unpublish affect kynurenate production is obscure, it merits further pro
analysis. Apparently, veratridine does not directly inhibit Eas
kynurenine aminotransferase in rat brain (unpublished upt
data quoted by Wu et al., 1992a), and analysis. Apparently, veratridine does not directly inh
kynurenine aminotransferase in rat brain (unpublis
data quoted by Wu et al., 1992a), and it is unlikely t
other actions of the alkaloid on glial cell function
account kynurenine aminotransferase in rat brain (unpublishe data quoted by Wu et al., 1992a), and it is unlikely the other actions of the alkaloid on glial cell function ca account for its effects because no diminution of kynuren data quoted by Wu et al., 1992a), and it is unlikely that other actions of the alkaloid on glial cell function can
account for its effects because no diminution of kynuren-
ate production was observed in excitotoxin-lesion other actions of the alkaloid on glial cell function ca
account for its effects because no diminution of kynurer
ate production was observed in excitotoxin-lesioned ar
imals (Wu et al., 1991) in which there is substantia
n account for its effects because no diminution of kynuren-
ate production was observed in excitotoxin-lesioned an-
imals (Wu et al., 1991) in which there is substantial in
neuronal loss compensated by astrocytic proliferati ate production was observed in excitotoxin-lesioned an-
imals (Wu et al., 1991) in which there is substantial into
neuronal loss compensated by astrocytic proliferation. 2.
Voltage-dependent sodium channels must be require tetrodotoxin. uronal loss compensated by astrocytic proliferat
bltage-dependent sodium channels must be required
ratridine to work because the effect is prevented
rodotoxin.
It seems possible, therefore, that neuronal depolar
on may res Voltage-dependent sodium channels must be required for
veratridine to work because the effect is prevented by
tetrodotoxin.
It seems possible, therefore, that neuronal depolarisa-
tion may result in the release of a factor

veratridine to work because the effect is prevented by
tetrodotoxin.
It seems possible, therefore, that neuronal depolarisa-
tion may result in the release of a factor that suppresses
kynurenate synthesis and/or efflux fro

QUINOLINIC AND KYNURENIC ACIDS
ward several ami- In support of this, potassium depolarisation is unable to
aminotransferase suppress kynurenate production in the absence of extersuppress kynurenate production is unable
The suppress kynurenate production in the absence of exter-
- suppress kynurenate production in the absence of exter-
- and calcium, possibly implying the need for the calcium NEXT CONS

In support of this, potassium depolarisation is unable

suppress kynurenate production in the absence of ext

nal calcium, possibly implying the need for the calciu

dependent excocytotic release of a neuronally In support of this, potassium depolarisation is unable to suppress kynurenate production in the absence of exter-
nal calcium, possibly implying the need for the calcium-
dependent excocytotic release of a neuronally deriv In support of this, potassium depol
suppress kynurenate production in
nal calcium, possibly implying the
dependent excocytotic release of
agent (Gramsbergen et al., 1991).
Wu et al. (1992a,b) proposed ppress kynurenate production in the absence of exter-
l calcium, possibly implying the need for the calcium-
pendent excocytotic release of a neuronally derived
ent (Gramsbergen et al., 1991).
Wu et al. (1992a,b) proposed

nal calcium, possibly implying the need for the calcium-
dependent excocytotic release of a neuronally derived
agent (Gramsbergen et al., 1991).
Wu et al. (1992a,b) proposed that glutamate or a
similar compound could be su dependent excocytotic release of a neuronally derived
agent (Gramsbergen et al., 1991).
Wu et al. (1992a,b) proposed that glutamate or a
similar compound could be such an agent. The absence
of veratridine's effect in lesio agent (Gramsbergen et al., 1991).
Wu et al. (1992a,b) proposed that glutamate or a
similar compound could be such an agent. The absence
of veratridine's effect in lesioned brain is then readily
understandable. This explana Wu et al. (1992a,b) proposed that glutamate or a similar compound could be such an agent. The absence of veratridine's effect in lesioned brain is then readily understandable. This explanation unfortunately leaves unresolv similar compound could be such an agent. The absence
of veratridine's effect in lesioned brain is then readily
understandable. This explanation unfortunately leaves
unresolved the paradox that kainate is effective in le-
s of veratridine's effect in lesioned brain is then readily understandable. This explanation unfortunately leaves unresolved the paradox that kainate is effective in lesioned but not normal brain. This may imply that kainate understandable. This explanation unfortunately le
unresolved the paradox that kainate is effective ir
sioned but not normal brain. This may imply that kai
has a direct stimulatory action on kynurenate produc
in glia but th unresolved the paradox that kainate is effective in le-
sioned but not normal brain. This may imply that kainate
has a direct stimulatory action on kynurenate production
in glia but that this can be balanced by the depolar sioned but not normal brain. This may imply that kainate
has a direct stimulatory action on kynurenate production
in glia but that this can be balanced by the depolarisa-
tion-induced release of the inhibitory factor from has a direct stimulatory action on kynurenate production
in glia but that this can be balanced by the depolarisa-
tion-induced release of the inhibitory factor from normal
neurones. It is likely that this issue will only b in glia but that this can be balanced by the depolarisation-induced release of the inhibitory factor from normal neurones. It is likely that this issue will only be resolved with the use of pure neuronal and glial cultures tion-induced release of the inhibitory factor from normal
neurones. It is likely that this issue will only be resolved
with the use of pure neuronal and glial cultures but does
receive some support from the recent discove neurones. It is likely that this issue will only be resolved with the use of pure neuronal and glial cultures but does receive some support from the recent discovery that receptors for excitatory amino acids do occur at le with the use of pure neuronal and glial cultures but does
receive some support from the recent discovery that
receptors for excitatory amino acids do occur at least on
some types of glial cells (Muller et al., 1992; Teichb receive some support from the recent discovery that
receptors for excitatory amino acids do occur at least on
some types of glial cells (Muller et al., 1992; Teichberg,
1991). In fact, Wu et al. (1992b) found that glutamat receptors for excitatory amino acids do occur at least on
some types of glial cells (Muller et al., 1992; Teichberg,
1991). In fact, Wu et al. (1992b) found that glutamate,
but not veratridine, will reduce kynurenate produ 1991). In fact, Wu et al. (1992b) found that glutamate, but not veratridine, will reduce kynurenate production in the lesioned hippocampus: glutamate is presumably acting directly on glial cells to suppress kynurenate formation. In a recent study, will reduce kynurenate production

the lesioned hippocampus: glutamate is presumably

ting directly on glial cells to suppress kynurenate for-

ation.

In a recent study, Wu et al. (1992b) attempted to

in the lesioned hippocampus: glutamate is presumably
acting directly on glial cells to suppress kynurenate for-
mation.
In a recent study, Wu et al. (1992b) attempted to
investigate the effects of manipulating experimental acting directly on glial cells to suppress kynurenate fo
mation.
In a recent study, Wu et al. (1992b) attempted
investigate the effects of manipulating experimental co
ditions on the levels of endogenous hippocampal kyn
re mation.

In a recent study, Wu et al. (1992b) attempted to

investigate the effects of manipulating experimental con-

ditions on the levels of endogenous hippocampal kynu-

renate. In contrast to the ability of veratridin In a recent study, Wu et al. (1992b) attempted to
investigate the effects of manipulating experimental con-
ditions on the levels of endogenous hippocampal kynu-
renate. In contrast to the ability of veratridine and
glutam investigate the effects of manipulating experimental conditions on the levels of endogenous hippocampal kynu-
renate. In contrast to the ability of veratridine and
glutamate to cause an almost 80% decrease of kynurenate
pr ditions on the levels of endogenous hippocampal kynu-
renate. In contrast to the ability of veratridine and
glutamate to cause an almost 80% decrease of kynurenate
production after preloading, less than half of this change renate. In contrast to the ability of veratridine and glutamate to cause an almost 80% decrease of kynurenate production after preloading, less than half of this change was observed for the endogenous material. This is an glutamate to cause an almost 80% decrease of kynurenate
production after preloading, less than half of this change
was observed for the endogenous material. This is an
intriguing finding which may, as the authors remark,
i production after preloading, less than half of this change
was observed for the endogenous material. This is an
intriguing finding which may, as the authors remark,
indicate the existence of at least two distinct pools of
 was observed for the endogenous material. This is an intriguing finding which may, as the authors remark, indicate the existence of at least two distinct pools of kynurenate, the more recently synthesised of which is avail intriguing finding which may, as the authors remark
indicate the existence of at least two distinct pools of
kynurenate, the more recently synthesised of which is
available for efflux. This, in turn, could have major
impli indicate the existence of at least two distinct pools of kynurenate, the more recently synthesised of which is available for efflux. This, in turn, could have major implications for understanding the biological role of kyn kynurenate, the more recently synthesised of which is available for efflux. This, in turn, could have major implications for understanding the biological role of kynurenate because it may imply the existence of a pool spec space. are the existence of a pool specifically earmarked for "release" into the extracellular space.

1. 3-Hydroxykynurenine. This metabolite has attracted relatively little attention despite the fact that it can

urenate because it may imply the existence of a pool
specifically earmarked for "release" into the extracellular
space.
1. 3-Hydroxykynurenine. This metabolite has attracted
relatively little attention despite the fact th specifically earmarked for "release" into the extracellular
space.
1. 3-Hydroxykynurenine. This metabolite has attracted
relatively little attention despite the fact that it can
produce convulsions and neuronal damage. How space.

1. 3-Hydroxykynurenine. This metabolite has attracted

relatively little attention despite the fact that it can

produce convulsions and neuronal damage. However,

Eastman et al. (1992) discovered the existence of 1. 3-Hydroxykynurenine. This metabolite has attracted
relatively little attention despite the fact that it can
produce convulsions and neuronal damage. However,
Eastman et al. (1992) discovered the existence of active
upt relatively little attention despite the fact that it of produce convulsions and neuronal damage. Howevel Eastman et al. (1992) discovered the existence of actuation solution and processes for the compound into brain slices produce convulsions and neuronal damage. However,
Eastman et al. (1992) discovered the existence of active
uptake processes for the compound into brain slices and
N18 RE-105-cultured neurones. Both sodium-dependent
and -in Eastman et al. (1992) discovered the existence of active
uptake processes for the compound into brain slices and
N18 RE-105-cultured neurones. Both sodium-dependent
and -independent systems were detected, the former
being uptake processes for the compound into brain slices an N18 RE-105-cultured neurones. Both sodium-dependent and -independent systems were detected, the formed being unique to central neurones; this duality may impfunctional N18 RE-105-cultured neurones. Both sodium-dep
and -independent systems were detected, the
being unique to central neurones; this duality may
functional compartmentation of 3-hydroxykynure
into two separable pools, as exist *2. Blood-brain barrier.* The ability may imply inctional compartmentation of 3-hydroxykynurenine to two separable pools, as exists for kynurenate.
2. *Blood-brain barrier*. The ability of L-kynurenine to in access to the

being unique to central neurones; this duality may imply
functional compartmentation of 3-hydroxykynurenine
into two separable pools, as exists for kynurenate.
2. Blood-brain barrier. The ability of L-kynurenine to
gain ac functional compartmentation of 3-hydroxykynurenine
into two separable pools, as exists for kynurenate.
2. Blood-brain barrier. The ability of L-kynurenine to
gain access to the CNS via the blood-brain barrier was
discovere into two separable pools, as exists for kynurenate.

2. Blood-brain barrier. The ability of L-kynurenine to

gain access to the CNS via the blood-brain barrier was

discovered by Joseph and Kadam (1979) and Gal and

Sherma 2. Blood-brain barrier. The ability of L-kynurenine to
gain access to the CNS via the blood-brain barrier was
discovered by Joseph and Kadam (1979) and Gal and
Sherman (1980) and has been studied more recently in
detail by gain access to the CNS via the blood-brain barrier was
discovered by Joseph and Kadam (1979) and Gal and
Sherman (1980) and has been studied more recently in
detail by Fukui et al. (1991). L-Kynurenine can cross the
barrie Sherman (1980) and has been studied more recently in detail by Fukui et al. (1991). L-Kynurenine can cross the barrier as a result of transport by the large neutral amino acid carrier. Kynurenic acid, on the other hand, ha

324 STONE
considered essentially unable to cross the barrier in dole
normal animals. The latter reservation is important be-STM

sTM

considered essentially unable to cross the barrier in

normal animals. The latter reservation is important be-

cause in many of the pathological states in which kynu-324
considered essentially unable to cross the barrier
normal animals. The latter reservation is important b
cause in many of the pathological states in which kynu-
renines may be implicated (encephalopathies, AIDS-r considered essentially unable to cross the barrier
normal animals. The latter reservation is important
cause in many of the pathological states in which ky
renines may be implicated (encephalopathies, AIDS
lated brain dama considered essentially unable to cross the barrier in
normal animals. The latter reservation is important be-
cause in many of the pathological states in which kynu-
renines may be implicated (encephalopathies, AIDS-re-
la normal animals. The latter reservation is important be-
cause in many of the pathological states in which kynu-
ist
renines may be implicated (encephalopathies, AIDS-re-
efflated brain damage, etc.) there is likely to be a cause in many of the pathological states in which kyr
renines may be implicated (encephalopathies, AIDS-
lated brain damage, etc.) there is likely to be a significated
weakening of the barrier's integrity. The barrier is k renines may be implicated (encephalopathies, AIDS-re-
lated brain damage, etc.) there is likely to be a significant reni
weakening of the barrier's integrity. The barrier is known
to be compromised, for example, in Alzheim weakening of the barrier's integrity. The barrier is known
to be compromised, for example, in Alzheimer's demen-
tia, raising the possibility that enhanced penetration by
kynurenate may occur in such conditions.
Several gr akening of the barrier's integrity. The barrier is known
be compromised, for example, in Alzheimer's demen-
i, raising the possibility that enhanced penetration by
nurenate may occur in such conditions.
Several groups have

to be compromised, for example, in Alzheimer's demen-
tia, raising the possibility that enhanced penetration by
kynurenate may occur in such conditions.
Several groups have measured kynurenate in CSF.
Here, the basal conce tia, raising the possibility that enhanced penetration by
kynurenate may occur in such conditions.
Several groups have measured kynurenate in CSF.
Here, the basal concentrations seem to be in the low
nanomolar range (1.13 kynurenate may occur in such conditions.

Several groups have measured kynurenate in CSF.

Here, the basal concentrations seem to be in the low

1 nanomolar range (1.13 nM in rat, 3.6 nM in human)

(Heyes and Quearry, 199 Several groups have measured kynurenate in CS
Here, the basal concentrations seem to be in the k
nanomolar range (1.13 nM in rat, 3.6 nM in huma
(Heyes and Quearry, 1990; Heyes et al., 1990a; Swartz
al., 1990b). Although s Here, the basal concentrations seem to be in the low
nanomolar range $(1.13 \text{ nM} \text{ in } \text{rat}, 3.6 \text{ nM} \text{ in } \text{human})$ sto
(Heyes and Quearry, 1990; Heyes et al., 1990a; Swartz et
al., 1990b). Although systemic administration o nanomolar range $(1.13 \text{ nm} \text{ in } \text{rat}, 3.6 \text{ nm} \text{ in } \text{human})$
(Heyes and Quearry, 1990; Heyes et al., 1990a; Swartz et al., 1990b). Although systemic administration of L-kyn-
urenine increased kynurenate levels about 3.5-fold urenine increased kynurenate lev
expected, the rather surprising of
that systemic kynurenate injection
almost 7-fold. This may indicate s
barrier permeability to kynurenate
The egress of kynurenate from pected, the rather surprising observation was made
at systemic kynurenate injection increased CSF levels
most 7-fold. This may indicate significant blood-brain
rrier permeability to kynurenate.
The egress of kynurenate fr

that systemic kynurenate injection increased CSF lev
almost 7-fold. This may indicate significant blood-bra
barrier permeability to kynurenate.
The egress of kynurenate from the CNS is probal
mediated by an acidic transpor The egress of kynurenate from the CNS is probably
mediated by an acidic transport system since the admin-
istration of probenecid, an inhibitor of this carrier, ele-
vates cerebral kynurenate levels both under resting conbarrier permeability to kynurenate.
The egress of kynurenate from the CNS is probably
mediated by an acidic transport system since the admin-
istration of probenecid, an inhibitor of this carrier, ele-
vates cerebral kynur The egress of kynurenate from the CNS is probably
mediated by an acidic transport system since the admin-
istration of probenecid, an inhibitor of this carrier, ele-
vates cerebral kynurenate levels both under resting conmediated by an acidic transport system since the administration of probenecid, an inhibitor of this carrier, elevates cerebral kynurenate levels both under resting conditions (Vecsei et al., 1992a,b) and following treatmen istration of probenecid, an inhibitor of this carrier, elevates cerebral kynurenate levels both under resting conditions (Vecsei et al., 1992a,b) and following treatment with tryptophan or indolepyruvic acid (Moroni et al. vates cerebral kynurenate levels both under resting conditions (Vecsei et al., 1992a,b) and following treatment
with tryptophan or indolepyruvic acid (Moroni et al., ciat
1991b). No evidence was obtained for the existence ditions (Vecsei et al., 1992a,b) and following treatment
with tryptophan or indolepyruvic acid (Moroni et al.,
1991b). No evidence was obtained for the existence of
active uptake processes for radiolabeled kynurenate in
b with tryptophan or indolepyruvic acid (Moroni et al., 1991b). No evidence was obtained for the existence of active uptake processes for radiolabeled kynurenate in brain slices (Turski and Schwarcz, 1988), and the same mate 1991b). No evidence was obtained for the existence of active uptake processes for radiolabeled kynurenate in brain slices (Turski and Schwarcz, 1988), and the same material injected directly into the hippocampus of unanaes active uptake processes for radiolabeled kynurenate in brain slices (Turski and Schwarcz, 1988), and the same material injected directly into the hippocampus of unanaesthetised rats was cleared into the rest of the brain, brain slices (Turski and Schwarcz, 1988), and the same
material injected directly into the hippocampus of unanaesthetised rats was cleared into the rest of the brain
the circulation, and, ultimately, the urine with no ev
d material injected directly into the hippocampus of un-
anaesthetised rats was cleared into the rest of the brain,
the circulation, and, ultimately, the urine with no evi-
dence of metabolism. The localisation of injected anaesthetised rats was cleared into the rest of the brain,
the circulation, and, ultimately, the urine with no evi-
dence of metabolism. The localisation of injected kynu-
renate to only soluble fractions of brain in this the circulation, and, ultimately, the urine with no evidence of metabolism. The localisation of injected kynu-
renate to only soluble fractions of brain in this study was
also interpreted to imply the absence both of uptak dence of metabolism. The localisation of injected kynu-
renate to only soluble fractions of brain in this study was
also interpreted to imply the absence both of uptake and
metabolism by subcellular organelles and of signi renate to only soluble fractions of brain in this study was
also interpreted to imply the absence both of uptake and
metabolism by subcellular organelles and of significant
binding to cellular membranes. This conclusion, w also interpreted to imply the absence both of uptake and
metabolism by subcellular organelles and of significant
binding to cellular membranes. This conclusion, which
is similar to that drawn from related studies of quinol metabolism by subcellular organelles and of significant
binding to cellular membranes. This conclusion, which
is similar to that drawn from related studies of quinolinic
acid, must be questioned in view of the known, albe binding to cellular membranes. This conclusion, which
is similar to that drawn from related studies of quinolinic at
acid, must be questioned in view of the known, albeit
low, affinity of kynurenate for amino acid receptor is similar to that drawn from related studies of quinolinic ated values
acid, must be questioned in view of the known, albeit leads
low, affinity of kynurenate for amino acid receptors and ACP
the subsequent demonstration low, affinity of kynurenate for amino acid receptors and
the subsequent demonstration of a relatively high affinity
for the strychnine-resistant allosteric site of the NMDA
receptor (see section VI.A). w, affinity of kynurenate for amino acid receptors and
e subsequent demonstration of a relatively high affinity
reflectively, to the metabolism of phosphatidylinositol lipids.
The NMDA-sensitive population of receptors is

the subsequent demonstration of a relatively high affinity
for the strychnine-resistant allosteric site of the NMDA
receptor (see section VI.A).
Additional studies in drug-free patients with diagnosed
senile dementia of th for the strychnine-resistant allosteric site of the NMDA
receptor (see section VI.A).
Additional studies in drug-free patients with diagnosed
senile dementia of the the Alzheimer type or Parkinson's
disease indicated that receptor (see section VI.A).
Additional studies in drug-free patients with diagnosed
senile dementia of the the Alzheimer type or Parkinson's
disease indicated that probenecid, administered in di-
vided doses to a total of Additional studies in drug-free patients with diagnosed
senile dementia of the the Alzheimer type or Parkinson's
disease indicated that probenecid, administered in di-
non
vided doses to a total of 100 mg/kg during 24 h senile dementia of the the Alzheimer type or Parkinson's disease indicated that probenecid, administered in divided doses to a total of 100 mg/kg during 24 hours, produced a significant, 4-fold increase of kynurenate in CS disease indicated that probenecid, administered in vided doses to a total of 100 mg/kg during 24 hou produced a significant, 4-fold increase of kynurenate CSF sampled 2 hours after the final dose (Vecsei et a 1992a). It wa vided doses to a total of 100 mg/kg during 24 hours, and neocortex (Collingridge and Lester, 1989; Bindman produced a significant, 4-fold increase of kynurenate in et al., 1991; Tsumoto, 1992) in which a brief repetitive C CSF sampled 2 hours after the final dose (Vecsei et al., 1992a). It was noted that such manipulations of endog-
enous kynurenate might be of therapeutic value in these
and other disorders in which the excessive activation amino acid receptors in these increase of synaptic efficacy, believed to form the neu-
enous kynurenate might be of therapeutic value in these ronal basis of learning and memory processes.
and other disorders in which the

enous kynurenate might be of therapeutic value in these romand other disorders in which the excessive activation of Namino acid receptors could be involved. These sease 3. Synthesis of kynurenate from indolepyruvate. An ap and other disorders in which the excessive activation of amino acid receptors could be involved.
3. Synthesis of kynurenate from indolepyruvate. An alternative route for the conversion of tryptophan to kynurenate, proposed amino acid receptors could be involved.

3. Synthesis of kynurenate from indolepyruvate. An

alternative route for the conversion of tryptophan to

kynurenate, proposed by Moroni and his group (1991b),

involves the oxidat

al., 1990b). Although systemic administration of L-kyn-
urenine increased kynurenate levels about 3.5-fold, as
expected, the rather surprising observation was made
that systemic kynurenate injection increased CSF levels
a urenine increased kynurenate levels about 3.5-fold, as
expected, the rather surprising observation was made
that systemic kynurenate injection increased CSF levels
almost 7-fold. This may indicate significant blood-brain
b NE
dolepyruvic acid and the subsequent conversion of the
latter to kynurenic acid. It was proposed that the admin-NE
dolepyruvic acid and the subsequent conversion of t
latter to kynurenic acid. It was proposed that the adm
istration of indolepyruvic acid might then provide a me WE
dolepyruvic acid and the subsequent conversion of the
latter to kynurenic acid. It was proposed that the admin-
istration of indolepyruvic acid might then provide a more
effective means (compared with tryptophan or L-ky dolepyruvic acid and the subsequent conversion of identicative means (compared with the provide a measured with tryptophan or L-kynu-
effective means (compared with tryptophan or L-kynu-
renine) of elevating kynurenate lev dolepyruvic acid and the subsequent conversion of the
latter to kynurenic acid. It was proposed that the admin-
istration of indolepyruvic acid might then provide a more
effective means (compared with tryptophan or L-kynulatter to kynurenic acid. It was proposed that the administration of indolepyruvic acid might then provide a more effective means (compared with tryptophan or L-kynurenine) of elevating kynurenate levels in the brain or, a istration of indolepyruvic acid might then provide a more
effective means (compared with tryptophan or L-kynu-
renine) of elevating kynurenate levels in the brain or, at
least, of increasing the ratio of kynurenate to quin renine) of elevating kynurenate levels in the brain or, at least, of increasing the ratio of kynurenate to quinolinate concentrations. Indolepyruvate is known to be a normal constituent of biological fluids that can be pro renine) of elevating kynurenate levels in the brain or, a
least, of increasing the ratio of kynurenate to quinolinate
concentrations. Indolepyruvate is known to be a norma
constituent of biological fluids that can be produ least, of increasing the ratio of kynurenate to quinolinat
concentrations. Indolepyruvate is known to be a norma
constituent of biological fluids that can be produced fro
tryptophan by the action of transaminase enzymes (K roda, 1950; Millard and Gal, 1971). Formation of indo-
lepyruvate could, therefore, represent an endogenous
step in tryptophan metabolism. Moroni et al. (1991b) constituent of biological fluids that can be produced from
tryptophan by the action of transaminase enzymes (Ku-
roda, 1950; Millard and Gal, 1971). Formation of indo-
lepyruvate could, therefore, represent an endogenous
s tryptophan by the action of transaminase enzymes (Kuroda, 1950; Millard and Gal, 1971). Formation of indolepyruvate could, therefore, represent an endogenous step in tryptophan metabolism. Moroni et al. (1991b) and Russi e roda, 1950; Millard and Gal, 1971). Formation of indo-
lepyruvate could, therefore, represent an endogenous
step in tryptophan metabolism. Moroni et al. (1991b)
and Russi et al. (1989) showed that indolepyruvate, in-
jecte lepyruvate could, therefore, represent an endogenous
step in tryptophan metabolism. Moroni et al. (1991b)
and Russi et al. (1989) showed that indolepyruvate, in-
jected systemically, can increase cerebral levels of kyn-
ur step in tryptophan metabolism. Moroni et al. (1991b)
and Russi et al. (1989) showed that indolepyruvate, in-
jected systemically, can increase cerebral levels of kyn-
urenines, including a striking increase in the ratio of and Russi et al. (1989) showed that indolepyruvate, injected systemically, can increase cerebral levels of kyn-
urenines, including a striking increase in the ratio of
kynurenate to tryptophan concentrations. This result,
 jected systemically, can increase cerebral levels of kyn-
urenines, including a striking increase in the ratio of
kynurenate to tryptophan concentrations. This result,
together with the discovery that the administration of urenines, including a striking increase in the ratio of kynurenate to tryptophan concentrations. This result, together with the discovery that the administration of radiolabeled indolepyruvate causes the appearance of labe kynurenate to tryptophan concentrations. This result, together with the discovery that the administration of radiolabeled indolepyruvate causes the appearance of labeled kynurenate rather than tryptophan, indicates strongl together with the discovery that the adm
radiolabeled indolepyruvate causes the
labeled kynurenate rather than tryptop
strongly that the metabolic flux is from i
to kynurenate and not back to tryptophar **IV. Pharmacology**
 IV. Pharmacology
 IV. Pharmacology
 IV. Pharmacology

rongly that the metabolic flux is from indolepyruvat

kynurenate and not back to tryptophan.

IV. Pharmacology

The pharmacology of kynurenines is intimately asso-

atted with that of the excitatory amino acids. The to kynurenate and not back to tryptophan.

IV. Pharmacology

The pharmacology of kynurenines is intimately asso-

ciated with that of the excitatory amino acids. The

endogenous excitatory amino acid transmitters, of which IV. Pharmacology
The pharmacology of kynurenines is intimately asso-
ciated with that of the excitatory amino acids. The
endogenous excitatory amino acid transmitters, of which
L-glutamate, L-aspartate, homocysteate, and c The pharmacology of kynurenines is intimately asso-
ciated with that of the excitatory amino acids. The
endogenous excitatory amino acid transmitters, of which
L-glutamate, L-aspartate, homocysteate, and cysteine
sulphinic The pharmacology of kynurenines is intimately asso-
ciated with that of the excitatory amino acids. The
endogenous excitatory amino acid transmitters, of which
L-glutamate, L-aspartate, homocysteate, and cysteine
sulphinic ciated with that of the excitatory amino acids. The
endogenous excitatory amino acid transmitters, of which
L-glutamate, L-aspartate, homocysteate, and cysteine
sulphinic acid are the primary candidates, appear to act
on s endogenous excitatory amino acid transmitters, of which
L-glutamate, L-aspartate, homocysteate, and cysteine
sulphinic acid are the primary candidates, appear to act
on several subtypes of neuronal receptor (Watkins and
Ev L-glutamate, L-aspartate, homocysteate, and cysteine
sulphinic acid are the primary candidates, appear to act
on several subtypes of neuronal receptor (Watkins and
Evans, 1981; Stone and Burton, 1988; Collingridge and
Lest sulphinic acid are the primary candidates, appear to act
on several subtypes of neuronal receptor (Watkins and
Evans, 1981; Stone and Burton, 1988; Collingridge and
Lester, 1989). These include receptors for which the
prim on several subtypes of neuronal receptor (Wat
Evans, 1981; Stone and Burton, 1988; Colling
Lester, 1989). These include receptors for w
primary agonists are exogenous materials,
NMDA, kainic acid, AMPA, 2-amino-4-phosphano Evans, 1981; Stone and Burton, 1988; Collingridge and
Lester, 1989). These include receptors for which the
primary agonists are exogenous materials, such as
NMDA, kainic acid, AMPA, 2-amino-4-phosphonobu-
tanoic acid, and primary agonists are exogenous materials, such as
NMDA, kainic acid, AMPA, 2-amino-4-phosphonobu-
tanoic acid, and ACPD. The first three receptors are
primarily ion channel-coupled receptors that are associ-
ated with the primary agonists are exogenous materials, such as NMDA, kainic acid, AMPA, 2-amino-4-phosphonobutanoic acid, and ACPD. The first three receptors are primarily ion channel-coupled receptors that are associated with the open NMDA, kainic acid, AMPA, 2-amino-4-phosphonobutanoic acid, and ACPD. The first three receptors are
primarily ion channel-coupled receptors that are associated with the opening of cation channels, which, in turn,
leads to d leads to depolarisation and excitation of neurones; the ACPD receptor is coupled primarily, although not exclusively, to the metabolism of phosphatidylinositol lipids. primarily ion channel-coupled receptors that are associated with the opening of cation channels, which, in turn, leads to depolarisation and excitation of neurones; the ACPD receptor is coupled primarily, although not excl ed with the opening of cation channels, which, in turn,
ads to depolarisation and excitation of neurones; the
CPD receptor is coupled primarily, although not exclu-
rely, to the metabolism of phosphatidylinositol lipids.
T

leads to depolarisation and excitation of neurones;
ACPD receptor is coupled primarily, although not ex
sively, to the metabolism of phosphatidylinositol lipi
The NMDA-sensitive population of receptors is
volved not only w ACPD receptor is coupled primarily, although not exclusively, to the metabolism of phosphatidylinositol lipids.
The NMDA-sensitive population of receptors is involved not only with the processes of synaptic transmission i sively, to the metabolism of phosphatidylinositol lipids.
The NMDA-sensitive population of receptors is in-
volved not only with the processes of synaptic transmis-
sion in many parts of the CNS but also in long-term
aspec The NMDA-sensitive population of receptors is in-
volved not only with the processes of synaptic transmis-
sion in many parts of the CNS but also in long-term
aspects of neuronal activity. The latter include the phe-
nomen volved not only with the processes of synaptic transmis-
sion in many parts of the CNS but also in long-term
aspects of neuronal activity. The latter include the phe-
nomenon of long-term potentiation in the hippocampus
an sion in many parts of the CNS but also in long-term
aspects of neuronal activity. The latter include the phe-
nomenon of long-term potentiation in the hippocampus
and neocortex (Collingridge and Lester, 1989; Bindman
et al aspects of neuronal activity. The latter include the phe-
nomenon of long-term potentiation in the hippocampus
and neocortex (Collingridge and Lester, 1989; Bindman
et al., 1991; Tsumoto, 1992) in which a brief repetitive
 nomenon of long-term potentiation in the hippocampus
and neocortex (Collingridge and Lester, 1989; Bindman
et al., 1991; Tsumoto, 1992) in which a brief repetitive
stimulation to afferent pathways induces a long-lasting
in and neocortex (Collingridge and Lester, 1989;
et al., 1991; Tsumoto, 1992) in which a brief
stimulation to afferent pathways induces a lo
increase of synaptic efficacy, believed to form
ronal basis of learning and memory p stimulation to afferent pathways induces a long-lasting

stimulation to afferent pathways induces a long-lasting
increase of synaptic efficacy, believed to form the neu-
ronal basis of learning and memory processes.
NMDA receptors are also involved in the plastic proc-
esses con increase of synaptic efficacy, believed to form the neu
ronal basis of learning and memory processes.
NMDA receptors are also involved in the plastic processes
concerned in the targeting of neurones and syn
apses and their ronal basis of learning and memory processes.
NMDA receptors are also involved in the plastic presses concerned in the targeting of neurones and s
apses and their adjustment during development, es
cially in the visual syst NMDA receptors are also involved in the plastic processes concerned in the targeting of neurones and synapses and their adjustment during development, especially in the visual system of vertebrates and invertebrates (see s esses concerned in the targeting of neurones and syn
apses and their adjustment during development, especially in the visual system of vertebrates and inverte
brates (see section VII). It is likely that comparabl
processes

PHARMACOLOGICAL REVIEWS

QUINOLINIC AND KYN
and, possibly, age-related changes in many parts of the tag
mi neuraxis.

QUINOLINIC AND KYN

At, possibly, age-related changes in many parts of the tag

auraxis. mind the other extreme, in a sense, NMDA receptors are un

volved in the determination of cell viability. Because are and, possibly, age-related changes in many parts of the
neuraxis.
At the other extreme, in a sense, NMDA receptors are
involved in the determination of cell viability. Because
the cation channels activated by NMDA receptor and, possibly, age-related changes in many parts of the
neuraxis.
At the other extreme, in a sense, NMDA receptors are
involved in the determination of cell viability. Because
the cation channels activated by NMDA receptor neuraxis.

At the other extreme, in a sense, NMDA receptors are

involved in the determination of cell viability. Because

the cation channels activated by NMDA receptors con-

duct calcium ions, as well as sodium and pota At the other extreme, in a sense, NMDA receptors a
involved in the determination of cell viability. Becau
the cation channels activated by NMDA receptors co
duct calcium ions, as well as sodium and potassium io
(Macdermott involved in the determination of cell viability. Because at
the cation channels activated by NMDA receptors con-
duct calcium ions, as well as sodium and potassium ions
m(Macdermott et al., 1986; Crowder et al., 1987), ove the cation channels activated by NMDA receptors conduct calcium ions, as well as sodium and potassium ions (Macdermott et al., 1986; Crowder et al., 1987), overactivation of those receptors results in an accumulation of in duct calcium ions, as well as sodium and potassium ions (Macdermott et al., 1986; Crowder et al., 1987), overactivation of those receptors results in an accumulation of intracellular calcium to a degree that is believed to (Macdermott et al., 1986; Crowder et al., 1987), overactivation of those receptors results in an accumulation of Intracellular calcium to a degree that is believed to activate destructive enzymes, such as phospholipases, tivation of those receptors results in an accumulation of N
intracellular calcium to a degree that is believed to acti-
vate destructive enzymes, such as phospholipases, pro-
teases, and protein kinases. Together, these en intracellular calcium to a degree that is believed to activate destructive enzymes, such as phospholipases, proteases, and protein kinases. Together, these enzymic hyprocesses result in the acute disruption of cell activi vate destructive enzymes, such as phospholipases, proteases, and protein kinases. Together, these enzymic processes result in the acute disruption of cell activity and, if maintained, cellular degeneration. This may be of processes result in the acute disruption of cell activity
and, if maintained, cellular degeneration. This may be of
importance, not only in explaining some cell death ocprocesses result in the acute disruption of cell activity
and, if maintained, cellular degeneration. This may be of
importance, not only in explaining some cell death oc-
curring with ageing but also the loss of neurones t and, if maintained, cellular degeneration. This may be a importance, not only in explaining some cell death of curring with ageing but also the loss of neurones the occurs in dementing disorders such as Alzheimer's disease importance, not only in explaining some cell death oc
curring with ageing but also the loss of neurones tha
occurs in dementing disorders such as Alzheimer's dis
ease, related neurodegenerative disorders such as Hun
tingto occurs in dementing disorders such as Alzheimer's disease, related neurodegenerative disorders such as Huntington's disease, and amyotrophic lateral sclerosis (motor neurone disease) and also the widespread neuronal ease, related neurodegenerative disorders such as Huntington's disease, and amyotrophic lateral sclerosis (motor neurone disease) and also the widespread neuronal damage that results from cerebral infarctions. In the latte tington's disease, and amyotrophic lateral sclerosis (motor neurone disease) and also the widespread neuronal damage that results from cerebral infarctions. In the latter case, the hypoxia or ischaemia is believed to resul tor neurone disease) and also the widespread neuronal
damage that results from cerebral infarctions. In the
latter case, the hypoxia or ischaemia is believed to result
in a massive efflux of glutamate, aspartate, and, poss damage that results from cerebral infarctions. In the latter case, the hypoxia or ischaemia is believed to result in a massive efflux of glutamate, aspartate, and, possibly, lother endogenous excitatory amino acids to an e latter case, the hypoxia or ischaemia is believed to result the
in a massive efflux of glutamate, aspartate, and, possibly, leve
other endogenous excitatory amino acids to an extent whe
that results in activation of NMDA r in a massive e
other endoge
that results in
excitotoxicity
section VI. *A. A. Quinolinic Acid*
 A. Quinolinic Acid
 A. Quinolinic Acid
 The initial excitemen

citotoxicity. These topics will be discussed in detail in
ction VI.
different conduction with the discovery of the initial excitement engendered by the discovery of (g
inolinic acid lay in the fact that it is a selective a section VI.

A. Quinolinic Acid

The initial excitement engendered by the discovery of

quinolinic acid lay in the fact that it is a selective agonist

for the NMDA population of receptors. The first report A. Quinolinic Acid
The initial excitement engendered by the discovery of
quinolinic acid lay in the fact that it is a selective agonist
for the NMDA population of receptors. The first report
of the excitatory activity of q and St

The initial excitement engendered by the discovery of (glutan

quinolinic acid lay in the fact that it is a selective agonist

for the NMDA population of receptors. The first report way as

of the excitatory activi The initial excitement engendered by the discovery of (a quinolinic acid lay in the fact that it is a selective agonist and for the NMDA population of receptors. The first report word the excitatory activity of quinolinic for the NMDA population of receptors. The first report
of the excitatory activity of quinolinic acid resulted from
experiments in the cerebral cortex of anaesthetised rats
(Stone and Perkins, 1981), in which it was demonst for the NMDA population of receptors. The first report
of the excitatory activity of quinolinic acid resulted from
experiments in the cerebral cortex of anaesthetised rats
(Stone and Perkins, 1981), in which it was demonst of the excitatory activity of quinolinic acid resulted from the experiments in the cerebral cortex of anaesthetised rats elective.
(Stone and Perkins, 1981), in which it was demonstrated move not only that quinolinic acid (Stone and Perkins, 1981), in which it was demonstrated moved between neocortex and spinal cord and, in several
not only that quinolinic acid would excite all 54 neurones animals, back to neocortex.
tested with an apparent (Stone and Perkins, 1981), in which it was demonstrated
not only that quinolinic acid would excite all 54 neurones
tested with an apparently similar potency to NMDA
itself but also that those excitations could be prevente not only that quinolinic acid would excite all 54 neurones
tested with an apparently similar potency to NMDA
itself but also that those excitations could be prevented
on 16 of 18 cells by the then newly described selective tested with an apparently similar potency to NMDA
itself but also that those excitations could be prevented to
on 16 of 18 cells by the then newly described selective al
NMDA receptor antagonist 2AP5 (Perkins et al., 1981) itself but also that those excitations could be prevente
on 16 of 18 cells by the then newly described selectiv
NMDA receptor antagonist 2AP5 (Perkins et al., 1981
glutamate diethyl ester was not effective. 2AP5 wa
active NMDA receptor antagonist 2AP5 (Perkins et al., 1981); sensitive to quinolinic acid. In contrast, Purkinje cells in glutamate diethyl ester was not effective. 2AP5 was the cerebellum were readily excited by glutamate, but a NMDA receptor antagonist 2AP5 (Perkins et al., 1981);
glutamate diethyl ester was not effective. 2AP5 was
active at doses having little effect on sensitivity to kain-
ate or quisqualate. A greater antagonistic potency of t glutamate diethyl ester was not effective. 2AP5 was active at doses having little effect on sensitivity to kainate or quisqualate. A greater antagonistic potency of the heptanoate antagonist 2AP7 was later observed in para active at doses having little effect on sensitivity to kain-
ate or quisqualate. A greater antagonistic potency of the (i)
heptanoate antagonist 2AP7 was later observed in par-
allel against responses to NMDA and quinolina ate or quisqualate. A greater antagonistic potency of the heptanoate antagonist 2AP7 was later observed in parallel against responses to NMDA and quinolinate (Stone, 1986a). Subsequent work using selective antagonists or c allel against responses to NMDA and quinolinate (Stone, mate and quinolinate, the latter was a less effective 1986a). Subsequent work using selective antagonists or excitant in more posteriorly located regions of the area, allel against responses to NMDA and quinolinate (Stone, 1986a). Subsequent work using selective antagonists or cross-desensitisation has confirmed the selectivity of action of quinolinic acid at NMDA receptors (Herrling et 1986a). Subsequent work using selective antagonists or exc
cross-desensitisation has confirmed the selectivity of ac-
tion of quinolinic acid at NMDA receptors (Herrling et bei
al., 1983; Perkins and Stone, 1983a,b; McLenn cross-desensitisation has confirmed the selectivity of action of quinolinic acid at NMDA receptors (Herrling et al., 1983; Perkins and Stone, 1983a,b; McLennan, 1984; Peet et al., 1986, 1987; Peters and Choi, 1987; Addae a al., 1983; Perkins and Stone, 1983a,b; McLennan, 1984; Peet et al., 1986, 1987; Peters and Choi, 1987; Addae and Stone, 1986; Martin and Lodge, 1987; Burton et al., 1987, 1988; Kiskin et al., 1990; Curras and Dingledine, 1 Peet et al., 1986, 1987; Peters and Choi, 1987; Addae and This initial study could be criticised on the grounds
Stone, 1986; Martin and Lodge, 1987; Burton et al., 1987, that the use of glutamate as a reference compound fa Peet et al., 1986, 1987; Peters and Cho
Stone, 1986; Martin and Lodge, 1987; 1
1988; Kiskin et al., 1990; Curras and
Considerable variation exists, howev
potencies of quinolinate and NMDA.
Although the technique of microio one, 1986; Martin and Lodge, 1987; Burton et al., 1987,
88; Kiskin et al., 1990; Curras and Dingledine, 1992). t
posiderable variation exists, however, in the relative r
tencies of quinolinate and NMDA.
Although the techni

1988; Kiskin et al., 1990; Curras and Dingledine, 1992).
Considerable variation exists, however, in the relative
potencies of quinolinate and NMDA.
Although the technique of microiontophoresis allows
compounds to be applie Although the technique of microiontophoresis allows
compounds to be applied in the vicinity of individual
neurones in the CNS (Stone, 1985a), it has the disadvan-

x

x intervals are being applied from a point

microelectrode source into an effectively unlimited vol-SUP TREATH T 325
tage that substances are being applied from a point
microelectrode source into an effectively unlimited vol-
ume. The concentrations of material within the tissue
are, therefore, largely unknown, as are the precise con tage that substances are being applied from a point
microelectrode source into an effectively unlimited volume. The concentrations of material within the tissue
are, therefore, largely unknown, as are the precise con-
cent microelectrode source into an effectively unlimited volume. The concentrations of material within the tissue are, therefore, largely unknown, as are the precise concentrations achieved at the cell surface. With these techmicroelectrode source into an effectively unlimited volume. The concentrations of material within the tissue
are, therefore, largely unknown, as are the precise concentrations achieved at the cell surface. With these techume. The concentrations of material within the tissue
are, therefore, largely unknown, as are the precise con-
centrations achieved at the cell surface. With these tech-
nical reservations in mind, however, it was calculat are, therefore, largely unknown, as are the precise concentrations achieved at the cell surface. With these technical reservations in mind, however, it was calculated that quinolinic acid was about one-quarter as active as centrations achieved at the cell surface. With these technical reservations in mind, however, it was calculated that quinolinic acid was about one-quarter as active as NMDA and approximately as active as glutamate and aspa that quinolinic acid was about one-quarter as active as NMDA and approximately as active as glutamate and aspartate (Stone and Perkins, 1981). It should be recalled, however, that the latter compounds have rapid high-affin that quinolinic acid was about one-quarter as active as NMDA and approximately as active as glutamate and aspartate (Stone and Perkins, 1981). It should be recalled, however, that the latter compounds have rapid high-affin aspartate (Stone and Perkins, 1981). It should be recalled, however, that the latter compounds have rapid high-affinity uptake systems for their removal, whereas quinolinic acid apparently does not.

1. Are quinolinate re partate (Stone and Perkins, 1981). It should b
lled, however, that the latter compounds have $\frac{1}{2}$
gh-affinity uptake systems for their removal, wh
inolinic acid apparently does not.
1. Are quinolinate receptors a sub

occurs in dementing disorders such as Alzheimer's dis-
ease, related neurodegenerative disorders such as Hun-
eisovered that neurones in different parts of the CNS
tington's disease, and amyotrophic lateral sclerosis (mo-
 called, however, that the latter compounds have rapid
high-affinity uptake systems for their removal, whereas
quinolinic acid apparently does not.
1. Are quinolinate receptors a subtype of N-methyl-D-
aspartate receptor? high-affinity uptake systems for their removal, whereas
quinolinic acid apparently does not.
1. Are quinolinate receptors a subtype of N-methyl-D-
aspartate receptor?. a. EXTRACELLULAR STUDIES. The
initial proposal that qu quinolinic acid apparently does not.

1. Are quinolinate receptors a subtype of N-methyl-D-

aspartate receptor?. a. EXTRACELLULAR STUDIES. The

initial proposal that quinolinic acid was a ligand for the

NMDA receptors re 1. Are quinolinate receptors a subtype of N-methyl-D-
aspartate receptor?. a. EXTRACELLULAR STUDIES. The
initial proposal that quinolinic acid was a ligand for the
NMDA receptors received a small setback when it was
disco aspartate receptor?. a. EXTRACELLULAR STUDIES. The
initial proposal that quinolinic acid was a ligand for the
NMDA receptors received a small setback when it was
discovered that neurones in different parts of the CNS
showe initial proposal that quinolinic acid was a ligand for the
NMDA receptors received a small setback when it was
discovered that neurones in different parts of the CNS
showed a differential sensitivity to NMDA and quinolinic NMDA receptors received a small setback when it was
discovered that neurones in different parts of the CNS
showed a differential sensitivity to NMDA and quinolinic
acid. For example, neurones in the cerebral cortex were
ab discovered that neurones in different parts of the CNS
showed a differential sensitivity to NMDA and quinolinic
acid. For example, neurones in the cerebral cortex were
about equally sensitive to glutamate and quinolinic ac showed a differential sensitivity to NMDA and quinolinic
acid. For example, neurones in the cerebral cortex were
about equally sensitive to glutamate and quinolinic acid,
the ratio of ejecting currents required to induce p acid. For example, neurones in the cerebral cortex were
about equally sensitive to glutamate and quinolinic acid,
the ratio of ejecting currents required to induce plateau
levels of firing of comparable amplitude being abo about equally sensitive to glutamate and quinolinic acid,
the ratio of ejecting currents required to induce plateau
levels of firing of comparable amplitude being about 0.8;
when the same micropipettes were used to test ne the ratio of ejecting currents required to induce plateau
levels of firing of comparable amplitude being about 0.8;
when the same micropipettes were used to test neurones
in the spinal cords of the same animals, however, levels of firing of comparable amplitude being about 0.8;
when the same micropipettes were used to test neurones
in the spinal cords of the same animals, however, most
of the neurones excited by glutamate were insensitive when the same micropipettes were used to test neurones
in the spinal cords of the same animals, however, most
of the neurones excited by glutamate were insensitive to
the iontophoresis of quinolinic acid, even though much
 in the spinal cords of the same animals, however, most
of the neurones excited by glutamate were insensitive to
the iontophoresis of quinolinic acid, even though much
higher ejecting currents were used in these cases (Perk of the neurones excited by glutamate were insensitive to
the iontophoresis of quinolinic acid, even though much
higher ejecting currents were used in these cases (Perkins
and Stone, 1983a). The ratio of equieffective curre the iontophoresis of quinolinic acid, even though much
higher ejecting currents were used in these cases (Perkins
and Stone, 1983a). The ratio of equieffective currents
(glutamate to quinolinate) on sensitive spinal cells higher ejecting currents were used in these cases (Perkins
and Stone, 1983a). The ratio of equieffective currents
(glutamate to quinolinate) on sensitive spinal cells was
approximately 0.14. The study was performed in such and Stone, 1983a). The ratio of equieffective currents (glutamate to quinolinate) on sensitive spinal cells was approximately 0.14. The study was performed in such a way as to minimise the variations that can occur between (glutamate to quinolinate) on sensitive spinal cells was approximately 0.14. The study was performed in such a way as to minimise the variations that can occur between the ejecting characteristics of different iontophoreti approximately 0.14. The study was performed in such a
way as to minimise the variations that can occur between
the ejecting characteristics of different iontophoretic
electrodes (Stone, 1985a) by using the same electrodes
 way as to minimise the varia
the ejecting characteristic
electrodes (Stone, 1985a) h
moved between neocortex a
animals, back to neocortex.
Differences of neuronal e ejecting characteristics of different iontophore ectrodes (Stone, 1985a) by using the same electro
oved between neocortex and spinal cord and, in seventimals, back to neocortex.
Differences of neuronal sensitivity were a

electrodes (Stone, 1985a) by using the same electrode moved between neocortex and spinal cord and, in sever animals, back to neocortex.
Differences of neuronal sensitivity were also encountered in other regions of the CNS. moved between neocortex and spinal cord and, in several

animals, back to neocortex.

Differences of neuronal sensitivity were also encoun-

tered in other regions of the CNS. In the hippocampus,

all neurones that were ex animals, back to neocortex.

Differences of neuronal sensitivity were also encoun-

tered in other regions of the CNS. In the hippocampus,

all neurones that were excited by glutamate were also

sensitive to quinolinic ac Differences of neuronal sensitivity were also encountered in other regions of the CNS. In the hippocampus, all neurones that were excited by glutamate were also sensitive to quinolinic acid. In contrast, Purkinje cells in tered in other regions of the CNS. In the hippocampus,
all neurones that were excited by glutamate were also
sensitive to quinolinic acid. In contrast, Purkinje cells in
the cerebellum were readily excited by glutamate, bu sensitive to quinolinic acid. In contrast, Purkinje cells in sensitive to quinolinic acid. In contrast, Purkinje cells the cerebellum were readily excited by glutamate, bonly one-third of them responded to quinolinic ac (Perkins and Stone, 1983a). Interestingly, although a cells tes the cerebellum were readily excited by glutamate, but
only one-third of them responded to quinolinic acid
(Perkins and Stone, 1983a). Interestingly, although all
cells tested in the striatum were sensitive to both gluta-
m only one-third of them responded to quinolinic acid (Perkins and Stone, 1983a). Interestingly, although all cells tested in the striatum were sensitive to both glutamate and quinolinate, the latter was a less effective exc (Perkins and Stone, 1983a). Interestingly, although all cells tested in the striatum were sensitive to both gluta-
mate and quinolinate, the latter was a less effective excitant in more posteriorly located regions of the a cells tested in the striatum were sensitive to both gluta mate and quinolinate, the latter was a less effective excitant in more posteriorly located regions of the area the glutamate to quinolinate equieffective current ra tum. citant in more posteriorly located regions of the area,
e glutamate to quinolinate equieffective current ratios
ing 0.75 in anterior regions and 0.33 in posterior stria-
m.
This initial study could be criticised on the gro

the glutamate to quinolinate equieffective current ratios
being 0.75 in anterior regions and 0.33 in posterior stria-
tum.
This initial study could be criticised on the grounds
that the use of glutamate as a reference comp being 0.75 in anterior regions and 0.33 in posterior stria-
tum.
This initial study could be criticised on the grounds
that the use of glutamate as a reference compound failed
to take account of glutamate's being a nonsele tum.
This initial study could be criticised on the grounds
that the use of glutamate as a reference compound failed
to take account of glutamate's being a nonselective ago-
nist at amino acid receptors. It is, therefore, p This initial study could be criticised on the grounds
that the use of glutamate as a reference compound failed
to take account of glutamate's being a nonselective ago-
nist at amino acid receptors. It is, therefore, possib that the use of glutamate as a reference compound failed
to take account of glutamate's being a nonselective ago-
nist at amino acid receptors. It is, therefore, possible that
receptors other than the quinolinate-sensitive to take account of glutamate's being a nonselective a
nist at amino acid receptors. It is, therefore, possible t
receptors other than the quinolinate-sensitive NMI
receptor population, such as those for quisqualic ac
kaina receptors other than the quinolinate-sensitive NMDA receptor population, such as those for quisqualic acid, kainate, or AMPA, were also activated and were responsible for the difference of sensitivity. In later experi-

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ments, therefore, a direct comparison was performed
between quinolinic acid and NMDA itself (Perkins and STONE
ments, therefore, a direct comparison was performed site
between quinolinic acid and NMDA itself (Perkins and of
Stone, 1983b). Results were obtained, however, that were fou STONE

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ments, therefore, a direct comparison was performed site

between quinolinic acid and NMDA itself (Perkins and of

Stone, 1983b). Results were obtained, however, that were fo

qualitatively identical with th ments, therefore, a direct comparison was performed
between quinolinic acid and NMDA itself (Perkins and
Stone, 1983b). Results were obtained, however, that were
qualitatively identical with those seen with glutamate
Only ments, therefore, a direct comparison was performed sites
between quinolinic acid and NMDA itself (Perkins and of bi
Stone, 1983b). Results were obtained, however, that were found
qualitatively identical with those seen w between quinolinic acid and NMDA itself (Perkins and Stone, 1983b). Results were obtained, however, that were qualitatively identical with those seen with glutamate. Only five of 23 spinal neurones sensitive to NMDA respon Stone, 1983b). Results were obtained, however, that were for qualitatively identical with those seen with glutamate. K_i Only five of 23 spinal neurones sensitive to NMDA responded to quinolinic acid, as did seven of 18 qualitatively identical with those seen with glutamate. For the positive of 23 spinal neurones sensitive to NMDA responded to quinolinic acid, as did seven of 18 neurones ein the cerebellum, whereas all neurones tested in responded to quinolinic acid, as did seven of 18 neurones
in the cerebellum, whereas all neurones tested in the
neocortex were sensitive to both agonists. Although
higher currents of NMDA were needed to excite neurones responded to quinolinic acid, as did seven of 18 neurones
in the cerebellum, whereas all neurones tested in the
neocortex were sensitive to both agonists. Although m
higher currents of NMDA were needed to excite neurones
e in the cerebellum, whereas all neurones tested in the neocortex were sensitive to both agonists. Although higher currents of NMDA were needed to excite neurones in the spinal cord than in neocortex, it has been pointed out neocortex were sensitive to both agonists. Although
higher currents of NMDA were needed to excite neurones
in the spinal cord than in neocortex, it has been pointed
out (Stone et al., 1989) that, because of the much longer in the spinal cord than in neocortex, it has been pointed
out (Stone et al., 1989) that, because of the much longer
duration of application of quinolinic acid in the spinal
cord compared with the cortex, and because substa in the spinal cord than in neocortex, it has been pointed
out (Stone et al., 1989) that, because of the much longer
duration of application of quinolinic acid in the spinal
cord compared with the cortex, and because substa out (Stone et al., 1989) that, because of the much longer centration of application of quinolinic acid in the spinal T
cord compared with the cortex, and because substantial ago:
elevations of firing rate were produced in duration of application of quinolinic acid in the spinal
cord compared with the cortex, and because substantial
elevations of firing rate were produced in the latter area,
a different sensitivity or density of NMDA recepto a different sensitivity or density of NMDA receptors in
the spinal cord could not have accounted for the lack of
quinolinic acid responses.
The explanation proposed for these results was that exations of firing rate were produced in the latter area,
different sensitivity or density of NMDA receptors in
e spinal cord could not have accounted for the lack of
inolinic acid responses.
The explanation proposed for t

a different sensitivity or density of NMDA receptors in or
the spinal cord could not have accounted for the lack of
quinolinic acid responses.
The explanation proposed for these results was that www.
two populations of NMD the spinal cord could not have accounted for the lack of
quinolinic acid responses.
The explanation proposed for these results was that
two populations of NMDA receptors might exist within
the CNS. One of these, referred t quinolinic acid responses. The explanation proposed for these results was that work work populations of NMDA receptors might exist within nat the CNS. One of these, referred to as the NMDA-1 site, I was proposed to be that The explanation proposed for these results was that
two populations of NMDA receptors might exist within
the CNS. One of these, referred to as the NMDA-1 site,
was proposed to be that site in the spinal cord and
cerebellum two populations of NMDA receptors might exist within natative CNS. One of these, referred to as the NMDA-1 site, E was proposed to be that site in the spinal cord and quin cerebellum activated preferentially by NMDA and no the CNS. One of these, referred to as the NMDA-1 site,
was proposed to be that site in the spinal cord and que
cerebellum activated preferentially by NMDA and not
and muinolinic acid. The NMDA-2 site, which would exist in was proposed to be that site in the spinal cord and
cerebellum activated preferentially by NMDA and not
quinolinic acid. The NMDA-2 site, which would exist in
the neocortex, hippocampus, and striatum, would then
be the sit cerebellum activated preferentially by NMDA and not
quinolinic acid. The NMDA-2 site, which would exist in
the neocortex, hippocampus, and striatum, would then
be the site sensitive to both NMDA and quinolinate
(Perkins an inolinic acid. The NMDA-2 site, which would exist in
e neocortex, hippocampus, and striatum, would then
the site sensitive to both NMDA and quinolinate
rekins and Stone, 1983a,b).
The difference of neuronal sensitivities

the neocortex, hippocampus, and striatum, would then
be the site sensitive to both NMDA and quinolinate
(Perkins and Stone, 1983a,b).
The difference of neuronal sensitivities was confirmed
in a subsequent independent ionto be the site sensitive to both NMDA and quinolinate re

(Perkins and Stone, 1983a,b).

The difference of neuronal sensitivities was confirmed with a subsequent independent iontophoretic study in an-

desthetised rats in whi (Perkins and Stone, 1983a,b). of
The difference of neuronal sensitivities was confirmed which a subsequent independent iontophoretic study in an-
described rats in which the excitatory activity of
NMDA and quinolinate was in a subsequent independent iontophoretic study in an-
aesthetised rats in which the excitatory activity of
NMDA and quinolinate was quantified in relation to the
sensitivity of neurones to quisqualic acid (McLennan,
1984) in a subsequent independent iontophoretic study in an-
aesthetised rats in which the excitatory activity of H
NMDA and quinolinate was quantified in relation to the on
sensitivity of neurones to quisqualic acid (McLennan, aesthetised rats in which the excitatory activity of R
NMDA and quinolinate was quantified in relation to the on t
sensitivity of neurones to quisqualic acid (McLennan, in v
1984). Whereas the relative activity of quisqual sensitivity of neurones to quisqualic acid (McLennan, 1984). Whereas the relative activity of quisqualate and NMDA (approximately 10:1) was comparable both in neocortex and spinal cord, quinolinic acid had approximately on sensitivity of neurones to quisqualic acid (McLennan, in 1984). Whereas the relative activity of quisqualate and NMDA (approximately 10:1) was comparable both in preocortex and spinal cord, quinolinic acid had approximatel 1984). Whereas the relative activity of quisqualate and Nl
NMDA (approximately 10:1) was comparable both in po
neocortex and spinal cord, quinolinic acid had approxi-
mately one-tenth the potency of NMDA in neocortex and
b mately one-tenth the potency of NMDA in neocortex and ketamine were found to be equally active against
but only one-third of this in spinal cord. Overall, the both agonists (Martin and Lodge, 1987). This was sup-
relative response and spinal cord, quinolinic acid had approximately one-tenth the potency of NMDA in neocortex but only one-third of this in spinal cord. Overall, the relative potency of NMDA compared with quinolinic acid ranged f mately one-tenth the potency of NMDA in neocortex
but only one-third of this in spinal cord. Overall, the
relative potency of NMDA compared with quinolinic acid
ranged from approximately 8 in cortex to 20 in spinal
cord (n but only one-third of this in spinal cord. Overall, the bot
relative potency of NMDA compared with quinolinic acid por
ranged from approximately 8 in cortex to 20 in spinal Bu
cord (not 37 as misprinted). This study also c relative potency of NMDA compared with quinolinic acid portanged from approximately 8 in cortex to 20 in spinal Bur cord (not 37 as misprinted). This study also confirmed evident belocked books of NMDA and quinolinic acid ranged from approximately 8 in cortex to 20 in spinal Bunder of (not 37 as misprinted). This study also confirmed even the selective blockade of NMDA and quinolinic acid de responses by similar doses of 2AP5 at levels that cord (not 37 as misprinted). This study also confirmed
the selective blockade of NMDA and quinolinic acid
responses by similar doses of 2AP5 at levels that had no
effect on quisqualic acid. If NMDA and quinolinate were
act the selective blockade of NMDA and quinolinic acid
responses by similar doses of 2AP5 at levels that had no
effect on quisqualic acid. If NMDA and quinolinate were
acting on different receptor populations, those receptors
 sponses by similar doses of 2AP5 at levels that had no
fect on quisqualic acid. If NMDA and quinolinate were
ting on different receptor populations, those receptors
ust share the same sensitivity to 2AP5.
The selectivity o effect on quisqualic acid. If NMDA and quinolinate were
acting on different receptor populations, those receptors ues,
must share the same sensitivity to 2AP5. The selectivity of quinolinic acid for NMDA receptors NM
is su

acting on different receptor populations, those receptors
must share the same sensitivity to 2AP5.
The selectivity of quinolinic acid for NMDA receptors
is supported by binding studies. Although attempts to
demonstrate the must share the same sensitivity to 2AP5. 00
The selectivity of quinolinic acid for NMDA receptors
is supported by binding studies. Although attempts to
indemonstrate the binding of labeled quinolinic acid itself
shave been The selectivity of quinolinic acid for NMDA receptors NM
is supported by binding studies. Although attempts to in in
demonstrate the binding of labeled quinolinic acid itself spi
have been singularly unsuccessful, the com is supported by binding studies. Although attempts to
demonstrate the binding of labeled quinolinic acid itself
have been singularly unsuccessful, the compound does
displace glutamate from hippocampal membranes with
an IC demonstrate the binding of labeled quinolinic acid itself spinal cord.
have been singularly unsuccessful, the compound does Electrophysiological responses to quinolinate are al-
displace glutamate from hippocampal membran have been singularly unsuccessful, the compound does
displace glutamate from hippocampal membranes with
an IC_{60} of 180 μ M (French et al., 1984) and can displace
the NMDA receptor antagonist 2AP5 with an IC_{60} of 3 an IC₅₀ of 180 μ M (French et al., 1984) and can displace
the NMDA receptor antagonist 2AP5 with an IC₅₀ of 350
 μ M (Olverman et al., 1984). This should be compared
with the inability of quinolinate to produce any an IC₅₀ of 180 μ M (French et al., 1984) and can displace an 1
the NMDA receptor antagonist 2AP5 with an IC₅₀ of 350 hype
 μ M (Olverman et al., 1984). This should be compared spin
with the inability of quinolinate μ M. (Olverman et al., 1984). This should be compared spinal cord (Martin and Lodge, 1987), but it is likely that with the inability of quinolinate to produce any detecta-
ble displacement of kainic acid at concentratio with the inability of quinolinate to produce any detecta-

NE
sites for glutamate in the postsynaptic density fraction
of brain homogenates. Here, Fagg and Matus (1984) NE
sites for glutamate in the postsynaptic density fraction
of brain homogenates. Here, Fagg and Matus (1984)
found that quinolinate would displace glutamate with a we
sites for glutamate in the postsynaptic density fraction
of brain homogenates. Here, Fagg and Matus (1984)
found that quinolinate would displace glutamate with a
 K_i of 91 μ M. K_i of 91 μ M. Exercise for glutamate in the postsynaptic density fractional brain homogenates. Here, Fagg and Matus (1 und that quinolinate would displace glutamate wi of 91 μ M.
Ffrench-Mullen et al. (1986) performed an iontopic inv

of brain homogenates. Here, Fagg and Matus (1984)
found that quinolinate would displace glutamate with a
 K_i of 91 μ M.
Ffrench-Mullen et al. (1986) performed an iontophor-
etic investigation of pyramidal cells in rat found that quinolinate would displace glutamate with a K_i of 91 μ M.
Ffrench-Mullen et al. (1986) performed an iontophor-
etic investigation of pyramidal cells in rat pyriform cor-
tex and observed that NMDA was appro K_i of 91 μ M.
French-Mullen et al. (1986) performed an iontophoretic investigation of pyramidal cells in rat pyriform contex and observed that NMDA was approximately 5-fold more active than quinolinate. Most interesti etic investigation of pyramidal cells in rat pyriform cortex and observed that NMDA was approximately 5-fold more active than quinolinate. Most interestingly, however, these authors reported that bath-applied 2AP5 etic investigation of pyramidal cells in rat pyriform cor-
tex and observed that NMDA was approximately 5-fold
more active than quinolinate. Most interestingly, how-
ever, these authors reported that bath-applied 2AP5
coul tex and observed that NMDA was ap
more active than quinolinate. Most i
ever, these authors reported that b
could block responses to NMDA at a
centration than it blocked quinolinate
The same combination of iontopl could block responses to NMDA at a 10-fold lower con-

centration than it blocked quinolinate.
The same combination of iontophoretically applied
agonists and superfused antagonists was used by Mag-
nusson et al. (1987) to examine the activity of quinolinate could block responses to NMDA at a 10-fold lower concentration than it blocked quinolinate.
The same combination of iontophoretically applied
agonists and superfused antagonists was used by Mag-
nusson et al. (1987) to exa centration than it blocked quinolinate.
The same combination of iontophoretically applied
agonists and superfused antagonists was used by Mag-
nusson et al. (1987) to examine the activity of quinolinate
on rat spinal cord The same combination of iontophoretically applied
agonists and superfused antagonists was used by Mag-
nusson et al. (1987) to examine the activity of quinolinate
on rat spinal cord in vitro. The same conclusion was
reach agonists and superfused antagonists was used by Mag-
nusson et al. (1987) to examine the activity of quinolinate
on rat spinal cord in vitro. The same conclusion was
reached, i.e., 2AP5 was a better antagonist of NMDA
tha nusson et al. (1987) to examine the activity of quinolin
on rat spinal cord in vitro. The same conclusion v
reached, i.e., 2AP5 was a better antagonist of NMI
than of quinolinate; the IC₅₀ values derived from t
work wer reached, i.e., 2AP5 was a better antagonist of NMDA
than of quinolinate; the IC_{50} values derived from this
work were 2 μ M against NMDA, 7 μ M against quinoli-
nate, and 20 μ M against kainate.
Evidence for some ached, i.e., 2AP5 was a better antagonist of NMDA
an of quinolinate; the IC₅₀ values derived from this
ork were 2 μ M against NMDA, 7 μ M against quinoli-
te, and 20 μ M against kainate.
Evidence for some distinct

than of quinolinate; the IC₅₀ values derived from this
work were 2 μ M against NMDA, 7 μ M against quinoli-
nate, and 20 μ M against kainate.
Evidence for some distinction between NMDA and
quinolinate receptors wa work were 2 μ M against NMDA, 7 μ M against quinol
nate, and 20 μ M against kainate.
Evidence for some distinction between NMDA an
quinolinate receptors was obtained without the use a
antagonists by comparing the po nate, and 20μ M against kainate.
Evidence for some distinction between NMDA and
quinolinate receptors was obtained without the use of
antagonists by comparing the potencies of NMDA, quin-
olinate, kainate, and quisquala Evidence for some distinction between NMDA and
quinolinate receptors was obtained without the use of
antagonists by comparing the potencies of NMDA, quin-
olinate, kainate, and quisqualate on the extracellularly
recorded d quinolinate receptors was obtained without the use of antagonists by comparing the potencies of NMDA, quinolinate, kainate, and quisqualate on the extracellularly recorded depolarisation of CA1 and dentate gyrus neurones (antagonists by comparing the potencies of NMDA, quin-
olinate, kainate, and quisqualate on the extracellularly
recorded depolarisation of CA1 and dentate gyrus neu-
rones (Stone, 1985b). This work concluded that the ratio
 olinate, kainate, and quisqualate on the extracellularly
recorded depolarisation of CA1 and dentate gyrus neu-
rones (Stone, 1985b). This work concluded that the ratio
of activity of NMDA on these populations was 2.19,
whe recorded depolarisation of CA1 and
rones (Stone, 1985b). This work conce
of activity of NMDA on these po
whereas quinolinate was relatively
dentate gyrus, with a ratio of 3.46.
Rather different conclusions were nes (Stone, 1985b). This work concluded that the ratio
activity of NMDA on these populations was 2.19,
nereas quinolinate was relatively less effective in the
ntate gyrus, with a ratio of 3.46.
Rather different conclusions

of activity of NMDA on these populations was 2.19,
whereas quinolinate was relatively less effective in the
dentate gyrus, with a ratio of 3.46.
Rather different conclusions were drawn from work
on the superfused rat cereb whereas quinolinate was relatively less effective in the
dentate gyrus, with a ratio of 3.46.
Rather different conclusions were drawn from work
on the superfused rat cerebral cortex and frog spinal cord
in vitro. Not only dentate gyrus, with a ratio of 3.46.
Rather different conclusions were drawn from work
on the superfused rat cerebral cortex and frog spinal cord
in vitro. Not only was quinolinate far less potent than
NMDA in producing de Rather different conclusions were drawn from work
on the superfused rat cerebral cortex and frog spinal cord
in vitro. Not only was quinolinate far less potent than
NMDA in producing depolarisation of the motor neurone
poo on the superfused rat cerebral cortex and frog spinal cord
in vitro. Not only was quinolinate far less potent than
NMDA in producing depolarisation of the motor neurone
pool (30- to 100-fold) but in both systems the compe in vitro. Not only was quinolinate far less potent than
NMDA in producing depolarisation of the motor neurone
pool (30- to 100-fold) but in both systems the competitive
antagonist 2AP5 and the channel blockers magnesium
an NMDA in producing depolarisation of the motor neurone
pool (30- to 100-fold) but in both systems the competitive
antagonist 2AP5 and the channel blockers magnesium
and ketamine were found to be equally active against
both on rat spinal cord in vitro. The same conclusion was
reached, i.e., 2AP5 was a better antagonist of NMDA
than of quinolinate; the Γ_{00} values derived from this
work were 2 μ M against kMDA, 7 μ M against quinoli-
 antagonist 2AP5 and the channel blockers magnesium
and ketamine were found to be equally active against
both agonists (Martin and Lodge, 1987). This was sup-
ported by work in slices of mouse neocortex in which
Burton et a and ketamine were found to be equally active against
both agonists (Martin and Lodge, 1987). This was sup-
ported by work in slices of mouse neocortex in which
Burton et al. (1987, 1988) obtained strong quantitative
evide both agonists (Martin and Lodge, 1987). This was sup-
ported by work in slices of mouse neocortex in which
Burton et al. (1987, 1988) obtained strong quantitative
evidence for the specificity of action of quinolinate by
d ported by work in slices of mouse neccortex in whi
Burton et al. (1987, 1988) obtained strong quantitatievidence for the specificity of action of quinolinate
demonstrating the close similarity between the pA_2 v
ues of Burton et al. (1987, 1988) obtained strong quantitative
evidence for the specificity of action of quinolinate by
demonstrating the close similarity between the pA₂ val-
ues of 2AP5 and kynurenate against NMDA and quinoevidence for the specificity of action of quinolinate by
demonstrating the close similarity between the pA_2 val-
ues of 2AP5 and kynurenate against NMDA and quino-
linate. Ibotenate showed significantly different pA_2 demonstrating the close similarity between the pA_2 values of 2AP5 and kynurenate against NMDA and quino-
linate. Ibotenate showed significantly different pA_2 values, which suggests an action either at different rece ues of 2AP5 and kynurenate against NMDA and quino-
linate. Ibotenate showed significantly different pA_2 val-
ues, which suggests an action either at different receptors
or at a subset of receptors. Herrling (1985) also linate. Ibotenate showed significantly different PA_2 values, which suggests an action either at different receptors
or at a subset of receptors. Herrling (1985) also blocked
NMDA and quinolinate, but not quisqualate, us or at a subset of receptors. Herrling (1985) also blocked
NMDA and quinolinate, but not quisqualate, using 2AP7 at a subset of receptors. Herrling (1985) also blocked
MDA and quinolinate, but not quisqualate, using 2AP7
studies of cat caudate nucleus neurones and in isolated
inal cord.
Electrophysiological responses to quinolinate a

NMDA and quinolinate, but not quisqualate, using 2AP7
in studies of cat caudate nucleus neurones and in isolated
spinal cord.
Electrophysiological responses to quinolinate are al-
most invariably of the depolarising type a in studies of cat caudate nucleus neurones and in isolated
spinal cord.
Electrophysiological responses to quinolinate are al-
most invariably of the depolarising type as expected of
an NMDA receptor agonist. It has been cl spinal cord.
Electrophysiological responses to quinolinate are almost invariably of the depolarising type as expected of
an NMDA receptor agonist. It has been claimed that
hyperpolarising responses could also be evoked in Electrophysiological responses to quinolinate are almost invariably of the depolarising type as expected of an NMDA receptor agonist. It has been claimed that hyperpolarising responses could also be evoked in the spinal co most invariably of the depolarising type as expected o
an NMDA receptor agonist. It has been claimed tha
hyperpolarising responses could also be evoked in th
spinal cord (Martin and Lodge, 1987), but it is likely tha
these an NMDA receptor agonist. It has been claimed that
hyperpolarising responses could also be evoked in the
spinal cord (Martin and Lodge, 1987), but it is likely that
these results were artifacts of the dilution of stock sol hyperpolarising responses could also be evoked in the spinal cord (Martin and Lodge, 1987), but it is likely that these results were artifacts of the dilution of stock solutions made in water; the reproduction of these ano these results were artifacts of the dilution of stock solu-

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QUINOLINIC AND K
The restriction of quinolinate's excitatory activity to
NMDA receptors was confirmed by Peters and Choi
(1987) using cultures of mouse cortex. The voltage de-QUINOLINIC AND
The restriction of quinolinate's excitatory activity to
NMDA receptors was confirmed by Peters and Choi
(1987) using cultures of mouse cortex. The voltage de-
pendence of the quinolinate-induced depolarisati The restriction of quinolinate's excitatory activity to to l
NMDA receptors was confirmed by Peters and Choi in (1987) using cultures of mouse cortex. The voltage de-
pendence of the quinolinate-induced depolarisation and The restriction of quinolinate's excitatory activity to

NMDA receptors was confirmed by Peters and Choi is

(1987) using cultures of mouse cortex. The voltage de-

pendence of the quinolinate-induced depolarisation and

i (1987) using cultures of mouse cortex. The voltage dependence of the quinolinate-induced depolarisation and its variation with magnesium concentration paralleled (1987) using cultures of mouse cortex. The voltage dependence of the quinolinate-induced depolarisation and
its variation with magnesium concentration paralleled
these properties of NMDA itself; superfusion with 2AP5,
keta pendence of the quinolinate-induced depolarisation aits variation with magnesium concentration parallel
these properties of NMDA itself; superfusion with 2AF
ketamine, or kynurenate, but not glutamate diethylest
or glutamy its variation with magnesium concentration paralleled
these properties of NMDA itself; superfusion with 2AP5,
ketamine, or kynurenate, but not glutamate diethylester
or glutamylaminomethylsulphonate, provided full block-
a ketamine, or kynurenate, but not glutamate diethylester
or glutamylaminomethylsulphonate, provided full block-
ade. Similarly, Ganong and Cotman (1986) reported that
2AP5 and 2AP7 would antagonise NMDA and quinoli-
nate wi or glutamylaminomethy
ade. Similarly, Ganong
2AP5 and 2AP7 would
nate without affecting
hippocampus in vitro.
Pharmacological evid e. Similarly, Ganong and Cotman (1986) reported that P5 and 2AP7 would antagonise NMDA and quinolitie without affecting kainate or quisqualate in the ppocampus in vitro.
Pharmacological evidence suggests that two molecules

2AP5 and 2AP7 would antagonise NMDA and quinoli-
nate without affecting kainate or quisqualate in the
hippocampus in vitro.
Pharmacological evidence suggests that two molecules
of NMDA are needed to activate receptors in t nate without affecting kainate or quisqualate in the thus
hippocampus in vitro. brain
pharmacological evidence suggests that two molecules quin
of NMDA are needed to activate receptors in the neo-
cortex (Williams et al., hippocampus in vitro.

Pharmacological evidence suggests that two molecules

of NMDA are needed to activate receptors in the neo-

cortex (Williams et al., 1988), a finding confirmed by

later reports of bimolecular kineti Pharmacological evidence suggests that two molecules
of NMDA are needed to activate receptors in the neo-
cortex (Williams et al., 1988), a finding confirmed by
later reports of bimolecular kinetics of NMDA in other
region of NMDA are needed to activate receptors in the necortex (Williams et al., 1988), a finding confirmed later reports of bimolecular kinetics of NMDA in other regions of the CNS (Benveniste and Mayer, 1991; Javet al., 1990; cortex (Williams et al., 1988), a finding confirmed by Nicter reports of bimolecular kinetics of NMDA in other seem regions of the CNS (Benveniste and Mayer, 1991; Javitt tret al., 1990; Clements and Westbrook, 1991). In n later reports of bimolecular kinetics of NMDA in oth
regions of the CNS (Benveniste and Mayer, 1991; Javi
et al., 1990; Clements and Westbrook, 1991). In neocc
tex, two molecules of quinolinate also seem to be need
to acti regions of the CNS (Benveniste and Mayer, 1991; Javitt et al., 1990; Clements and Westbrook, 1991). In neocortex, two molecules of quinolinate also seem to be needed to activate the receptor (Williams et al., 1988), an obs et al., 1990; Clemer
tex, two molecules
to activate the rece
vation consistent
lation of receptors.
b. BINDING STUI k, two molecules of quinolinate also seem to be needed
activate the receptor (Williams et al., 1988), an obser-
tion consistent with activation of an identical popu-
ion of receptors.
b. BINDING STUDIES. The cerebellum app

to activate the receptor (Williams et al., 1988), an observation consistent with activation of an identical population of receptors.
b. BINDING STUDIES. The cerebellum appears to possess a form of NMDA receptor pharmacolog vation consistent with activation of an identical popu-
lation of receptors.
b. BINDING STUDIES. The cerebellum appears to pos-
sess a form of NMDA receptor pharmacologically dis-
and
tinct from the cortex and hippocampus, is the complete sensitivity of receptors.

Sensitivity to quinolinate. Both binding and molecular

binding and molecular

biological studies now lend support to this distinction. b. BINDING STUDIES. The cerebellum appears to possess a form of NMDA receptor pharmacologically distinct from the cortex and hippocampus, showing no sensitivity to quinolinate. Both binding and molecular biological studies sess a form of NMDA receptor pharmacologically distinct from the cortex and hippocampus, showing no
sensitivity to quinolinate. Both binding and molecular
biological studies now lend support to this distinction.
When recep tinct from the cortex and hippocampus, showing no
sensitivity to quinolinate. Both binding and molecular list
biological studies now lend support to this distinction. 1
When receptors were expressed in *Xenopus* oocytes fo sensitivity to quinolinate. Both binding and molecular ling
biological studies now lend support to this distinction. 198
When receptors were expressed in *Xenopus* oocytes fol-
lowing the injection of mRNA from guinea pig biological studies now lend support to this distinctic
When receptors were expressed in *Xenopus* oocytes f
lowing the injection of mRNA from guinea pig forebra
or cerebellum, only the former exhibited modulation
glycine (When receptors were expressed in *Xenopus* oocytes fol-
lowing the injection of mRNA from guinea pig forebrain
or cerebellum, only the former exhibited modulation by
glycine (Sekiguchi et al., 1990). The binding of dizocil lowing the injection of mRNA from guinea pig forebrain depotor cerebellum, only the former exhibited modulation by potenty glycine (Sekiguchi et al., 1990). The binding of dizociliantly prime at hippocampal membranes is mo or cerebellum, only the former exhibited modulation by
glycine (Sekiguchi et al., 1990). The binding of dizocil-
pine at hippocampal membranes is more easily displaced
by competitive NMDA antagonist than it is in cerebellu glycine (Sekiguchi et al., 1990). The binding of dizocilpine at hippocampal membranes is more easily displaced
by competitive NMDA antagonist than it is in cerebellum
(Yoneda and Ogita, 1991). The density of dizocilpine
si pine at hippocampal membranes is more easily displace
by competitive NMDA antagonist than it is in cerebellur
(Yoneda and Ogita, 1991). The density of dizocilpin
sites is also lower in cerebellar tissue (Ebert et al., 1991 by competitive NMDA antagonist than it is in cerebellum act

(Yoneda and Ogita, 1991). The density of dizocilpine this

sites is also lower in cerebellar tissue (Ebert et al., 1991). pro

Spermidine lacks the ability to en (Yoneda and Ogita, 1991). The density of dizocilpinosites is also lower in cerebellar tissue (Ebert et al., 1991). Spermidine lacks the ability to enhance dizocilpine bind ing in cerebellum, whereas this action can be easi reso is also lower in cerebellar tissue (Ebert et al., 1991). potentially position of the ability to enhance dizocilpine bind-
g in cerebellum, whereas this action can be easily (Horostrated in hippocampal or neocortical m Spermidine lacks the ability to enhance dizocilpine ling in cerebellum, whereas this action can be edemonstrated in hippocampal or neocortical membr.
Although these and a number of other studies stro
suggest the existence

ing in cerebellum, whereas this action can be easi
demonstrated in hippocampal or neocortical membrane
Although these and a number of other studies strong
suggest the existence of pharmacologically distinguish
ble forms of demonstrated in hippocampal or neocortical membranes. in
Although these and a number of other studies strongly
suggest the existence of pharmacologically distinguisha-
in
ble forms of the NMDA receptor in the brain, few wo Although these and a number of other studies strongly
suggest the existence of pharmacologically distinguisha-
ble forms of the NMDA receptor in the brain, few work-
ers have tested quinolinate. Monaghan and Beaton
(1991) suggest the existence of pharmacologically distinguisha-
ble forms of the NMDA receptor in the brain, few work-
tras have tested quinolinate. Monaghan and Beaton
(1991) showed that quinolinate is significantly more ac-
tiv ble forms of the NMDA receptor in the brain, few wolvers have tested quinolinate. Monaghan and Beat (1991) showed that quinolinate is significantly more itive in displacing glutamate binding from forebrain the cerebellar p ers have tested quinolinate. Monaghan and Beat (1991) showed that quinolinate is significantly more ative in displacing glutamate binding from forebrain the cerebellar preparations. This autoradiographic investigation thus (1991) showed that quinolinate is significan
tive in displacing glutamate binding from for
cerebellar preparations. This autoradiograp
gation thus provides independent support for
sion drawn from electrophysiological data.

cerebellar preparations. This autoradiographic investigation thus provides independent support for the conclusion drawn from electrophysiological data. Conclusion drawn from electrophysiological data. Conception is being d gation thus provides independent support for the conclumedity in the structure of distinct NMDA plate.

Definitive evidence for the existence of distinct NMDA plate

receptor molecules is being developed. Several groups in sion drawn from electrophysiological data.

Definitive evidence for the existence of distinct NMDA

receptor molecules is being developed. Several groups

have begun to clone and analyse the structure of NMDA

receptors (M Definitive evidence for the existence of distinct NMDA
receptor molecules is being developed. Several groups is
have begun to clone and analyse the structure of NMDA
receptors (Moriyoshi et al., 1991; Monyer et al., 1992; receptor molecules is being developed. Several groups in
have begun to clone and analyse the structure of NMDA sp
receptors (Moriyoshi et al., 1991; Monyer et al., 1992; in
Meguro et al., 1992; Kutsuwada et al., 1992; Sugi have begun to clone and analyse the structure of NMDA spil
receptors (Moriyoshi et al., 1991; Monyer et al., 1992; in t
Meguro et al., 1992; Kutsuwada et al., 1992; Sugihara et hip
al., 1992). The results of the latter gro Meguro et al., 1992; Kutsuwada et al., 1992; Sugihara et hippocampal study, however, entirely supported the view al., 1992). The results of the latter group, however, serve from the caudate experiments that the actions of al., 1992). The results of the latter group, however, serve

QUINOLINIC AND KYNURENIC ACIDS
The restriction of quinolinate's excitatory activity to to be pharmacologically distinguishable when expressed ketamine, or kynurenate, but not glutamate diethylester whereas NR2B localises to forebrain, and NR2C exists
or glutamylaminomethylsulphonate, provided full block-
primarily in the cerebellum. When combined with NR1
ade. S to be pharmacologically distinguishable when expressed in 327
it obe pharmacologically distinguishable when expressed
in oocytes (Sugihara et al., 1992). On the other hand, the
molecular species studied by Monyer et al. (1992) show 327
to be pharmacologically distinguishable when expressed
in oocytes (Sugihara et al., 1992). On the other hand, the
molecular species studied by Monyer et al. (1992) show
a differential anatomical distribution that may w to be pharmacologically distinguishable when expressed
in oocytes (Sugihara et al., 1992). On the other hand, the
molecular species studied by Monyer et al. (1992) show
a differential anatomical distribution that may well to be pharmacologically distinguishable when expressed
in oocytes (Sugihara et al., 1992). On the other hand, the
molecular species studied by Monyer et al. (1992) show
a differential anatomical distribution that may well molecular species studied by Monyer et al. (1992) show
a differential anatomical distribution that may well re-
late to the pharmacology of quinolinate. Their NR2A
subunit is distributed in forebrain and cerebellum, molecular species studied by Monyer et al. (1992) show
a differential anatomical distribution that may well re-
late to the pharmacology of quinolinate. Their NR2A
subunit is distributed in forebrain and cerebellum,
wherea a differential anatomical distribution that may well re-
late to the pharmacology of quinolinate. Their NR2A
subunit is distributed in forebrain and cerebellum,
whereas NR2B localises to forebrain, and NR2C exists
primaril late to the pharmacology of quinolinate. Their NR2A
subunit is distributed in forebrain and cerebellum,
whereas NR2B localises to forebrain, and NR2C exists
primarily in the cerebellum. When combined with NR1
subunits, eac subunit is distributed in forebrain and cerebellum,
whereas NR2B localises to forebrain, and NR2C exists
primarily in the cerebellum. When combined with NR1
subunits, each of the NR2 species is able to form a
functional re whereas NR2B localises to forebrain, and NR2C existiprimarily in the cerebellum. When combined with NR:
subunits, each of the NR2 species is able to form a
functional receptor/channel complex. The possibility is
thus raise primarily in the cerebellum. When combined with NR1 subunits, each of the NR2 species is able to form a functional receptor/channel complex. The possibility is thus raised that it is the NR2B subunit, found in fore-
brain quinolinate.

Further evidence for the activation of a subset of NMDA receptors by quinolinate will be discussed in thus raised that it is the NR2B subunit, found in fore-
brain but not cerebellum, that confers sensitivity to
quinolinate.
Further evidence for the activation of a subset of
NMDA receptors by quinolinate will be discussed brain but not cerebellum, that confers sensitivity to
quinolinate.
Further evidence for the activation of a subset of
NMDA receptors by quinolinate will be discussed in
section VI.A, but taken together, the evidence from e quinolinate.
Further evidence for the activation of a subset of
NMDA receptors by quinolinate will be discussed in
section VI.A, but taken together, the evidence from elec-
tropharmacological, binding, molecular biology, a Further evidence for the activation of a subset of NMDA receptors by quinolinate will be discussed in section VI.A, but taken together, the evidence from electropharmacological, binding, molecular biology, and neurotoxicit NMDA receptors by quinolinate will be discussed in
section VI.A, but taken together, the evidence from elec-
tropharmacological, binding, molecular biology, and neu-
rotoxicity studies provide an almost overwhelming ar-
gu section VI.A, but taken together, the evidence from electropharmacological, binding, molecular biology, and neu-
rotoxicity studies provide an almost overwhelming ar-
gument for the existence of distinct subtypes of the
NM tropharmacological, binding, molecular biology, and neu-
rotoxicity studies provide an almost overwhelming ar-
gument for the existence of distinct subtypes of the
NMDA receptor, some of which are pharmacologically
disting rotoxicity studies provide an almost overwhelming argument for the existence of distinct subtypes of the NMDA receptor, some of which are pharmacologically distinguishable and some of which are responsible for neuronal sen ment for the existence of distinct subtypes of the
 2. Intracellular studies. The effects of quinolinic acids.

2. *Intracellular studies*. The effects of quinolinic acid

2. *Intracellular studies*. The effects of quino

NMDA receptor, some of which are pharmacologically
distinguishable and some of which are responsible for
neuronal sensitivity to quinolinic and kynurenic acids.
2. Intracellular studies. The effects of quinolinic acid
and neuronal sensitivity to quinolinic and kynurenic acids.
2. Intracellular studies. The effects of quinolinic acid
and NMDA were compared using intracellular recording
techniques on neurones of the cat caudate nucleus (Herrneuronal sensitivity to quinolinic and kynurenic acids.

2. Intracellular studies. The effects of quinolinic acid

and NMDA were compared using intracellular recording

techniques on neurones of the cat caudate nucleus (He 2. Intracellular studies. The effects of quinolinic acid
and NMDA were compared using intracellular recording
techniques on neurones of the cat caudate nucleus (Herr-
ling et al., 1983) and hippocampus (Peet et al., 1986,
 NMDA receptors by quinolinate will be discussed in extraction VI.A, but taken together, the evidence from electropharmacological, binding, molecular biology, and neurotoxicity studies provide an almost overwhelming argume techniques on neurones of the cat caudate nucleus (Herr-
ling et al., 1983) and hippocampus (Peet et al., 1986,
1987; Ganong et al., 1983; Ganong and Cotman, 1986).
Whereas glutamate and quisqualate induced a steady
depola ling et al., 1983) and hippocampus (Peet et al., 1986, 1987; Ganong et al., 1983; Ganong and Cotman, 1986).
Whereas glutamate and quisqualate induced a steady depolarisation with an increasing frequency of action potential 1987; Ganong et al., 1983; Ganong and Cotman, 1986).
Whereas glutamate and quisqualate induced a steady
depolarisation with an increasing frequency of action
potential generation, NMDA and quinolinic acid usually
induced p Whereas glutamate and quisqualate induced a steady
depolarisation with an increasing frequency of action
potential generation, NMDA and quinolinic acid usually
induced periodic depolarisation plateaux with apparent
increas depolarisation with an increasing frequency of action
potential generation, NMDA and quinolinic acid usually
induced periodic depolarisation plateaux with apparent
increases of membrane resistance, on which groups of
actio potential generation, NMDA and quinolinic acid usually
induced periodic depolarisation plateaux with apparent
increases of membrane resistance, on which groups of
action potentials were generated. In all cells exhibiting
 induced periodic depolarisation plateaux with apparent
increases of membrane resistance, on which groups of
action potentials were generated. In all cells exhibiting
this type of response in the caudate, $L-\alpha$ -aminoadipat increases of membrane resistance, on which groups of
action potentials were generated. In all cells exhibiting
this type of response in the caudate, $L-\alpha$ -aminoadipate
proved able to block both NMDA and quinolinate in
par action potentials were generated. In all cells exhibiting
this type of response in the caudate, $L-\alpha$ -aminoadipate
proved able to block both NMDA and quinolinate in
parallel with no change of sensitivity to quisqualate
(H this type of response in the caudate, $L-\alpha$ -aminoadipate
proved able to block both NMDA and quinolinate in
parallel with no change of sensitivity to quisqualate
(Herrling et al., 1983); on a small proportion of neurones
i proved able to block both NMDA and quinolinate in
parallel with no change of sensitivity to quisqualate
(Herrling et al., 1983); on a small proportion of neurones
in which plateaux were not induced, $L-\alpha$ -aminoadipate
sho parallel with no change of sensitivity to quisqual.
(Herrling et al., 1983); on a small proportion of neuroin which plateaux were not induced, $L-\alpha$ -aminoadip showed no antagonism, a finding consistent with the involvemen (Herrling et al., 1983); of
in which plateaux were
showed no antagonism,
involvement of non-NM
trations of the agonists.
The plateaux of depole which plateaux were not induced, $L-\alpha$ -aminoadipate
owed no antagonism, a finding consistent with the
volvement of non-NMDA receptors at some concen-
stions of the agonists.
The plateaux of depolarisation induced by NMDA

tive in displacing glutamate binding from forebrain than
cerebellar preparations. This autoradiographic investi-
gation thus provides independent support for the conclu-
medium superfusing hippocampal slices by the divalen showed no antagonism, a finding consistent with the
involvement of non-NMDA receptors at some concen-
trations of the agonists.
The plateaux of depolarisation induced by NMDA and
quinolinate appeared to be mediated partly involvement of non-NMDA receptors at some con
trations of the agonists.
The plateaux of depolarisation induced by NMDA
quinolinate appeared to be mediated partly by an in
of calcium into the neurones, because these depolar trations of the agonists.
The plateaux of depolarisation induced by NMDA and
quinolinate appeared to be mediated partly by an influx
of calcium into the neurones, because these depolarisa-
tions could be prevented by repla The plateaux of depolarisation induced by NMDA and
quinolinate appeared to be mediated partly by an influx
of calcium into the neurones, because these depolarisa-
tions could be prevented by replacing calcium in the
medium quinolinate appeared to be mediated partly by an influx
of calcium into the neurones, because these depolarisa-
tions could be prevented by replacing calcium in the
medium superfusing hippocampal slices by the divalent
cat of calcium into the neurones, because these depolarisations could be prevented by replacing calcium in the medium superfusing hippocampal slices by the divalent cation channel blocker cobalt (Peet et al., 1986). The platea tions could be prevented by replacing calcium in the
medium superfusing hippocampal slices by the divalent
cation channel blocker cobalt (Peet et al., 1986). The
plateau were correspondingly insensitive to tetrodotoxin
in medium superfusing hippocampal slices by the divalent
cation channel blocker cobalt (Peet et al., 1986). The
plateau were correspondingly insensitive to tetrodotoxin
in hippocampus slices, whereas the superimposed sodium
s cation channel blocker cobalt (Peet et al., 1986). The
plateau were correspondingly insensitive to tetrodotoxin
in hippocampus slices, whereas the superimposed sodium
spikes could be converted to long-duration calcium spik plateau were correspondingly insensitive to tetrodotoxin
in hippocampus slices, whereas the superimposed sodium
spikes could be converted to long-duration calcium spikes
in the presence of this sodium channel blocker. This in hippocampus slices, whereas the superimposed sodius
spikes could be converted to long-duration calcium spik
in the presence of this sodium channel blocker. Th
hippocampal study, however, entirely supported the vio
from spikes could be converted to long-duration calcium spikes
in the presence of this sodium channel blocker. This
hippocampal study, however, entirely supported the view
from the caudate experiments that the actions of quino-NMDA. from the caudate experiments that the actions of quino-

linic acid were qualitatively identical with those of

NMDA.

3. Patch-clamp studies. Using cultured rat hippocampal

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neurones under patch-clamp conditions, Tsuzuki et al. (1989)
(1989a,b) examined the characteristics of quinolinative diagram
(1989a,b) examined the characteristics of quinolin
induced ion channel currents. Channel conductanc STONI

neurones under patch-clamp conditions, Tsuzuki et al.

(1989a,b) examined the characteristics of quinolinate-

induced ion channel currents. Channel conductances of tra-

40 to 46 pS were recorded at membrane potent neurones under patch-clamp conditions, Tsuzuki et al.
(1989a,b) examined the characteristics of quinolinate-
induced ion channel currents. Channel conductances of the
40 to 46 pS were recorded at membrane potentials of m
neurones under patch-clamp conditions, Tsuzuki et al. (1989a,b) examined the characteristics of quinolinate-
induced ion channel currents. Channel conductances of
40 to 46 pS were recorded at membrane potentials of
-40 to (1989a,b) examined the characteristics of quinolinate-
induced ion channel currents. Channel conductances of
 40 to 46 pS were recorded at membrane potentials of mm
 -40 to -80 mV, quite similar to those induced by NM induced ion channel currents. Channel conductances of the 40 to 46 pS were recorded at membrane potentials of -40 to -80 mV, quite similar to those induced by NMDA; k the action of quinolinate was sensitive to $2AP5$. 40 to 46 pS were recorded at membrane potentials of -40 to -80 mV, quite similar to those induced by NMDA;
the action of quinolinate was sensitive to $2AP5$. In a
later study, McLarnon and Curry (1990) expanded this
in the action of quinolinate was sensitive to 2AP5. In a wh
later study, McLarnon and Curry (1990) expanded this Sir
information on single-channel properties. Quinolinate ure
opened channels with a mean conductance of 39 pS i later study, McLarnon and Curry (1990) expanded this Sim
information on single-channel properties. Quinolinate ure
opened channels with a mean conductance of 39 pS in com
the absence of magnesium, a value similar to that s information on single-channel properties. Quinolinate uppened channels with a mean conductance of 39 pS in combine the absence of magnesium, a value similar to that seen compression the preceding study. Channel open times opened channels with a mean conductance of 39 pS in com
the absence of magnesium, a value similar to that seen colo
in the preceding study. Channel open times were seen to aspect
decrease with membrane hyperpolarisation a the absence of magnesium, a value similar to that seen
in the preceding study. Channel open times were seen to
decrease with membrane hyperpolarisation at the rate of
0.6 ms/20 mV or with the addition of magnesium. At 30
 in the preceding study. Channel open times were see
decrease with membrane hyperpolarisation at the ra
0.6 ms/20 mV or with the addition of magnesium. μ
 μ M magnesium, open time was reduced about 70%
though the condu decrease with membrane hyperpolarisation at the rate of $0.6 \text{ ms}/20 \text{ mV}$ or with the addition of magnesium. At 30 μ M magnesium, open time was reduced about 70%. Alection the conductances of NMDA- and quinolinate appe 0.6 ms/20 mV or with the addition of magnesium. At 30 μ M magnesium, open time was reduced about 70%. Although the conductances of NMDA- and quinolinate-opened channels were similar, the open time was less for quinolina μ M magnesium, open time was reduced about 70%. A though the conductances of NMDA- and quinolinat opened channels were similar, the open time was less faultion quinolinate than for NMDA. Using patch-clamped hip pocampal though the conductances of NMDA- and quinolinate-
opened channels were similar, the open time was less for
quinolinate than for NMDA. Using patch-clamped hip-
pocampal neurones, Kiskin et al. (1990) examined cross-
desensi opened channels were similar, the open time was less for
quinolinate than for NMDA. Using patch-clamped hip-
also
pocampal neurones, Kiskin et al. (1990) examined cross-
relea
desensitisation between excitatory amino acids receptors. desensitisation between excitatory amino acids and concluded that quinolinate was a selective agonist at NMDA receptors.
4. *Myenteric plexus*. There is some evidence that glu-
tamate may, via the activation of NMDA-like r cluded that quinolinate was a selective agonist at NMDA

cluded that quinolinate was a selective agonist at NMDA
receptors.
4. Myenteric plexus. There is some evidence that glu-
tamate may, via the activation of NMDA-like receptors,
depolarise neurones in the myenteric plexus an receptors.
4. Myenteric plexus. There is some evidence that glue
tamate may, via the activation of NMDA-like receptors
depolarise neurones in the myenteric plexus and, thus
indirectly induce contractions of intestinal smoo 4. Myenteric plexus. There is some evidence that glutamate may, via the activation of NMDA-like receptors depolarise neurones in the myenteric plexus and, thus indirectly induce contractions of intestinal smooth muscle (Mo tamate may, via the activation of NMDA-like receptors, Whistopolarise neurones in the myenteric plexus and, thus, of indirectly induce contractions of intestinal smooth mus-
cile (Moroni et al., 1986d). The contractions c depolarise neurones in the myenteric plexus and, thus,
indirectly induce contractions of intestinal smooth mus-
cle (Moroni et al., 1986d). The contractions can be mim-
icked by NMDA, but not kainate or quisqualate, and
pr indirectly induce contractions of intestinal smooth mus-
cle (Moroni et al., 1986d). The contractions can be mim-
icked by NMDA, but not kainate or quisqualate, and
prevented by 2AP5 or high magnesium concentrations
as wel cle (Moroni et al., 1986d). The contractions can be mim-
icked by NMDA, but not kainate or quisqualate, and glu
prevented by 2AP5 or high magnesium concentrations am
as well as by atropine or hyoscine (Moroni et al., 1986d icked by NMDA, but not kainate or quisqualate, and glu
prevented by 2AP5 or high magnesium concentrations am
as well as by atropine or hyoscine (Moroni et al., 1986d; Stc
Wiley et al., 1991). Both glutamate and NMDA can pr prevented by 2AP5 or high magnesium concentrations
as well as by atropine or hyoscine (Moroni et al., 1986d;
Wiley et al., 1991). Both glutamate and NMDA can
induce the release of radiolabeled acetylcholine and
GABA from t as well as by atropine or hyoscine (Moroni et al., 1986d;
Wiley et al., 1991). Both glutamate and NMDA can
induce the release of radiolabeled acetylcholine and
GABA from the plexus (Wiley et al., 1991). The presence
of NMD Wiley et al., 1991). Both glutamate and NMDA can
induce the release of radiolabeled acetylcholine and
GABA from the plexus (Wiley et al., 1991). The presence
of NMDA receptors in this preparation would thus ex-
plain the f induce the release of radiolabeled acetylcholine and GABA from the plexus (Wiley et al., 1991). The presence of NMDA receptors in this preparation would thus explain the findings of Luzzi et al. (1988) that quinolinate cou GABA from the plexus (Wiley et al., 1991). The presence second MMDA receptors in this preparation would thus ex-
plain the findings of Luzzi et al. (1988) that quinolinate si
could also cause contraction of ileal muscle. of NMDA receptors in this preparation would thus ex-
plain the findings of Luzzi et al. (1988) that quinolinate
could also cause contraction of ileal muscle. Of special
interest was the observation that kynurenate and 7-
c plain the findings of Luzzi et al. (1988) that quinolinate sinc
could also cause contraction of ileal muscle. Of special of 2
interest was the observation that kynurenate and 7-Stor
chlorokynurenate could antagonise glutam could also cause contraction of ileal muscle. Of special of interest was the observation that kynurenate and 7- Stochlorokynurenate could antagonise glutamate but that this action appeared to be noncompetitive; this was in interest was the observation that kynurenate and
chlorokynurenate could antagonise glutamate but th
this action appeared to be noncompetitive; this was
marked contrast to the competitive blockade seen wii
2AP5. Glycine was chlorokynurenate could antagonise glutamate but that Although it was not possible in vivo to use compounds
this action appeared to be noncompetitive; this was in such as tetrodotoxin to determine the proportion of
marked c marked contrast to the competitive blockade seen w
2AP5. Glycine was able to enhance sensitivity to glu
mate. Together, these data indicate the presence not or
of functional NMDA receptors but also of the exister
of a kynu binding domain (Luzzi et al., 1988; Moroni et al., 1989b; mate. Together, these dof functional NMDA reprise to a kynurenate-sensitional metal. 1989).
Reggiani et al., 1989). *nding domain (Luzzi et al., 1988; Moroni et al., 1989b;* weggiani et al., 1989).

component al., 1989).
 Neurochemical Effects of Kynurenines
 1. Effects on uptake and release of amino acids. Since a a me of the pharm

B. Neurochemical Effects of Kynurenines

Reggiani et al., 1989). comes comes comes comes comes and Reflects of Kynurenines and nelease of amino acids. Since acid
and nelease of amino acids. Since acid
some of the pharmacological effects of quinolinic acid (Comes B. Neurochemical Effects of Kynurenines
1. Effects on uptake and release of amino acids. Since
some of the pharmacological effects of quinolinic acid
appear to be dependent on the presence of afferent
innervation, it is po B. Neurocnemical Effects of Kynurentnes
1. Effects on uptake and release of amino acids. Since
some of the pharmacological effects of quinolinic acid
appear to be dependent on the presence of afferent
innervation, it is po 1. Effects on uptake and release of amino acids. Since accome of the pharmacological effects of quinolinic acid (C appear to be dependent on the presence of afferent innervation, it is possible that quinolinic acid recepto some of the pharmacological effects of quinolinic acid appear to be dependent on the presence of afferent innervation, it is possible that quinolinic acid receptors exist on synaptic terminals and that it is the evoked rel appear to be dependent on the presence of affer
innervation, it is possible that quinolinic acid recept
exist on synaptic terminals and that it is the evol
release of factors from those terminals that contribu
to, or is re innervation, it is possible that quinolinic acid receptors po
exist on synaptic terminals and that it is the evoked at
release of factors from those terminals that contributes in
to, or is required for, the excitotoxicity. release of factors from those terminals that contributes inducing a degree of excitotoxicity. The remarkable se-
to, or is required for, the excitotoxicity. Similar depend-lectivity of quinolinic acid in vivo, therefore, r

the action of quinolinate was sensitive to 2AP5. In a which were effective inhibitors of this transport system.

later study, McLarnon and Curry (1990) expanded this Similar inactivity was shown by L-kynurenine and kyn-

i various parts of the CNS. However, quinolinic acid has
been found to have no effect on the apparent uptake of NE
various parts of the CNS. However, quinolinic acid has
been found to have no effect on the apparent uptake of
tritiated L-aspartate, even at concentrations as high as 1 NE
various parts of the CNS. However, quinolinic acid has
been found to have no effect on the apparent uptake of
tritiated L-aspartate, even at concentrations as high as 1
mM (Connick and Stone, 1985). This is in contrast various parts of the CNS. However, quinolinic acid has
been found to have no effect on the apparent uptake of
tritiated L-aspartate, even at concentrations as high as 1
mM (Connick and Stone, 1985). This is in contrast to
 various parts of the CNS. However, quinolinic acid been found to have no effect on the apparent uptake
tritiated L-aspartate, even at concentrations as high and
mM (Connick and Stone, 1985). This is in contrast
kainic acid been found to have no effect on the apparent uptake of tritiated L-aspartate, even at concentrations as high as 1 mM (Connick and Stone, 1985). This is in contrast to kainic acid and its more potent analogue, dihydrokainat tritiated L-aspartate, even at concentrations as high as imm (Connick and Stone, 1985). This is in contrast to kainic acid and its more potent analogue, dihydrokainate which were effective inhibitors of this transport syst mM (Connick and Stone, 1985). This is in contrast to kainic acid and its more potent analogue, dihydrokainate, which were effective inhibitors of this transport system. Similar inactivity was shown by L-kynurenine and kynu kainic acid and its more potent analogue, dihydrokain
which were effective inhibitors of this transport syst
Similar inactivity was shown by L-kynurenine and k
urenic acid, although nicotinic acid and dipicolinic a
compoun which were effective inhibitors of this transport system.
Similar inactivity was shown by L-kynurenine and kynurenic acid, although nicotinic acid and dipicolinic acid,
compounds showing very little effect in most pharma-
 Similar inactivity
urenic acid, althou
compounds showi
cological tests (St
aspartate uptake.
Because Ferkan enic acid, although nicotinic acid and dipicolinic acid,
mpounds showing very little effect in most pharma-
logical tests (Stone 1984), were weak inhibitors of L-
partate uptake.
Because Ferkany and Coyle (1983) were able

compounds showing very little effect in most pharma-
cological tests (Stone 1984), were weak inhibitors of L-
aspartate uptake.
Because Ferkany and Coyle (1983) were able to show
that kainic acid could promote the release cological tests (Stone 1984), were weak inhibitors of L-
aspartate uptake.
Because Ferkany and Coyle (1983) were able to show
that kainic acid could promote the release of endogenous
excitatory amino acids from various reg aspartate uptake.
Because Ferkany and Coyle (1983) were able to show
that kainic acid could promote the release of endogenous
excitatory amino acids from various regions of rat brain
at concentrations that had little effec Because Ferkany and Coyle (1983) were able to show
that kainic acid could promote the release of endogenous
excitatory amino acids from various regions of rat brain
at concentrations that had little effect on the release o that kainic acid could promote the release of endogenous
excitatory amino acids from various regions of rat brain
at concentrations that had little effect on the release of
tritiated L-aspartate, the effects of quinolinic at concentrations that had little effect on the release of tritiated L-aspartate, the effects of quinolinic acid were also tested on preloaded and endogenous amino acid release from hippocampal slices. In contrast to the c tritiated L-aspartate, the effects of quinolinic acid were firmed effects of kainic acid, neither NMDA nor quinoalso tested on preloaded and endogenous amino acid
release from hippocampal slices. In contrast to the con-
firmed effects of kainic acid, neither NMDA nor quino-
linic acid had any effect on the basal or potassium-
induce release from hippocampal slices. In contrast to the con-
firmed effects of kainic acid, neither NMDA nor quino-
linic acid had any effect on the basal or potassium-
induced release of endogenous glutamate, aspartate, gly-
 firmed effects of kainic acid, neither NMDA nor quino-
linic acid had any effect on the basal or potassium-
induced release of endogenous glutamate, aspartate, gly-
cine, or GABA (Connick and Stone, 1986, 1988a,b).
When st linic acid had any effect on the basal or potassium-
induced release of endogenous glutamate, aspartate, gly-
cine, or GABA (Connick and Stone, 1986, 1988a,b).
When studies were performed on the neocortical surface
of anae induced release of endogenous glutamate, aspartate, gly-
cine, or GABA (Connick and Stone, 1986, 1988a,b).
When studies were performed on the neocortical surface
of anaesthetised rats, the presence of 1 mM quinolinic
acid cine, or GABA (Connick and Stone, 1986, 1988a,b).
When studies were performed on the neocortical surface
of anaesthetised rats, the presence of 1 mM quinolinic
acid in a cortical cup was found to stimulate, significantly
a When studies were performed on the neocortical surface
of anaesthetised rats, the presence of 1 mM quinolinic
acid in a cortical cup was found to stimulate, significantly
and specifically, the release of endogenous asparta of anaesthetised rats, the presence of 1 mM quinolinic
acid in a cortical cup was found to stimulate, significantly
and specifically, the release of endogenous aspartate and
glutamate, with no significant effect on seven o acid in a cortical cup was found to stimulate, significantly
and specifically, the release of endogenous aspartate and
glutamate, with no significant effect on seven other
amino acids, including glycine and GABA (Connick a and specifically, the release of endogenous aspartate and glutamate, with no significant effect on seven oth amino acids, including glycine and GABA (Connick and Stone, 1988a). Higher concentrations of quinolinic ac produc glutamate, with no significant effect on seven other
amino acids, including glycine and GABA (Connick and
Stone, 1988a). Higher concentrations of quinolinic acid
produced up to a 400% increase of aspartate and gluta-
mate amino acids, including glycine and GABA (Connick and
Stone, 1988a). Higher concentrations of quinolinic acid
produced up to a 400% increase of aspartate and gluta-
mate release with only a 50% increase in the release of
se Stone, 1988a). Higher concentrations of quinolinic acid
produced up to a 400% increase of aspartate and gluta-
mate release with only a 50% increase in the release of
serine, glycine, and taurine. This action was mediated
 produced up to a 400% increase of aspartate and gluta-
mate release with only a 50% increase in the release of
serine, glycine, and taurine. This action was mediated
through the NMDA population of glutamate receptors
since mate release with only a 50% increase in the release of serine, glycine, and taurine. This action was mediated through the NMDA population of glutamate receptors since it could be prevented by the simultaneous presence of through the NMDA population of glutamate receptors since it could be prevented by the simultaneous presence of 2AP5. Purine release is also increased (Perkins and Stone, 1983c). since it could be prevented by the simultaneous presence since it could be prevented by the simultaneous presence
of 2AP5. Purine release is also increased (Perkins and
Stone, 1983c).
Although it was not possible in vivo to use compounds
such as tetrodotoxin to determine the pro

marked contrast to the competitive blockade seen with amino acid release that was due to quinolinic acid action 2AP5. Glycine was able to enhance sensitivity to gluta-

acidy on nerve terminals, it was found that kainic ac of 2AP5. Purine release is also increased (Perkins and
Stone, 1983c).
Although it was not possible in vivo to use compounds
such as tetrodotoxin to determine the proportion of
amino acid release that was due to quinolinic Stone, 1983c).
Although it was not possible in vivo to use compound
such as tetrodotoxin to determine the proportion of
amino acid release that was due to quinolinic acid action
directly on nerve terminals, it was found th Although it was not possible in vivo to use compounds such as tetrodotoxin to determine the proportion camino acid release that was due to quinolinic acid actio directly on nerve terminals, it was found that kainic acid i such as tetrodotoxin to determine the proportion of
amino acid release that was due to quinolinic acid action
directly on nerve terminals, it was found that kainic acid-
induced release in the same in vivo experimental par amino acid release that was due to quinolinic acid action
directly on nerve terminals, it was found that kainic acid-
induced release in the same in vivo experimental para-
digm was profoundly different. At 1 mM, kainic ac directly on nerve terminals, it was found that kainic acid-
induced release in the same in vivo experimental para-
digm was profoundly different. At 1 mM, kainic acid
produced no apparent release of any amino acids,
wherea induced release in the same in vivo experimental para-
digm was profoundly different. At 1 mM , kainic acid
produced no apparent release of any amino acids,
whereas a concentration of 5 mM , comparable to the
concen digm was profoundly different. At 1 mM, kainic acid
produced no apparent release of any amino acids,
whereas a concentration of 5 mM, comparable to the
concentration of quinolinic acid that gave the 4-fold
increase of glut produced no apparent release of any amino acids,
whereas a concentration of 5 mM, comparable to the
concentration of quinolinic acid that gave the 4-fold
increase of glutamate and aspartate release, now induced
an approxim whereas a concentration of 5 mM, comparable to the concentration of quinolinic acid that gave the 4-fold increase of glutamate and aspartate release, now induced an approximately 60% increase of all of the eight amino concentration of quinolinic increase of glutamate and aspian approximately 60% increased
an approximately 60% increased
acids analysed, including no
(Connick and Stone, 1988a).
This is the pattern that wo crease of glutamate and aspartate release, now induce
approximately 60% increase of all of the eight amin
ids analysed, including nontransmitter compound
connick and Stone, 1988a).
This is the pattern that would be expecte

an approximately 60% increase of all of the eight an acids analysed, including nontransmitter compour (Connick and Stone, 1988a).
This is the pattern that would be expected for a cound producing nonselective activation and acids analysed, including nontransmitter compounds
(Connick and Stone, 1988a).
This is the pattern that would be expected for a com-
pound producing nonselective activation and depolaris-
ation of all neurones within the c (Connick and Stone, 1988a).
This is the pattern that would be expected for a com-
pound producing nonselective activation and depolaris-
ation of all neurones within the cortex and probably
inducing a degree of excitotoxic This is the pattern that would be expected for a compound producing nonselective activation and depolaris-
ation of all neurones within the cortex and probably
inducing a degree of excitotoxicity. The remarkable se-
lectiv pound producing nonselective activation and depolaris-
ation of all neurones within the cortex and probably
inducing a degree of excitotoxicity. The remarkable se-
lectivity of quinolinic acid in vivo, therefore, remains t lectivity of quinolinic acid in vivo, therefore, remains to

QUINOLINIC AND P
for quinolinic acid are restricted to glutamate- and/or
aspartate-releasing neurones.

QUINOLINIC AND K
for quinolinic acid are restricted to glutamate- and/or
aspartate-releasing neurones.
The evidence from autoradiographic studies indicates
that NMDA displacement of glutamate from its binding for quinolinic acid are restricted to glutamate- and/or we aspartate-releasing neurones. first The evidence from autoradiographic studies indicates of that NMDA displacement of glutamate from its binding desites can be dem for quinolinic acid are restricted to glutamate- and/
aspartate-releasing neurones.
The evidence from autoradiographic studies indicat
that NMDA displacement of glutamate from its bindi
sites can be demonstrated primarily aspartate-releasing neurones.
The evidence from autoradiographic studies indicates
that NMDA displacement of glutamate from its binding
sites can be demonstrated primarily in the more super-
ficial layers of the neocortex, The evidence from autoradiographic studies indicates
that NMDA displacement of glutamate from its binding
sites can be demonstrated primarily in the more super-
ficial layers of the neocortex, whereas kainate receptors
are sites can be demonstrated primarily in the more super-
ficial layers of the neocortex, whereas kainate receptors
from rat cortex slices unless glycine is present (Fink et
are found primarily in the deeper layers (Greenamyr sites can be demonstrated primarily in the more super-
ficial layers of the neocortex, whereas kainate receptors
fare found primarily in the deeper layers (Greenamyre et
al., 1985). This may mean that higher concentrations ficial layers of the neocortex, whereas kainate receptors
are found primarily in the deeper layers (Greenamyre et
al., 1985). This may mean that higher concentrations of
kainic acid are required to penetrate to the deeper are found primarily in the deeper layers (Greenamyre et al.
al., 1985). This may mean that higher concentrations of
kainic acid are required to penetrate to the deeper layers stu
to induce a quasi-physiological release of al., 1985). This may mean that higher concentrations of kainic acid are required to penetrate to the deeper layers sto induce a quasi-physiological release of endogenous limino acids. Those same concentrations, however, ar kainic acid are required to penetrate to the deeper layers sto induce a quasi-physiological release of endogenous liamino acids. Those same concentrations, however, are for likely to reach a level in the more superficial p to induce a quasi-physiological release of endogenous
amino acids. Those same concentrations, however, are
likely to reach a level in the more superficial parts of
cortex, nearer the collecting pial cup, to cause a degree
 amino acids. Those same concentrations, however, are for likely to reach a level in the more superficial parts of B cortex, nearer the collecting pial cup, to cause a degree word cell damage and nonspecific membrane permea likely to reach a level in the more superficial parts of cortex, nearer the collecting pial cup, to cause a degre
of cell damage and nonspecific membrane permeability
to all amino acids; this could be the cause of the obse cortex, nearer the collecting pial cup, to cause a degre
of cell damage and nonspecific membrane permeabilit
to all amino acids; this could be the cause of the observe
nonspecificity of the kainate-induced release. It is, of cell damage and nonspecific membrane permeability neurotoxic actions of quinolinate, but structure activity
to all amino acids; this could be the cause of the observed analyses have indicated sufficient comparability b to all amino acids; this could be the cause of the observed nonspecificity of the kainate-induced release. It is, however, an important question of whether there is a similarly selective distribution of NMDA and/or quinoli nonspecificity of the kainate-induced release. It is, lever, an important question of whether there is a s
larly selective distribution of NMDA and/or quino
acid receptors on excitatory amino acid-releasing
rones in parts

larly selective distribution of NMDA and/or quinolinic
acid receptors on excitatory amino acid-releasing neu-
rones in parts of the CNS other than the neocortex.
Other attempts to examine the effects of quinolinic
acid on acid receptors on excitatory amino acid-releasing neu-
rones in parts of the CNS other than the neocortex. dif-
Other attempts to examine the effects of quinolinic NN
acid on amino acid release have focussed on the techniq rones in parts of the CNS other than the neocortex. different of the ratempts to examine the effects of quinolinic Nlacid on amino acid release have focussed on the technique abof microdialysis. Local perfusion of quinolin Other attempts to examine the effects of quinolinic N
acid on amino acid release have focussed on the technique
of microdialysis. Local perfusion of quinolinic acid into
the rat hippocampus caused no detectable change in t acid on amino acid release have focussed on the technique
of microdialysis. Local perfusion of quinolinic acid into
the rat hippocampus caused no detectable change in the
efflux of endogenous glutamate and aspartate, altho of microdialysis. Local perfusion of quinolinic acid into
the rat hippocampus caused no detectable change in the
efflux of endogenous glutamate and aspartate, although eit
taurine efflux was increased to more than twice th efflux of endogenous glutamate and aspartate, although
taurine efflux was increased to more than twice the basal
levels (Vezzani et al., 1985; Lu et al., 1991). Using the
same technique, Lehmann's group (1985), using the r efflux of endogenous glutamate and aspartate, although eith
taurine efflux was increased to more than twice the basal nat
levels (Vezzani et al., 1985; Lu et al., 1991). Using the tive
same technique, Lehmann's group (1985 taurine efflux was increased to more than twice the basal nevels (Vezzani et al., 1985; Lu et al., 1991). Using the tisame technique, Lehmann's group (1985), using the rabbit hippocampus, also reported a substantial increa levels (Vezzani et al., 1985; Lu et al., 1991). Using the ti
same technique, Lehmann's group (1985), using the rab-
bit hippocampus, also reported a substantial increase in re
the efflux of taurine in response to the appli same technique, Lehmann's group (1985), using the rab-
bit hippocampus, also reported a substantial increase in rost
the efflux of taurine in response to the application of ical
either NMDLA or quinolinic acid. The amounts bit hippocampus, also reported a substantial increase in
the efflux of taurine in response to the application of
either NMDLA or quinolinic acid. The amounts release
were extraordinary: taurine release was increased to
120 the efflux of taurine in response to the application of ic
either NMDLA or quinolinic acid. The amounts released
were extraordinary: taurine release was increased to
1200% and phosphoethanolamine to 2400% of their rest-
in either NMDLA or quinolinic acid. The amounts released
were extraordinary: taurine release was increased to a
1200% and phosphoethanolamine to 2400% of their rest-
ing levels in response to 5 mM NMDLA. The efflux of c
other were extraordinary: taurine release was increased to a 1200% and phosphoethanolamine to 2400% of their resting levels in response to 5 mM NMDLA. The efflux of cother amino acids was not quoted in this report, although it 1200% and phosphoethanolamine to 2400% of their rest-
ing levels in response to 5 mM NMDLA. The efflux of
other amino acids was not quoted in this report, although
it was stated that "most other amino acids rose by 20-
 1 ing levels in response to 5 mM NMDLA. The efflux of counter and poster and phosphoethanolamine levels to 100% " (Lehmann et al., 1985). Quinolinic acid increased aptitudes are extracellular taurine and phosphoethanolami other amino acids was not quoted in this report it was stated that "most other amino acids 100%" (Lehmann et al., 1985). Quinolinic actracellular taurine and phosphoethanolam about 60% of those achieved with NMDLA. The fai was stated that "most other amino acids rose by 20–
0%" (Lehmann et al., 1985). Quinolinic acid increased atracellular taurine and phosphoethanolamine levels to nout 60% of those achieved with NMDLA. The failure to demonst

 100% " (Lehmann et al., 1985). Quinolinic acid increased a extracellular taurine and phosphoethanolamine levels to nabout 60% of those achieved with NMDLA. The failure to demonstrate an effect of NMDA or the quinolinic about 60% of those achieved with NMDLA. evaluate the failure to demonstrate an effect of NMDA or the qualitative cid on endogenous amino acid uptake or difference using any technique other than the cortical cup 11 is disap The failure to demonstrate an effect of NMDA or taluation and pulled pulled action of displaces using any technique other than the cortical cup 198 is disappointing, although the qualitative similarity of Cai the results i quinolinic acid on endogenous amino acid uptake or
release using any technique other than the cortical cup
is disappointing, although the qualitative similarity of
the results is consistent with the action of quinolinic ac release using any technique other than the cortical cup 198
is disappointing, although the qualitative similarity of Cai
the results is consistent with the action of quinolinic acid pro
at NMDA receptors. In addition, the is disappointing, although the qualitative similarity of the results is consistent with the action of quinolinic acid at NMDA receptors. In addition, the results clearly support the discrimination between quinolinic acid a the results is consistent with the action of quinolinic acid
at NMDA receptors. In addition, the results clearly sup-
port the discrimination between quinolinic acid and
kainic acid which evokes a pronounced amino acid reat NMDA receptors. In addition, the results clearly support the discrimination between quinolinic acid and kainic acid which evokes a pronounced amino acid release in vitro or, rather more nonselectively, in vivo. Thus, al port the discrimination between quinolinic acid and kainic acid which evokes a pronounced amino acid re-
lease in vitro or, rather more nonselectively, in vivo.
Thus, although some of the neurodegenerative properties
of qu kainic acid which evokes a pronounced amino acid re-
lease in vitro or, rather more nonselectively, in vivo.
Thus, although some of the neurodegenerative properties
of quinolinic acid do resemble those of kainic acid rathe Thus, although some of the neurodegenerative properties
of quinolinic acid do resemble those of kainic acid rather
more than NMDLA, including their dependence on af-
ferent innervation, this aspect of their excitotoxic pro Thus, although some of the neurodegenerative properties as of quinolinic acid do resemble those of kainic acid rather emore than NMDLA, including their dependence on afferent innervation, this aspect of their excitotoxic p of quinolinic acid do resemble those of kainic acid
more than NMDLA, including their dependence
ferent innervation, this aspect of their excitotoxic
erties cannot easily be explained by a common relation on the same endoge ore than NMDLA, including their dependence on af-
rent innervation, this aspect of their excitotoxic prop-
ties cannot easily be explained by a common releasing
role of the same endogenous amino acid pool.
One avenue that ferent innervation, this aspect of their excitotoxic properties cannot easily be explained by a common releasing action on the same endogenous amino acid pool.
One avenue that remains to be explored is the role of glycine.

YNURENIC ACIDS
when using microdialysis, glycine may be removed suf-
ficiently quickly by perfusion to deplete NMDA receptors Ficheral Corrections

The using microdialysis, glycine may be removed suf-

ficiently quickly by perfusion to deplete NMDA receptors

of their glycine requirement. In the cortical cup, this 329
when using microdialysis, glycine may be removed suf-
ficiently quickly by perfusion to deplete NMDA receptors
of their glycine requirement. In the cortical cup, this
depletion is less likely to occur. It is interestin when using microdialysis, glycine may be removed suf-
ficiently quickly by perfusion to deplete NMDA receptors
of their glycine requirement. In the cortical cup, this
depletion is less likely to occur. It is interesting, f ficiently quickly by perfusion to deplete NMDA receptors
of their glycine requirement. In the cortical cup, this ficiently quickly by perfusion to deplete NMDA receptors of their glycine requirement. In the cortical cup, this depletion is less likely to occur. It is interesting, for example, that NMDA does not release noradrenaline f of their gly
depletion is
example, tl
from rat co
al., 1990).
In parall example, that NMDA does not release noradrenaline
from rat cortex slices unless glycine is present (Fink et
al., 1990).
In parallel with these conventional neurochemical from rat cortex slices unless glycine is present (Fink et

from rat cortex slices unless glycine is present (Fink et al., 1990).

In parallel with these conventional neurochemical

studies have been investigations of the effects of quino-

linate on the physical state of cell memb al., 1990).
In parallel with these conventional neurochemical
studies have been investigations of the effects of quino-
linate on the physical state of cell membranes in general,
focusing on that of human erythrocytes (Far In parallel with these conventional neurochemical
studies have been investigations of the effects of quino-
linate on the physical state of cell membranes in general,
focusing on that of human erythrocytes (Farmer and
Butt studies have been investigations of the effects of quino-
linate on the physical state of cell membranes in general,
focusing on that of human erythrocytes (Farmer and
Butterfield, 1984; Farmer et al., 1984). It remains un linate on the physical state of cell membranes in general,
focusing on that of human erythrocytes (Farmer and
Butterfield, 1984; Farmer et al., 1984). It remains unclear
whether these effects are relevant to the excitatory Butterfield, 1984; Farmer et al., 1984). It remains unclear whether these effects are relevant to the excitatory or Butterfield, 1984; Farmer et al., 1984). It remains uncles
whether these effects are relevant to the excitatory of
neurotoxic actions of quinolinate, but structure activit
analyses have indicated sufficient comparability b whether these effects are relevant to the excitatory or
neurotoxic actions of quinolinate, but structure activity
analyses have indicated sufficient comparability between
toxicity and spin resonance changes of membrane flu neurotoxic act

analyses have

toxicity and s

ity to merit ful

et al., 1988).

2. Effects of *2. Effects on other neuroactive agents.* All ally set we arrive that is a prior in the prior of the prior of the proof of the proof of the proof al., 1988).

2. Effects on other neuroactive agents. Despite the ficulty of

Other attempts to examine the effects of quinolinic NMDLA on amino acid release, both of these agents are id on amino acid release have focussed on the technique able to produce a release of acetylcholine from striatal toxicity and spin resonance changes of membrane fluid-
ity to merit further study (Farmer et al., 1984; Nonneman
et al., 1988).
2. Effects on other neuroactive agents. Despite the
difficulty of demonstrating effects of qui ity to merit further study (Farmer et al., 1984; Nonneman
et al., 1988).
2. Effects on other neuroactive agents. Despite the
difficulty of demonstrating effects of quinolinic acid and
NMDLA on amino acid release, both of t et al., 1988).

2. Effects on other neuroactive agents. Despite the

difficulty of demonstrating effects of quinolinic acid and

NMDLA on amino acid release, both of these agents are

able to produce a release of acetylcho 2. Effects on other neuroactive agents. Despite the difficulty of demonstrating effects of quinolinic acid and NMDLA on amino acid release, both of these agents are able to produce a release of acetylcholine from striate s difficulty of demonstrating effects of quinolinic acid and

NMDLA on amino acid release, both of these agents are

able to produce a release of acetylcholine from striatal

slices. Lehmann et al. (1983) detected a release NMDLA on amino acid release, both of these agents
able to produce a release of acetylcholine from stris
slices. Lehmann et al. (1983) detected a release of re
olabeled acetylcholine from rat striatal slices induced
either able to produce a release of acetylcholine from striats slices. Lehmann et al. (1983) detected a release of rad olabeled acetylcholine from rat striatal slices induced beither NMDLA (ED₅₀ approximately 70 μ M) or quin slices. Lehmann et al. (1983) detected a release of radi-
olabeled acetylcholine from rat striatal slices induced by
either NMDLA (ED₅₀ approximately 70 μ M) or quinoli-
nate (ED₅₀ about 2 mM); both agents were bloc olabeled acetylcholine from rat striatal slices induced by

either NMDLA (ED₅₀ approximately 70 μ M) or quinoli-

nate (ED₅₀ about 2 mM); both agents were blocked selec-

tively by 2AP5 or 2AP7. Quinolinate was rela either NMDLA (ED₅₀ approximately 70 μ M) or q
nate (ED₅₀ about 2 mM); both agents were blocked
tively by 2AP5 or 2AP7. Quinolinate was relative
effective than NMDLA in the caudal striatum th
rostral slices, a findin nate (ED₅₀ about 2 mM); both agents were blocked
tively by 2AP5 or 2AP7. Quinolinate was relativel
effective than NMDLA in the caudal striatum th
rostral slices, a finding that mirrors the electrophys
ical gradient noted It is not possible to deduce from the selective than NMDLA in the caudal striatum than in stral slices, a finding that mirrors the electrophysiologies and striatum there is not possible to deduce from this work whether the

effective than NMDLA in the caudal striatum than in
rostral slices, a finding that mirrors the electrophysiolog-
ical gradient noted by Perkins and Stone (1983b).
It is not possible to deduce from this work whether the
act rostral slices, a finding that mirrors the electrophysiolog-
ical gradient noted by Perkins and Stone (1983b).
It is not possible to deduce from this work whether the
actions of NMDLA and quinolinate were on cell bodies
or It is not possible to deduce from this work whether the actions of NMDLA and quinolinate were on cell bodies or directly on cholinergic neurone terminals. Release could have occurred indirectly after the depolarisation of noncholinergic excitatory interneurones.

about 60% of those achieved with NMDLA. evoke a release of noradrenaline (Fink et al., 1990; Pit-
The failure to demonstrate an effect of NMDA or taluga and Raiteri, 1992), cholecystokinin (Bandopa-
quinolinic acid on endo More recent work, using either tetrodotoxin or syn-
aptosomes, suggests the presence of NMDA receptors on or directly on cholinergic neurone terminals. Release
could have occurred indirectly after the depolarisation of
noncholinergic excitatory interneurones.
More recent work, using either tetrodotoxin or syn-
aptosomes, sugge could have occurred indirectly after the depolarisation of
noncholinergic excitatory interneurones.
More recent work, using either tetrodotoxin or syn-
aptosomes, suggests the presence of NMDA receptors on
nerve terminals. noncholinergic excitatory interneurones.
More recent work, using either tetrodotoxin or syn-
aptosomes, suggests the presence of NMDA receptors on
nerve terminals. NMDA under these conditions can
evoke a release of noradre More recent work, using either tetrodotoxin or aptosomes, suggests the presence of NMDA receptor
nerve terminals. NMDA under these conditions
evoke a release of noradrenaline (Fink et al., 1990;
taluga and Raiteri, 1992), aptosomes, suggests the presence of NMDA receptors on
nerve terminals. NMDA under these conditions can
evoke a release of noradrenaline (Fink et al., 1990; Pit-
taluga and Raiteri, 1992), cholecystokinin (Bandopa-
dhyay an nerve terminals. NMDA under these conditions can
evoke a release of noradrenaline (Fink et al., 1990; Pit-
taluga and Raiteri, 1992), cholecystokinin (Bandopa-
dhyay and de Belleroche, 1991), GABA (Reynolds et al.,
1989), evoke a release of noradrenaline (Fink et al., 1990; Pittaluga and Raiteri, 1992), cholecystokinin (Bandopa-
dhyay and de Belleroche, 1991), GABA (Reynolds et al., 1989), and dopamine both in vitro (Mount et al., 1991;
Cai taluga and Raiteri, 1992), cholecystokinin (Bandop dhyay and de Belleroche, 1991), GABA (Reynolds et a 1989), and dopamine both in vitro (Mount et al., 1991) a
Cai et al., 1991) and in vivo (Krebs et al., 1991) a
probably dhyay and de Belleroche, 1991), GABA (Reynolds et al., 1989), and dopamine both in vitro (Mount et al., 1991; Cai et al., 1991) and in vivo (Krebs et al., 1991) and probably in part by a direct depolarisation of the termin 1989), and dopamine both in vitro (Mount et al., 1992)
Cai et al., 1991) and in vivo (Krebs et al., 1991) a
probably in part by a direct depolarisation of the tern
nals (Overton and Clark, 1991). Many of these neuror
presu probably in part by a direct depolarisation of the terminals (Overton and Clark, 1991). Many of these neurones presumably represent sites at which endogenous quino-
linate would also act if present in sufficiently high con probably in part by a direct depolarisation of the terminals (Overton and Clark, 1991). Many of these neurones
presumably represent sites at which endogenous quino-
linate would also act if present in sufficiently high con nals (Overton and Clark, 1991). Many of these neurones
presumably represent sites at which endogenous quino-
linate would also act if present in sufficiently high con-
centrations. The depolarising activity of quinolinate efflux from neurones in vitro (Luini et al., 1985).
 3. *Luteinising hormone.* Possible effects of quinolinate, but not NMDA, on 5HT-releasing neurones have been

also shown by this compound's ability to increase sodium
efflux from neurones in vitro (Luini et al., 1985).
3. Luteinising hormone. Possible effects of quinolinate,
but not NMDA, on 5HT-releasing neurones have been
report also shown by this compound's ability to increase sodium
efflux from neurones in vitro (Luini et al., 1985).
3. *Luteinising hormone*. Possible effects of quinolinate,
but not NMDA, on 5HT-releasing neurones have been
repo efflux from neurones in vitro (Luini et al., 1985).
3. Luteinising hormone. Possible effects of quinolinate,
but not NMDA, on 5HT-releasing neurones have been
reported by Johnson et al. (1985a). This group has shown
that t 3. Luteinising hormone. Possible effects of quinolinate,
but not NMDA, on 5HT-releasing neurones have been
reported by Johnson et al. (1985a). This group has shown
that the intracisternal administration of quinolinate into but not NMDA, on 5HT-releasing neurones have been
reported by Johnson et al. (1985a). This group has shown
that the intracisternal administration of quinolinate into
female rats induced the secretion of luteinising hormone

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were not effective (Mason et al., 1983). Subsequent work par
revealed that this action was lost after disturbances of in STONE
were not effective (Mason et al., 1983). Subsequent work
revealed that this action was lost after disturbances of ir
5HT neurones, either by the use of the 5HT neurotoxin STON

were not effective (Mason et al., 1983). Subsequent work

revealed that this action was lost after disturbances of

5HT neurones, either by the use of the 5HT neurotoxin

5,7-dihydroxytryptamine, the 5HT antagonist m were not effective (Mason et al., 1983). Subsequent werevealed that this action was lost after disturbances
5HT neurones, either by the use of the 5HT neuroto.
5,7-dihydroxytryptamine, the 5HT antagonist methergide, or the were not effective (Mason et al., 1983). Subsequen
revealed that this action was lost after disturbar
5HT neurones, either by the use of the 5HT neur
5,7-dihydroxytryptamine, the 5HT antagonist m
ergide, or the 5HT synthes revealed that this action was lost after disturbances of SHT neurones, either by the use of the 5HT neurotoxii 5,7-dihydroxytryptamine, the 5HT antagonist methys ergide, or the 5HT synthesis inhibitor *p*-chlorophenyla lan 5HT neurones, either by the use of the 5HT neurotor
5,7-dihydroxytryptamine, the 5HT antagonist methy
ergide, or the 5HT synthesis inhibitor p-chloropheny
lanine (Johnson et al., 1985b). Depletion of brain ca
cholamines, 5,7-dihydroxytryptamine, the 5HT antagonist methysergide, or the 5HT synthesis inhibitor *p*-chlorophenyla-
lanine (Johnson et al., 1985b). Depletion of brain cate-
cholamines, on the other hand, did not affect the luteinergide, or the 5HT synthesis inhibitor *p*-chlorophenyla
lanine (Johnson et al., 1985b). Depletion of brain cate
cholamines, on the other hand, did not affect the luteir
ising hormone stimulation by quinolinate, and, mos
i lanine (Johnson et al., 1985b)
cholamines, on the other hand
ising hormone stimulation by
intriguing of all, the stimulatio
fected by any amine depletion.
Although it is not possible t olamines, on the other hand, did not affect the lutein-
ng hormone stimulation by quinolinate, and, most
triguing of all, the stimulation by NMDLA was unaf-
ted by any amine depletion.
Although it is not possible to infer

ising hormone stimulation by quinolinate, and, most
intriguing of all, the stimulation by NMDLA was unaf-
fected by any amine depletion.
Although it is not possible to infer from this whether
quinolinate was acting at the fected by any amine depletion.

Although it is not possible to infer from this whether

quinolinate was acting at the level of the raphe nuclei or

at 5HT terminals, it would seem potentially rewarding

to study quinolinat Although it is not possible to infer from this whether poundlinate was acting at the level of the raphe nuclei or that 5HT terminals, it would seem potentially rewarding at to study quinolinate activity on isolated or disr quinolinate was acting at the level of the raphe nuclei or test
at 5HT terminals, it would seem potentially rewarding agai
to study quinolinate activity on isolated or disrupted cell
and
systems from these regions. Because at 5HT terminals, it would seem potentially rewarding at to study quinolinate activity on isolated or disrupted cell asystems from these regions. Because the injection of requinolinate directly into the hypothalamus is abl to study quinolinate activity on isolated or disrupted cell and systems from these regions. Because the injection of requinolinate directly into the hypothalamus is able to set elicit a release of luteinising hormone, as w systems from these regions. Because the injection of quinolinate directly into the hypothalamus is able to elicit a release of luteinising hormone, as well as prolactin and growth hormone (Nemeroff et al., 1985), it would and growth hormone (
seem more likely that tone.

C. *Kynurenic Acid*

Following the demon

em more likely that the action of quinolinate is a local
e.
Explorer demonstration of the excitatory activity
Following the demonstration of the excitatory activity
quinolinic acid, other components of the kynurenine one.

C. Kynurenic Acid

Following the demonstration of the excitatory activity

of quinolinic acid, other components of the kynurenine

pathway were examined on single neurones in vivo and ple

pathway the demonstration of the excitatory activity

pathway were examined on single neurones in vivo and

pathway were examined on single neurones in vivo and

on hippocampal slices to determine whether other com-
 C. *Kyndrenic Acid*
Following the demonstration of the excitatory activity
of quinolinic acid, other components of the kynurenine
pathway were examined on single neurones in vivo and
on hippocampal slices to determine whet Following the demonstration of the excitatory activity
of quinolinic acid, other components of the kynurenine
pathway were examined on single neurones in vivo and
on hippocampal slices to determine whether other com-
pound of quinolinic acid, other components of the kynurenine
pathway were examined on single neurones in vivo an
on hippocampal slices to determine whether other com
pounds had related pharmacological activity. Wheree
most of th pathway were examined on single neurones in vivo and
on hippocampal slices to determine whether other com-
pounds had related pharmacological activity. Whereas
most of the other kynurenines, including L-kynurenine,
3-hydro on hippocampal slices to determine whether other compounds had related pharmacological activity. Whereas most of the other kynurenines, including L-kynurenine, 3-hydroxykynurenine, anthranilic acid, nicotinic acid, and dip pounds had related pharmacological activity. Whereas an most of the other kynurenines, including L-kynurenine, eff
3-hydroxykynurenine, anthranilic acid, nicotinic acid, IC
and dipicolinic acid had no discernible effect on most of the other kynurenines, including L-kynurenine, 3-hydroxykynurenine, anthranilic acid, nicotinic acid, and dipicolinic acid had no discernible effect on neuronal firing, kynurenic acid was able to effectively block 3-hydroxykynurenine, anthranilic acid, nicotinic acid, and dipicolinic acid had no discernible effect on neuronal firing, kynurenic acid was able to effectively block the actions of NMDA, quisqualate, and kainic acid in th and dipicolinic acid had no discernible effect on neuronal
firing, kynurenic acid was able to effectively block the
actions of NMDA, quisqualate, and kainic acid in the rat
neocortex (Perkins and Stone, 1982). In the origi firing, kynurenic acid was able to effectively block the actions of NMDA, quisqualate, and kainic acid in the raneocortex (Perkins and Stone, 1982). In the original experiments, kynurenic acid was equally effective a block actions of NMDA, quisqualate, and kainic acid in the rat depressed kainate responses by no more than 25% (Gan-
neocortex (Perkins and Stone, 1982). In the original ong and Cotman, 1986). Kynurenate also distinguishes
exper experiments, kynurenic acid was equally effective at kainate and quisqualate receptors in the vertebrate retina
blocking responses to quinolinic acid, NMDA, and quis-
qualic acid on cortical neurones. In contrast to this A experiments, kynurenic acid was equally effective at left blocking responses to quinolinic acid, NMDA, and quisqualic acid on cortical neurones. In contrast to this nonselective depressant action, however, kynurenic acid l blocking responses to quinolinic acid, NMDA, and quis-
qualic acid on cortical neurones. In contrast to this
nonselective depressant action, however, kynurenic acid
was able to block excitatory amino acid sensitivity at
le qualic acid on cortical neurones. In contrast to this nonselective depressant action, however, kynurenic acid was able to block excitatory amino acid sensitivity at levels that had no effect on excitation produced by acety nonselective depressant action, however, kynurenic acid was able to block excitatory amino acid sensitivity a levels that had no effect on excitation produced by ace tylcholine. Later analysis of the action of kynurenic ac was able to block excitatory amino acid sensitivity
levels that had no effect on excitation produced by a
tylcholine. Later analysis of the action of kynurenic ac
as well as 3-hydroxyanthranilic acid, picolinic acid,
kynur levels that had no effect on excitation produced by a
tylcholine. Later analysis of the action of kynurenic ac
as well as 3-hydroxyanthranilic acid, picolinic acid,
kynurenine, and xanthurenic acid, using isolated hipp
cam tylcholine. Later analysis of the action of kynurenic acid, rot as well as 3-hydroxyanthranilic acid, picolinic acid, L-
hynurenine, and xanthurenic acid, using isolated hippo-
of campal slices, confirmed that pharmacologi as well as 3-hydroxyanthranilic acid, picolinic acid, kynurenine, and xanthurenic acid, using isolated hipp campal slices, confirmed that pharmacological anta mist activity at amino acid receptors resided only in kynurenic murenine, and xanthurenic acid, using isolated hippompal slices, confirmed that pharmacological antagest activity at amino acid receptors resided only in the murenic acid molecule (Perkins and Stone, 1984). The early evide

campal slices, confirmed that pharmacological antagonist activity at amino acid receptors resided only in the kynurenic acid molecule (Perkins and Stone, 1984).
The early evidence for a nonspecific blockade of excitatory a mist activity at amino acid receptors resided only in the symurenic acid molecule (Perkins and Stone, 1984).
The early evidence for a nonspecific blockade of excitatory amino acid sensitivity on some neurones was late
conf kynurenic acid molecule (Perkins and Stone, 1984).
The early evidence for a nonspecific blockade of excitory amino acid sensitivity on some neurones was latticonfirmed by work in the spinal cord, hippocampuneocortex, and c The early evidence for a nonspecific blockade of excitiatory amino acid sensitivity on some neurones was later kyr confirmed by work in the spinal cord, hippocampus, response
neocortex, and caudate nucleus (Peet et al., 19 atory amino acid sensitivity on some neurones was lat
confirmed by work in the spinal cord, hippocamp
neocortex, and caudate nucleus (Peet et al., 1986; He:
ling, 1985; Curry et al., 1986) in which kynurenic ac
was found c confirmed by work in the spinal cord, hippocampus,
neocortex, and caudate nucleus (Peet et al., 1986; Herr-
ling, 1985; Curry et al., 1986) in which kynurenic acid
was found capable of antagonising responses to quino-
lini *Coortex, and caudate nucleus (Peet et al., 1986; Herr-shippeg, 1985; Curry et al., 1986) in which kynurenic acid ind as found capable of antagonising responses to quino-
ic acid, NMDA, kainic acid, or quisqualate. In Sele*

ling, 1985; Curry et al., 1986) in which kynurenic acid in was found capable of antagonising responses to quino-
linic acid, NMDA, kainic acid, or quisqualate.
1. Selectivity of kynurenate. Evidence has shown a comore sele was found capable of antagonising responses to quilinic acid, NMDA, kainic acid, or quisqualate.
1. Selectivity of kynurenate. Evidence has shown
more selective action of kynurenic acid in other parts
the CNS. Kynurenate w linic acid, NMDA, kainic acid, or quisqualate.

1. Selectivity of kynurenate. Evidence has shown

more selective action of kynurenic acid in other parts of

the CNS. Kynurenate was, for example, a more consist

ent antagon

NE
pared with quisqualate on neurones of the visual cortex
in anaesthetised cats (Tsumoto et al., 1986), although IE
pared with quisqualate on neurones of the visual cortex
in anaesthetised cats (Tsumoto et al., 1986), although
responses to acetylcholine were totally unaffected by the responses to acetylcholine were totally unaffected by the antagonist. Similarly, in the caudate nucleus of anaesthead by the antagonist. Similarly, in the caudate nucleus of anaesthead by the same set $\frac{1}{2}$ pared with quisqualate on neurones of the visual co
in anaesthetised cats (Tsumoto et al., 1986), altho
responses to acetylcholine were totally unaffected by
antagonist. Similarly, in the caudate nucleus of anaes
etised ca pared with quisqualate on neurones of the visual cortex
in anaesthetised cats (Tsumoto et al., 1986), although
responses to acetylcholine were totally unaffected by the
antagonist. Similarly, in the caudate nucleus of anae in anaesthetised cats (Tsumoto et al., 1986), although
responses to acetylcholine were totally unaffected by the
antagonist. Similarly, in the caudate nucleus of anaesth-
etised cats, Herrling (1985) reported that on sever responses to acetylcholine were totally unaffected by
antagonist. Similarly, in the caudate nucleus of anaes
etised cats, Herrling (1985) reported that on several c
excitation produced by NMDA was more sensitive
kynurenate tagonist. Similarly, in the caudate nucleus of anaest ised cats, Herrling (1985) reported that on several celestiation produced by NMDA was more sensitive nurenate than were responses to quisqualic acid. In other regions o

intriguing of all, the stimulation by NMDLA was unaf-
fected by any amine depletion.
Atthough it is not possible to infer from this whether particularly so in the hippocampus, slices of which were
quinolinate was acting a etised cats, Herrling (1985) reported that on several cells
excitation produced by NMDA was more sensitive to
kynurenate than were responses to quisqualic acid.
In other regions of the CNS, there is a clearer differ-
ence excitation produced by NMDA was more sensitive to
kynurenate than were responses to quisqualic acid.
In other regions of the CNS, there is a clearer differ-
ence in sensitivity between NMDA and non-NMDA
receptors to kynure kynurenate than were responses to quisqualic acid.
In other regions of the CNS, there is a clearer difference in sensitivity between NMDA and non-NMDA
receptors to kynurenic acid blockade. This seems to be
particularly so In other regions of the CNS, there is a clearer difference in sensitivity between NMDA and non-NMDA receptors to kynurenic acid blockade. This seems to be particularly so in the hippocampus, slices of which were tested wi ence in sensitivity between NMDA and non-NMDA receptors to kynurenic acid blockade. This seems to be particularly so in the hippocampus, slices of which were tested with 100 μ M concentrations of kynurenic acid against receptors to kynurenic acid blockade. This seems to be particularly so in the hippocampus, slices of which were tested with 100μ M concentrations of kynurenic acid against depolarisations produced by NMDLA, kainate, and particularly so in the hippocampus, slices of which were tested with 100μ M concentrations of kynurenic acid against depolarisations produced by NMDLA, kainate, and quisqualate (Ganong et al., 1983). The former was redu tested with 100 μ M concentrations of kynurenic acid against depolarisations produced by NMDLA, kainate, and quisqualate (Ganong et al., 1983). The former was reduced preferentially, although the pooled data from the se against depolarisations produced by NMDLA, kainate, and quisqualate (Ganong et al., 1983). The former was reduced preferentially, although the pooled data from the set of neurones tested indicate that the difference is cle reduced preferentially, although the pooled data from the set of neurones tested indicate that the difference is clearly not absolute but merely relative. Similar results were achieved by Peet et al. (1986) in a quantitati set of neurones tested indicate that the difference is clearly not absolute but merely relative. Similar results were achieved by Peet et al. (1986) in a quantitative study using intracellular techniques in the hippocampal set of neurones tested indicate that the difference is clearly not absolute but merely relative. Similar result were achieved by Peet et al. (1986) in a quantitative study using intracellular techniques in the hippocampasl clearly not absolute but merely relative. Similar results
were achieved by Peet et al. (1986) in a quantitative
study using intracellular techniques in the hippocampal
slice. Here, kynurenic acid proved able to block comwere achieved by Peet et al. (1986) in a quantitative study using intracellular techniques in the hippocampaslice. Here, kynurenic acid proved able to block completely the sensitivity of CA1 pyramidal neurones to NMDA and study using intracellular t
slice. Here, kynurenic aci
pletely the sensitivity of
NMDA and quinolinic aci
qualic acid was unaffected
A related study was p ce. Here, kynurenic acid proved able to block com-
etely the sensitivity of CA1 pyramidal neurones to
MDA and quinolinic acid, whereas sensitivity to quis-
alic acid was unaffected.
A related study was performed using DC p

pletely the sensitivity of CA1 pyramidal neurones to NMDA and quinolinic acid, whereas sensitivity to quisqualic acid was unaffected.
A related study was performed using DC potential recording from the hippocampal slice wi NMDA and quinolinic acid, whereas sensitivity to quisqualic acid was unaffected.

A related study was performed using DC potential

recording from the hippocampal slice with the conclusion

that kynurenic acid would block qualic acid was unaffected.

A related study was performed using DC potential

recording from the hippocampal slice with the conclusion

that kynurenic acid would block responses to NMDA

and quinolinic acid at concentrati A related study was performed using DC potential
recording from the hippocampal slice with the conclusion
that kynurenic acid would block responses to NMDA
and quinolinic acid at concentrations that had little
effect on qu recording from the hippocampal slice with the conclusion
that kynurenic acid would block responses to NMDA
and quinolinic acid at concentrations that had little
effect on quisqualic acid or glutamate responses. The
IC₅₀ that kynurenic acid would block responses to NMDA
and quinolinic acid at concentrations that had little
effect on quisqualic acid or glutamate responses. The
IC₅₀ for kynurenate against NMDA or quinolinate was
approxima and quinolinic acid at concentrations that had little effect on quisqualic acid or glutamate responses. The IC_{50} for kynurenate against NMDA or quinolinate was approximately 100 μ M, whereas kynurenate depressed kain effect on quisqualic acid or glutamate responses. The IC_{50} for kynurenate against NMDA or quinolinate wapproximately 100 μ M, whereas kynurenate depressed kainate responses by only 75% at 1 mM, and quisquala depresse IC₅₀ for kynurenate against NMDA or quinolinate was
approximately 100 μ M, whereas kynurenate depressed
kainate responses by only 75% at 1 mM, and quisqualate
depressed kainate responses by no more than 25% (Gan-
ong approximately 100 μ M, whereas kynurenate depressed kainate responses by only 75% at 1 mM, and quisqualate depressed kainate responses by no more than 25% (Ganong and Cotman, 1986). Kynurenate also distinguishes kainate kainate responses by onl
depressed kainate respor
ong and Cotman, 1986).
kainate and quisqualate :
(Coleman et al., 1986).
A further quantitative pressed kainate responses by no more than 25% (Gan-
g and Cotman, 1986). Kynurenate also distinguishes
inate and quisqualate receptors in the vertebrate retina
coleman et al., 1986).
A further quantitative analysis was per

ong and Cotman, 1986). Kynurenate also distinguishes
kainate and quisqualate receptors in the vertebrate retina
(Coleman et al., 1986).
A further quantitative analysis was performed using
hemisected frog spinal cord in whi kainate and quisqualate receptors in the vertebrate retina
(Coleman et al., 1986).
A further quantitative analysis was performed using
hemisected frog spinal cord in which DC recordings were
made of the ventral root potent (Coleman et al., 1986).
A further quantitative analysis was performed using
hemisected frog spinal cord in which DC recordings were
made of the ventral root potentials (Herrling, 1985). This
reflects the depolarisation of hemisected frog spinal cord in which DC recordings were
made of the ventral root potentials (Herrling, 1985). This
reflects the depolarisation of ventral horn motor neu-
rones and can be used to provide a quantitative mea hemisected frog spinal cord in which DC recordings were
made of the ventral root potentials (Herrling, 1985). This
reflects the depolarisation of ventral horn motor neu-
rones and can be used to provide a quantitative mea made of the ventral root potentials (Herrling, 1985). This
reflects the depolarisation of ventral horn motor neu-
rones and can be used to provide a quantitative measure
of neuronal depolarisation. In this system, the pA reflects the depolarisation of ventral horn motor neu
rones and can be used to provide a quantitative measur-
of neuronal depolarisation. In this system, the pA_2 value
of kynurenic acid against NMDA depolarisation was rones and can be used to provide a quantitative measure
of neuronal depolarisation. In this system, the pA_2 value
of kynurenic acid against NMDA depolarisation was 4.6,
whereas the corresponding value was 4.0 against q of neuronal depolarisation. In this system, the pA_2 value
of kynurenic acid against NMDA depolarisation was 4.6,
whereas the corresponding value was 4.0 against quis-
qualic acid. This difference of sensitivity was rep of kynurenic acid against NMDA depolarisation was 4.6,
whereas the corresponding value was 4.0 against quis-
qualic acid. This difference of sensitivity was replicated
qualitatively by Elmslie and Yoshikami (1985). It is
i whereas the corresponding value was 4.0 against quisi-
qualic acid. This difference of sensitivity was replicate
qualitatively by Elmslie and Yoshikami (1985). It is
interesting to note that, in view of the dual nature of
 qualic acid. This difference of sensitivity was replicated
qualitatively by Elmslie and Yoshikami (1985). It is
interesting to note that, in view of the dual nature of
kynurenic acid antagonism (section IV.C.5), the dose-
 qualitatively by Elmslie and Yoshikami (1985). It is
interesting to note that, in view of the dual nature of
kynurenic acid antagonism (section IV.C.5), the dose-
response curves to all agonists in the spinal cord were
shi interesting to note that, in view of the dual nature of kynurenic acid antagonism (section IV.C.5), the dose-
response curves to all agonists in the spinal cord were
shifted by kynurenate in a parallel fashion, normally
in kynurenic acid antagonism (section IV.C
response curves to all agonists in the spin
shifted by kynurenate in a parallel fashi
indicating that the antagonism involved a
competitive mechanism (Herrling, 1985).
In the hippoca sponse curves to all agonists in the spinal cord were
ifted by kynurenate in a parallel fashion, normally
dicating that the antagonism involved an essentially
mpetitive mechanism (Herrling, 1985).
In the hippocampus of ana

shifted by kynurenate in a parallel fashion, norm
indicating that the antagonism involved an essenti
competitive mechanism (Herrling, 1985).
In the hippocampus of anaesthetised rats, a car
comparison of the peak responses indicating that the antagonism involved an essentially
competitive mechanism (Herrling, 1985).
In the hippocampus of anaesthetised rats, a careful
comparison of the peak responses produced by microion-
tophoretically appli competitive mechanism (Herrling, 1985).
In the hippocampus of anaesthetised rats, a careful
comparison of the peak responses produced by microion-
tophoretically applied agonists indicated that kynurenic
acid could almost comparison of the peak responses produced by microion-
tophoretically applied agonists indicated that kynurenic
acid could almost abolish responses to NMDA at doses
that produced minimal reduction in sensitivity to quis-

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qualic acid (Perkins and Stone, 1985). This study also bot
indicated that two other agonists generally believed to K_d quinolatic acid (Perkins and Stone, 1985). This study also bother indicated that two other agonists generally believed to K_d of the NMDA population of receptors, iboquinolinic acid (Perkins and Stone, 1985). This study also
indicated that two other agonists generally believed to
be selective for the NMDA population of receptors, ibo-
tenic acid and DL-homocysteic acid, were also more qualic acid (Perkins and Stone, 1985). This study also be
indicated that two other agonists generally believed to K,
be selective for the NMDA population of receptors, ibo-
sitenic acid and DL-homocysteic acid, were also m indicated that two other agonists generally believed to
be selective for the NMDA population of receptors, ibo-
tenic acid and DL-homocysteic acid, were also more
sensitive to kynurenic acid blockade than quisqualic acid.
 indicated that two other agonists generally believed to
be selective for the NMDA population of receptors, ibo-
tenic acid and DL-homocysteic acid, were also more
sensitive to kynurenic acid blockade than quisqualic acid.
 be selective for the NMDA population of receptors, it tenic acid and DL-homocysteic acid, were also mosensitive to kynurenic acid blockade than quisqualic ac
This result is derived from an analysis of the to
neuronal popul tenic acid and DL-homocysteic acid, were also more In sensitive to kynurenic acid blockade than quisqualic acid. On This result is derived from an analysis of the total μ l neuronal population studied, however, and it i Sensitive to kynurenic acid blockade than quisqualic acid. onis

This result is derived from an analysis of the total μ M)

neuronal population studied, however, and it is impor-

3.

tant to note that no consistent dif This result is derived from an analysis of the total μ N
neuronal population studied, however, and it is impor-
tant to note that no consistent differentiation between st
NMDA and kainate could be detected on these cell neuronal population studied, however, and it is impor-
tant to note that no consistent differentiation between
NMDA and kainate could be detected on these cells. In
the same study, more than half the neurones tested
showed tant to note that no consistent differentiation between st
NMDA and kainate could be detected on these cells. In
the same study, more than half the neurones tested m
showed some evidence of a differentiation by kynurenic 1 NMDA and kainate could be detected on these cells. In
the same study, more than half the neurones tested m
showed some evidence of a differentiation by kynurenic 19
acid of responses to quinolinic acid and NMDA, a finding the same study, more than half the neurones tested mshowed some evidence of a differentiation by kynurenic 19 acid of responses to quinolinic acid and NMDA, a finding acthat could support the view that subpopulations of re showed some evidence of a differentiation by kynureniacid of responses to quinolinic acid and NMDA, a findin
that could support the view that subpopulations c
NMDA receptors may exist. In the dentate gyrus, somevidence fo acid of responses to quinolinic acid and NMDA, a finding
that could support the view that subpopulations of
NMDA receptors may exist. In the dentate gyrus, some
evidence for a differential action against NMDA or quin-
oli that could support the view that subpopulations of NMDA receptors may exist. In the dentate gyrus, some evidence for a differential action against NMDA or quinolinate has also been offered in that at 100μ M kynurenate r NMDA receptors may exist. In the dentate gyrus, some evidence for a differential action against NMDA or quinolinate has also been offered in that at 100μ M kynurenate reduced responses to NMDA by 66%, but responses to q 1983). nate has also been offered in that at 100μ M kynurent expedience reduced responses to NMDA by 66%, but response quinolinate were reduced by only 32% (Ganong et also salid mem-
Kynurenic acid had no direct effect on neur

ate reduced responses to NMDA by 66%, but responses con
to quinolinate were reduced by only 32% (Ganong et al., tra
1983).
Kynurenic acid had no direct effect on neuronal mem-
brane properties, including membrane resistan to quinolinate were reduced by only 32% (Ganong et a
1983).
Kynurenic acid had no direct effect on neuronal mesopherane properties, including membrane resistance a
threshold for action potential initiation or action potent 1983).
Kynurenic acid had no direct effect on neuronal membrane properties, including membrane resistance and
threshold for action potential initiation or action poten-
tial configuration (Ganong et al., 1983; Herrling, 19 Kynurenic acid had no direct effect on neuronal mem-
brane properties, including membrane resistance and
threshold for action potential initiation or action poten-
tial configuration (Ganong et al., 1983; Herrling, 1985; A brane properties, including membrane resistance and
threshold for action potential initiation or action poten-
tial configuration (Ganong et al., 1983; Herrling, 1985;
Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewi thereshold for action potential initiation or action potential configuration (Ganong et al., 1983; Herrling, 1985; A

Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewis celet al., 1989), even at concentrations several tial configuration (Ganong et al., 1983; Herrling, 1985; A
Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewis cet al., 1989), even at concentrations severalfold higher a
than those that are effective in blocking excit

et al., 1989), even at concentrations severalfold higher and
than those that are effective in blocking excitatory amino of
acid receptors. the
2. Kynurenic acid and kainate receptors. Although po
much experimental emphasis than those that are effective in blocking excitatory amino
acid receptors.
2. Kynurenic acid and kainate receptors. Although
much experimental emphasis has been placed on the
interaction of kynurenate with the NMDA recepto acid receptors. the complements of the section of kynurenic acid and kainate receptors. Although potention of kynurenate with the NMDA receptors, model interesting data have also been produced on other amino acid receptors 2. Kynurenic acid and kainate receptors. Although
much experimental emphasis has been placed on the
interaction of kynurenate with the NMDA receptors,
interesting data have also been produced on other amino
acid receptors. much experimental emphasis has been placed on the exitent exitent interaction of kynurenate with the NMDA receptors, mether interesting data have also been produced on other amino
acid receptors. In many regions of the CNS interaction of kynurenate with the NMDA receptors, m
interesting data have also been produced on other amino
acid receptors. In many regions of the CNS, responses on
to kainate and quisqualate are relatively resistant to t interesting data have also been produced on other amino
acid receptors. In many regions of the CNS, responses or insensitivity to kynurenate might help distinguish
to kainate and quisqualate are relatively resistant to the acid receptors. In many regions of the CNS, responses or
to kainate and quisqualate are relatively resistant to the ph
attentions of kynurenate. One of the areas in which this me
is particularly noticeable is at CA3 neuron to kainate and quisqualate are relatively resistant to the phattentions of kynurenate. One of the areas in which this measure is particularly noticeable is at CA3 reurones in the cate hippocampus, where both kainate and qu attentions of kynurenate. One of the areas in which this
is particularly noticeable is at CA3 neurones in the
hippocampus, where both kainate and quisqualate are
virtually insensitive to kynurenate. The CA3 region is
pecul is particularly noticeable is at CA3 neurones in the cate
hippocampus, where both kainate and quisqualate are A
virtually insensitive to kynurenate. The CA3 region is Rai
peculiar for its exceptionally high density of kain hippocampus, where both kainate and quisqualate are An invirtually insensitive to kynurenate. The CA3 region is Raigorn peculiar for its exceptionally high density of kainate Four divergentors, many of which are believed t virtually insensitive to kynurenate. The CA3 region is Raiffeculiar for its exceptionally high density of kainate For
receptors, many of which are believed to be located on ing
the synaptic terminals of mossy fibres projec peculiar for its exceptionally high density of kainate Freceptors, many of which are believed to be located on ir
the synaptic terminals of mossy fibres projecting from at
the dentate gyrus. It is probably this feature of receptors, many of which are believed to be located on ing
the synaptic terminals of mossy fibres projecting from add
the dentate gyrus. It is probably this feature of the CA3 aci
region that also confers the extraordinary the synaptic terminals of mossy fibres projecting from
the dentate gyrus. It is probably this feature of the CA3
region that also confers the extraordinary sensitivity of
athe postsynaptic neurones to locally applied kaina the dentate gyrus. It is probably this feature of the CA3
region that also confers the extraordinary sensitivity of
the postsynaptic neurones to locally applied kainate (de
Montigny and Tardif, 1981). If the mossy fibre pr region that also confers the extraordinary sensitivity of ant
the postsynaptic neurones to locally applied kainate (de
Montigny and Tardif, 1981). If the mossy fibre projection the
is destroyed by lesioning with colchicine the postsynaptic neurones to locally applied kainate (decloses to Montigny and Tardif, 1981). If the mossy fibre projection the neuron is destroyed by lesioning with colchicine, then the sen-
sitivity to kainate declines t Montigny and Tardif, 1981). If the mossy fibre project
is destroyed by lesioning with colchicine, then the s
sitivity to kainate declines to a level comparable w
that of CA1 neurones. In addition, kynurenate can r
block re is destroyed by lesioning with colchicine, then the sen-
sitivity to kainate declines to a level comparable with
could suppress NMDA-induced biting and that γ -L-glu-
that of CA1 neurones. In addition, kynurenate can no sitivity to kainate declines to a level comparable with that of CA1 neurones. In addition, kynurenate can no
block responses to kainate, although actions of quisque
ate remain unimpressed (Stone, 1990). These resu
strongly that of CA1 neurones. In addition, kynurenate can now tand block responses to kainate, although actions of quisqual-
ate remain unimpressed (Stone, 1990). These results eff
strongly suggest that kynurenate may be able to d block responses to kainate, although actions of quisqual-
ate remain unimpressed (Stone, 1990). These results et
strongly suggest that kynurenate may be able to distin-
guish between two subtypes of receptor for kainate, o ate remain unimpressed (Stone, 1990). These results
strongly suggest that kynurenate may be able to distin-
guish between two subtypes of receptor for kainate, one
group located on the postsynaptic CA3 pyramidal cells
and strongly suggest that kynurenate may be able to distinguish between two subtypes of receptor for kainate, or group located on the postsynaptic CA3 pyramidal cel and sensitive to kynurenate and the second population located guish between two sub
group located on the pand sensitive to kynum
located on mossy fibre
renate (Stone, 1990).
Evans et al. (1987) and sensitive to kynurenate and the second population
located on mossy fibre terminals and resistant to kynu-
renate (Stone, 1990).
Evans et al. (1987) analysed the effect of kynurenate

YNURENIC ACIDS 331
both on cord motoneurones and on C fibre afferents. The $K_{\rm d}$ of kynurenate was significantly different at these two **XNURENIC ACIDS** 331

both on cord motoneurones and on C fibre afferents. The
 K_d of kynurenate was significantly different at these two

sites, suggesting that different receptors may be involved. Similarly vertex supports and that different at these two being that different receptors may be involved.
In the same study, kynurenate was a more potent antised.
In the same study, kynurenate was a more potent antised. both on cord motoneurones and on C fibre afferents. T
 K_d of kynurenate was significantly different at these t
sites, suggesting that different receptors may be involve
In the same study, kynurenate was a more potent ant K_d of kynurenate was significantly different at these two sites, suggesting that different receptors may be involved.
In the same study, kynurenate was a more potent antagonist of kainate $(K_d 164 \mu M)$ than of quisqualat *3. Suggesting that different receptors may be involved.*
 3. Kynurenate was a more potent antag-
 3. Kynurenic acid and metabotropic sites. In several
 3. Kynurenic acid and metabotropic sites. In several
 dies, r

In the same study, kynurenate was a more potent antagonist of kainate $(K_d 164 \mu M)$ than of quisqualate $(K_d 258 \mu M)$.
3. Kynurenic acid and metabotropic sites. In several studies, responses to glutamate have been found to onist of kainate $(K_d 164 \mu)$ than of quisqualate $(K_d 258 \mu)$.
3. Kynurenic acid and metabotropic sites. In several studies, responses to glutamate have been found to be
relatively insensitive to kynurenate (Ganong and Cot μ M).
3. Kynurenic acid and metabotropic sites. In several studies, responses to glutamate have been found to be relatively insensitive to kynurenate (Ganong and Cotman, 1986; Talman, 1989; Pawlowski-Dahm and Gordon, 19 3. Kynurenic acid and metabotropic sites. In several studies, responses to glutamate have been found to be relatively insensitive to kynurenate (Ganong and Cotman, 1986; Talman, 1989; Pawlowski-Dahm and Gordon, 1992), a fi studies, responses to glutamate have been found to be relatively insensitive to kynurenate (Ganong and Cotman, 1986; Talman, 1989; Pawlowski-Dahm and Gordon, 1992), a finding that may be explicable in terms of an action of relatively insensitive to kynurenate (Ganong and Cotman, 1986; Talman, 1989; Pawlowski-Dahm and Gordon, 1992), a finding that may be explicable in terms of an action of both quisqualate and glutamate at metabotropic recept man, 1986; Talman, 1989; Pawlowski-Dahm and Gordon, 1992), a finding that may be explicable in terms of an action of both quisqualate and glutamate at metabotropic receptor sites. Although these receptors are primarily rec 1992), a finding that may be explicable in terms action of both quisqualate and glutamate at metabot receptor sites. Although these receptors are prince recognised as stimulators of phosphatidylinosito drolysis, they (or a action of both quisqualate and glutamate at metabotropic
receptor sites. Although these receptors are primarily
recognised as stimulators of phosphatidylinositol hy-
drolysis, they (or a subtype) also modify electrophysio receptor sites. Although these receptors are primarily
recognised as stimulators of phosphatidylinositol hy-
drolysis, they (or a subtype) also modify electrophysio-
logical activity by mediating slow changes of potassium
 recognised as stimulators of phosphatidylinositol hydrolysis, they (or a subtype) also modify electrophysiological activity by mediating slow changes of potassium conductance and, thus, late components of synaptic transmis drolysis, they (or a subtype) also modify electrophysio-
logical activity by mediating slow changes of potassium
conductance and, thus, late components of synaptic
transmission (Stone, 1992). They are, however, resistant
t conductance and, thus, late components of synaptic transmission (Stone, 1992). They are, however, resistant to kynurenate in some CNS areas (Desai and Conn, 1990; Salt and Eaton, 1991).

drolysis, they (or a subtype) also modify electrophysio-
logical activity by mediating slow changes of potassium
conductance and, thus, late components of synaptic
cransmission (Stone, 1992). They are, however, resistant
 transmission (Stone, 1992). They are, however, resistant
to kynurenate in some CNS areas (Desai and Conn,
1990; Salt and Eaton, 1991).
Before its emergence as a selective ligand for the
metabotropic glutamate receptor, the to kynurenate in some CNS areas (Desai and Con.
1990; Salt and Eaton, 1991).
Before its emergence as a selective ligand for the
metabotropic glutamate receptor, the pharmacology (ACPD was examined by Curry et al. (1987) us 1990; Salt and Eaton, 1991).
Before its emergence as a selective ligand for the
metabotropic glutamate receptor, the pharmacology of
ACPD was examined by Curry et al. (1987) using intra-
cellular recordings from CA1 pyrami Before its emergence as a selective ligand for the
metabotropic glutamate receptor, the pharmacology of
ACPD was examined by Curry et al. (1987) using intra-
cellular recordings from CA1 pyramidal cells. Both $(+)$ -
and $($ metabotropic glutamate receptor, the pharmacology of
ACPD was examined by Curry et al. (1987) using intra-
cellular recordings from CA1 pyramidal cells. Both (+)-
and (-)-isomers of ACPD were found to induce a pattern
of m ACPD was examined by Curry et al. (1987) using intra-
cellular recordings from CA1 pyramidal cells. Both $(+)$ -
and $(-)$ -isomers of ACPD were found to induce a pattern
of maintained firing to that seen with kainate and unl cellular recordings from CA1 pyramidal cells. Both (+)-
and (-)-isomers of ACPD were found to induce a pattern
of maintained firing to that seen with kainate and unlike
the rhythmic burst firing obtained with NMDA. In supand $(-)$ -isomers of ACPD were found to induce a pattern
of maintained firing to that seen with kainate and unlike
the rhythmic burst firing obtained with NMDA. In sup-
port of this, $2AP5$ had no effect on ACPD or kainate
 of maintained fir
the rhythmic bu
port of this, 2A
excitation, but k
mers of ACPD.
It is clearly ar port of this, 2AP5 had no effect on ACPD or kainate excitation, but kynurenate blocked kainate and the isomers of ACPD.

port of this, 2AP5 had no effect on ACPD or kainate excitation, but kynurenate blocked kainate and the isomers of ACPD.
It is clearly an exciting possibility that the sensitivity or insensitivity to kynurenate might help d excitation, but kynurenate blocked kainate and the isomers of ACPD.
It is clearly an exciting possibility that the sensitivity
or insensitivity to kynurenate might help distinguish
pharmacologically between two excitatory mers of ACPD.
It is clearly an exciting possibility that the sensitivity
or insensitivity to kynurenate might help distinguish
pharmacologically between two excitatory subtypes of
metabotropic receptor, most probably diffe It is clearly an exciting possibility that the sens
or insensitivity to kynurenate might help distin
pharmacologically between two excitatory subty
metabotropic receptor, most probably differentia
cated in spinal cord and insensitivity to kynurenate might help distinguish
armacologically between two excitatory subtypes of
etabotropic receptor, most probably differentially lo-
ted in spinal cord and diencephalon respectively.
An intriguing

pharmacologically between two excitatory subtypes of
metabotropic receptor, most probably differentially lo-
cated in spinal cord and diencephalon respectively.
An intriguing set of observations was reported by
Raigorodsky metabotropic receptor, most probably differentially cated in spinal cord and diencephalon respectively.
An intriguing set of observations was reported
Raigorodsky and Urca (1990) in the mouse spinal co
Four different excit cated in spinal cord and diencephalon respectively.

An intriguing set of observations was reported by

Raigorodsky and Urca (1990) in the mouse spinal cord.

Four different excitatory amino acid antagonists, includ-

ing An intriguing set of observations was reported by
Raigorodsky and Urca (1990) in the mouse spinal cord.
Four different excitatory amino acid antagonists, includ-
ing 2AP5, kynurenate, and γ -L-glutamylglycine, were
admi Raigorodsky and Urca (1990) in the mouse spinal cord.
Four different excitatory amino acid antagonists, including 2AP5, kynurenate, and γ -L-glutamylglycine, were administered intrathecally, and their effects on amino a ing 2AP5, kynurenate, and γ -L-glutamylglycine, were administered intrathecally, and their effects on amino acid-induced biting were determined. Since all of these antagonists prevented NMDA-induced bites at the same do ing 2AP5, kynurenate, and γ -L-glutamylglycine, were administered intrathecally, and their effects on amino acid-induced biting were determined. Since all of these antagonists prevented NMDA-induced bites at the same do administered intrathecally, and their effects on amino
acid-induced biting were determined. Since all of these
antagonists prevented NMDA-induced bites at the same
doses that produced antinociception, the results favoured
 acid-induced biting were determined. Since all of these
antagonists prevented NMDA-induced bites at the same
doses that produced antinociception, the results favoured
the need for NMDA receptors in pain sensitivity. In
ad antagonists prevented NMDA-induced bites at the sandoses that produced antinociception, the results favoure
the need for NMDA receptors in pain sensitivity. And is addition, however, the authors noted that quisquala
could doses that produced antinociception, the results favoured
the need for NMDA receptors in pain sensitivity. In
addition, however, the authors noted that quisqualate
could suppress NMDA-induced biting and that γ -L-glu-
t addition, however, the authors noted that quisqualate addition, however, the authors noted that quisqualat could suppress NMDA-induced biting and that γ -L-glu tamylglycine was less effective as an antinociceptive than 2AP5 at doses producing comparable blockade of NMD/eff could suppress NMDA-induced biting and that γ -L-glutamylglycine was less effective as an antinociceptive that 2AP5 at doses producing comparable blockade of NMD.
effects, whereas kynurenate showed no such discrepancy.
 tamylglycine was less effective as an antinociceptive the 2AP5 at doses producing comparable blockade of NM effects, whereas kynurenate showed no such discreparables preferentially with a subpoputamylglycine interacts pre 2AP5 at doses producing comparable blockade of NMDA effects, whereas kynurenate showed no such discrepancy.
Based on these findings, the authors suggested that γ -L-glutamylglycine interacts preferentially with a subpop effects, whereas kynurenate showed no such discrepared as Based on these findings, the authors suggested that γ glutamylglycine interacts preferentially with a subpolation of quisqualate sites able to modulate NMDA sit Based on these findings, the authors suggested that γ -L-
glutamylglycine interacts preferentially with a subpopu-
lation of quisqualate sites able to modulate NMDA sen-
sitivity. Kynurenate would then be regarded as no glutamylglycine interacts preferentially with a subpopulation of quisqualate sites able to modulate NMDA sensitivity. Kynurenate would then be regarded as nonselective for any quisqualate receptor subtype. This is an inter lation of quisqualate sites ab
sitivity. Kynurenate would the
tive for any quisqualate ree
interesting proposal that cou
or autoradiographic studies.

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4. *Kynurenic acid and synaptic transmission.* Since the STON:
4. Kynurenic acid and synaptic transmission. Since the
recognition that kynurenate was able to block most types
of amino acid receptors on many cells at appropriate d sro
4. Kynurenic acid and synaptic transmission. Since the
recognition that kynurenate was able to block most types
of amino acid receptors on many cells at appropriate
concentrations, it has become a popular antagonist be 4. Kynurenic acid and synaptic transmission. Since the recognition that kynurenate was able to block most types of amino acid receptors on many cells at appropriate concentrations, it has become a popular antagonist be-cau 4. Kynurenic acid and synaptic transmission. Since the recognition that kynurenate was able to block most typ of amino acid receptors on many cells at appropriation concentrations, it has become a popular antagonist leause recognition that kynurenate was able to block most types
of amino acid receptors on many cells at appropriate
concentrations, it has become a popular antagonist be-
cause of its ease of use, efficacy, and inexpensiveness.
 of amino acid receptors on many cells at appropriate
concentrations, it has become a popular antagonist be-
cause of its ease of use, efficacy, and inexpensiveness.
Although it would be impracticable to list the hundreds
o concentrations, it has become a popular antagonist be-
cause of its ease of use, efficacy, and inexpensiveness. to e
Although it would be impracticable to list the hundreds the
of research reports of studies using kynurena cause of its ease of use, efficacy, and inexpensiveness.
Although it would be impracticable to list the hundreds
of research reports of studies using kynurenate, the fol-
lowing compilation encompasses a number of studies

of research reports of studies using kynurenate, the fol-
lowing compilation encompasses a number of studies in
which kynurenate helped to yield new insights or ideas.
a. SPINAL CORD. The demonstration that kynurenic ph
ac lowing compilation encompasses a number of studies in act which kynurenate helped to yield new insights or ideas. two a. SPINAL CORD. The demonstration that kynurenic phacid was an amino acid antagonist led naturally to it which kynurenate helped to yield new insights or ideas. two
a. SPINAL CORD. The demonstration that kynurenic pha
acid was an amino acid antagonist led naturally to its dep
testing as a blocker of synaptic transmission. An a. SPINAL CORD. The demonstration that kynurenic pha
acid was an amino acid antagonist led naturally to its dep
testing as a blocker of synaptic transmission. An early relie
such report was of the blockade of monosynaptic acid was an amino acid antagonist led naturally to its cordination of the blockade of monosynaptic and polysynaptic potentials recorded from ventral roots in cominescted spinal cords from neonatal rats (Ganong et Sal., 19 testing as a blocker of synaptic transmission. An early resuch report was of the blockade of monosynaptic and nolysynaptic potentials recorded from ventral roots in definisected spinal cords from neonatal rats (Ganong et polysynaptic potentials recorded from ventral roots in
hemisected spinal cords from neonatal rats (Ganong et
al., 1983). Kynurenate (100 μ M) was very effective in this
preparation and reduced the potentials by 50%.
The hemisected spinal cords from neonatal rats (Ganong et

al., 1983). Kynurenate (100 μ M) was very effective in this preparation and reduced the potentials by 50%.
The specificity of kynurenate's antagonistic properties bon transmission, sometimes in doubt because of the very preparation and reduced the potentials by 50%. Since The specificity of kynurenate's antagonistic properties but
on transmission, sometimes in doubt because of the very to 1
high proportion of synapses that seem to use exc The specificity of kynurenate's antagonistic properties
on transmission, sometimes in doubt because of the very
high proportion of synapses that seem to use excitatory
amino acid transmitters, was nicely demonstrated in a
 on transmission, sometimes in doubt because of the very
high proportion of synapses that seem to use excitatory
amino acid transmitters, was nicely demonstrated in a
comparison of the ventral root responses to dorsal root
 high proportion of synapses that seem to use excitatory
amino acid transmitters, was nicely demonstrated in a
comparison of the ventral root responses to dorsal root
stimulation with the dorsal root response to ventral ro amino acid transmitters, was nicely demonstrated in a onto
comparison of the ventral root responses to dorsal root NM
stimulation with the dorsal root response to ventral root pres
stimulation in frog spinal cord (Elmslie comparison of the ventral root responses to dorsal root NM
stimulation with the dorsal root response to ventral root pre
stimulation in frog spinal cord (Elmslie and Yoshikami, syn
1985). At 500 μ M, kynurenate blocked stimulation with the dorsal root response to ventral root
stimulation in frog spinal cord (Elmslie and Yoshikami,
1985). At 500 μ M, kynurenate blocked the former by
>90% without affecting action potential profiles but stimulation in frog spinal cord (Elmslie and Yoshikami, 1985). At 500 μ M, kynurenate blocked the former by $>90\%$ without affecting action potential profiles but had no effect in the second paradigm, even at 2.5 mM. A 1985). At 500 μ M, kynurenate blocked the former by $>90\%$ without affecting action potential profiles but had no effect in the second paradigm, even at 2.5 mM. At effective doses, kynurenate also blocked ventral root >90% without affecting action potential profiles but had cord.
no effect in the second paradigm, even at 2.5 mM. At ulation
effective doses, kynurenate also blocked ventral root the responses to all amino acid agonists, NM no effect in the second paradigm, even at 2.5 mM. A effective doses, kynurenate also blocked ventral roo responses to all amino acid agonists, NMDA, kainate quisqualate, aspartate, and glutamate, although NMD/was in gener effective doses, kynurenate also blocked ventral root responses to all amino acid agonists, NMDA, kainate, quisqualate, aspartate, and glutamate, although NMDA was in general more susceptible to blockade than quisqualate. responses to all amino acid agonists, NMDA, kainate, quisqualate, aspartate, and glutamate, although NMDA was in general more susceptible to blockade than quisqualate. At lower concentrations, approximately 100μ M, some quisqualate, aspartate, and glutamate, a
was in general more susceptible to bloc!
qualate. At lower concentrations, approx
some enhancement of responses to quis
corded (Elmslie and Yoshikami, 1985).
The early epsp evoked i is in general more susceptible to blockade than quis-
alate. At lower concentrations, approximately 100μ M,
me enhancement of responses to quisqualate was re-
rded (Elmslie and Yoshikami, 1985).
The early epsp evoked in qualate. At lower concentrations, approximately 100μ M, some enhancement of responses to quisqualate was recorded (Elmslie and Yoshikami, 1985).
The early epsp evoked in motor neurones of the rat neonatal spinal cord in

some enhancement of responses to quisqualate was recorded (Elmslie and Yoshikami, 1985). We was the early epsp evoked in motor neurones of the rat can neonatal spinal cord in vitro in response to low-intensity lyistimulati corded (Elmslie and Yoshikami, 1985). We
The early epsp evoked in motor neurones of the rat
neonatal spinal cord in vitro in response to low-intensity ly
stimulation of Ia afferent nerves was unaffected by 2AP5 pl
but bloc The early epsp evoked in motor neurones of the rat
neonatal spinal cord in vitro in response to low-intensity
stimulation of Ia afferent nerves was unaffected by 2AP5
but blocked by kynurenate. The same concentration of
ky neonatal spinal cord in vitro in response to low-intensity lyist
imulation of Ia afferent nerves was unaffected by 2AP5 plication blocked by kynurenate. The same concentration of tain
kynurenate blocked sensitivity to glut stimulation of Ia afferent nerves was unaffected by 2AP5
but blocked by kynurenate. The same concentration of
kynurenate blocked sensitivity to glutamate but not car-
bachol (Jahr and Yoshioka, 1986) and did not modify
ven but blocked by kynurenate. The same concentration of tainty as to the effective concentration achieved at the kynurenate blocked sensitivity to glutamate but not car-
heuronal surface, although in the same experiments no b kynurenate blocked sensitivity to glutamate but not obachol (Jahr and Yoshioka, 1986) and did not moventral root-evoked responses in the motor neuro:
This confirmed the selectivity of the synaptic block to those sites at w bachol (Jahr and Yoshioka, 1986) and did not modify characterized responses in the motor neurones. duce
This confirmed the selectivity of the synaptic blockade and
to those sites at which glutamate, rather than acetylcho ventral root-evoked responses in the motor neurone
This confirmed the selectivity of the synaptic blockad
to those sites at which glutamate, rather than acetylch
line, is believed to be the transmitter and helped
exclude a renate. exclude a general presynaptic inhibitory action of kynu-
renate.
Perfusion of the central canal of the cat spinal cord in In more recent work, Cherubini et al. (1988a) used
Perfusion of the central canal of the cat spinal

line, is believed to be the transmitter and helped to exclude a general presynaptic inhibitory action of kynurenate.
Perfusion of the central canal of the cat spinal cord in situ was developed as a means of delivering kynu exclude a general presynaptic inhibitory action of kynu-
renate.
Perfusion of the central canal of the cat spinal cord in
situ was developed as a means of delivering kynurenate
to the cord and simultaneously stimulating af renate.

Perfusion of the central canal of the cat spinal cord

situ was developed as a means of delivering kynurent

to the cord and simultaneously stimulating afferent

puts (Walmsley and Nicol, 1991). Intracellular reco Perfusion of the central canal of the cat spinal cord
situ was developed as a means of delivering kynurena
to the cord and simultaneously stimulating afferent i
puts (Walmsley and Nicol, 1991). Intracellular recor
ings wer situ was developed as a means of delivering kynurenat
to the cord and simultaneously stimulating afferent in
puts (Walmsley and Nicol, 1991). Intracellular record
ings were made of monosynaptic epsps in dorsal spinc
cerebe to the cord and simultaneously stimulating afferent in-
puts (Walmsley and Nicol, 1991). Intracellular record-
ings were made of monosynaptic epsps in dorsal spino-
nerebellar tract neurones evoked by stimulation of hind-
 puts (Walmskings were madeler
tracerebellar tracerebellar
himb muscle no
by kynurenate
Jahr and Jes gs were made of monosynaptic epsps in dorsal spino-
rebellar tract neurones evoked by stimulation of hind-
nb muscle nerves. The epsps could be totally abolished
that monosynaptic epsps
shahr and Jessell (1985) found that cerebellar tract neurones evoked by stimulation of hind-
limb muscle nerves. The epsps could be totally abolished
by kynurenate.
Jahr and Jessell (1985) found that monosynaptic epsps
recorded in cultured dorsal horn neuron

NE
mation of synaptic contacts from dorsal root ganglion
cells were sensitive to kynurenate. The excitation of NE
mation of synaptic contacts from dorsal root ganglion
cells were sensitive to kynurenate. The excitation of
dorsal horn neurones by glutamate, kainate, and quis-NE
mation of synaptic contacts from dorsal root ganglior
cells were sensitive to kynurenate. The excitation of
dorsal horn neurones by glutamate, kainate, and quis-
qualate was also blocked. In contrast, NMDA was unable mation of synaptic contacts from dorsal root ganglion
cells were sensitive to kynurenate. The excitation of
dorsal horn neurones by glutamate, kainate, and quis-
qualate was also blocked. In contrast, NMDA was unable
to ex mation of synaptic contacts from dorsal root ganglion
cells were sensitive to kynurenate. The excitation of
dorsal horn neurones by glutamate, kainate, and quis-
qualate was also blocked. In contrast, NMDA was unable
to ex cells were sensitive to kynurenate. The excit
dorsal horn neurones by glutamate, kainate, a
qualate was also blocked. In contrast, NMDA was
to excite the dorsal horn cells, and 2AP5 did no
the epsps or sensitivity to exoge rsal horn neurones by glutamate, kainate, and quis-
alate was also blocked. In contrast, NMDA was unable
excite the dorsal horn cells, and 2AP5 did not modify
e epsps or sensitivity to exogenous glutamate.
In the spinal co

hemisected spinal cords from neonatal rats (Ganong et Sillar and Roberts (1991) have now shown that this same
al., 1983). Kynurenate (100 μ M) was very effective in this pattern exists in the spinal cord of *Xenopus* em qualate was also blocked. In contrast, NMDA was unable
to excite the dorsal horn cells, and 2AP5 did not modify
the epsps or sensitivity to exogenous glutamate.
In the spinal cord, as in most regions of the CNS, the
activa to excite the dorsal horn cells, and 2AP5 did not modify
the epsps or sensitivity to exogenous glutamate.
In the spinal cord, as in most regions of the CNS, the
activation of amino acid-releasing synapses results in
two-co the epsps or sensitivity to exogenous glutamate.
In the spinal cord, as in most regions of the CNS, the
activation of amino acid-releasing synapses results in
two-component synaptic potentials, including an early
phase med In the spinal cord, as in most regions of the CNS, the activation of amino acid-releasing synapses results in two-component synaptic potentials, including an early phase mediated by non-NMDA receptors. The resulting depola activation of amino acid-releasing synapses results in
two-component synaptic potentials, including an early
phase mediated by non-NMDA receptors. The resulting
depolarisation is then presumed to provide a sufficient
relie two-component synaptic potentials, including an early
phase mediated by non-NMDA receptors. The resulting
depolarisation is then presumed to provide a sufficient
relief from the voltage-dependent blockade of ion chan-
nels phase mediated by non-NMDA receptors. The resulting
depolarisation is then presumed to provide a sufficient
relief from the voltage-dependent blockade of ion chan-
nels by magnesium to permit a late, secondary phase of
dep depolarisation is then presumed to provide a sufficient
relief from the voltage-dependent blockade of ion chan-
nels by magnesium to permit a late, secondary phase of
depolarisation mediated primarily by NMDA receptors.
Si relief from the voltage-dependent blockade of ion channels by magnesium to permit a late, secondary phase of depolarisation mediated primarily by NMDA receptors.
Sillar and Roberts (1991) have now shown that this same patt nels by magnesium to permit a late, secondary phase of
depolarisation mediated primarily by NMDA receptors.
Sillar and Roberts (1991) have now shown that this same
pattern exists in the spinal cord of *Xenopus* embryos,
si depolarisation mediated primarily by NMDA receptors.
Sillar and Roberts (1991) have now shown that this same
pattern exists in the spinal cord of *Xenopus* embryos,
since evoked epsps can be fully suppressed by kynurenate
 Sillar and Roberts (1991) have now shown that this same
pattern exists in the spinal cord of *Xenopus* embryos,
since evoked epsps can be fully suppressed by kynurenate
but only partly by 2AP5. Spontaneous potentials appea pattern exists in the spinal cord of *Xenopus* embryos, since evoked epsps can be fully suppressed by kynurenate but only partly by 2AP5. Spontaneous potentials appear to fall into either the fast or slow categories, sugge since evoked epsps can be fully suppressed by kynurenate
but only partly by 2AP5. Spontaneous potentials appear
to fall into either the fast or slow categories, suggesting
that individual synapses may release their transmi to fall into either the fast or slow categories, suggesting
that individual synapses may release their transmitter
onto receptors that are almost exclusively either of the
NMDA or the non-NMDA type; evoked epsps are thus
p Sillar and Roberts (1991) have now shown that this same
pattern exists in the spinal cord of *Xenopus* embryos,
since evoked epsps can be fully suppressed by kyuremate
but only partly by 2AP5. Spontaneous potentials appea synapses.

Kynurenate is also effective in the nonmammalian cord. In isolated CNS preparations of the lamprey, stimthe reticular formation to spinal motor neurones evokes synapses.

Kynurenate is also effective in the nonmammalian

cord. In isolated CNS preparations of the lamprey, stim-

ulation of the Muller or Mauthner cells projecting from

the reticular formation to spinal motor neuron Extreme is also effective in the nonmammalian

cord. In isolated CNS preparations of the lamprey, stim-

ulation of the Muller or Mauthner cells projecting from

the reticular formation to spinal motor neurones evokes

ep cord. In isolated CNS preparations of the lamprey, stitulation of the Muller or Mauthner cells projecting free the reticular formation to spinal motor neurones evology is in the latter which could be totally blocked kynure ulation of the Muller or Mauthner cells projecting from
the reticular formation to spinal motor neurones evokes
epsps in the latter which could be totally blocked by
kynurenate (Buchanan et al., 1987). Only a late compo-
 2AP5. sps in the latter which could be totally blocked by
nurenate (Buchanan et al., 1987). Only a late compo-
nt of the synaptic potential could be prevented by
R5.
b. BASAL GANGLIA. In anaesthetised cats, kynurenate
as found t kynurenate (Buchanan et al., 1987). Only a late component of the synaptic potential could be prevented by 2AP5.
b. BASAL GANGLIA. In anaesthetised cats, kynurenate was found to prevent the excitation of neurones in the cau

nent of the synaptic potential could be prevented b
2AP5.
b. BASAL GANGLIA. In anaesthetised cats, kynurenat
was found to prevent the excitation of neurones in th
caudate nucleus in response to stimulation of the over-
lyi 2AP5.
b. BASAL GANGLIA. In anaesthetised cats, kynurenate
was found to prevent the excitation of neurones in the
caudate nucleus in response to stimulation of the over-
lying neocortex (Herrling, 1985). Kynurenate was ap-
 plied by microiontophoresis in this study, raising uncerwas found to prevent the excitation of neurones in the caudate nucleus in response to stimulation of the over-
lying neocortex (Herrling, 1985). Kynurenate was ap-
plied by microiontophoresis in this study, raising uncer-
 caudate nucleus in response to stimulation of the over-
lying neocortex (Herrling, 1985). Kynurenate was ap-
plied by microiontophoresis in this study, raising uncer-
tainty as to the effective concentration achieved at t plied by microiontophoresis in this study, raising uncerplied by microiontophoresis in this study, raising uncertainty as to the effective concentration achieved at the neuronal surface, although in the same experiments no change of resting membrane potential or artificially in tainty as to the effective concentration achieved at the
neuronal surface, although in the same experiments no
change of resting membrane potential or artificially in-
duced action potentials was seen in the cells recorde neuronal surface, although in the same experiments no
change of resting membrane potential or artificially in-
duced action potentials was seen in the cells recorded,
and the NMDA-selective antagonist 2AP7 was found to
be change of resting membrane potential or artificially in-
duced action potentials was seen in the cells recorded,
and the NMDA-selective antagonist 2AP7 was found to
be ineffective in preventing synaptic activation. This
st duced action potentials was seen in the cells record and the NMDA-selective antagonist 2AP7 was found be ineffective in preventing synaptic activation. The strongly supported the view that non-NMDA recept were involved in and the NMDA-s
be ineffective in
strongly supporte
were involved in
triatal projection.
In more recen strongly supported the view that non-NMDA receptors

strongly supported the view that non-NMDA receptors
were involved in mediating the effects of the corticos-
triatal projection.
In more recent work, Cherubini et al. (1988a) used
local electrical stimulation in slices of r were involved in mediating the effects of the corticostriatal projection.
In more recent work, Cherubini et al. (1988a) used
local electrical stimulation in slices of rat striatum to
evoke epsps. Superfusion with kynurenat triatal projection.
In more recent work, Cherubini et al. (1988a) used
local electrical stimulation in slices of rat striatum to
evoke epsps. Superfusion with kynurenate then sup-
pressed these epsps by up to 80%, whereas In more recent work, Cherubini et al. (1988a) use
local electrical stimulation in slices of rat striatum
evoke epsps. Superfusion with kynurenate then sup
pressed these epsps by up to 80%, whereas 2AP7 an
nicotinic antagon local electrical stimulation in slices of rat striatum to evoke epsps. Superfusion with kynurenate then suppressed these epsps by up to 80%, whereas 2AP7 and micotinic antagonists had no effect, implicating a kynurenate-se evoke epsps. Superfusion with kynurenate then sup
pressed these epsps by up to 80%, whereas 2AP7 and
nicotinic antagonists had no effect, implicating a kynurenate-sensitive amino acid in neurotransmission within
the striat pressed these epsps by up to 80%, whereas 2AP7 and
nicotinic antagonists had no effect, implicating a kynu-
renate-sensitive amino acid in neurotransmission within
the striatum. Only after depolarisation or in zero mag-
ne nicotinic antagonists had no effect, implicating a kynu-
renate-sensitive amino acid in neurotransmission within
the striatum. Only after depolarisation or in zero mag-
nesium did 2AP7 cause reduction. Similar results were the striatum. Only after depolarisation or in zero magnesium did 2AP7 cause reduction. Similar results were seen by Walsh et al. (1989). Calabresi et al. (1991) used a rat corticostriatal slice preparation to show that kyn

REVIEWS PHARMACOLOGICAL primate, the commo
1984). Across this ran
urenate is remarkabl
rability of amino aci
across these species.
Robinson et al. (19

QUINOLINIC AND KYNU
urenate would reduce corticostriatally evoked epsps by
up to 88%. Although this clearly stands comparison with sugg QUINOLINIC AND KYN
urenate would reduce corticostriatally evoked epsps by
up to 88%. Although this clearly stands comparison with
Cherubini et al. (1988a), it is perhaps surprising that ant QUINOLINIC AND K

urenate would reduce corticostriatally evoked epsps by

up to 88%. Although this clearly stands comparison with

Cherubini et al. (1988a), it is perhaps surprising that

intrastriatally elicited potential urenate would reduce corticostriatally evoked epsps by red
up to 88%. Although this clearly stands comparison with sug
Cherubini et al. (1988a), it is perhaps surprising that anti
intrastriatally elicited potentials were r 48%.

Cherubini et al. (1988a), it is perhaps surprising that
intrastriatally elicited potentials were reduced by only
48%.
c. HIPPOCAMPUS. Excitation of several of the major
afferent pathways into the hippocampal formation prointrastriatally elicited potentials were reduced by only that are susceptible to block are susceptible to blockade by kynurenate. These pathways include the lateral per-48%.

c. HIPPOCAMPUS. Excitation of several of the major

afferent pathways into the hippocampal formation pro-

duce synaptic potentials that are susceptible to blockade

by kynurenate. These pathways include the lateral c. HIPPOCAMPUS. Excitation of several of the may afferent pathways into the hippocampal formation piduce synaptic potentials that are susceptible to blocks by kynurenate. These pathways include the lateral potent path to t afferent pathways into the hippocampal formation pro-
duce synaptic potentials that are susceptible to blockade
by kynurenate. These pathways include the lateral per-
forant path to the dentate gyrus, the mossy fibre proje duce synaptic potentials that are susceptible to blockad
by kynurenate. These pathways include the lateral pe
forant path to the dentate gyrus, the mossy fibre proje
tion to CA3 pyramidal cells, and the Schaeffer collatera by kynurenate. These pathways include the lateral perstrant path to the dentate gyrus, the mossy fibre projec-
forant path to the dentate gyrus, the mossy fibre projec-
ion to CA3 pyramidal cells, and the Schaeffer collate forant path to the dentate gyrus, the mossy fibre projec-
tion to CA3 pyramidal cells, and the Schaeffer collateral/
commissural pathways traveling to the CA1 region (Gan-
ong et al., 1983; Harris and Cotman, 1985; Stone tion to CA3 pyramidal cells, and the Schaeffer collateral/
commissural pathways traveling to the CA1 region (Gan-
ong et al., 1983; Harris and Cotman, 1985; Stone and
Perkins, 1984). The potency of kynurenic acid is quite commissural pathways traveling to the CA1 region (Gas ong et al., 1983; Harris and Cotman, 1985; Stone are Perkins, 1984). The potency of kynurenic acid is qui consistent in these pathways with an ED_{50} of approx mately ong et al., 1983; Harris and Cotman, 1985; Stone and
Perkins, 1984). The potency of kynurenic acid is quite
consistent in these pathways with an ED_{50} of approxi-
mately 500 μ M. The blockade of transmission by kynu-
 consistent in these pathways with an ED_{50} of approximately 500 μ M. The blockade of transmission by kynurenate is not accompanied by any changes of membrane properties of CA1 pyramidal neurones; neither membrane pote consistent in these pathways with an ED_{50} of approxi-
mately 500 μ M. The blockade of transmission by kynu-
renate is not accompanied by any changes of membrane at t
properties of CA1 pyramidal neurones; neither memmately 500 μ M. The blockade of transmission by kynu-
renate is not accompanied by any changes of membrane at t
properties of CA1 pyramidal neurones; neither mem-
mechane potential nor input resistance were modified by renate is not accompanied by any changes of membrane aproperties of CA1 pyramidal neurones; neither mem-
brane potential nor input resistance were modified by reported intophoretically applied kynurenate. This ability to l properties of CA1 pyramidal neurones; neither mem-
brane potential nor input resistance were modified by
incomplomentially applied kynurenate. This ability to lon
block hippocampal transmission has now been reported unc
ac brane potential nor input resistance were modified by
iontophoretically applied kynurenate. This ability to
block hippocampal transmission has now been reported
across a wide range of species ranging from mice to a
primate iontophoretically applied kynurenate. This ability to block hippocampal transmission has now been reported across a wide range of species ranging from mice to aprimate, the common marmoset (Stone and Perkins 1984). Across block hippocampal transmission has now been report
across a wide range of species ranging from mice to
primate, the common marmoset (Stone and Perki
1984). Across this range, the inhibitory potency of ky
urenate is remarka across a wide range of species ranging from mice to a
primate, the common marmoset (Stone and Perkins,
1984). Across this range, the inhibitory potency of kyn-
urenate is remarkably constant and suggests a compa-
rability 84). Across this range, the inhibitory potency of kynemate is remarkably constant and suggests a compability of amino acid receptors for neurotransmission ross these species.
Robinson et al. (1984) used several different e urenate is remarkably constant and suggests a com
rability of amino acid receptors for neurotransmiss
across these species.
Robinson et al. (1984) used several different electr
placements in the hippocampus to reveal that

rability of amino acid receptors for neurotransmission
across these species.
Robinson et al. (1984) used several different electrode
placements in the hippocampus to reveal that kynuren-
ate exhibits marked variations of p across these species.
Robinson et al. (1984) used several different electrode
placements in the hippocampus to reveal that kynuren-
ate exhibits marked variations of pharmacology in dif-
ferent regions of the tissue. They Robinson et al. (1984) used several different electrode
placements in the hippocampus to reveal that kynuren-
ate exhibits marked variations of pharmacology in dif-
ferent regions of the tissue. They reported, for example placements in the hippocampus to reveal that kynurenate exhibits marked variations of pharmacology in different regions of the tissue. They reported, for example, that neurotransmission to the CA1 neurones was blocked by ate exhibits marked variations of pharmacology in different regions of the tissue. They reported, for example, that neurotransmission to the CA1 neurones was blocked by kynurenate with an IC₅₀ of 365 μ M, whereas the ferent regions of the tissue. They reported, for example,
that neurotransmission to the CA1 neurones was blocked
by kynurenate with an IC₅₀ of 365 μ M, whereas the medial
and lateral perforant paths to the dentate gyr that neurotransmission to the CA1 neurones was blocked
by kynurenate with an IC₅₀ of 365 μ M, whereas the medial
and lateral perforant paths to the dentate gyrus granule
cells were blocked with IC₅₀ values of 280 an and lateral perforant paths to the dentate gyrus granule cells were blocked with IC_{50} values of 280 and 130 μ M, respectively, potencies that are significantly different from that demonstrated in the CA1 region. In c cells were blocked with IC_{50} values of 280 and 130 μ M, are respectively, potencies that are significantly different components. That fraction of measured into two distinct components. That fraction of measured into respectively, potencies that are significantly different cell
from that demonstrated in the CA1 region. In contrast, car
the mossy fibre input to the CA3 pyramids could be
resolved into two distinct components. That fracti the mossy fibre input to the CA3 pyramids could be resolved into two distinct components. That fraction of the input that traveled to the stratum radiatum of CA3 was sensitive to kynurenate, acting with a potency comparabl the mossy fibre input to the CA3 pyramids resolved into two distinct components. That friest the input that traveled to the stratum radiatum was sensitive to kynurenate, acting with a poten parable to that experienced in t

With recording electrodes nearer to the CA3 pyramidal the input that traveled to the stratum radiatum of CA3 was sensitive to kynurenate, acting with a potency comparable to that experienced in the CA1 region.
With recording electrodes nearer to the CA3 pyramidal cell layer, was sensitive to kynurenate, acting with a potency com-
parable to that experienced in the CA1 region.
With recording electrodes nearer to the CA3 pyramidal
cell layer, in stratum lucidum, the synaptic potentials
were foun parable to that experienced in the CA1 region. simple with recording electrodes nearer to the CA3 pyramidal neu cell layer, in stratum lucidum, the synaptic potentials rece were found to be insensitive to kynurenate even a With recording electrodes nearer to the CA3 pyramida
cell layer, in stratum lucidum, the synaptic potentials
were found to be insensitive to kynurenate even at con
centrations as high as 10 mM, but this sensitivity to
kynu cell layer, in stratum lucidum, the synaptic potentials red were found to be insensitive to kynurenate even at concentrations as high as 10 mM, but this sensitivity to relay
hurrenate was strongly dependent on the precise were found to be insensitive to kynurenate even at concentrations as high as 10 mM, but this sensitivity to relay
kynurenate was strongly dependent on the precise loca-
tion of the stimulating electrode within or outside o centrations as high as 10 mM, but this sensitivity to kynurenate was strongly dependent on the precise location of the stimulating electrode within or outside of the hilus region of the dentate gyrus. This may explain the kynurenate was strongly dependent on the precise location of the stimulating electrode within or outside of the hilus region of the dentate gyrus. This may explain the difference between the report of Robinson et al. (1984 tion of the stimulating electrode within or outside of the more superficial layers II and III, as well as those in the hilus region of the dentate gyrus. This may explain the deeper parts of layer VI, showed little respons hilus region of the dentate a
difference between the repo
and that of Ganong et al.
responses in both stratum raa
were sensitive to kynurenate
Spontaneous miniature e fference between the report of Robinson et al. (1984)
d that of Ganong et al. (1983), who reported that
sponses in both stratum radiatum and stratum lucidum
re sensitive to kynurenate.
Spontaneous miniature epsps recorded

et al., 1986). The mean amplitude of these potentials was

up to 88%. Although this clearly stands comparison with suggesting a purely postsynaptic site of action of the
Cherubini et al. (1988a), it is perhaps surprising that antagonist. At comparable doses, kynurenate was shown
i quinolinic and kynurenic acids
evoked epsps by reduced by kynurenate with no change in frequency, SUPER TREST TREAD TRIMURE SUPPOSE METHOD SUPPOSE THE SUPERENT CONSERVED SUPPOSE SUPPOSE THE ALGONISH TRIMUS AT A comparable doses, kynurenate was shown 333
reduced by kynurenate with no change in frequency,
suggesting a purely postsynaptic site of action of the
antagonist. At comparable doses, kynurenate was shown
to block transmission from the mossy fibres onto CA3 reduced by kynurenate with no change in frequency, suggesting a purely postsynaptic site of action of the antagonist. At comparable doses, kynurenate was shown to block transmission from the mossy fibres onto CA3 cells. cells.

Only one report has appeared of the differential activity of kynurenate on the Schaffer collateral and commissural components of the CA1 afferent fibres traveling in antagonist. At comparable doses, kynurenate was shot block transmission from the mossy fibres onto C cells.
Cells. Only one report has appeared of the differential act
ity of kynurenate on the Schaffer collateral and comm
 to block transmission from the mossy fibres onto CA3
cells.
Only one report has appeared of the differential activ-
ity of kynurenate on the Schaffer collateral and commis-
sural components of the CA1 afferent fibres trave cells.

Only one report has appeared of the differential activ-

ity of kynurenate on the Schaffer collateral and commis-

sural components of the CA1 afferent fibres traveling in

stratum radiatum. This study was performe Only one report has appeared of the differential activity of kynurenate on the Schaffer collateral and commissural components of the CA1 afferent fibres traveling in stratum radiatum. This study was performed in vivo becau ity of kynurenate on the Schaffer collateral and commissural components of the CA1 afferent fibres traveling in stratum radiatum. This study was performed in vivo because this represents the only realistic opportunity for sural components of the CA1 afferent fibres travel
stratum radiatum. This study was performed in
because this represents the only realistic opportuni
stimulating selectively the commissural fibre port
the pathway. Kynurena stratum radiatum. This study was performed in vivo
because this represents the only realistic opportunity for
stimulating selectively the commissural fibre portion of
the pathway. Kynurenate, applied by microiontopho-
resi because this represents the only realistic opportunity for
stimulating selectively the commissural fibre portion of
the pathway. Kynurenate, applied by microiontopho-
resis, effectively blocked the excitatory responses, al stimulating selectively the commissural fibre portion
the pathway. Kynurenate, applied by microiontoph
resis, effectively blocked the excitatory responses,
though doses had to be used that were not selective f
NMDA, implyi the pathway. Kynurenate, applied by microiontophoresis, effectively blocked the excitatory responses, although doses had to be used that were not selective for NMDA, implying the involvement of non-NMDA receptors (Perkins resis, effectively blocked the excitatory responses, although doses had to be used that were not selective for NMDA, implying the involvement of non-NMDA receptors (Perkins and Stone, 1985). Although disappointing at the t though doses had to be used that were not selective for NMDA, implying the involvement of non-NMDA receptors (Perkins and Stone, 1985). Although disappointing at the time, this can now be understood in terms of the mediati NMDA, implying the involvement of non-NMDA receptors (Perkins and Stone, 1985). Although disappointing
at the time, this can now be understood in terms of the
mediation of low frequency transmission by non-NMDA
receptors, tors (Perkins and Stone, 1985). Although disappointing
at the time, this can now be understood in terms of the
mediation of low frequency transmission by non-NMDA
receptors, with recruitment of NMDA receptors for
longer la at the time, this can now be understood in terms of mediation of low frequency transmission by non-NMI receptors, with recruitment of NMDA receptors longer latency components of synaptic potentials of under circumstances i mediation of low frequency transmission by non-NMDA
receptors, with recruitment of NMDA receptors for
longer latency components of synaptic potentials only
under circumstances in which the voltage-dependent
blockade of ion receptors, with recruitment of NMDA receptors for
longer latency components of synaptic potentials only
under circumstances in which the voltage-dependent
blockade of ion channels by magnesium is relieved. Un-
fortunately, longer latency components of synaptic potentials only
under circumstances in which the voltage-dependent
blockade of ion channels by magnesium is relieved. Un-
fortunately, no clear correlation could be established
between under circumstances in which the voltage-dependent
blockade of ion channels by magnesium is relieved. Un-
fortunately, no clear correlation could be established
between the blockade of synaptic transmission and the
selecti blockade of ion channels by magnesium is relieved. Unfortunately, no clear correlation could be established between the blockade of synaptic transmission and the selective blockade of any of the exogenous agonists; doses o fortunately, no clear correlation could be established between the blockade of synaptic transmission and the selective blockade of any of the exogenous agonists; doses of kynurenate needed to block synaptic excitation redu 1985). lective blockade of any of the exogenous agonists; doses
kynurenate needed to block synaptic excitation re-
ced sensitivity to all the agonists (Perkins and Stone,
85).
Excitatory synaptic transmission has also been
ocked

of kynurenate needed to block synaptic excitation duced sensitivity to all the agonists (Perkins and Storus)
1985).
Excitatory synaptic transmission has also be
blocked by kynurenate in hippocampal efferent projec-
tions t duced sensitivity to all the agonists (Perkins and S
1985).
Excitatory synaptic transmission has also
blocked by kynurenate in hippocampal efferent p
tions to the septum (Stevens and Cotman, 1986).
The effects of kynurenat 85).
Excitatory synaptic transmission has also
ocked by kynurenate in hippocampal efferent pr
ons to the septum (Stevens and Cotman, 1986).
The effects of kynurenate on epileptiform electrop
logical activity is discussed i Excitatory synaptic transmission has a blocked by kynurenate in hippocampal efferentions to the septum (Stevens and Cotman, 1984). The effects of kynurenate on epileptiform elevation VI.E. d. NEOCORTEX. Kynurenate has comp

and lateral perforant paths to the dentate gyrus granule
cells were blocked with IC_{50} values of 280 and 130 μ M, activation of different populations of sensory receiving
respectively, potencies that are significantly responses in both stratum radiatum and stratum lucidum cortical pathway to IV and VI results in the activation
were sensitive to kynurenate.
Spontaneous miniature epsps recorded in CA3 neu-
of excitatory amino acid recepto ocked by kynurenate in hippocampal efferent projections to the septum (Stevens and Cotman, 1986).
The effects of kynurenate on epileptiform electrophys-
logical activity is discussed in section VI.E.
d. NEOCORTEX. Kynurena tions to the septum (Stevens and Cotman, 1986).
The effects of kynurenate on epileptiform electrophys-
iological activity is discussed in section VI.E.
d. NEOCORTEX. Kynurenate has complex effects on the
activation of diff The effects of kynurenate on epileptiform electrophysiological activity is discussed in section VI.E.
d. NEOCORTEX. Kynurenate has complex effects on the
activation of different populations of sensory receiving
cells in th iological activity is discussed in section VI.E.
d. NEOCORTEX. Kynurenate has complex effects on the
activation of different populations of sensory receiving
cells in the neocortex. This phenomenon has been most
carefully d. NEOCORTEX. Kynurenate has complex effects on the
activation of different populations of sensory receiving
cells in the neocortex. This phenomenon has been most
carefully examined in the cat visual cortex by Tsumoto
et a activation of different populations of sensory receiving
cells in the neocortex. This phenomenon has been most
carefully examined in the cat visual cortex by Tsumoto
et al. (1986), who found that kynurenate applied by
micr cells in the neocortex. This phenomenon has been most
carefully examined in the cat visual cortex by Tsumoto
et al. (1986), who found that kynurenate applied by
microiontophoresis could suppress the activation of cor-
tica carefully examined in the cat visual cortex by Tsumoto
et al. (1986), who found that kynurenate applied by
microiontophoresis could suppress the activation of cor-
tical neurones by visual stimuli. However, kynurenate
was et al. (1986), who found that kynurenate applied by
microiontophoresis could suppress the activation of cor-
tical neurones by visual stimuli. However, kynurenate
was substantially more effective against activation of
simp microiontophoresis could suppress the activation of cor-
tical neurones by visual stimuli. However, kynurenate
was substantially more effective against activation of
simple cells compared with complex and special complex
n tical neurones by visual stimuli. However, kynurenate
was substantially more effective against activation of
simple cells compared with complex and special complex
neurones. Similarly, the activation of cells in the primar was substantially more effective against activation
simple cells compared with complex and special comple
neurones. Similarly, the activation of cells in the prima
receiving layers of neocortex (layers IVa,b,c) had the
act simple cells compared with complex and special complex
neurones. Similarly, the activation of cells in the primary
receiving layers of neocortex (layers IVa,b,c) had their
activity substantially depressed by locally applie receiving layers of neocortex (layers IVa,b,c) had their
activity substantially depressed by locally applied kynureceiving layers of neocortex (layers IVa,b,c) had their
activity substantially depressed by locally applied kynu-
renate with a slightly smaller rate of success than the
upper reaches of layer VI. In contrast, neurones in activity substantially depressed by locally applied kynu renate with a slightly smaller rate of success than the upper reaches of layer VI. In contrast, neurones in the more superficial layers II and III, as well as those upper reaches of layer VI. In contrast, neurones in the upper reaches of layer VI. In contrast, neurones in
more superficial layers II and III, as well as those in
deeper parts of layer VI, showed little response to k
urenate. Although these observations are supportive
the view more superficial layers II and III, as well as those in the deeper parts of layer VI, showed little response to kynurenate. Although these observations are supportive of the view that primary afferent input along the genic deeper parts of layer VI, showed little response to kyr
urenate. Although these observations are supportive the view that primary afferent input along the genicule
cortical pathway to IV and VI results in the activatio
of urenate. Although these observations are supportive
the view that primary afferent input along the genicu
cortical pathway to IV and VI results in the activat
of excitatory amino acid receptors, the interesting qu
tion is the view that primary afferent in
cortical pathway to IV and VI re
of excitatory amino acid receptor
tion is raised of the identity of t
to other regions of the neocortex.
Kynurenic acid is also able to

Kynurenic acid is also able to block somatosensory

334
evoked cortical potentials in the anaesthetised rat after moto
topical application to the pial surface (Addae and Stone, ever, STC
evoked cortical potentials in the anaesthetised rat after
topical application to the pial surface (Addae and Stone,
1988). 1988). oked cortical potentials in the anaesthetised rat after
pical application to the pial surface (Addae and Stone,
88).
e. OLFACTORY SYSTEM. Jacobson and Hamberger
986) showed that kynurenate could block electrically

evoked cortical potentials in the anaesthetised rat after
topical application to the pial surface (Addae and Stone,
1988).
e. OLFACTORY SYSTEM. Jacobson and Hamberger
(1986) showed that kynurenate could block electrically
 topical application to the pial surface (Addae and Stone,
1988).

e. OLFACTORY SYSTEM. Jacobson and Hamberger
(1986) showed that kynurenate could block electrically

evoked synaptic transmission in the rat olfactory bulb,
 pies (1988). Philopology SPSTEM. Jacobson and Hamberger metals (1996) showed that kynurenate could block electrically expoked synaptic transmission in the rat olfactory bulb, not collins (1990) performed a detailed investi e. OLFACTORY SYSTEM. Jacobson and Hamberger m
(1986) showed that kynurenate could block electrically expoked synaptic transmission in the rat olfactory bulb, no
and Collins (1990) performed a detailed investigation of
mono evoked synaptic transmission in the rat olfactory bulb, and Collins (1990) performed a detailed investigation of monosynaptic and polysynaptic pathways in the mouse evoked synaptic transmission in the rat olfactory bulb,
and Collins (1990) performed a detailed investigation of
monosynaptic and polysynaptic pathways in the mouse
olfactory cortex slice. In these studies, 7-chlorokynuren and Collins (1990) performed a detailed investigation of himonosynaptic and polysynaptic pathways in the mouse analoffactory cortex slice. In these studies, 7-chlorokynuren- of conte was able to reduce the later polysynapt olfactory cortex slice. In these studies, 7-chlorokynurenate was able to reduce the later polysynaptic components of evoked field potentials, an effect that was reversed by glycine or L-serine. Conversely, 7-chlorokynurena olfactory cortex slice. In these studies, 7-chlorokynuren
ate was able to reduce the later polysynaptic component
of evoked field potentials, an effect that was reversed by
glycine or L-serine. Conversely, 7-chlorokynurena of evoked field potentials, an effect that was reversed by glycine or L-serine. Conversely, 7-chlorokynurenate could prevent the potentiation of neurotransmission induced by NMDA.
f. CEREBELLUM. There is general agreement evoked field potentials, an effect that was reversed by
vcine or L-serine. Conversely, 7-chlorokynurenate
uld prevent the potentiation of neurotransmission in-
ced by NMDA.
f. CEREBELLUM. There is general agreement that gl

glycine or L-serine. Conversely, 7-chlorokynurenate m
could prevent the potentiation of neurotransmission in-
duced by NMDA.
f. CEREBELLUM. There is general agreement that glu-
ktamate or aspartate is the major transmitter could prevent the potentiation of neurotransmission in-
duced by NMDA.
f. CEREBELLUM. There is general agreement that glu-
tamate or aspartate is the major transmitter of climbing
fibre and parallel fibres in the cerebellu to
f. CEREBELLUM. There is general agreement that glu-
tamate or aspartate is the major transmitter of climbing cal
fibre and parallel fibres in the cerebellum (Stone, 1979). NN
The cerebellum was one region of the isolate f. CEREBELLUM. There is general agreement that glu-
tamate or aspartate is the major transmitter of climbing ca
fibre and parallel fibres in the cerebellum (Stone, 1979). N
The cerebellum was one region of the isolated fro tamate or aspartate is the major transmitter of climbing
fibre and parallel fibres in the cerebellum (Stone, 1979).
The cerebellum was one region of the isolated frog brain
studied by Cochran (1983). Here, kynurenate block fibre and parallel fibres in the cerebellum (Stone, 1979). NM
The cerebellum was one region of the isolated frog brain i.
studied by Cochran (1983). Here, kynurenate blocked elec
Purkinje cell responses to either climbing The cerebellum was one region of the isolated frog brain studied by Cochran (1983). Here, kynurenate blocked electricinie cell responses to either climbing fibre or parallel in fibre activation at doses that antagonised r studied by Coch
Purkinje cell resp
fibre activation
NMDA and quin
than quisqualate
Kano et al. (1 rkinje cell responses to either climbing fibre or parallel
re activation at doses that antagonised responses to
MDA and quinolinate to a substantially greater degree
an quisqualate.
Kano et al. (1988) attempted to clarify

fibre activation at doses that antagonised responses to NMDA and quinolinate to a substantially greater degree
than quisqualate.
Kano et al. (1988) attempted to clarify the receptors
involved in transmission from the paral NMDA and quinolinate to a substantially greater degree of k
than quisqualate. example to clarify the receptors i.
Kano et al. (1988) attempted to clarify the receptors i.
involved in transmission from the parallel fibres t than quisqualate.

Kano et al. (1988) attempted to clarify the receptors

involved in transmission from the parallel fibres to Pur-

kinje cells in the rabbit cerebellum. 2AP5 was unable to

affect these Purkinje cell res Kano et al. (1988) attempted to clarify the receptot
involved in transmission from the parallel fibres to Pu
kinje cells in the rabbit cerebellum. 2AP5 was unable
affect these Purkinje cell responses, whereas kynurena
and involved in transmission from the parallel fibres to Pur
kinje cells in the rabbit cerebellum. 2AP5 was unable to
affect these Purkinje cell responses, whereas kynurenate
and γ -L-glutamylglycine did so in parallel with kinje cells in the rabbit cerebellum. $2AP5$ was unable to affect these Purkinje cell responses, whereas kynurenate and γ -L-glutamylglycine did so in parallel with the block ade of sensitivity to glutamate, aspartate, q affect these Purkinje cell responses, whereas kynurenate by and γ -L-glutamylglycine did so in parallel with the block-
ade of sensitivity to glutamate, aspartate, quisqualate, on
and kainate. This group claimed that re and γ -L-glutamylglycine did so in parallel with the block-
ade of sensitivity to glutamate, aspartate, quisqualate,
and kainate. This group claimed that responses to quis-
qualate and glutamate and parallel fibre stimu ade of sensitivity to glutamate, aspartate, quisqualate, and kainate. This group claimed that responses to quisqualate and glutamate and parallel fibre stimulation were significantly less sensitive to kynurenate than respo and kainate. This group claimed that responses to quis qualate and glutamate and parallel fibre stimulation were significantly less sensitive to kynurenate than response to kainate and aspartate, leading them to conclude t qualate and glutamate and parallel fibre stimulation w
significantly less sensitive to kynurenate than respon
to kainate and aspartate, leading them to conclude t
the quisqualate receptor was involved. However, all c
pound significantly less sensitive to kynurenate than responses
to kainate and aspartate, leading them to conclude that
in the quisqualate receptor was involved. However, all com-
pounds in this study were applied by microiontop to kainate and aspartate, leading them to conclude that
the quisqualate receptor was involved. However, all com-
pounds in this study were applied by microiontophoresis,
and the conclusions must, therefore, be viewed with the quisqualate receptor was involved. However, all compounds in this study were applied by microiontophoresis, and the conclusions must, therefore, be viewed with the caveat that any differential distribution of receptor pounds in this study were apend the conclusions must, the caveat that any differential populations along the extermay affect the interpretation. d the conclusions must, therefore, be viewed with the
veat that any differential distribution of receptor sub-
pulations along the extensive dendritic arborisations
we affect the interpretation.
Recent evidence also sugges

caveat that any differential distribution of receptor sub-
populations along the extensive dendritic arborisations ve
may affect the interpretation. Su
Recent evidence also suggests that an excitatory amino or
acid may ser populations along the extensive dendritic arborisations
may affect the interpretation.
Recent evidence also suggests that an excitatory amino
acid may serve as the transmitter from mossy fibre
afferents to granule cells. T may affect the interpretation. Summer and the surface also suggests that an excitatory amino or acid may serve as the transmitter from mossy fibre to afferents to granule cells. The population potentials recorded from the Recent evidence also suggests that an excitatory amino
acid may serve as the transmitter from mossy fibre
afferents to granule cells. The population potentials re-
corded from the granule cell region in response to white
m acid may serve as the transmitter from mossy fibre
afferents to granule cells. The population potentials re-
corded from the granule cell region in response to white
matter stimulation could be completely blocked by per-
f afferents to granule cells. The population potentials recorded from the granule cell region in response to white matter stimulation could be completely blocked by perfusion with kynurenate (although a high concentration of matter stimulation could be completely blocked by per-
fusion with kynurenate (although a high-concentration
of 3 mM was used) or CNQX. No NMDA-mediated
components were detectable unless high-frequency stim-
ulation was us matter stimulation could be completely blocked by j
fusion with kynurenate (although a high concentra
of 3 mM was used) or CNQX. No NMDA-media
components were detectable unless high-frequency st
ulation was used (Garthwait sion with kynurenate (although a high concentration c 3 mM was used) or CNQX. No NMDA-mediated mponents were detectable unless high-frequency stim-
httion was used (Garthwaite and Brodbelt, 1989). a
g. RED NUCLEUS. In the

of 3 mM was used) or CNQX. No NMDA-mediated niscomponents were detectable unless high-frequency stim-
ulation was used (Garthwaite and Brodbelt, 1989). at g. RED NUCLEUS. In the cat red nucleus in vivo, Davies
et al. (198 components were detectable unless high-frequency stim-
ulation was used (Garthwaite and Brodbelt, 1989).
g. RED NUCLEUS. In the cat red nucleus in vivo, Davies
et al. (1986) confirmed the ability of kynurenate to block
all ulation was used (Garthwaite and Brodbelt, 1989).

g. RED NUCLEUS. In the cat red nucleus in vivo, Davies

et al. (1986) confirmed the ability of kynurenate to block

all of the excitatory amino acids tested, glutamate, as g. RED NUCLEUS. In the cat red nucleus in vivo, Davies
et al. (1986) confirmed the ability of kynurenate to block
oll of the excitatory amino acids tested, glutamate, as-
partate, NMDA, kainate, and quisqualate. Synaptic e et al. (1986) confirmed the ability of kynurenate to block
all of the excitatory amino acids tested, glutamate, as-
partate, NMDA, kainate, and quisqualate. Synaptic ex-
citation of rubral neurones, induced by stimulation all of the excitatory amino acids tested, glutamate, partate, NMDA, kainate, and quisqualate. Synaptic citation of rubral neurones, induced by stimulation nucleus interpositus, were blocked by iontophoretical applied kynur citation of rubral neurones, induced by stimulation of nucleus interpositus, were blocked by iontophoretically applied kynurenate but not 2AP5. Excitatory postsynaptic potentials evoked by stimulation of the sensori-

NE
motor neocortex could be less clearly categorised. How
ever, the potencies of 2AP5 and *p*-chlorobenzoyl-*ci*a ever, the potencies could be less clearly categorised ever, the potencies of 2AP5 and *p*-chlorobenz
piperazine-2,3-dicarboxylate in blocking synaptic WE
motor neocortex could be less clearly categorised. However, the potencies of 2AP5 and p-chlorobenzoyl-ci
piperazine-2,3-dicarboxylate in blocking synaptic trans-
mission did not correlate with their abilities to bloc motor neocortex could be less clearly categorised. How-
ever, the potencies of 2AP5 and *p*-chlorobenzoyl-cis-
piperazine-2,3-dicarboxylate in blocking synaptic trans-
mission did not correlate with their abilities to bloc motor neocortex could be less clearly categorised. How-
ever, the potencies of 2AP5 and *p*-chlorobenzoyl-cis-
piperazine-2,3-dicarboxylate in blocking synaptic trans-
mission did not correlate with their abilities to bloc ever, the potencies of 2AP5 and *p*-chlorobenzoyl-cis-
piperazine-2,3-dicarboxylate in blocking synaptic trans-
mission did not correlate with their abilities to bloc-
exogenous amino acids. Unfortunately, kynurenate was
n berazine-2,3-dicarboxylate in blocking synaptic transsion did not correlate with their abilities to block
ogenous amino acids. Unfortunately, kynurenate was
t tested against the corticorubral synaptic potentials.
h. THALAM

mission did not correlate with their abilities to block
exogenous amino acids. Unfortunately, kynurenate was
not tested against the corticorubral synaptic potentials.
h. THALAMUS. In the ventrobasal thalamic complex of
ana exogenous amino acids. Unfortunately, kynurenate was
not tested against the corticorubral synaptic potentials.
h. THALAMUS. In the ventrobasal thalamic complex of
anaesthetised rats, kynurenate prevented the activation
of not tested against the corticorubral synaptic potentials.

h. THALAMUS. In the ventrobasal thalamic complex of

anaesthetised rats, kynurenate prevented the activation

of cells in response to NMDA or quisqualate applicati h. THALAMUS. In the ventrobasal thalamic complex
anaesthetised rats, kynurenate prevented the activation
of cells in response to NMDA or quisqualate application
and blocked responses to physiological stimulation
afferent p anaesthetised rats, kynurenate prevented the activation
of cells in response to NMDA or quisqualate application
and blocked responses to physiological stimulation of
afferent pathways, including that initiated by the moveof cells in response to NMDA or quisqualate application
and blocked responses to physiological stimulation of
afferent pathways, including that initiated by the move-
ment of hairs or vibrissae. 2AP5, however, blocked the
 and blocked responses to physiological stimulation of
afferent pathways, including that initiated by the move-
ment of hairs or vibrissae. 2AP5, however, blocked the
physiological responses but had no effect on responses
t afferent pathways, including that initiated by the meant of hairs or vibrissae. 2AP5, however, blocked physiological responses but had no effect on responto electrical stimulation (Salt, 1986). It is not clear NMDA recepto ment of hairs or vibrissae. 2AP5, however, blocked the
physiological responses but had no effect on responses
to electrical stimulation (Salt, 1986). It is not clear why
NMDA receptors should be activated only physiologica physiological responses but had no effect on ret
to electrical stimulation (Salt, 1986). It is not ck
NMDA receptors should be activated only phy
cally and not artificially, but it would appear th
NMDA receptors are involv electrical stimulation (Salt, 1986). It is not clear why
MDA receptors should be activated only physiologi-
lly and not artificially, but it would appear that non-
MDA receptors are involved in both responses.
i. HYPOTHALA

NMDA receptors should be activated only physiologically and not artificially, but it would appear that non-NMDA receptors are involved in both responses.

i. HYPOTHALAMUS. In rat hypothalamic slices, local

electrical stim cally and not artificially, but it would appear that non-

NMDA receptors are involved in both responses.

i. HYPOTHALAMUS. In rat hypothalamic slices, local

electrical stimulation evoked epsps in supraoptic nucleus

meu NMDA receptors are involved in both responses.

i. HYPOTHALAMUS. In rat hypothalamic slices, local

electrical stimulation evoked epsps in supraoptic nucleus

neurones that were blocked by kynurenate (250 to 300
 μ M). U i. HYPOTHALAMUS. In rat hypothalamic slices, local
electrical stimulation evoked epsps in supraoptic nucleus
neurones that were blocked by kynurenate (250 to 300
 μ M). Unfortunately, it is difficult to assess the select electrical stimulation evoked epsps in sum
neurones that were blocked by kynuren
 μ M). Unfortunately, it is difficult to asses
of kynurenate in this work because ne
ramined (Gribkoff and Dudek, 1988).
j. MIDBRAIN: DOPAM (250 to 300

M). Unfortunately, it is difficult to assess the selectivity

kynurenate in this work because no agonists were

amined (Gribkoff and Dudek, 1988).

j. MIDBRAIN: DOPAMINERGIC NEURONES. In the ventral

gmental a

 μ M). Unfortunately, it is difficult to assess the selectivity
of kynurenate in this work because no agonists were
examined (Gribkoff and Dudek, 1988).
j. MIDBRAIN: DOPAMINERGIC NEURONES. In the ventral
tegmental area o of kynurenate in this work because no agonists were
examined (Gribkoff and Dudek, 1988).
j. MIDBRAIN: DOPAMINERGIC NEURONES. In the ventral
tegmental area of anaesthetised rats, neurones tend to
exhibit a pattern of burst examined (Gribkoff and Dudek, 1988).

j. MIDBRAIN: DOPAMINERGIC NEURONES. In the ventra

tegmental area of anaesthetised rats, neurones tend to

exhibit a pattern of burst firing that seems to be imposed

by external synap j. MIDBRAIN: DOPAMINERGIC NEURONES. In the ventral
tegmental area of anaesthetised rats, neurones tend to
exhibit a pattern of burst firing that seems to be imposed
by external synaptic influences. The application of kyntegmental area of anaesthetised rats, neurones tend to
exhibit a pattern of burst firing that seems to be imposed
by external synaptic influences. The application of kyn-
urenate icv is able to convert this bursting patter exhibit a pattern of burst firing that seems to be imposed
by external synaptic influences. The application of kyn-
urenate icv is able to convert this bursting pattern into
one of regular firing with no change of overall by external synaptic influences. The application of kynurenate icv is able to convert this bursting pattern in
one of regular firing with no change of overall firing
frequency (Grenhoff et al., 1988). When applied eith
by urenate icv is able to convert this bursting pattern into
one of regular firing with no change of overall firing
frequency (Grenhoff et al., 1988). When applied either
by microiontophoresis or local pressure ejection, kynu frequency (Grenhoff et al., 1988). When applied either
by microiontophoresis or local pressure ejection, kynu-
renate induces a similar regularisation of firing of cells
in the ventral tegmental area or substantia nigra pa frequency (Grenhoff et al., 1988). When applied either
by microiontophoresis or local pressure ejection, kynu-
renate induces a similar regularisation of firing of cells
in the ventral tegmental area or substantia nigra pa by microiontophoresis or local pressure ejection, kynu-
renate induces a similar regularisation of firing of cells
in the ventral tegmental area or substantia nigra pars
compacta (Charlety et al., 1991). Kynurenate was mor renate induces a similar regularisation of firing of cells
in the ventral tegmental area or substantia nigra pars
compacta (Charlety et al., 1991). Kynurenate was more
efficacious after icv administration, possibly because in the ventral tegmental area or substantia nigra pars
compacta (Charlety et al., 1991). Kynurenate was more
efficacious after icv administration, possibly because of
its greater access to distal synapses bearing dendrites compacta (Charlety et al., 1991). Kynurenate was more efficacious after icv administration, possibly because of its greater access to distal synapses bearing dendrites and to effects on neuronal populations projecting to t efficacious after icv administration, possibly because of
its greater access to distal synapses bearing dendrites
and to effects on neuronal populations projecting to the
ventral tegmental area and substantia nigra. Becaus its greater access to distal synapses bearing dendrite and to effects on neuronal populations projecting to the ventral tegmental area and substantia nigra. Because the substantia nigra and ventral tegmentum represent the and to effects on neuronal populations projecting to the ventral tegmental area and substantia nigra. Because the substantia nigra and ventral tegmentum represent the origins of dopaminergic neurones projecting to the stri ventral tegmental area and substantia nigra. Because the
substantia nigra and ventral tegmentum represent the
origins of dopaminergic neurones projecting to the stria-
tum and mesolimbic regions, respectively, it is proba substantia nigra and ventral tegmentum represent the
origins of dopaminergic neurones projecting to the stria-
tum and mesolimbic regions, respectively, it is probable
that amino acid inputs to these cells (probably from
p origins of dopaminergic neurones projecting to the stria-
tum and mesolimbic regions, respectively, it is probable
that amino acid inputs to these cells (probably from
prefrontal neocortex) play a critical role in determin tum and mesolimbic regions, respectively, it is probat
that amino acid inputs to these cells (probably from
prefrontal neocortex) play a critical role in determini
major aspects of locomotor and limbic behaviours.
deed, re that amino acid inputs to these cells (probably from
prefrontal neocortex) play a critical role in determining
major aspects of locomotor and limbic behaviours. In-
deed, recent reports that excitatory amino acid antago-
m major aspects of locomotor and limbic behaviours. In-
deed, recent reports that excitatory amino acid antago-
nists are effective in locomotor disorders, such as Par-
kinson's disease, may be partly explicable by an action deed, recent reports that excitatory amino acid antago-

Also of interest were subsequent studies of the activity
of the neuroleptic drug haloperidol on the ventral tegnists are effective in locomotor disorders, such as Parkinson's disease, may be partly explicable by an action
at these sites.
Also of interest were subsequent studies of the activity
of the neuroleptic drug haloperidol on kinson's disease, may be partly explicable by an action
at these sites.
Also of interest were subsequent studies of the activity
of the neuroleptic drug haloperidol on the ventral teg-
mental neurones in chloral hydrate-an at these sites.

Also of interest were subsequent studies of the activity

of the neuroleptic drug haloperidol on the ventral teg-

mental neurones in chloral hydrate-anaesthetised rats.

Here, the acute administration of Also of interest were subsequent studies of the activity
of the neuroleptic drug haloperidol on the ventral teg-
mental neurones in chloral hydrate-anaesthetised rats.
Here, the acute administration of haloperidol is known of the neuroleptic drug haloperidol on the ventral teg-
mental neurones in chloral hydrate-anaesthetised rats.
Here, the acute administration of haloperidol is known
to cause excitation of the dopaminergic neurones, an
act Here, the acute administration of haloperidol is known
to cause excitation of the dopaminergic neurones, an
action that may lead to overdepolarisation and, thus,
inactivation of the cells, thereby contributing to the
antip to cause excitation of the dopaminergic neurones, an

PHARMACOLOGICAL REVIEWS

QUINOLINIC AND
demonstrated that icy kynurenate was able to prevent
this excitatory action of haloperidol, implying that it was QUINOLINIC AND KYI
demonstrated that icv kynurenate was able to prevent at
this excitatory action of haloperidol, implying that it was
mediated indirectly by the activation of amino acid re-QUINOLINIC AND
demonstrated that icv kynurenate was able to prevent
this excitatory action of haloperidol, implying that it was
mediated indirectly by the activation of amino acid re-
leasing neurones to the ventral tegmen demonstrated that icv kynurenate was abthis excitatory action of haloperidol, implyimediated indirectly by the activation of a leasing neurones to the ventral tegmentum.

k. LOCUS COERULEUS. Local stimulation

this excitatory action of haloperidol, implying that it we
mediated indirectly by the activation of amino acid re
leasing neurones to the ventral tegmentum.
k. LOCUS COERULEUS. Local stimulation of the ra
locus coeruleus i mediated indirectly by the activation of amino acid re-
leasing neurones to the ventral tegmentum.

k. LOCUS COERULEUS. Local stimulation of the rat

locus coeruleus in a slice preparation resulted in depo-

larising post leasing neurones to the ventral tegmentum. The k. LOCUS COERULEUS. Local stimulation of the rat ula locus coeruleus in a slice preparation resulted in depolarising postsynaptic potentials that were depressed by ula kynure k. LOCUS COERULEUS. Local stimulation of the ralocus coeruleus in a slice preparation resulted in depolarising postsynaptic potentials that were depressed by kynurenate $(55\%$ reduction at 500μ M). Kynurenate also bloc larising postsynaptic potentials that were depressed by ulation of a regular intrinsically generated rhythm by an
kynurenate $(55\%$ reduction at 500μ M). Kynurenate also incoming amino acid-releasing pathway.
blocked r larising postsynaptic potentials that were depressed by universate (55% reduction at 500 μ M). Kynurenate also is blocked responses to superfusion with NMDA or quisqualate, whereas 2AP5 blocked selectively responses to kynurenate $(55\%$ reduction at 500μ M). Kynurenate also incoblocked responses to superfusion with NMDA or quisqualate, whereas $2AP5$ blocked selectively responses to blook NMDA and had no effect on the synaptic potenti blocked responses to superfusion with NMDA or quis-
qualate, whereas 2AP5 blocked selectively responses to
NMDA and had no effect on the synaptic potential. This
was taken as favouring the involvement of non-NMDA
receptors qualate, whereas 2AP5 blocked selectively responses to bloc NMDA and had no effect on the synaptic potential. This Kukwas taken as favouring the involvement of non-NMDA cardiffectors in the production of the epsps (Cherubi was taken as favouring the involvement of non-NMDA
receptors in the production of the epsps (Cherubini et
al., 1988b). It was emphasised that kynurenate had no
effect on neuronal membrane properties at effective an-
tagoni was taken as favouring the involvement of non-NMDA creceptors in the production of the epsps (Cherubini et al., 1988b). It was emphasised that kynurenate had no peffect on neuronal membrane properties at effective antagoni receptors in the production of the epsps (Cherubini et ad., 1988b). It was emphasised that kynurenate had no peffect on neuronal membrane properties at effective antagonistic concentrations. The excitatory projection a fro al., 1988b). It was emphasised that kynurenate had no
effect on neuronal membrane properties at effective an-
tagonistic concentrations. The excitatory projection
from ventrolateral medulla to neurones of the locus
coerule effect on neuronal
tagonistic concent
from ventrolateral
coeruleus is also bl
ton-Jones, 1986).
l. RAPHE NUCLE gonistic concentrations. The excitatory projection
om ventrolateral medulla to neurones of the locus
eruleus is also blocked by kynurenate (Ennis and As-
n-Jones, 1986).
l. RAPHE NUCLEUS. Richter and Behbehani (1991)
ovide

from ventrolateral medulla to neurones of the locus
coeruleus is also blocked by kynurenate (Ennis and As-
ton-Jones, 1986).
l. RAPHE NUCLEUS. Richter and Behbehani (1991)
provided evidence for an amino acid-mediated link coeruleus is also blocked by kynurenate (Ennis and Asimpton-Jones, 1986).

I. RAPHE NUCLEUS. Richter and Behbehani (1991) of

provided evidence for an amino acid-mediated link be-

tween the mesencephalic nucleus cuneiform 1. RAPHE NUCLEUS. Richter and Behbehani (1991) of h
provided evidence for an amino acid-mediated link be-
tween the mesencephalic nucleus cuneiformis and the of l
nucleus raphe magnus in anaesthetised rats. Activation inv provided evidence for an amino acid-mediated link be-
tween the mesencephalic nucleus cuneiformis and the of k
nucleus raphe magnus in anaesthetised rats. Activation invo
of this projection leads to excitatory responses on tween the mesencephalic nucleus cuneiformis and t
nucleus raphe magnus in anaesthetised rats. Activati
of this projection leads to excitatory responses on
proportion of raphe neurones, which could be blocked
kynurenic acid nucleus raphe magnus in anaesthetised rats. Activation inv
of this projection leads to excitatory responses on a in t
proportion of raphe neurones, which could be blocked by of l
kynurenic acid. The role of this projectio of this projection leads to excitatory responses on a in
proportion of raphe neurones, which could be blocked by
dividential rationale for the development of
indicate some potential rationale for the development of
amino a proportion of raphe neurones, which could be blocked by
kynurenic acid. The role of this projection as a compo-
nent of descending nocisponsive control pathways may
indicate some potential rationale for the development of

indicate some potential rationale for the development of
amino acid receptor ligands with analgesic properties.
m. HINDBRAIN CARDIOVASCULAR AREAS. Kynurenic
acid was used by Sun and Guyenet (1987) to assess the
involvement amino acid receptor ligands with analgesic properties. F.
m. HINDBRAIN CARDIOVASCULAR AREAS. Kynurenic reacid was used by Sun and Guyenet (1987) to assess the thinvolvement of excitatory amino acids in the sympathetic in
e m. HINDBRAIN CARDIOVASCULAR AREAS. Kynurenic relation of excitatory amino acids in the sympathetic in involvement of excitatory amino acids in the sympathetic in effects of stimulating vagal afferent fibres. Injection of K acid was used by Sun and Guyenet (1987) to assess the
involvement of excitatory amino acids in the sympathetic
effects of stimulating vagal afferent fibres. Injection of
kynurenate directly into the retrofacial portion of involvement of excitatory amino acids in the sympathetive
fects of stimulating vagal afferent fibres. Injection c
kynurenate directly into the retrofacial portion of th
nucleus PGCL of rats (in the ventrolateral medulla
bl kynurenate directly into the retrofacial portion of the yielding a 91% reduction of synaptic potentials.

nucleus PGCL of rats (in the ventrolateral medulla) Urbanski and Sapru (1988) explored, in anaesthetised

blocked th kynurenate directly into the retrofacial portion of the nucleus PGCL of rats (in the ventrolateral medulla) blocked the pressor effects of high-frequency vagal stimulation as well as the excitatory effect of this stimulati nucleus PGCL of rats (in the ventrolateral medulla)
blocked the pressor effects of high-frequency vagal stim-
ulation as well as the excitatory effect of this stimulation
on firing frequency of neurones in the PGCL nucleus blocked the pressor effects of high-frequency vagal stim-
ulation as well as the excitatory effect of this stimulation
on firing frequency of neurones in the PGCL nucleus.
Kynurenate also prevented the excitation of PGCL n ulation as well as the excitatory effect of this stimulation sit
on firing frequency of neurones in the PGCL nucleus. act
Kynurenate also prevented the excitation of PGCL neu-
prones induced by single-pulse stimulation of on firing frequency of neurones in the PGCL nucleus. acti
Kynurenate also prevented the excitation of PGCL neu-
presences induced by single-pulse stimulation of the vagus
when applied by microiontophoresis, confirming the Kynurenate also prevented the excitation of PGCL neu-
rones induced by single-pulse stimulation of the vagus
when applied by microiontophoresis, confirming the
soresence of the necessary amino acid receptors on PGCL
Neells rones induced by single-pulse stimulation of the value when applied by microiontophoresis, confirming
presence of the necessary amino acid receptors on PG
cells themselves. Kynurenate prevented excitation
PGCL neurones ind when applied by microiontophoresis, confirming the sor area. If this region were first blocked by kynurenate, presence of the necessary amino acid receptors on PGCL NTS stimulation induced a pressor response that could cel presence of the necessary amino acid receptors on PGCL
cells themselves. Kynurenate prevented excitation of
PGCL neurones induced by stimulation of the hypothal-
amus (Sun and Guyenet, 1986) and thereby blocked
activation cells themselves. Kynurenate prevented excitation of the PGCL neurones induced by stimulation of the hypothal-
amus (Sun and Guyenet, 1986) and thereby blocked B
activation of sympathetic afferent activity without af-
fect amus (Sun and Guyenet, 1986) and thereby blocked
activation of sympathetic afferent activity without af-
fecting arterial pressure or baseline firing of the PGCL
neurones.
Sun et al. (1988) assessed the effects of intracis activation of sympathetic afferent activity without
fecting arterial pressure or baseline firing of the PG
neurones.
Sun et al. (1988) assessed the effects of intracisterna
applied kynurenate on a number of autonomic param

fecting arterial pressure or baseline firing of the PGC
neurones.
Sun et al. (1988) assessed the effects of intracisternal
applied kynurenate on a number of autonomic parameters
in anaesthetised rats or in in vitro prepara meurones.

Sun et al. (1988) assessed the effects of intracisternally

applied kynurenate on a number of autonomic parame

ters in anaesthetised rats or in in vitro preparations

Following an early increase of blood press Sun et al. (1988) assessed the effects of intracisternally applied kynurenate on a number of autonomic parameters in anaesthetised rats or in in vitro preparations.
Following an early increase of blood pressure, all sympa applied kynurenate on a number of autonomic parame-
ters in anaesthetised rats or in in vitro preparations.
Following an early increase of blood pressure, all sym-
pathetic reflexes were abolished by kynurenate ($5 \mu \text{mol}$ ters in anaesthetised rats or in in vitro preparations. times following an early increase of blood pressure, all sympathetic reflexes were abolished by kynurenate $(5 \mu \text{mol})$, all including the arterial baroreceptor refle Following an early increase of blood pressure, all sym-que pathetic reflexes were abolished by kynurenate $(5 \mu \text{mol})$, also including the arterial baroreceptor reflex and the vagal sure depressor and pressor reflexes. Cor

this excitatory action of haloperidol, implying that it was inhibitory neurones and a loss of any reactivity of PGCL
mediated indirectly by the activation of amino acid re-
leasing neurones to the ventral tegmentum.
the ca attributed to disinhibition by the reduced activation of individually actions
inhibitory neurones and a loss of any reactivity of PGCL
inhibitory neurones and a loss of any reactivity of PGCL
neurones to changes in systemic blood pressure. As in 335

attributed to disinhibition by the reduced activation of

inhibitory neurones and a loss of any reactivity of PGCL

neurones to changes in systemic blood pressure. As in

the case of ventral tegmental neurones, the no attributed to disinhibition by the reduced activation of inhibitory neurones and a loss of any reactivity of PGC neurones to changes in systemic blood pressure. As is the case of ventral tegmental neurones, the normal irre attributed to disinhibition by the reduced activation of inhibitory neurones and a loss of any reactivity of PGCL
neurones to changes in systemic blood pressure. As in
the case of ventral tegmental neurones, the normal irr inhibitory neurones and a loss of any reactivity of PGCl
neurones to changes in systemic blood pressure. As is
the case of ventral tegmental neurones, the normal irreg
ular firing pattern of the cells was changed to a regu neurones to changes in systemic blood pressure. As in
the case of ventral tegmental neurones, the normal irreg-
ular firing pattern of the cells was changed to a regular
one after kynurenate administration, implying the mo one after kynurenate administration, implying the modar firing pattern of the cells was changed to a regular
e after kynurenate administration, implying the mod-
ation of a regular intrinsically generated rhythm by an
coming amino acid-releasing pathway.
When administered in

ton-Jones, 1986). Findings suggest the involvement in baroreceptor reflexes
1. RAPHE NUCLEUS. Richter and Behbehani (1991) of kynurenate-sensitive receptors at the level of both the
provided evidence for an amino acid-medi one after kynurenate administration, implying the modulation of a regular intrinsically generated rhythm by an
incoming amino acid-releasing pathway.
When administered into the NTS, kynurenate can
block arterial barorecept ulation of a regular intrinsically generated rhythm by an
incoming amino acid-releasing pathway.
When administered into the NTS, kynurenate can
block arterial baroreceptor reflexes (Guyenet et al., 1987;
Kubo and Kihara, 1 incoming amino acid-releasing pathway.
When administered into the NTS, kynurenate can
block arterial baroreceptor reflexes (Guyenet et al., 1987;
Kubo and Kihara, 1991), as well as the vagally mediated
cardioinhibitory ref When administered into the NTS, kynurenate can
block arterial baroreceptor reflexes (Guyenet et al., 1987;
Kubo and Kihara, 1991), as well as the vagally mediated
cardioinhibitory reflex in response to elevated systemic
ar block arterial baroreceptor reflexes (Guyenet et al., 1987;
Kubo and Kihara, 1991), as well as the vagally mediated
cardioinhibitory reflex in response to elevated systemic
arterial pressure, implicating an amino acid-rele Kubo and Kihara, 1991), as well as the vagally mediated
cardioinhibitory reflex in response to elevated systemic
arterial pressure, implicating an amino acid-releasing
pool of neurones projecting to the NTS in both types o cardioinhibitory reflex in response to elevated systemic
arterial pressure, implicating an amino acid-releasing
pool of neurones projecting to the NTS in both types of
response. The injection of kynurenate into PGCL was
ab arterial pressure, implicating an amino acid-releasing
pool of neurones projecting to the NTS in both types of
response. The injection of kynurenate into PGCL was
able to block excitation produced by glutamate, without
mod pool of neurones projecting to the NTS in both types of
response. The injection of kynurenate into PGCL was
able to block excitation produced by glutamate, without
modifying baroreceptor reflexes, whereas administration
in response. The injection of kynurenate into PGCL was
able to block excitation produced by glutamate, without
modifying baroreceptor reflexes, whereas administration
into the ventrolateral medulla did so. Together, these
fin able to block excitation produced by glutamate, without
modifying baroreceptor reflexes, whereas administration
into the ventrolateral medulla did so. Together, these
findings suggest the involvement in baroreceptor reflex modifying baroreceptor reflexes, whereas administration
into the ventrolateral medulla did so. Together, these
findings suggest the involvement in baroreceptor reflexes
of kynurenate-sensitive receptors at the level of bot into the ventrolateral medulla did so. Together, these
findings suggest the involvement in baroreceptor reflexes
of kynurenate-sensitive receptors at the level of both the
NTS and the ventrolateral medulla. The greater act findings suggest the involvement in baroreceptor reflexes
of kynurenate-sensitive receptors at the level of both the
NTS and the ventrolateral medulla. The greater activity
of kynurenate compared with dizocilpine indicates NTS and the ventrolateral medulla. The greater activity of kynurenate compared with dizocilpine indicates the
involvement of both NMDA and non-NMDA receptors
in the NTS (Kubo and Kihara, 1991). The effectiveness
of kynurenate, when administered intrathecally, further
indicates of kynurenate compared with dizocilpine indicates the
involvement of both NMDA and non-NMDA receptors
in the NTS (Kubo and Kihara, 1991). The effectiveness
of kynurenate, when administered intrathecally, further
indicates involvement of both NMDA and non-NMDA receptors
in the NTS (Kubo and Kihara, 1991). The effectiveness
of kynurenate, when administered intrathecally, further
indicates a role for amino acid receptors in the control
of effe response. The injection of kynurenate into PGCL was able to block excitation produced by glutamate, without modifying baroceptor reflexes, whereas administration into the ventrolateral medulla did so. Together, these find of efferent sympathetic activity (Verberne et al., 1990).

indicate some potential rationale for the development of
amino acid receptor ligands with analgesic properties. Felder (1988) showed directly that perfusion with kynu-
m. HINDBRAIN CARDIOVASCULAR AREAS. Kynurenic renate wo indicates a role for amino acid receptors in the control
of efferent sympathetic activity (Verberne et al., 1990).
Using a slice preparation of the rat NTS, Miller and
Felder (1988) showed directly that perfusion with kynu of efferent sympathetic activity (Verberne et al., 1990).
Using a slice preparation of the rat NTS, Miller and
Felder (1988) showed directly that perfusion with kynu-
renate would block synaptic responses to stimulation of Using a slice preparation of the rat NTS, Miller and Felder (1988) showed directly that perfusion with kynu-
renate would block synaptic responses to stimulation of
the solitary tract by recording single-neurone activatio Felder (1988) showed directly that perfusion with kynurenate would block synaptic responses to stimulation of the solitary tract by recording single-neurone activation in response to electrical stimulation of the pathway. renate would block synaptic responses to stimulation of the solitary tract by recording single-neurone a
in response to electrical stimulation of the
Kynurenate (300 μ M) was very effective in thi
yielding a 91% reducti e solitary tract by recording single-neurone activation
response to electrical stimulation of the pathway.
ynurenate $(300 \ \mu\text{M})$ was very effective in this system,
elding a 91% reduction of synaptic potentials.
Urbansk

in response to electrical stimulation of the pathway.

Kynurenate (300 μ M) was very effective in this system,

yielding a 91% reduction of synaptic potentials.

Urbanski and Sapru (1988) explored, in anaesthetised

rat Kynurenate (300 μ M) was very effective in this system,

yielding a 91% reduction of synaptic potentials.

Urbanski and Sapru (1988) explored, in anaesthetised

rats, the connectivity between some of these brainstem

si yielding a 91% reduction of synaptic potentials.
Urbanski and Sapru (1988) explored, in anaesthetised
rats, the connectivity between some of these brainstem
sites involved in baroreflexes. Glutamate was used to
activate th Urbanski and Sapru (1988) explored, in anaesthetise
rats, the connectivity between some of these brainste
sites involved in baroreflexes. Glutamate was used
activate the NTS and to induce a decrease of bloo
pressure and he rats, the connectivity between some of these brainst
sites involved in baroreflexes. Glutamate was used
activate the NTS and to induce a decrease of blo
pressure and heart rate, these being prevented by kyr
renate injected activate the NTS and to induce a decrease of blood
pressure and heart rate, these being prevented by kynu-
renate injected into the ventrolateral medullary depresactivate the NTS and to induce a decrease of blood
pressure and heart rate, these being prevented by kynu-
renate injected into the ventrolateral medullary depres-
sor area. If this region were first blocked by kynurenate, pressure and heart rate, these being prevented by kynu-
renate injected into the ventrolateral medullary depres-
sor area. If this region were first blocked by kynurenate
NTS stimulation induced a pressor response that cou renate injected into the ventrolater
sor area. If this region were first ble
NTS stimulation induced a pressor
then be prevented by kynurenate i
trolateral medullary pressor area.
Blessing (1989) and Talman (19 r area. If this region were first blocked by kynurenate,
IS stimulation induced a pressor response that could
en be prevented by kynurenate injected into the ven-
blateral medullary pressor area.
Blessing (1989) and Talman

NTS stimulation induced a pressor response that could
then be prevented by kynurenate injected into the ven-
trolateral medullary pressor area.
Blessing (1989) and Talman (1989) used kynurenate
and 2AP5 in an analysis of b then be prevented by kynurenate injected into the ven-
trolateral medullary pressor area.
Blessing (1989) and Talman (1989) used kynurenate
and 2AP5 in an analysis of baroreceptor reflexes in the
rabbit and rat medulla, re trolateral medullary pressor area.
Blessing (1989) and Talman (1989) used kynurenat
and 2AP5 in an analysis of baroreceptor reflexes in th
rabbit and rat medulla, respectively. Either agent, at
dose of 5 nmol, injected int Blessing (1989) and Talman (1989) used kynurenate
and 2AP5 in an analysis of baroreceptor reflexes in the
rabbit and rat medulla, respectively. Either agent, at a
dose of 5 nmol, injected into the rabbit ventrolateral
medu and 2AP5 in an analysis of baroreceptor reflexes in the rabbit and rat medulla, respectively. Either agent, at dose of 5 nmol, injected into the rabbit ventrolaters medulla caused a block of the vasodepressor effect coloca rabbit and rat medulla, respectively. Either agent, at a dose of 5 nmol, injected into the rabbit ventrolateral medulla caused a block of the vasodepressor effect of locally applied NMDLA but not of glutamate. In addition, medulla caused a block of the vasodepressor effect of locally applied NMDLA but not of glutamate. In addition, the depressor and renal sympathoinhibitory consequences of stimulating the aortic depressor nerve wer also abol locally applied NMDLA but not of glutamate. In a
tion, the depressor and renal sympathoinhibitory con
quences of stimulating the aortic depressor nerve v
also abolished, but the results of modulating blood p
sure, which co tion, the depressor and renal sympathoinhibitory consequences of stimulating the aortic depressor nerve were
also abolished, but the results of modulating blood pres-
sure, which comprise qualitatively the same cardiovas-
 quences of stimulating the aortic depressor nerve were
also abolished, but the results of modulating blood pres-
sure, which comprise qualitatively the same cardiovas-
cular effects, were essentially unchanged. The same pr

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to NMDA and kainate with no effect on glutamate, was be
seen in the rat preparation (Talman, 1989). 336
to NMDA and kainate with no effect on glut.
seen in the rat preparation (Talman, 1989).
Despite the obvious efficacy of kynurenate

6

NMDA and kainate with no effect on glutamate, v

en in the rat preparation (Talman, 1989).

Despite the obvious efficacy of kynurenate in prevent-

g synaptic activation, there is substantial confus to NMDA and kainate with no effect on glutamate, was been in the rat preparation (Talman, 1989). In Despite the obvious efficacy of kynurenate in prevent-
ing synaptic activation, there is substantial confusion asurroundin to NMDA and kainate with no effect on glutamate, was
seen in the rat preparation (Talman, 1989).
Despite the obvious efficacy of kynurenate in prevent-
ing synaptic activation, there is substantial confusion
surrounding th seen in the rat preparation (Talman, 1989). mindless in the obvious efficacy of kynurenate in prevent-
ing synaptic activation, there is substantial confusion and
surrounding the identity of the kynurenate sensitive H2
tra Despite the obvious efficacy of kynurenate in prevent-
ing synaptic activation, there is substantial confusion an
surrounding the identity of the kynurenate sensitive Hz
transmitter released by baroreceptor afferents to th ing synaptic activation, there is substantial confusion surrounding the identity of the kynurenate sensitivend
transmitter released by baroreceptor afferents to the NTS. Although kynurenate injected directly into the NTS i surrounding the identity of the kynurenate sensitive
transmitter released by baroreceptor afferents to the
NTS. Although kynurenate injected directly into the
NTS is able to block baroreceptor reflex activity (Guye-
net et transmitter released by baroreceptor afferents to the NTS. Although kynurenate injected directly into the NTS is able to block baroreceptor reflex activity (Guyenet et al., 1987; Blessing, 1989; Le Galloudec et al., 1989; NTS. Although kynurenate injected directly into the a p
NTS is able to block baroreceptor reflex activity (Guye-
net et al., 1987; Blessing, 1989; Le Galloudec et al., 1989; for
Leone and Gordon, 1989; Talman, 1989; Kubo a NTS is able to block baroreceptor reflex activity (Guynet et al., 1987; Blessing, 1989; Le Galloudec et al., 198
Leone and Gordon, 1989; Talman, 1989; Kubo and K
hara, 1991), it appears to do so with little effect c
respon net et al., 1987; Blessing, 1989; Le Galloudec et al., 1989; folcone and Gordon, 1989; Talman, 1989; Kubo and Kihara, 1991), it appears to do so with little effect on is responses produced by exogenously administered gluta Leone and Gordon, 1989; Talman, 1989; Kubo and Ki-
hara, 1991), it appears to do so with little effect on is
responses produced by exogenously administered gluta-
imate. When discussing this apparent paradox, Leone ar
and hara, 1991), it appears to do so with little effect on responses produced by exogenously administered glutamate. When discussing this apparent paradox, Leone and Gordon (1989) and Pawlowski-Dahm and Gordon (1992) have prop responses produced by exogenously administered glutt
mate. When discussing this apparent paradox, Leor
and Gordon (1989) and Pawlowski-Dahm and Gordo
(1992) have proposed two explanations. The simple
explanation may be tha mate. When discussing this apparent paradox, Leonand Gordon (1989) and Pawlowski-Dahm and Gordo (1992) have proposed two explanations. The simple explanation may be that a transmitter other than glut mate, but sensitive to and Gordon (1989) and Pawlowski-Dahm and Gordon [1992) have proposed two explanations. The simplest texplanation may be that a transmitter other than glutamate, but sensitive to kynurenate, is involved in transmission. Alt explanation may be that a transmitter other than glut mate, but sensitive to kynurenate, is involved in tran mission. Alternatively, exogenous glutamate may act receptors that are not sensitive to kynurenate as well a or i mate, but sensitive to kynurenate, is involved in trans-
mission. Alternatively, exogenous glutamate may act at 2A
receptors that are not sensitive to kynurenate as well as, ful
or instead of, receptors activated by transm mission. Alternatively, exogenous glutamate may act are
receptors that are not sensitive to kynurenate as well a
or instead of, receptors activated by transmitter gluta-
mate. In studies of anaesthetised rats, Pawlowski-Da receptors that are not sensitive to kynurenate as well as, full or instead of, receptors activated by transmitter gluta-
mate. In studies of anaesthetised rats, Pawlowski-Dahm the and Gordon (1992) reported that the effica mate. In studies of anaesthetised rats, Pawlowski-Dahm
and Gordon (1992) reported that the efficacy of gluta-
mate in producing depressor responses from the NTS mate. In studies of anaesthetised rats, Pawlowski-Da
and Gordon (1992) reported that the efficacy of glumate in producing depressor responses from the N
was mimicked by the metabotropic receptor ago:
ACPD, although neither and Gordon (1992) reported that the efficacy of gluta-
mate in producing depressor responses from the NTS
was mimicked by the metabotropic receptor agonist
ACPD, although neither action was blocked by kynuren-
ate. This ob mate in producing depressor responses from the NT
was mimicked by the metabotropic receptor agoni
ACPD, although neither action was blocked by kynure
ate. This observation is consistent with the presence
metabotropic sites ate. This observation is consistent with the presence of cometabotropic sites that could mediate effects of exoge-
nous glutamate because the electrophysiological recoponses via these receptors seem to be kynurenate rebust metabotropic sites that could mediate effects of exogenous glutamate because the electrophysiological responses via these receptors seem to be kynurenate resistant (Salt and Eaton, 1991). It is likely that this particular sponses via these receptors seem to be kynurenate resistant (Salt and Eaton, 1991). It is likely that this particular problem will remain unresolved until the advent of selective antagonists at the metabotropic receptors.

particular problem will remain unresolved until the advent of selective antagonists at the metabotropic receptors.

tors.

n. AUDITORY AND VESTIBULAR SYSTEMS. Synaptically veroked field potentials were blocked in a number regions of selective antagonists at the metabotropic recep-
tors. pre-
n. AUDITORY AND VESTIBULAR SYSTEMS. Synaptically ves-
evoked field potentials were blocked in a number of lula-
regions of the isolated frog brain by k tors.

n. AUDITORY AND VESTIBULAR SYSTEMS. Synaptica

evoked field potentials were blocked in a number

regions of the isolated frog brain by kynurenate in

study by Cochran (1983). Field potentials in the vesti

ular nerv n. AUDITORY AND VESTIBULAR SYSTEMS. Synapticall
evoked field potentials were blocked in a number c
regions of the isolated frog brain by kynurenate in
study by Cochran (1983). Field potentials in the vestit
ular nerve, olf evoked field potentials were blocked in a number of regions of the isolated frog brain by kynurenate in a study by Cochran (1983). Field potentials in the vestibular nerve, olfactory bulb, and tectum of this preparation, r regions of the isolated frog brain by kynurenate in a ara
study by Cochran (1983). Field potentials in the vestib-
blow ular nerve, olfactory bulb, and tectum of this preparation, tial
resulting from stimulation of afferen study by Cochran (1983). Field potentials in the vestib-
ular nerve, olfactory bulb, and tectum of this preparation, tia
resulting from stimulation of afferent fibres were pre-
wented by kynurenate. In a later study of iso ular nerve, olfactory bulb, and tectum of this preparation, ties resulting from stimulation of afferent fibres were prevented by kynurenate. In a later study of isolated frog medulla, the synaptic responses to stimulation resulting from stimulation of afferent fibres were prevented by kynurenate. In a later study of isolated frog medulla, the synaptic responses to stimulation of the eighth nerve revealed that kynurenate was more active than vented by kynurenate. In a later study of isolated frog medulla, the synaptic responses to stimulation of the eighth nerve revealed that kynurenate was more active than 2AP5 in blocking synaptically evoked responses (Cochr medulla, the synaptic responses to stimulation of the ireighth nerve revealed that kynurenate was more active of
than 2AP5 in blocking synaptically evoked responses re
(Cochran et al., 1984), again supporting the concept t eighth nerve revealed that kynurenate was more active than 2AP5 in blocking synaptically evoked response (Cochran et al., 1984), again supporting the concept the non-NMDA receptors were important in this form conceptron fr than 2AP5 in blocking synaptically evoked respo
(Cochran et al., 1984), again supporting the concept
non-NMDA receptors were important in this form
neurotransmission. Similarly, transmission from c
lear nerve afferents to (Cochran et al., 1984), again supporting the concept the
non-NMDA receptors were important in this form oneurotransmission. Similarly, transmission from coclear
neurotransmission. Similarly, transmission from coclear
nerve non-NMDA receptors were important in this form
neurotransmission. Similarly, transmission from codear nerve afferents to cells in the nucleus magnocel
laris of the isolated chick medulla was blocked by kyr
renate, whereas neurotransmission. Similarlear nerve afferents to cells
laris of the isolated chick m
renate, whereas selective N!
tive (Jackson et al., 1985).
Both kynurenate and 2A In the nucleus magnocellu-

is of the isolated chick medulla was blocked by kynu-

merate, whereas selective NMDA blockers were ineffec-

duce

(Jackson et al., 1985).

Both kynurenate and 2AP5, however, were able to (Ga

laris of the isolated chick medulla was blocked by kynu-
renate, whereas selective NMDA blockers were ineffec-
tive (Jackson et al., 1985).
Both kynurenate and 2AP5, however, were able to
block the transmission at afferent renate, whereas selective NMDA blockers were ineffec-
tive (Jackson et al., 1985). puls
Both kynurenate and 2AP5, however, were able to (Ga
block the transmission at afferent synapses between hair ling
cells and neurones i tive (Jackson et al., 1985).
Both kynurenate and 2AP5, however, were able
block the transmission at afferent synapses between ha
cells and neurones in the frog vestibular apparatus in
study by Annoni et al. (1984). The rat Both kynurenate and 2AP5, however, were able to ((block the transmission at afferent synapses between hair linells and neurones in the frog vestibular apparatus in a 19 study by Annoni et al. (1984). The rather strange obs block the transmission at afferent synapses between hair ling
cells and neurones in the frog vestibular apparatus in a
study by Annoni et al. (1984). The rather strange obser-
the vation was reported from this study that t

NE
be frequency dependent. At 1 mM kynurenic acid, tran
mission was completely abolished only from stimulatio NE
be frequency dependent. At 1 mM kynurenic acid, trans-
mission was completely abolished only from stimulation
frequencies of approximately 3 Hz, whereas at a 2 mM Frequency dependent. At 1 mM kynurenic acid, transmission was completely abolished only from stimulation
frequencies of approximately 3 Hz, whereas at a 2 mM
antagonist, suppression of transmission appeared at 1 be frequency dependent. At 1 mM kynurenic acid, transmission was completely abolished only from stimulation
frequencies of approximately 3 Hz, whereas at a 2 mM
antagonist, suppression of transmission appeared at 1
Hz; at be frequency dependent. At 1 mM kynurenic acid, transmission was completely abolished only from stimulation
frequencies of approximately 3 Hz, whereas at a 2 mM
antagonist, suppression of transmission appeared at 1
Hz; at mission was completely abolished only from stimulation
frequencies of approximately 3 Hz, whereas at a 2 mM
antagonist, suppression of transmission appeared at 1
Hz; at 2.5 mM antagonist, blockade occurred at 0.5 Hz.
The a frequencies of approximately 3 Hz, whereas at a 2 m
antagonist, suppression of transmission appeared at
Hz; at 2.5 mM antagonist, blockade occurred at 0.5 H
The authors proposed that this interaction might refle
a presynap antagonist, suppression of transmission appeared at 1
Hz; at 2.5 mM antagonist, blockade occurred at 0.5 Hz.
The authors proposed that this interaction might reflect
a presynaptic component in the pharmacology of kynu-
ren Hz; at 2.5 mM antagonist, blockade occurred at
The authors proposed that this interaction might
a presynaptic component in the pharmacology of
renate, but to date there has been no supporting e
for this suggestion from oth he authors proposed that this interaction might reflect
presynaptic component in the pharmacology of kynu-
nate, but to date there has been no supporting evidence
r this suggestion from other neuronal systems.
Perfusion of

explanation may be that a transmitter other than gluta-
mot only spontaneous activity in the afferent nerve but
mate, but sensitive to kynurenate, is involved in trans-
mission. Alternatively, exogenous glutamate may act a presynaptic component in the pharmacology of kynu-
renate, but to date there has been no supporting evidence
for this suggestion from other neuronal systems.
Perfusion of the vestibular system of the axolotl in an
isolat renate, but to date there has been no supporting evidence
for this suggestion from other neuronal systems.
Perfusion of the vestibular system of the axolotl in an
isolated head preparation with excitatory amino acids
induc for this suggestion from other neuronal systems.
Perfusion of the vestibular system of the axolotl in an
isolated head preparation with excitatory amino acids
induced activation of afferent fibres to the CNS. Kainate
and q Perfusion of the vestibular system of the axolotl in an isolated head preparation with excitatory amino acids induced activation of afferent fibres to the CNS. Kainate and quisqualate were substantially more potent in this isolated head preparation with excitatory amino acids
induced activation of afferent fibres to the CNS. Kainate
and quisqualate were substantially more potent in this
preparation than was NMDA. Of a series of antagonists
t induced activation of afferent fibres to the CNS. Kainate
and quisqualate were substantially more potent in this
preparation than was NMDA. Of a series of antagonists
tested, kynurenate was the most potent agent in blockin and quisqualate were substantially more potent in this preparation than was NMDA. Of a series of antagonists tested, kynurenate was the most potent agent in blocking not only spontaneous activity in the afferent nerve but preparation than was NMDA. Of a series of antagonists
tested, kynurenate was the most potent agent in blocking
not only spontaneous activity in the afferent nerve but
also activity evoked physiologically by tilting the hea tested, kynurenate was the most potent agent in blocking
not only spontaneous activity in the afferent nerve but
also activity evoked physiologically by tilting the head.
2AP5 was the least effective antagonist. It seems not only spontaneous activity in the afferent nerve but
also activity evoked physiologically by tilting the head.
2AP5 was the least effective antagonist. It seems that a
full blockade of evoked activity was achieved with also activity evoked physiologically by tilting the head.
2AP5 was the least effective antagonist. It seems that a
full blockade of evoked activity was achieved with ap-
proximately 5 μ M kynurenate which, taking into a 2AP5 was the least effective antagonist. It seems that a full blockade of evoked activity was achieved with approximately 5 μ M kynurenate which, taking into account the authors' (Soto and Vega, 1988) estimate of drug d full blockade of evoked activity was achieved with
proximately 5μ M kynurenate which, taking into acco
the authors' (Soto and Vega, 1988) estimate of d
dilution in their perfusion system, indicates a far hig
potency tha oximately 5 μ M kynurenate which, taking into accouse authors' (Soto and Vega, 1988) estimate of drution in their perfusion system, indicates a far high tency than reported in any other system to date.
There is strong n

ACPD, although neither action was blocked by kynuren-
ate. This observation is consistent with the presence of cells and primary afferent axons in the mammalian sy-
metabotropic sites that could mediate effects of exoge-
n the authors' (Soto and Vega, 1988) estimate of drug
dilution in their perfusion system, indicates a far higher
potency than reported in any other system to date.
There is strong neurochemical evidence for a trans-
mitter r dilution in their perfusion system, indicates a far higher potency than reported in any other system to date.
There is strong neurochemical evidence for a transmitter role for amino acids between sensory receptor cells and potency than reported in any other system to date.
There is strong neurochemical evidence for a transmitter role for amino acids between sensory receptor
cells and primary afferent axons in the mammalian sys-
tem. Bobbin a There is strong neurochemical evidence for a transmitter role for amino acids between sensory receptorells and primary afferent axons in the mammalian system. Bobbin and Ceasar (1987) found that kynurenat could abolish the mitter role for amino acids between sensory receptor
cells and primary afferent axons in the mammalian sys-
tem. Bobbin and Ceasar (1987) found that kynurenate
could abolish the potentials recorded in the scala vesti-
buli cells and primary afferent axons in the mammalian system. Bobbin and Ceasar (1987) found that kynurenate could abolish the potentials recorded in the scala vestibuli of the guinea pig cochlea. The potentials were induced p tem. Bobbin and Ceasar (1987) found that kynure
could abolish the potentials recorded in the scala v
buli of the guinea pig cochlea. The potentials were
duced physiologically by sound stimulation, drugs b
perfused through uld abolish the potentials recorded in the scala vesti-
li of the guinea pig cochlea. The potentials were in-
ced physiologically by sound stimulation, drugs being
rfused through the cochlea in artificial perilymph.
Stimul

tors.
n. AUDITORY AND VESTIBULAR SYSTEMS. Synaptically vestibular nuclei. Lewis et al. (1989) recorded intracel-
evoked field potentials were blocked in a number of lularly from the medial vestibular nucleus in such prepbuli of the guinea pig cochlea. The potentials were in-
duced physiologically by sound stimulation, drugs being
perfused through the cochlea in artificial perilymph.
Stimulation of the eighth nerve entering brain slice
pre duced physiologically by sound stimulation, drugs be
perfused through the cochlea in artificial perilymph.
Stimulation of the eighth nerve entering brain s
preparations of the rat evokes epsps in neurones of
vestibular nuc perfused through the cochlea in artificial perilymph.
Stimulation of the eighth nerve entering brain slice
preparations of the rat evokes epsps in neurones of the
vestibular nuclei. Lewis et al. (1989) recorded intrace
lul Stimulation of the eighth nerve entering brain slice
preparations of the rat evokes epsps in neurones of the
vestibular nuclei. Lewis et al. (1989) recorded intracel-
lularly from the medial vestibular nucleus in such prep preparations of the rat evokes epsps in neurones of t
vestibular nuclei. Lewis et al. (1989) recorded intrac
lularly from the medial vestibular nucleus in such pre
arations and noted that kynurenate, but not 2AP5, co
block vestibular nuclei. Lewis et al. (1989) recorded intracel-
lularly from the medial vestibular nucleus in such prep-
arations and noted that kynurenate, but not 2AP5, could
block the epsps. No changes of resting membrane pot block the epsps. No changes of resting membrane potential input resistance or action potential configuration were seen.

o. OPTIC PATHWAYS. Kynurenate is effective in blocking excitatory transmission in the retinotectal pa

ial input resistance or action potential configuration
were seen.

o. OPTIC PATHWAYS. Kynurenate is effective in block-

ing excitatory transmission in the retinotectal pathway

of goldfish (Langdon and Freeman, 1987) and were seen.

o. OPTIC PATHWAYS. Kynurenate is effective in bl

ing excitatory transmission in the retinotectal path

of goldfish (Langdon and Freeman, 1987) and in bloc

responses to optic nerve stimulation of the suprach
 o. OPTIC PATHWAYS. Kynurenate is effective in block-
ing excitatory transmission in the retinotectal pathway
of goldfish (Langdon and Freeman, 1987) and in blocking
responses to optic nerve stimulation of the suprachias-
m

of goldfish (Langdon and Freeman, 1987) and in blockin
responses to optic nerve stimulation of the suprachias
matic nucleus (Cahill and Menaker, 1987).
5. Site of action of kynurenic acid. Present evidence
strongly suggest responses to optic nerve stimulation of the suprachias-
matic nucleus (Cahill and Menaker, 1987).
5. Site of action of kynurenic acid. Present evidence
strongly suggests that kynurenate is a selective phar-
macological age matic nucleus (Cahill and Menaker, 1987).
5. Site of action of kynurenic acid. Present evidence
strongly suggests that kynurenate is a selective phar-
macological agent. The absence of any effect on neuronal
membrane prope 5. Site of action of kynurenic acid. Present evidence
strongly suggests that kynurenate is a selective phar-
macological agent. The absence of any effect on neuronal
membrane properties or action potential initiation pro-
 strongly suggests that kynurenate is a selective phar-
macological agent. The absence of any effect on neuronal
membrane properties or action potential initiation pro-
duced by intracellularly applied depolarising current
 macological agent. The absence of any effect on neurons
membrane properties or action potential initiation preduced by intracellularly applied depolarising currer
pulses clearly indicates the absence of nonspecific action
 membrane properties or action potential initiation pro-
duced by intracellularly applied depolarising current
pulses clearly indicates the absence of nonspecific actions
(Ganong et al., 1983; Ganong and Cotman, 1986; Herrduced by intracellularly applied depolarising currer
pulses clearly indicates the absence of nonspecific action
(Ganong et al., 1983; Ganong and Cotman, 1986; Her
ling, 1985; Brady and Swann, 1988; Cherubini et al
1988a,b; pulses clearly indicates the absence of nonspecific actions (Ganong et al., 1983; Ganong and Cotman, 1986; Herr-
ling, 1985; Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewis et al., 1989). Several groups have none-
 (Ganong et al., 1983; Ganong and Cotman, 1986; Herr-
ling, 1985; Brady and Swann, 1988; Cherubini et al.,
1988a,b; Lewis et al., 1989). Several groups have none-
theless been interested in the possibility that kynurenate
m ling, 1985; Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewis et al., 1989). Several groups have none-
theless been interested in the possibility that kynurenate
may have a component of its action at presynaptic ter-

PHARMACOLOGICAL REVIEWS

QUINOLINIC AND KY
tors. Jackson et al. (1985), for instance, noted a degree
of frequency dependence of kynurenate's ability to block of QUINOLINIC AND KYN
tors. Jackson et al. (1985), for instance, noted a degree gly
of frequency dependence of kynurenate's ability to block of
transmission from the cochlear nerve in chicks and pro-QUINOLINIC AND
tors. Jackson et al. (1985), for instance, noted a degree
of frequency dependence of kynurenate's ability to block
transmission from the cochlear nerve in chicks and pro-
posed the possibility of a presynapt tors. Jackson et al. (1985), for instance, noted a
of frequency dependence of kynurenate's ability t
transmission from the cochlear nerve in chicks a
posed the possibility of a presynaptic mechanism
Such a possibility was rs. Jackson et al. (1985), for instance, noted a degree frequency dependence of kynurenate's ability to bloch ansmission from the cochlear nerve in chicks and pro sed the possibility of a presynaptic mechanism.
Such a poss

of frequency dependence of kynurenate's ability to block of a
transmission from the cochlear nerve in chicks and pro-
with
posed the possibility of a presynaptic mechanism.
Such a possibility was tested using paired pulse transmission from the cochlear nerve in chicks and posed the possibility of a presynaptic mechanism.
Such a possibility was tested using paired pulse in bition in the perforant path of hippocampal slices
Harris and Cotman posed the possibility of a presynaptic mechanism. Such a possibility was tested using paired pulse inhibition in the perforant path of hippocampal slices by Denvirsi and Cotman (1985), who concluded that kynurenties are re bition in the perforant path of hippocampal slices by Harris and Cotman (1985), who concluded that kynurenate reduced the size of both the first and second evoked responses to an approximately equal extent. There was, ther bition in the perforant path of hippocampal slices by De
Harris and Cotman (1985), who concluded that kynuren-
ate reduced the size of both the first and second evoked
responses to an approximately equal extent. There was, Harris and Cotman (1985), who concluded that kynuren-
ate reduced the size of both the first and second evoked
responses to an approximately equal extent. There was, in
therefore, no change in the relative magnitude of the ate reduced the size of both the first and second evoked
responses to an approximately equal extent. There was, in
therefore, no change in the relative magnitude of the
cansistent with the action of kynurenate limited to t responses to an appro
therefore, no change
paired pulse depressio
consistent with the ac
postsynaptic surface.
A preliminary quan erefore, no change in the relative magnitude of
ired pulse depression, this observation being enti
msistent with the action of kynurenate limited to
stsynaptic surface.
A preliminary quantal analysis of synaptic transm
on

paired pulse depression, this observation being entirely esseconsistent with the action of kynurenate limited to the ami
postsynaptic surface. period analysis of synaptic transmis-
in the medial performed by the medial per consistent with the action of kynurenate limited to the postsynaptic surface.
A preliminary quantal analysis of synaptic transmission in the medial perforant path was performed left Brooks et al. (1986) to probe the site o postsynaptic surface. per perture in the medial performat path was performed by or sign in the medial performat path was performed by or or Brooks et al. (1986) to probe the site of action of kynu-be renate in greater deta A preliminary quantal analysis of synaptic transmistion in the medial performat path was performed by chooks et al. (1986) to probe the site of action of kynumetering greater detail. The variance method was used an conjunc sion in the medial perforant path was performed by Brooks et al. (1986) to probe the site of action of kynu-
renate in greater detail. The variance method was used
in conjunction with intracellular recordings of epsps
evok Brooks et al. (1986) to probe the site of action of kynurenate in greater detail. The variance method was used
in conjunction with intracellular recordings of epsps
evoked in granule cells of the dentate gyrus by medial
pe renate in greater detail. The variance method was used
in conjunction with intracellular recordings of epsps
evoked in granule cells of the dentate gyrus by medial
perforant path stimulation. The results indicated a de-
in in conjunction with intracellular recordings of epevoked in granule cells of the dentate gyrus by me
perforant path stimulation. The results indicated a
crease of mean quantal size but not of the number
quanta released per evoked in granule cells of the dentate gyrus by mediperforant path stimulation. The results indicated a d crease of mean quantal size but not of the number quanta released per stimulus in the presence of kynure ate, a find perforant path stimulation. The results indicated a decrease of mean quantal size but not of the number of quanta released per stimulus in the presence of kynurenate, a finding explicable in terms of an action of kynurenat sites. ianta released per stimulus in the presence of kynures, a finding explicable in terms of an action of kynunate restricted to postsynaptic and not presynapties.
Despite the preceding work, there remains the possity of a pre

ate, a finding explicable in terms of an action of kynu-
renate restricted to postsynaptic and not presynaptic actios.
sites.
bility of a presynaptic action of kynurenate under some st
circumstances. Gaiarsa et al. (1990) renate restricted to postsynaptic and not presynapties.
Sites.
Despite the preceding work, there remains the positive of a presynaptic action of kynurenate under son
circumstances. Gaiarsa et al. (1990) described the occur sites.
Despite the preceding work, there remains the possi-
bility of a presynaptic action of kynurenate under some
circumstances. Gaiarsa et al. (1990) described the occur-
rence of giant depolarising postsynapti potentia Despite the preceding work, there remains the possi-
bility of a presynaptic action of kynurenate under some str
circumstances. Gaiarsa et al. (1990) described the occur-
tonce of giant depolarising postsynapti potentials bility of a presynaptic action of kynurenate under some
circumstances. Gaiarsa et al. (1990) described the occur-
rence of giant depolarising postsynapti potentials in neo-
natal rat CA3 neurones, which appear to involve t circumstances. Gaiarsa et al. (1990) described the occur-
rence of giant depolarising postsynapti potentials in neo-
natal rat CA3 neurones, which appear to involve the
activation of NMDA receptors on GABA-releasing ter-
m rence of giant depolarising postsynapti potentials in neo-
natal rat CA3 neurones, which appear to involve the
activation of NMDA receptors on GABA-releasing ter-
minals, the NMDA receptors facilitating or inducing the
rel natal rat CA3 neurones, which appear to involve the an activation of NMDA receptors on GABA-releasing ter-
minals, the NMDA receptors facilitating or inducing the Frelease of transmitter. Whereas neither glycine nor L-
ser activation of NMDA receptors on GABA-releasing ter-
minals, the NMDA receptors facilitating or inducing the
release of transmitter. Whereas neither glycine nor L-
serine were able to modify NMDA-induced currents in
the CA3 minals, the NMDA receptors facilitating or inducing release of transmitter. Whereas neither glycine nor serine were able to modify NMDA-induced currents the CA3 cells themselves, they did enhance the frequent of the depola release of transmitter. Whereas neither glycine nor L- the offerine were able to modify NMDA-induced currents in that the CA3 cells themselves, they did enhance the frequency stryc of the depolarising potentials consistent serine were able to modify NMDA-induced currents in the CA3 cells themselves, they did enhance the frequency strof the depolarising potentials consistent with a facilita-
for the depolarising potentials consistent with a f the CA3 cells themselves, they did enhance the frequency stry
of the depolarising potentials consistent with a facilita-
tory action at the presynaptic population of NMDA was
receptors. 7-Chlorokynurenate was shown to redu of the depolarising potentials consistent with a factory action at the presynaptic population of Γ receptors. 7-Chlorokynurenate was shown to redupostsynaptic effect of NMDA, this being revers glycine or L-serine, but, tory action at the presynaptic population of NMDA was far higher than as a general competitive antagonist
receptors. 7-Chlorokynurenate was shown to reduce the of amino acids in general, the dissociation constant for
post receptor. glycine or L-serine, but, unfortunately, 7-chlorokynuren-
ate was not examined against the presynaptic NMDA (fig. 2).
receptor. The realisation that kynurenate had complicated ac-
Since there is evidence for strychnine-re glycine or L-serine, but, unfortunately, 7-chlorokynuren-
ate was not examined against the presynaptic NMDA (fig
receptor.
Since there is evidence for strychnine-resistant glycine
sites that are not sensitive to kynurenate

ate was not examined against the presynaptic NMDA (fig.

receptor. T

Since there is evidence for strychnine-resistant glycine tion

sites that are not sensitive to kynurenate in the cord wou

(Danysz et al., 1990), it wil receptor.

Since there is evidence for strychnine-resistant glycine tis

sites that are not sensitive to kynurenate in the cord w

(Danysz et al., 1990), it will be of some importance to co

establish whether there is any Since there is evidence for strychnine-resistant glycine
sites that are not sensitive to kynurenate in the cord
(Danysz et al., 1990), it will be of some importance to
constablish whether there is any correlation between t (Danysz et al., 1990), it will be of some importance to establish whether there is any correlation between these kynurenate-resistant sites and presynaptically located populations of glycine-modulated NMDA receptors. There Nanysz et al., 1990), it will be of some importance to
tablish whether there is any correlation between these
nurenate-resistant sites and presynaptically located
pulations of glycine-modulated NMDA receptors.
There is als establish whether there is any correlation between th
kynurenate-resistant sites and presynaptically loca
populations of glycine-modulated NMDA receptors.
There is also an increasing body of evidence consist
with the locat

kynurenate-resistant sites and presynaptically located k
populations of glycine-modulated NMDA receptors. k
There is also an increasing body of evidence consistent b
with the location of NMDA receptors on other presyn-
apt populations of glycine-modulated NMDA receptors.
There is also an increasing body of evidence consistent
with the location of NMDA receptors on other presyn-
aptic terminals that are capable of modulating the release
of tr There is also an increasing body of evidence consistent
with the location of NMDA receptors on other presyn-
aptic terminals that are capable of modulating the release
of transmitters, including acetylcholine (Adamson et a with the location of NMDA receptors on other presynaptic terminals that are capable of modulating the release
of transmitters, including acetylcholine (Adamson et al., 1990), noradrenaline (Fink et al., 1990), dopamine (Kr aptic terminals that are capable of modulating the release
of transmitters, including acetylcholine (Adamson et al.,
1990), noradrenaline (Fink et al., 1990), dopamine (Krebs
et al., 1991; Overton and Clark, 1991), and glu of transmitters, including acetylcholine (Adamson et al., with
1990), noradrenaline (Fink et al., 1990), dopamine (Krebs age
et al., 1991; Overton and Clark, 1991), and glutamate enti
tiself (Connick and Stone, 1988b; Garc

y

y is a 337 symmetry assumed as a 337 symmetry assumed) the existence

of a glycine allosteric site analogous to that associated YNURENIC ACIDS
glycine, indicating (it is currently assumed) the existence
of a glycine allosteric site analogous to that associated
with the postsynaptic NMDA receptor. If this site is as 337
glycine, indicating (it is currently assumed) the existence
of a glycine allosteric site analogous to that associated
with the postsynaptic NMDA receptor. If this site is as
sensitive to kynurenate as that on postsynap glycine, indicating (it is currently assumed) the existence of a glycine allosteric site analogous to that associate with the postsynaptic NMDA receptor. If this site is a sensitive to kynurenate as that on postsynaptic me glycine, indicating (it is currently assumed) the existence
of a glycine allosteric site analogous to that associated
with the postsynaptic NMDA receptor. If this site is as
sensitive to kynurenate as that on postsynaptic of a glycine allosteric site analogous to that associated
with the postsynaptic NMDA receptor. If this site is as
sensitive to kynurenate as that on postsynaptic mem-
branes, as it appears to be in some cases (Ransom and
D with the postsynaptic NMDA receptor. If this site
sensitive to kynurenate as that on postsynaptic i
branes, as it appears to be in some cases (Ranson
Deschennes, 1989), then kynurenate may well pro
have some ability to mod msitive to kynurenate as that on postsynaptic
anes, as it appears to be in some cases (Ranson
eschennes, 1989), then kynurenate may well prove
some ability to modulate transmitter release.
Kynurenate was not able to modify

branes, as it appears to be in some cases (Ransom a Deschennes, 1989), then kynurenate may well prove have some ability to modulate transmitter release.
Kynurenate was not able to modify depolarisation induced excitatory a Deschennes, 1989), then kynurenate may well prove to
have some ability to modulate transmitter release.
Kynurenate was not able to modify depolarisation-
induced excitatory amino acid release from the hippo-
campus (Connic have some ability to modulate transmitter release.

Kynurenate was not able to modify depolarisation-

induced excitatory amino acid release from the hippo-

campus (Connick and Stone, 1988a,b). It is of course

essential, Kynurenate was not able to modify depolarisation-
induced excitatory amino acid release from the hippo-
campus (Connick and Stone, 1988a,b). It is of course
essential, in view of the activity of kynurenate at several
amino induced excitatory amino acid release from the hippo-
campus (Connick and Stone, 1988a,b). It is of course
essential, in view of the activity of kynurenate at several
amino acid receptors, that care is taken to restrict ex campus (Connick and Stone, 1988a,b). It is of course essential, in view of the activity of kynurenate at several amino acid receptors, that care is taken to restrict experimental conditions to those in which only one recep essential, in view of the activity of kynurenate at several
amino acid receptors, that care is taken to restrict ex-
perimental conditions to those in which only one receptor
type is involved. This may require the use of t amino acid receptors, that care is taken to restrict ex-
perimental conditions to those in which only one receptor
type is involved. This may require the use of tetrodotoxin
or of synaptosomes, but without these precaution perimental conditions to those in which only one receptor
type is involved. This may require the use of tetrodotoxin
or of synaptosomes, but without these precautions it may
be difficult to exclude indirect effects of agon type is involved. This may require the use of tetrodotoxir
or of synaptosomes, but without these precautions it may
be difficult to exclude indirect effects of agonists and
antagonists at various synaptic loci and may lead or of synaptosomes, but without these precautions it may
be difficult to exclude indirect effects of agonists and
antagonists at various synaptic loci and may lead to
ambiguous results (Bandopadhyay and de Belleroche,
1991 antagonists at various synaptic loci and may lead to ambiguous results (Bandopadhyay and de Belleroche, 1991). These considerations are becoming ever more important with the realisation that non-NMDA recepantagonists at various synaptic loci and may lead to ambiguous results (Bandopadhyay and de Belleroche, 1991). These considerations are becoming ever more important with the realisation that non-NMDA receptors may also exi ambiguous results (Bandopadhyay and de Belleroche
1991). These considerations are becoming ever mor
important with the realisation that non-NMDA recep
tors may also exist on nerve terminals and that they ma
also be blocked 91). These considerations are becoming ever more poortant with the realisation that non-NMDA receptre may also exist on nerve terminals and that they may so be blocked by kynurenate (Carrozza et al., 1991).
6. *Glycine sit*

important with the realisation that non-NMDA receptors may also exist on nerve terminals and that they may also be blocked by kynurenate (Carrozza et al., 1991).
6. Glycine site. The requirement of NMDA receptor activation tors may also exist on nerve terminals and that they may
also be blocked by kynurenate (Carrozza et al., 1991).
6. Glycine site. The requirement of NMDA receptor
activation for the occupation of a positive allosteric site
 also be blocked by kynurenate (Carrozza et al., 1991).

6. Glycine site. The requirement of NMDA receptor

activation for the occupation of a positive allosteric site

by low micromolar concentrations of glycine was first
 6. Glycine site. The requirement of NMDA recept activation for the occupation of a positive allosteric sipply low micromolar concentrations of glycine was find postulated by Johnson and Ascher (1987). This is strychnine-in by low micromolar concentrations of glycine was first postulated by Johnson and Ascher (1987). This is a strychnine-insensitive site, and studies of NMDA receptors expressed in *Xenopus* oocytes after the injection of postulated by Johnson and Ascher (1987). This is a
strychnine-insensitive site, and studies of NMDA recep-
tors expressed in *Xenopus* occytes after the injection of
rat brain mRNA indicate that the presence of glycine is
 strychnine-insensitive site, and stutors expressed in *Xenopus* occytes
rat brain mRNA indicate that the
an essential prerequisite for NMI
(Kleckner and Dingledine, 1988).
Following the description of this Following the description of the description of the description of the description of this glycine is
essential prerequisite for NMDA receptor function of the description of this glycine requirement
e observation was made an essential prerequisite for NMDA receptor function (Kleckner and Dingledine, 1988).
Following the description of this glycine requirement, the observation was made by Kessler et al. (1987, 1989)

or of synaptosomes, but without these preceautions it may
be difficult to exclude indirect effects of agonists and
antagonists at various synaptic loci and may lead to
ambiguous results (Bandopadhyay and de Belleroche,
19 an essential prerequisite for NMDA receptor function

(Kleckner and Dingledine, 1988).

Following the description of this glycine requirement,

the observation was made by Kessler et al. (1987, 1989)

that kynurenic acid c (Kleckner and Dingledine, 1988).
Following the description of this glycine requirement,
the observation was made by Kessler et al. (1987, 1989)
that kynurenic acid could displace glycine from its
strychnine-insensitive bin Following the description of this glycine requirement,
the observation was made by Kessler et al. (1987, 1989)
that kynurenic acid could displace glycine from its
strychnine-insensitive binding site responsible for this
mo that kynurenic acid could displace glycine from its
strychnine-insensitive binding site responsible for this
modulatory effect. The activity of kynurenate at this site that kynurenic acid could displace glycine from its
strychnine-insensitive binding site responsible for this
modulatory effect. The activity of kynurenate at this site
was far higher than as a general competitive antagonis strychnine-insensitive binding site responsible for this modulatory effect. The activity of kynurenate at this site was far higher than as a general competitive antagonist of amino acids in general, the dissociation const modulatory effect. The activity of kynurenate at this site was far higher than as a general competitive antagonist of amino acids in general, the dissociation constant for the strychnine-resistant glycine site being in th was far hi
of amino
the strych
15 to 35
(fig. 2).
The rea amino acids in general, the dissociation constant for
e strychnine-resistant glycine site being in the range
it to 35 μ M (Watson et al., 1988; Kessler et al., 1989)
g. 2).
The realisation that kynurenate had complicate

the strychnine-resistant glycine site being in the range 15 to 35 μ M (Watson et al., 1988; Kessler et al., 1989) (fig. 2).
The realisation that kynurenate had complicated actions on the NMDA complex in which low concen 15 to 35 μ M (Watson et al., 1988; Kessler et al., 1989)

(fig. 2).

The realisation that kynurenate had complicated ac-

tions on the NMDA complex in which low concentrations

would act selectively at the glycine site, (fig. 2).
The realisation that kynurenate had complicated a
tions on the NMDA complex in which low concentratio
would act selectively at the glycine site, whereas high
concentrations would act directly at the NMDA reco
nit The realisation that kynurenate had complicated actions on the NMDA complex in which low concentrations would act selectively at the glycine site, whereas higher concentrations would act directly at the NMDA recognition si tions on the NMDA complex in which low concentrations
would act selectively at the glycine site, whereas higher
concentrations would act directly at the NMDA recog-
nition site, followed. Birch et al. (1988a,b) observed th would act selectively at the glycine site, whereas higher
concentrations would act directly at the NMDA recog-
nition site, followed. Birch et al. (1988a,b) observed that
kynurenate would act as a competitive antagonist of concentrations would act directly at the NMDA recognition site, followed. Birch et al. (1988a,b) observed that kynurenate would act as a competitive antagonist of kainate and AMPA without any selectivity between them but t nition site, followed. Birch et al. (1988a,b) observed t
kynurenate would act as a competitive antagonist
kainate and AMPA without any selectivity between th
but that it provided a nonsurmountable antagonism
NMDA in the ra kynurenate would act as a competitive antagonist of
kainate and AMPA without any selectivity between them
but that it provided a nonsurmountable antagonism of
NMDA in the rat hemisected spinal cord. The nonsur-
mountable a kainate and AMPA without any selectivity between them
but that it provided a nonsurmountable antagonism of
NMDA in the rat hemisected spinal cord. The nonsur-
mountable antagonism could be reversed by superfusion
with L-se but that it provided a nonsurmountable antagonism
NMDA in the rat hemisected spinal cord. The nonse
mountable antagonism could be reversed by superfusi
with L-serine or glycine, and in the presence of the
agents, kynurenat NMDA in the rat hemisected spinal cord. The non
mountable antagonism could be reversed by superfu
with L-serine or glycine, and in the presence of t
agents, kynurenate then acted only as a weak and ap
ently competitive ant mountable antagonism could be reversed by superfusion
with L-serine or glycine, and in the presence of these
agents, kynurenate then acted only as a weak and appar-
ently competitive antagonist (Birch et al., 1988a,b).
The with L-serine or glycine, and in the presence of these agents, kynurenate then acted only as a weak and apparently competitive antagonist (Birch et al., 1988a,b).
There is some evidence that the glycine site may not be ful

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FIG. 2. Schematic representation of the NMDA receptor/channel complex indicating the presence of modulatory binding sites for phencyclidine (PCP) and dizocilpine (MK801), glycine, polyamines, and zinc. Positive (enhancing FIG. 2. Schematic representation of the NMDA receptor/channel complex indicating the presence of modulatory binding sites for phencycli-
dine (PCP) and dizocilpine (MK801), glycine, polyamines, and zinc. Positive (enhanci FIG. 2. Schematic representation of the NMDA receptor/channel complex indicating the presence of modulatory binding sites for phencydine (PCP) and dizocilpine (MK801), glycine, polyamines, and zinc. Positive (enhancing) o plus and minus signs, respectively. Kynurenic acid acts partly as an antagonist at the strychinine-resistant glycine site (IC₅₀ approximately 20 μ M) and partly as an antagonist at the NMDA-binding site itself.
because

AM) and partly as an antagonist at the NMDA-binding site itself.

because glycine or L-serine can potentiate responses me-

diated by NMDA receptors (Salt, 1989; Thomson et al.,

1989; Gaiarsa et al., 1990; Stone, 1991). C because glycine or L-serine can potentiate responses me-
diated by NMDA receptors (Salt, 1989; Thomson et al.,
1989; Gaiarsa et al., 1990; Stone, 1991). Collins (1990)
reported that both glycine and L-serine could potentia because glycine or L-serine can potentiate responses me-
diated by NMDA receptors (Salt, 1989; Thomson et al., rena
1989; Gaiarsa et al., 1990; Stone, 1991). Collins (1990) by
reported that both glycine and L-serine could diated by NMDA receptors (Salt, 1989; Thomson et al., 1989; Gaiarsa et al., 1990; Stone, 1991). Collins (1990) b
reported that both glycine and L-serine could potentiate m
polysynaptically mediated excitation of neurones i 1989; Gaiarsa et al., 1990; Stone, 1991). Collins (1990)
reported that both glycine and L-serine could potentiate
polysynaptically mediated excitation of neurones in
slices of mouse olfactory cortex, believed to be mediate reported that both glycine and L-serine could potentiate
polysynaptically mediated excitation of neurones in
slices of mouse olfactory cortex, believed to be mediated
by NMDA receptors. No effect was noted on short la-
ten polysynaptically mediated excitation of neurones in
slices of mouse olfactory cortex, believed to be mediated
by NMDA receptors. No effect was noted on short la-
tency components of these responses or on monosynaptic
respo slices of mouse olfactory cortex, believed to be mediate
by NMDA receptors. No effect was noted on short la
tency components of these responses or on monosynapti
responses involving non-NMDA receptors. Of some sur
prise, h by NMDA receptors. No effect was noted on short la-
tency components of these responses or on monosynaptic
responses involving non-NMDA receptors. Of some sur-
prise, however, was the finding that the effects of exog-
enou tency components of these responses or on monosynaptic
responses involving non-NMDA receptors. Of some sur-
prise, however, was the finding that the effects of exog-
enously bath-applied NMDA were not changed by gly-
cine responses involving non-NMDA receptors. Of some sur-
prise, however, was the finding that the effects of exog-
enously bath-applied NMDA were not changed by gly-
cine or L-serine. This may indicate that exogenous
NMDA inte prise, however, was the finding that the effects of exogenously bath-applied NMDA were not changed by gly-
cine or L-serine. This may indicate that exogenous
NMDA interacts with a population of receptors different
from tha enously bath-applied NMDA were not changed by gly-
cine or L-serine. This may indicate that exogenous
NMDA interacts with a population of receptors different
from that reached by synaptically released transmitter
and that cine or L-serine. This may indicate that exogenous
NMDA interacts with a population of receptors different
from that reached by synaptically released transmitter
and that the latter, but not the former, possesses a glycine NMDA interacts with a population of
from that reached by synaptically re
and that the latter, but not the former,
modulatory site that is not normally
glycine (or other endogenous ligand).
Even in those situations in which by synaptically released transmitter in that the latter, but not the former, possesses a glycine odulatory site that is not normally fully occupied by wine (or other endogenous ligand). Even in those situations in which gl

and that the latter, but not the former, possesses a glycine modulatory site that is not normally fully occupied by glycine (or other endogenous ligand). Even in those situations in which glycine does not enhance basal NMD modulatory site that is not normally fully occupied
glycine (or other endogenous ligand).
Even in those situations in which glycine does non-
enhance basal NMDA sensitivity, the interaction is
tween kynurenate and the glyc glycine (or other endogenous ligand).

Even in those situations in which glycine does not

enhance basal NMDA sensitivity, the interaction be-

tween kynurenate and the glycine site can be demon-

strated by effecting a p Even in those situations in which glycine does not
enhance basal NMDA sensitivity, the interaction be-
tween kynurenate and the glycine site can be demon-
strated by effecting a partial antagonism of NMDA by
kynurenate or enhance basal NMDA sensitivity, the interaction be-
tween kynurenate and the glycine site can be demon-
strated by effecting a partial antagonism of NMDA by
kynurenate or its analogues that can then be reversed by
glycine strated by effecting a partial antagonism of NMDA by
kynurenate or its analogues that can then be reversed by
glycine or L-serine (Pralong et al., 1992; Stone, 1991).
a. GLYCINE-BINDING SITE. Similar findings were re-
por

kynurenate or its analogues that can then be reversed by glycine or L-serine (Pralong et al., 1992; Stone, 1991).

a. GLYCINE-BINDING SITE. Similar findings were reported by Danysz et al. (1989a,b) that kynurenate dispeti glycine or L-serine (Pralong et al., 1992; Stone, 1991).

a. GLYCINE-BINDING SITE. Similar findings were re-

ported by Danysz et al. (1989a,b) that kynurenate dis-

placement of glycine binding occurred with an IC_{50} o a. GLYCINE-BINDING SITE. Similar findings were reported by Danysz et al. (1989a,b) that kynurenate displacement of glycine binding occurred with an IC_{50} of 43 μ M in rat telencephalon, whereas the IC_{50} for kynuren placement of glycine binding occurred with an IC_{50} of 43
 μ M in rat telencephalon, whereas the IC_{50} for kynurenate it

against glutamate binding was 3 times higher. Evidence 1

for an action of kynurenate at the μ M in rat telencephalon, whereas the IC₅₀ for kynurenate against glutamate binding was 3 times higher. Evidence for an action of kynurenate at the NMDA recognition site was also reported from binding studies because against glutamate binding was 3 times higher. Evidence It for an action of kynurenate at the NMDA recognition w
site was also reported from binding studies because it si
displaces 2AP5 binding (Watkins and Olverman, 1988). for an action of kynurenate at the NMDA recognition
site was also reported from binding studies because it
displaces 2AP5 binding (Watkins and Olverman, 1988).
Glycine was also able to stimulate dizocilpine binding
and rev site was also re
displaces 2AP5
Glycine was als
and reversed the
tamate binding.

gonist at the strychinine-resistant glycine site $(IC_{60}$ approximately 20
 $\frac{33}{12}$

On postsynaptically located receptors at least, kynu-

renate has a dual mode of action, partly blocking NMDA

by an action at its r On postsynaptically located receptors at least, kynu-
renate has a dual mode of action, partly blocking NMDA
by an action at its recognition site on the receptor
molecule and partly by displacing glycine from its allo-On postsynaptically located receptors at least, kynu-
renate has a dual mode of action, partly blocking NMDA
by an action at its recognition site on the receptor-
molecule and partly by displacing glycine from its allo-
st On postsynaptically located receptors at least, kynu-
renate has a dual mode of action, partly blocking NMDA
by an action at its recognition site on the receptor
molecule and partly by displacing glycine from its allo-
ste renate has a dual mode of action, partly blocking NMDA
by an action at its recognition site on the receptor
molecule and partly by displacing glycine from its allo-
steric modulatory site associated with the receptor
(Kemp by an action at its recognition site on the receptor molecule and partly by displacing glycine from its allosteric modulatory site associated with the receptor (Kemp et al., 1988; Evans et al., 1987; Mayer et al., 1988; As molecule an
steric mod
(Kemp et al
Ascher et a
al., 1989).
NMDA r eric modulatory site associated with the receptotemp et al., 1988; Evans et al., 1987; Mayer et al., 1988
scher et al., 1988; Henderson et al., 1990; Reynolds e
, 1989).
NMDA responses, studied using the patch-clamp tech-q (Kemp et al., 1988; Evans et al., 1987; Mayer et al., 1986; Henderson et al., 1990; Reynol
al., 1989).
NMDA responses, studied using the patch-clamp in cortical cultures, were antagonised noncon
itively by kynurenate with

Ascher et al., 1988; Henderson et al., 1990; Reynolds et al., 1989).

NMDA responses, studied using the patch-clamp tech-

nique in cortical cultures, were antagonised noncompet-

itively by kynurenate with an IC₅₀ of 7 al., 1989).
NMDA responses, studied using the patch-clamp tech-
nique in cortical cultures, were antagonised noncompet-
itively by kynurenate with an IC_{50} of 70 μ M, whereas
kainate responses were antagonised competi NMDA responses, studied using the patch-clamp tech-
nique in cortical cultures, were antagonised noncompet-
itively by kynurenate with an IC_{50} of 70 μ M, whereas
kainate responses were antagonised competitively at
hi nique in cortical cultures, were antagonised noncompet-
itively by kynurenate with an IC_{50} of 70 μ M, whereas
kainate responses were antagonised competitively at
higher concentrations (ID₅₀ 500 μ M). The kynurena Ethery by ayhutchace with an $1C_{50}$ of 10μ m, whereas
kainate responses were antagonised competitively at
higher concentrations $(ID_{50} 500 \mu)$. The kynurenate
antagonism of NMDA was reversed by glycine (Bertolino
et

ported by Danysz et al. (1989a,b) that kynurenate dis-
placement of glycine binding occurred with an IC_{50} of 43
 μ M in rat telencephalon, whereas the IC_{50} for kynurenate
in the presence of 400 μ M glycine (Pulla higher concentrations $(ID_{50} 500 \mu M)$. The kynuren
antagonism of NMDA was reversed by glycine (Bertol
et al., 1989).
A number of careful quantitative studies have
tempted to elucidate the nature of kynurenate's anta
nist antagonism of NMDA was reversed by glycine (Bertolino
et al., 1989).
A number of careful quantitative studies have at-
tempted to elucidate the nature of kynurenate's antago-
nistic properties against NMDA. When sodium flu et al., 1989).
A number of careful quantitative studies have attempted to elucidate the nature of kynurenate's antagonistic properties against NMDA. When sodium fluxes stimulated by NMDA in rat hippocampal slices were exa A number of careful quantitative studies have attempted to elucidate the nature of kynurenate's antagonistic properties against NMDA. When sodium fluxes stimulated by NMDA in rat hippocampal slices were examined, glycine tempted to elucidate the nature of kynurenate's antag
nistic properties against NMDA. When sodium flux
stimulated by NMDA in rat hippocampal slices we
examined, glycine at 150μ M was found to enhance the
effect in norma nistic properties against NMDA. When sodium fluxes
stimulated by NMDA in rat hippocampal slices were
examined, glycine at 150 μ M was found to enhance this
effect in normal medium and also to reverse the kynu-
renic aci examined, glycine at 150 μ M was found to enhance this effect in normal medium and also to reverse the kynurenic acid-induced inhibition. In the absence of glycine, the kynurenic acid antagonism appeared to be noncomexamined, glycine at 150 μ M was found to enhance this effect in normal medium and also to reverse the kynurenic acid-induced inhibition. In the absence of glycine, the kynurenic acid antagonism appeared to be noncompet effect in normal medium and also to reverse the kynu-
renic acid-induced inhibition. In the absence of glycine,
the kynurenic acid antagonism appeared to be noncom-
petitive with a dose-response Schild slope of 0.6 which
 renic acid-induced inhibition. In the absence of glycine, the kynurenic acid antagonism appeared to be noncompetitive with a dose-response Schild slope of 0.6 which increased to 1 in the presence of 100μ M glycine and 1 the kynurenic acid antagonism appeared to be noncom-
petitive with a dose-response Schild slope of 0.6 which
increased to 1 in the presence of 100μ M glycine and 1.9
in the presence of 400μ M glycine (Pullan and Cler, petitive with a dose-response Schild slope of 0.6 which
increased to 1 in the presence of 100 μ M glycine and 1.9
in the presence of 400 μ M glycine (Pullan and Cler, 1989).
It was concluded that these results are mos increased to 1 in the presence of 100 μ M glycine and 1.9 in the presence of 400 μ M glycine (Pullan and Cler, 1989).
It was concluded that these results are most consistent with a model in which kynurenic acid is act in the presence of 400μ M glycine (Pullan and Cler, 1989 It was concluded that these results are most consiste with a model in which kynurenic acid is acting at two sites, one of which involves a competitive action at t It was concluded i
with a model in v
sites, one of which
NMDA recognitio
acts with glycine.
In cortical slice th a model in which kynurenic acid is acting at two
ces, one of which involves a competitive action at the
MDA recognition site and the second at which it inter-
ts with glycine.
In cortical slices, the depolarising effect sites, one of which involves a competitive action at the NMDA recognition site and the second at which it inter-
acts with glycine.
In cortical slices, the depolarising effect of NMDA could be reduced by kynurenic acid, bu

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quinolinic
could be reversed either by glycine added at concentions ranging from 1μ M to 1 mm or by L-serine but quinolations ranging from 1 μ M to 1 mM or by L-serine but not by L-serine or GABA. There was no ability of glycine or QUINOLINIC AND KYI
could be reversed either by glycine added at concentra-
tions ranging from $1 \mu M$ to $1 \mu M$ or by L-serine but not
to the L-serine or GABA. There was no ability of glycine or
L-serine to reverse kynuren could be reversed either by glycine added at concentrations ranging from $1 \mu M$ to $1 \mu M$ or by L-serine but not by L-serine or GABA. There was no ability of glycine or L-serine to reverse kynurenate's blockade of respons could be reversed either by glycine added at concentrations ranging from $1 \mu M$ to $1 \mu M$ or by L-serine but not by L-serine or GABA. There was no ability of glycine or L-serine to reverse kynurenate's blockade of respons tions ranging from $1 \mu M$ to $1 \mu M$ or by L-serine b
by L-serine or GABA. There was no ability of gly
L-serine to reverse kynurenate's blockade of resp
to quisqualate (Fletcher et al., 1989). The antage
actions of kynuren by L-serine or GABA. There was no ability of glycine or L-serine to reverse kynurenate's blockade of responses kto quisqualate (Fletcher et al., 1989). The antagonistic that actions of kynurenate or its analogues 7-chloro L-serine to reverse kynurenate's blockade of respons
to quisqualate (Fletcher et al., 1989). The antagonis
actions of kynurenate or its analogues 7-chlorokynure
ate or 5,7-dichlorokynurenate are also reversed by glyci
or L to quisqualate (Fletcher et al., 1989). The antagonistic
actions of kynurenate or its analogues 7-chlorokynuren-
ate or 5,7-dichlorokynurenate are also reversed by glycine
or L-serine in other electrophysiological studies, actions of kynurenate or its analogues 7-chlorokynurenate are also reversed by glycior L-serine in other electrophysiological studies, including neocortex and spinal cord (Brugger et al., 19
Pralong et al., 1992), and 7-ch ate or 5,7-dichlorokynurenate are also reversed by glycine
or L-serine in other electrophysiological studies, includ-
ing neocortex and spinal cord (Brugger et al., 1990;
Pralong et al., 1992), and 7-chlorokynurenate antag or L-serine in other electrophysiological stting neocortex and spinal cord (Brugger
Pralong et al., 1992), and 7-chlorokynure
nism is also reversed when blocking NMD*l*
of dopamine release (Mount et al., 1991).
It is often It is ofter assumed that the potency of the potency along et al., 1992), and 7-chlorokynurenate antagorm is also reversed when blocking NMDA stimulation dopamine release (Mount et al., 1991).
It is often assumed that the p

Pralong et al., 1992), and 7-chlorokynurenate antago-
it is in is also reversed when blocking NMDA stimulation
of dopamine release (Mount et al., 1991). for
it is often assumed that the potency of kynurenate's
action at th mism is also reversed when blocking NMDA stimulation
of dopamine release (Mount et al., 1991).
It is often assumed that the potency of kynurenate's
action at the glycine site results in its being the sole or
main mechanism of dopamine release (Mount et al., 1991).
It is often assumed that the potency of kynurenate's
action at the glycine site results in its being the sole of
main mechanism by which it antagonises responses me
diated through It is often assumed that the potency of kynurenate's laction at the glycine site results in its being the sole or main mechanism by which it antagonises responses mediated through NMDA receptors. This has led to erro-
neou action at the glycine site results in its being the sole or nist of main mechanism by which it antagonises responses me-
diated through NMDA receptors. This has led to erro-
Shala neous conclusions about the role of glycin main mechanism by which it antagonises responses me-
diated through NMDA receptors. This has led to erro-
neous conclusions about the role of glycine (Dalkara et
al., 1992). Because kynurenate also acts at the NMDA
recogni diated through NMDA receptors. This has led to erro-

meous conclusions about the role of glycine (Dalkara et

al., 1992). Because kynurenate also acts at the NMDA

the recognition site, failure of glycine to reverse kynur neous conclusions about the role of glycine (Dalkara et al., 1992). Because kynurenate also acts at the NMDA recognition site, failure of glycine to reverse kynurenate antagonism cannot be taken to imply saturation of the al., 1992). Because kynurenate also acts at the NMDA recognition site, failure of glycine to reverse kynurenate antagonism cannot be taken to imply saturation of the glycine site unless low concentrations of the antagonist experiments.

glycine site unless low concentrations of the antagonis
are used. This cannot be guaranteed in iontophoreti
experiments.
There also appears to be a glycine site sensitive t
blockade by kynurenate linked to the control of p are used. This cannot be guaranteed in iontophoretic
experiments.
There also appears to be a glycine site sensitive to
blockade by kynurenate linked to the control of phos-
phoinositol hydrolysis. In guinea pig brain slice experiments.
There also appears to be a glycine site sensitive to
blockade by kynurenate linked to the control of phos-
phoinositol hydrolysis. In guinea pig brain slices, Kendall
and Robinson (1990) found that the suppres There also appears to be a glycine site sensitive to but r
blockade by kynurenate linked to the control of phos-
bindiphoinositol hydrolysis. In guinea pig brain slices, Kendall led th
and Robinson (1990) found that the su blockade by kynurenate linked to the control of phos-
phoinositol hydrolysis. In guinea pig brain slices, Kendall
and Robinson (1990) found that the suppression of car-
bachol-stimulated phosphoinositol turnover by NMDA
wa phoinositol hydrolysis. In guinea pig brain slices, Kendall lector and Robinson (1990) found that the suppression of car-
bachol-stimulated phosphoinositol turnover by NMDA words prevented by 7-chlorokynurenate but that th and Robinson (1990) found that the suppression of carbachol-stimulated phosphoinositol turnover by NMDA was prevented by 7-chlorokynurenate but that this antagonism was then reversed by glycine. Interestingly, the inhibito bachol-stimulated phosphoinositol turnover by NMDA
was prevented by 7-chlorokynurenate but that this an-
tagonism was then reversed by glycine. Interestingly, the
inhibitory effect of glutamate against carbachol was not
pr was prevented by 7-chlorokynurenate but that the tagonism was then reversed by glycine. Interesting inhibitory effect of glutamate against carbachol v
prevented by 7-chlorokynurenate; this may be a
instance of glutamate's inhibitory effect of glutamate against carbachol was not
prevented by 7-chlorokynurenate; this may be another
instance of glutamate's acting at the kynurenate-insen-
sitive metabotropic receptor.

instance of glutamate's acting at the kynurenate-insensitive metabotropic receptor.
The stimulation by NMDA of phencyclidine binding
to the channel site is also enhanced by either glycine or
L-serine in a strychnine-resist instance of glutamate's acting at the kynurenate-insensitive metabotropic receptor.
The stimulation by NMDA of phencyclidine binding
to the channel site is also enhanced by either glycine or
L-serine in a strychnine-resist Issume that the simulation by NMDA of phencyclidine binding The stimulation by NMDA of phencyclidine binding The to the channel site is also enhanced by either glycine or presence in a strychnine-resistant fashion (Snell e The stimulation by NMDA of phencyclidine binding The to the channel site is also enhanced by either glycine or pre-
L-serine in a strychnine-resistant fashion (Snell et al., du-
1987; Reynolds et al., 1987; Kloog et al., 1 to the channel site is also enhanced by either glycine on L-serine in a strychnine-resistant fashion (Snell et al. 1987; Reynolds et al., 1987; Kloog et al., 1988). The implication of a close structural relationship betwee L-serine in a strychnine-resistant fashion (Snell et al., 1987; Reynolds et al., 1987; Kloog et al., 1988). The implication of a close structural relationship between the preceptor and channel is supported by the ability o implication of a close structural relationship b
receptor and channel is supported by the abilurenate to reduce binding of the phencyclidir
N-1-(2-thienyl)cyclohexyl)piperidine and of
(Kessler et al., 1989; Reynolds et al. ceptor and channel is supported by the ability of kyn-

enate to reduce binding of the phencyclidine analogue the

1-(2-thienyl)cyclohexyl)piperidine and of dizocilpine sit

essler et al., 1989; Reynolds et al., 1989). is

urenate to reduce binding of the phencyclidine analogue the N-1-(2-thienyl)cyclohexyl)piperidine and of dizocilpine site, including L-serine and L-kynurenine, which reglycine site, including L-serine and L-kynurenine, whic N-1-(2-thienyl)cyclohexyl)piperidine and of dizocilpine s

(Kessler et al., 1989; Reynolds et al., 1989).

Compounds other than glycine may be active at the

glycine site, including L-serine and L-kynurenine, which

at mil (Kessler et al., 1989; Reynolds et al., 1989). is a
Compounds other than glycine may be active at the responses to plycine site, including L-serine and L-kynurenine, which nent
at millimolar concentrations can reverse the Compounds other than glycine may be active at the glycine site, including L-serine and L-kynurenine, which at millimolar concentrations can reverse the inhibitory effect of kynurenate on neuronal responses to NMDA (Stone, glycine site, including L-serine and L-kynurenine, which
at millimolar concentrations can reverse the inhibitory
effect of kynurenate on neuronal responses to NMDA
(Stone, 1991). Similarly, it has been claimed that β -
 at millimolar concentrations can reverse the inhibiteffect of kynurenate on neuronal responses to NMI (Stone, 1991). Similarly, it has been claimed that methylaminoalanine, one of the putatively neuroto components of cycad effect of kynurenate on neuronal responses to NMDA
(Stone, 1991). Similarly, it has been claimed that β -
methylaminoalanine, one of the putatively neurotoxic
components of cycad seeds responsible for the Parkin-
son's-A (Stone, 1991). Similarly, it has been claimed that β -
methylaminoalanine, one of the putatively neurotoxic the
components of cycad seeds responsible for the Parkin-
son's-Alzheimer's motor neurone disease complex of Pa methylaminoalanine, one of the putatively neurotoxic this
components of cycad seeds responsible for the Parkin-
son's-Alzheimer's motor neurone disease complex of Pa-
the
cific Islanders can also reverse the inhibitory act components of cycad seeds responsible for the Parkin-
son's-Alzheimer's motor neurone disease complex of Pa-
cific Islanders can also reverse the inhibitory action of
kynurenate on glutamate-stimulated calcium influx into
 son's-Alzheimer's motor neurone disease complex of Pacific Islanders can also reverse the inhibitory action of pix-
higher such an effect of physical such an effect of discultured cerebellar neurones (Copani et al., 1991) cific Islanders can also reverse the inhibitory action of kynurenate on glutamate-stimulated calcium influx into cultured cerebellar neurones (Copani et al., 1991). It would be important to confirm whether such an effect

MOTHER SET STRING AND STRING AND MONDRENIC ACIDS
preparations of the CNS and whether it could contribute
to the neurotoxic properties of β -methylaminoalanine. $\begin{array}{l} \textsc{ynew} \textsc$

b. 339

b. 7-CHLOROKYNURENATE. The 7-chloro analogue of

the neurotoxic properties of β -methylaminoalanine.

b. 7-CHLOROKYNURENATE. The 7-chloro analogue of

nurenic acid appears to have a greater selectivity for preparations of the CNS and whether it could contribute
to the neurotoxic properties of β -methylaminoalanine.
b. 7-CHLOROKYNURENATE. The 7-chloro analogue of
kynurenic acid appears to have a greater selectivity for
the preparations of the CNS and whether it could contribute
to the neurotoxic properties of β -methylaminoalanine.
b. 7-CHLOROKYNURENATE. The 7-chloro analogue of
kynurenic acid appears to have a greater selectivity for
the to the neurotoxic properties of β -methylaminoalaning
b. 7-CHLOROKYNURENATE. The 7-chloro analogue
kynurenic acid appears to have a greater selectivity
the glycine site compared with the NMDA recognit
site. In rat corte b. 7-CHLOROKYNURENATE. The 7-chloro analogue of kynurenic acid appears to have a greater selectivity for the glycine site compared with the NMDA recognition site. In rat cortex, the IC₅₀ against glycine is approximately kynurenic acid appears to have a greater selectivity for
the glycine site compared with the NMDA recognition
site. In rat cortex, the IC_{50} against glycine is approxi-
mately 0.56 μ M, whereas at the recognition site, the glycine site compared with the NMDA recognition
site. In rat cortex, the IC_{50} against glycine is approxi-
mately 0.56 μ M, whereas at the recognition site, it is 169
 μ M (Kemp et al., 1988). This selectivity ra site. In rat cortex, the IC₅₀ against glycine is app
mately 0.56 μ M, whereas at the recognition site, it is
 μ M (Kemp et al., 1988). This selectivity ratio of
compares with a ratio of only about 4 for kynurenic
its mately 0.56 μ M, whereas at the recognition site, it is 169 μ M (Kemp et al., 1988). This selectivity ratio of >100 compares with a ratio of only about 4 for kynurenic acid itself and explains the increasing use of 7- μ M (Kemp et al., 1988). This selectivity ratio of $>$ compares with a ratio of only about 4 for kynurenic a itself and explains the increasing use of 7-chloroky renate as a selective antagonist for the glycine site. fo compares with a ratio of only about 4 for kynurenic a
itself and explains the increasing use of 7-chlorokyi
renate as a selective antagonist for the glycine site.
for kynurenate itself, the inhibitory effects of 7-chlo
kyn itself and explains the increasing use of 7-chlorokynu-
renate as a selective antagonist for the glycine site. As
for kynurenate itself, the inhibitory effects of 7-chloro-
kynurenate against dizocilpine binding or as an a renate as a selective antagonist for the glycine site. As for kynurenate itself, the inhibitory effects of 7-chloro-kynurenate against dizocilpine binding or as an antagonist of glutamate neurotoxicity in hippocampal cell for kynurenate itself, t
kynurenate against diz
nist of glutamate neur
tures can be reversed
Shalaby et al., 1989).
Danysz et al. (1989b nurenate against dizocilpine binding or as an antagotat of glutamate neurotoxicity in hippocampal cell culties can be reversed by glycine (Sircar et al., 1989; alaby et al., 1989).
Danysz et al. (1989b) and Kloog et al. (1

glycine site unless low concentrations of the antagonist displace glycine from its binding sites, HA966 was less
are used. This cannot be guaranteed in iontophoretic effective than 7-chlorokynurenate in displacing gluta-
e mist of glutamate neurotoxicity in hippocampal cell curres can be reversed by glycine (Sircar et al., 198
Shalaby et al., 1989).
Danysz et al. (1989b) and Kloog et al. (1990) explor
the differences in mechanism of action b tures can be reversed by glycine (Sircar et al., 19
Shalaby et al., 1989).
Danysz et al. (1989b) and Kloog et al. (1990) exploit
the differences in mechanism of action between 7-ch
rokynurenate and another putative glycine Shalaby et al., 1989).

Danysz et al. (1989b) and Kloog et al. (1990) explored

the differences in mechanism of action between 7-chlo-

rokynurenate and another putative glycine site antago-

mist HA966. Although both com Danysz et al. (1989b) and Kloog et al. (1990) explored
the differences in mechanism of action between 7-chlo-
rokynurenate and another putative glycine site antago-
nist HA966. Although both compounds were able to
displace the differences in mechanism of action between 7-chlorokynurenate and another putative glycine site antage in displace glycine from its binding sites, HA966 was leffective than 7-chlorokynurenate in displacing glut mate bi rokynurenate and another putative glycine site antagonist HA966. Although both compounds were able to displace glycine from its binding sites, HA966 was less effective than 7-chlorokynurenate in displacing glutamate bindin mist HA966. Although both compounds were able to
displace glycine from its binding sites, HA966 was less
effective than 7-chlorokynurenate in displacing gluta-
mate binding or dizocilpine binding. Conversely, HA966,
but no displace glycine from its binding sites, HA966 was less
effective than 7-chlorokynurenate in displacing gluta-
mate binding or dizocilpine binding. Conversely, HA966,
but not 7-chlorokynurenate, was able to facilitate the
 effective than 7-chlorokynurenate in displacing glutamate binding or dizocilpine binding. Conversely, HA966, but not 7-chlorokynurenate, was able to facilitate the binding of the competitive NMDA antagonist CPP. This led t mate binding or dizocilpine binding. Conversely, HA966,
but not 7-chlorokynurenate, was able to facilitate the
binding of the competitive NMDA antagonist CPP. This
led the authors to conclude that 7-chlorokynurenate and
HA but not 7-chlorokynurenate, was able to facilitate the binding of the competitive NMDA antagonist CPP. This led the authors to conclude that 7-chlorokynurenate and HA9 do not act in an identical fashion but may possibly wo led the authors to conclude that 7-chlorokynurenate and HA9 do not act in an identical fashion but may possibly work through overlapping sites associated with the glycine receptor. I the authors to conclude that 7-chlorokynurenate and
A9 do not act in an identical fashion but may possible of
the through overlapping sites associated with the gly
ne receptor.
Several of these findings have been confirm

inhibitory effect of glutamate against carbachol was not derson et al. (1990) using cultured cortical neurones. The
prevented by 7-chlorokynurenate; this may be another dissociation constant of 230 nM was in agreement wit HA9 do not act in an identical fashion but may possibly
work through overlapping sites associated with the gly-
cine receptor.
Several of these findings have been confirmed by Hen-
derson et al. (1990) using cultured corti work through overlapping sites associated with the glycine receptor.

Several of these findings have been confirmed by Hen-

derson et al. (1990) using cultured cortical neurones. The

dissociation constant of 230 nM was i cine receptor.

Several of these findings have been confirmed by Hen-

derson et al. (1990) using cultured cortical neurones. The

dissociation constant of 230 nM was in agreement with

that determined in previous studies Several of these findings have been confirmed by Henderson et al. (1990) using cultured cortical neurones. The dissociation constant of 230 nM was in agreement with that determined in previous studies (Kemp et al., 1988; K derson et al. (1990) using cultured cortical neurones. The dissociation constant of 230 nM was in agreement with that determined in previous studies (Kemp et al., 1988; Kleckner and Dingledine, 1989; Benveniste et al., 19 dissociation constant of 230 nM was in agreement with
that determined in previous studies (Kemp et al., 1988;
Kleckner and Dingledine, 1989; Benveniste et al., 1990).
The dissociation constant for kynurenate itself was ap that determined in previous studies (Kemp et al., Kleckner and Dingledine, 1989; Benveniste et al., 1
The dissociation constant for kynurenate itself wa
proximately 60 times greater, at approximately 1⁸
due to its activi eckner and Dingledine, 1989; Benveniste et al., 1990).
he dissociation constant for kynurenate itself was ap-
oximately 60 times greater, at approximately 15 μ M,
e to its activity at the NMDA recognition site.
An inter

implication of a close structural relationship between the glycine site in NMDA receptor activation by Sircar and
receptor and channel is supported by the ability of kyn-
urenate to reduce binding of the phencyclidine anal The dissociation constant for kynurenate itself was approximately 60 times greater, at approximately 15 μ M,
due to its activity at the NMDA recognition site.
An interesting light has been shed on the role of the
glycin proximately 60 times greater, at approximately 15 μ M, due to its activity at the NMDA recognition site.
An interesting light has been shed on the role of the glycine site in NMDA receptor activation by Sircar and Zukin due to its activity at the NMDA recognition site.

An interesting light has been shed on the role of the

glycine site in NMDA receptor activation by Sircar and

Zukin (1991). This group began from the premise that

the bi An interesting light has been shed on the role of the glycine site in NMDA receptor activation by Sircar and Zukin (1991). This group began from the premise that the binding of dizocilpine to the phencyclidine receptor sit glycine site in NMDA receptor activation by Sircar and

Zukin (1991). This group began from the premise that

the binding of dizocilpine to the phencyclidine receptor

site within the NMDA receptor-associated ion channel
 Zukin (1991). This group began from the premise the binding of dizocilpine to the phencyclidine receptite within the NMDA receptor-associated ion channels is a measure of the activation of those channels response to recept the binding of dizocilpine to the phencyclidine receptosite within the NMDA receptor-associated ion channels is a measure of the activation of those channels is response to receptor activation. An initial rapid component o site within the NMDA receptor-associated ion channel
is a measure of the activation of those channels in
response to receptor activation. An initial rapid compo-
nent of the binding reflects the activation of the chan-
nel is a measure of the activation of those channels in
response to receptor activation. An initial rapid compo-
nent of the binding reflects the activation of the chan-
nels. 7-Chlorokynurenate was found to abolish this rapid response to receptor activation. An initial rapid component of the binding reflects the activation of the channels. 7-Chlorokynurenate was found to abolish this rapid, transient component of dizocilpine binding, and this w nent of the binding reflects the activation of the chan-
nels. 7-Chlorokynurenate was found to abolish this rapid,
transient component of dizocilpine binding, and this was
reversed by the presence of glycine. The implicati nels. 7-Chlorokynurenate was found to abolish this rapid, transient component of dizocilpine binding, and this was
reversed by the presence of glycine. The implication of
this work is that the role of the glycine site is t transient component of dizocilpine binding, and this was
reversed by the presence of glycine. The implication of
this work is that the role of the glycine site is to modulate
the probability of opening up the associated io reversed by the presence of glycine. The implicat
this work is that the role of the glycine site is to moothe probability of opening up the associated ion cha
the glycine site is, therefore, considered to be an ab
prerequi this work is that the role of the glycine site is to modulate
the probability of opening up the associated ion channel;
the glycine site is, therefore, considered to be an absolute
prerequisite for the activation of the io

the probability of opening up the associated ion channel;
the glycine site is, therefore, considered to be an absolute
prerequisite for the activation of the ion channels.
Most recently, Hatta et al. (1992) rather confused the glycine site is, therefore, considered to be an absolut
prerequisite for the activation of the ion channels.
Most recently, Hatta et al. (1992) rather confused th
picture of a two-site model for 7-chlorokynurenate b
de prerequisite for the activation of the ion channels.
Most recently, Hatta et al. (1992) rather confused the
picture of a two-site model for 7-chlorokynurenate by
demonstrating that this compound, together with a num-
ber o

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STOI
but also magnesium-stimulated binding of N-1-(2-
thienyl)cyclohexyl)piperidine. Therefore, there may be a STONE
but also magnesium-stimulated binding of N-1-(2- kyn
thienyl)cyclohexyl)piperidine. Therefore, there may be a at t
third site of action for these compounds, a proposal made c STONE
but also magnesium-stimulated binding of N-1-(2- ky
thienyl)cyclohexyl)piperidine. Therefore, there may be a at
third site of action for these compounds, a proposal made
earlier by other groups (Reynolds et al., 1989 thienyl)cyclohexyl)piperidine. Therefore, there may be a
third site of action for these compounds, a proposal made
earlier by other groups (Reynolds et al., 1989).
Bashir et al. (1990) reported that 7-chlorokynurenate third site of action for these compounds, a proposal made
earlier by other groups (Reynolds et al., 1989).
Bashir et al. (1990) reported that 7-chlorokynurenate
could suppress the NMDA receptor-mediated component

thienyl)cyclohexyl)piperidine. Therefore, there may be a
third site of action for these compounds, a proposal made
earlier by other groups (Reynolds et al., 1989).
Bashir et al. (1990) reported that 7-chlorokynurenate
coul third site of action for these compounds, a proposal made
earlier by other groups (Reynolds et al., 1989).
Bashir et al. (1990) reported that 7-chlorokynurenate
could suppress the NMDA receptor-mediated component is
of syn earlier by other groups (Reynolds et al., 1989).

Bashir et al. (1990) reported that 7-chlorokynurenate to

could suppress the NMDA receptor-mediated component in

of synaptic transmission in rat CA1 cells and that this (Bashir et al. (1990) reported that 7-chlorokynurer
could suppress the NMDA receptor-mediated compon
of synaptic transmission in rat CA1 cells and that
could be reversed by D-serine. In addition, the induc
of LTP was said t could suppress the NMDA receptor-mediated component
of synaptic transmission in rat CA1 cells and that this (199
could be reversed by D-serine. In addition, the induction same
of LTP was said to be prevented by 7-chlorokyn of synaptic transmission in rat CA1 cells and that this (1990)
could be reversed by D-serine. In addition, the induction same f
of LTP was said to be prevented by 7-chlorokynurenate, the ma
but this effect, too, could be could be reversed by D-serine. In addition, the induction sate of LTP was said to be prevented by 7-chlorokynurenate, the but this effect, too, could be reversed by D-serine. In prigrallel experiments, Abe et al. (1990) o of LTP was said to be prevented by 7-chlorokynurenate, but this effect, too, could be reversed by D-serine. In parallel experiments, Abe et al. (1990) observed that low concentrations of glycine (approximately 50 μ M) w but this effect, too, could be reversed by D-serine. In purallel experiments, Abe et al. (1990) observed that low Ir concentrations of glycine (approximately 50 μ M) would glenhance the transient potentiating effect of parallel experiments, Abe et al. (1990) observed that low
concentrations of glycine (approximately 50 μ M) would
enhance the transient potentiating effect of a short tet-
anus in stratum radiatum to the extent that LTP enhance the transient potentiating effect of a short than
anus in stratum radiatum to the extent that LTP v
induced. This phenomenon was not seen in 2AP5, continuing the involvement of NMDA receptors. Also
interest in thi anus in stratum radiatum to the extent that LTP wisternational value of NMDA receptors. Also interest in this report was the claim that higher concertrations of glycine (approximately 500 μ M) would facilitate normal un induced. This phenomenon was not seen in 2AP5, confirming the involvement of NMDA receptors. Also of interest in this report was the claim that higher concentrations of glycine (approximately 500 μ M) would facilitate n firming the involvement of NMDA receptors. Also of
interest in this report was the claim that higher concen-
trations of glycine (approximately 500 μ M) would facili-
tate normal unpotentiated orthodromic population
spi interest in this report was the claim that if trations of glycine (approximately 500 μ M tate normal unpotentiated orthodromispikes, an observation also made by Tl (1989), Collins (1990), and Stone (1991). Glycine facil The interiors of glycine (approximately 500 μ M) would facili-
te normal unpotentiated orthodromic population glycites, an observation also made by Thomson et al. (
989), Collins (1990), and Stone (1991).
Glycine facili

tate normal unpotentiated orthodromic population signals spikes, an observation also made by Thomson et al. (1989), Collins (1990), and Stone (1991).

Glycine facilitates LTP in CA1 neurones (Tauck and spotentiates LTP in spikes, an observation also made by Thomson et al.
(1989), Collins (1990), and Stone (1991).
Glycine facilitates LTP in CA1 neurones (Tauck and
Ashbeck, 1990) and potentiates the facilitation of LTP
by the sulphydryl-reduc (1989), Collins (1990), and Stone (1991).

Glycine facilitates LTP in CA1 neurones (Tauck and

Ashbeck, 1990) and potentiates the facilitation of LTP

by the sulphydryl-reducing agent dithiothreitol. The ac-

tion of glyci Glycine facilitates LTP in CA1 neurones (Tauck and Ashbeck, 1990) and potentiates the facilitation of LTl by the sulphydryl-reducing agent dithiothreitol. The action of glycine was blocked by kynurenate. In addition Woodwa Ashbeck, 1990) and potentiates the facilitation of LTP
by the sulphydryl-reducing agent dithiothreitol. The ac-
tion of glycine was blocked by kynurenate. In addition,
Woodward and Blair (1991) reported that dithiothreitol by the sulphydryl-reducing agent dithiothreitol. The action of glycine was blocked by kynurenate. In addition,
Woodward and Blair (1991) reported that dithiothreitol singreatly enhances NMDA stimulation of noradrenaline r tion of glycine was blocked by kynurenate. In addition,
Woodward and Blair (1991) reported that dithiothreitol
greatly enhances NMDA stimulation of noradrenaline
release from rat cortex slices and reduces the potency of
b Woodward and Blair (1991) reported that dithiothreif
greatly enhances NMDA stimulation of noradrenali
release from rat cortex slices and reduces the potency
both 7-chlorokynurenate and 2AP5 to antagonise t
NMDA effect. Thi greatly enhances NMDA stimulation of noradrenaline
release from rat cortex slices and reduces the potency of
both 7-chlorokynurenate and 2AP5 to antagonise the
NMDA effect. This may indicate that the redox modu-
latory si both 7-chlorokynurenate and 2AP5 to antagonise the NMDA effect. This may indicate that the redox modulatory site of the NMDA recognition site or the glycine/
kynurenate site. NMDA effect. This may indicate that the redox modulatory site of the NMDA receptor complex is located distal to either the NMDA recognition site or the glycine/
kynurenate site.
Using cultured cerebellar granule cells, Rab distal to either the NMDA recognition site or the glycine/
kynurenate site.
Using cultured cerebellar granule cells, Rabe and Ta-
bakoff (1990) reported that glycine and D-serine increase

latory site of the NMDA receptor complex is located
distal to either the NMDA recognition site or the glycine/
kynurenate site.
Using cultured cerebellar granule cells, Rabe and Ta-
bakoff (1990) reported that glycine and distal to either the NMDA recognition site or the glycine/

kynurenate site.

Using cultured cerebellar granule cells, Rabe and Ta-

bakoff (1990) reported that glycine and D-serine increase

NMDA-mediated stimulation of kynurenate site.

Using cultured cerebellar granule cells, Rabe and Ta-

bakoff (1990) reported that glycine and D-serine increase

NMDA-mediated stimulation of calcium influx and, in

addition, partially reverse ethanol's Using cultured cerebellar granule cells, Rabe and Tabakoff (1990) reported that glycine and D-serine increase
NMDA-mediated stimulation of calcium influx and, in
addition, partially reverse ethanol's ability to block the
N bakoff (1990) reported that glycine and D-serine increase
NMDA-mediated stimulation of calcium influx and, in
addition, partially reverse ethanol's ability to block the
NMDA-induced calcium influx. Because comparable in-
t NMDA-mediated stimulation of calcium influx and, in
addition, partially reverse ethanol's ability to block the
NMDA-induced calcium influx. Because comparable in-
teractions were not seen in the case of kainate-stimulated addition, partially reverse ethanol's ability to block the NMDA-induced calcium influx. Because comparable interactions were not seen in the case of kainate-stimulated calcium movements it was concluded that the effects of NMDA-induced calcium influx. Because comparable in-
teractions were not seen in the case of kainate-stimulated
calcium movements it was concluded that the effects of
ethanol may be partly dependent on local concentrations teractions were not seen in the case of kainate-stimulated
calcium movements it was concluded that the effects of
ethanol may be partly dependent on local concentrations
of glycine at the NMDA receptors. The ability of gly calcium movements it was concluded that the effects
ethanol may be partly dependent on local concentratio
of glycine at the NMDA receptors. The ability of glyc:
to potentiate NMDA on acutely isolated pyramidal no
rones fro ethanol may be partly dependent on local concentration
of glycine at the NMDA receptors. The ability of glycin
to potentiate NMDA on acutely isolated pyramidal net
rones from rat hippocampus at low micromolar concer
tratio glycine at the NMDA receptors. The ability of glycine
potentiate NMDA on acutely isolated pyramidal neu-
nes from rat hippocampus at low micromolar concen-
tions was also shown by Chizhmakov et al. (1989).
There appears to

to potentiate NMDA on acutely isolated pyramidal no
rones from rat hippocampus at low micromolar conce
trations was also shown by Chizhmakov et al. (1989).
There appears to be a close functional relationsl
between the NMDA rones from rat hippocampus at low micromolar contrations was also shown by Chizhmakov et al. (1989)
There appears to be a close functional relation
between the NMDA recognition site and the gly-
binding site because 2AP5 c trations was also shown by Chizhmakov et al. (1989).
There appears to be a close functional relations
between the NMDA recognition site and the glycin
binding site because 2AP5 can displace the strychnin
resistant glycine There appears to be a close functional relationship
between the NMDA recognition site and the glycine-
binding site because 2AP5 can displace the strychnine-
resistant glycine binding by approximately 50% (Mona-
han et al. between the NMDA recognition site and the glycine-
binding site because 2AP5 can displace the strychnine-
resistant glycine binding by approximately 50% (Mona-
han et al., 1990); this occurred at concentrations similar
to binding site because 2AP5 can displace the strychnine-
resistant glycine binding by approximately 50% (Mona-
han et al., 1990); this occurred at concentrations similar the
to those effective in displacing NMDA itself or bi resistant glycine binding by approximately 50% (Monahan et al., 1990); this occurred at concentrations similar
to those effective in displacing NMDA itself or binding
to the dizocilpine sensitive channel site. The effect o han et al., 1990); this occurred at concentrations similar the chose effective in displacing NMDA itself or binding sp
to the dizocilpine sensitive channel site. The effect of po
2AP5 (and related compounds) was reversed b to those effective in displacing NMDA itself or binding spermidine, a fact that distinguishes this site from the
to the dizocilpine sensitive channel site. The effect of polyamine site associated with the NMDA receptor
2AP

kynurenate at the NMDA recognition site from effects

concentrations of glycine (approximately 50 μ M) would
enhance the transient potentiating effect of a short tet-
anus in stratum radiatum to the extent that LTP was
model in which kynurenate maintains the NMDA recep-
in NE

kynurenate at the NMDA recognition site from effec

at the glycine site.

c. DESENSITISATION. The glycine site, and thus kynu-

renate, may play a role in regulating desensitisation kynurenate at the NMDA recognition site from effects
at the glycine site.
c. DESENSITISATION. The glycine site, and thus kynu-
renate, may play a role in regulating desensitisation of
the NMDA receptor. Using patch-clamp t kynurenate at the NMDA recognition site from effects
at the glycine site.
c. DESENSITISATION. The glycine site, and thus kynu-
renate, may play a role in regulating desensitisation of
the NMDA receptor. Using patch-clamp t at the glycine site.

c. DESENSITISATION. The glycine site, and thus kynu-

renate, may play a role in regulating desensitisation of

the NMDA receptor. Using patch-clamp techniques on

isolated rat hippocampal neurones, C c. DESENSITISATION. The glycine site, and thus kynu-
renate, may play a role in regulating desensitisation of
the NMDA receptor. Using patch-clamp techniques on
isolated rat hippocampal neurones, Chizhmakov et al.
(1990) r renate, may play a role in regulating desensitisation of
the NMDA receptor. Using patch-clamp techniques on
isolated rat hippocampal neurones, Chizhmakov et al.
(1990) reported that glycine was unable to induce the
same fa the NMDA receptor. Using patch-clamp techniques on isolated rat hippocampal neurones, Chizhmakov et al. (1990) reported that glycine was unable to induce the same facilitation of NMDA responses when applied in the maintain isolated rat hippocampal neurones, Chizhmakov et al. (1990) reported that glycine was unable to induce the same facilitation of NMDA responses when applied in the maintained presence of NMDA, implying a possible primary d (1990) reported that glycine was unable to induce the same facilitation of NMDA responses when applied in the maintained presence of NMDA, implying a possible primary desensitisation of the glycine recognition site. In th same facilitation of NMDA responses when applied in
the maintained presence of NMDA, implying a possible
primary desensitisation of the glycine recognition site.
In the presence of kynurenate (250 μ M), this loss of
gly the maintained presence of NMDA, implying a possible
primary desensitisation of the glycine recognition site.
In the presence of kynurenate $(250 \mu M)$, this loss of
glycine sensitivity did not occur. One possible view of
 primary desensitisation of the glycine recognition sit
In the presence of kynurenate $(250 \mu M)$, this loss
glycine sensitivity did not occur. One possible view
the data proposed by the authors was of a two-sta
model in wh In the presence of kynurenate $(250 \mu M)$, this loss of glycine sensitivity did not occur. One possible view of the data proposed by the authors was of a two-state model in which kynurenate maintains the NMDA receptor in a glycine sensitivity did not occur. One possible view of
the data proposed by the authors was of a two-state
model in which kynurenate maintains the NMDA recep-
tor in a conformation exhibiting sensitivity to glycine. It
is the data proposed by the authors was of a two-state model in which kynurenate maintains the NMDA receptor in a conformation exhibiting sensitivity to glycine. It is difficult to accept this conclusion, however, given the h model in which kynurenate maintains the NMDA receptor in a conformation exhibiting sensitivity to glycine. It is difficult to accept this conclusion, however, given the high concentration of kynurenate that would certainly is difficult to accept this conclusion, however, given the
high concentration of kynurenate that would certainly
have affected the NMDA recognition site as well as the
glycine site.
On the other hand, Shirasaki et al. (199 difficult to accept this conclusion, however, given the gh concentration of kynurenate that would certainly we affected the NMDA recognition site as well as the voine site.
On the other hand, Shirasaki et al. (1990) found

high concentration of kynurenate that would certainly
have affected the NMDA recognition site as well as the
glycine site.
On the other hand, Shirasaki et al. (1990) found that
glycine was able to potentiate the inward cur have affected the NMDA recognition site as well as the glycine site.

On the other hand, Shirasaki et al. (1990) found that

glycine was able to potentiate the inward current re-

sponses to NMDA, i.e., both the early tran glycine site.

On the other hand, Shirasaki et al. (1990) found that

glycine was able to potentiate the inward current re-

sponses to NMDA, i.e., both the early transient response

and the later, slower response assumed On the other hand, Shirasaki et al. (1990) found that
glycine was able to potentiate the inward current re-
sponses to NMDA, i.e., both the early transient response
and the later, slower response assumed because of partia glycine was able to potentiate the inward current re-
sponses to NMDA, i.e., both the early transient response
and the later, slower response assumed because of partial
desensitisation of the receptor. Glycine was unable sponses to NMDA, i.e., both the early transient response
and the later, slower response assumed because of partial
desensitisation of the receptor. Glycine was unable to
prevent the loss of the transient component induced and the later, slower response assumed because of partial desensitisation of the receptor. Glycine was unable to prevent the loss of the transient component induced by preincubation with NMDA. This might be read as consist desensitisation of the receptor. Glycine was unable to
prevent the loss of the transient component induced by
preincubation with NMDA. This might be read as con-
sistent with the work of Chizhmakov et al. (1990) in that
NM prevent the loss of the transient component induced by
preincubation with NMDA. This might be read as con-
sistent with the work of Chizhmakov et al. (1990) in that
NMDA desensitisation might involve the loss of glycine
se preincubation with NMDA. This might be read as consistent with the work of Chizhmakov et al. (1990) in that NMDA desensitisation might involve the loss of glycine sensitivity. It is clearly important to pursue a comparison sistent with the work of Chizhmakov et al. (1990) in that
NMDA desensitisation might involve the loss of glycine
sensitivity. It is clearly important to pursue a comparison
between these studies, in particular to examine t tor in a conformation exhibiting sensitivity to glycine. It
is difficult to accept this conclusion, however, given the
high concentration of kynurenate that would certainly
have affected the NMDA recognition site as well tween these studies, in particular to examine the ef-
tts of blocking the glycine site at concentrations of
nurenate known to be selective, e.g., approximately 20
4.
A comparison was made of the relationship between
e glyc

fects of blocking the glycine site at concentrations of

kynurenate known to be selective, e.g., approximately 20
 μ M.

A comparison was made of the relationship between

the glycine site and the polyamine site of the kynurenate known to be selective, e.g., approximately 20 μ M.
A comparison was made of the relationship between
the glycine site and the polyamine site of the NMDA
receptor. The enhancement of dizocilpine binding in-
du μ M.
A comparison was made of the relationship between
the glycine site and the polyamine site of the NMDA
receptor. The enhancement of dizocilpine binding in-
duced by spermidine, for example, is further enhanced
by gl A comparison was made of the relationship between
the glycine site and the polyamine site of the NMD/
receptor. The enhancement of dizocilpine binding in
duced by spermidine, for example, is further enhancee
by glutamate, the glycine site and the polyamine site of the NMDA
receptor. The enhancement of dizocilpine binding in-
duced by spermidine, for example, is further enhanced
by glutamate, not glycine, whereas 7-chlorokynurenate
reduces t receptor. The enhancement of dizocilpine binding in-
duced by spermidine, for example, is further enhanced
by glutamate, not glycine, whereas 7-chlorokynurenate
reduces the spermidine effect in a manner that is reversed
by duced by spermidine, for example, is further enhanced
by glutamate, not glycine, whereas 7-chlorokynurenate
reduces the spermidine effect in a manner that is reversed
by glycine. Together with other data, the conclusion wa reduces the spermidine effect in a manner that is reversed
by glycine. Together with other data, the conclusion was
drawn that the actions of glutamate and glycine site
ligands appear to be quite distinct and to show littl interaction (Nussenzveig et al., 1991).
Spermine can enhance strychnine-resistant glycine drawn that the actions of glutamate and glycine site
ligands appear to be quite distinct and to show little
interaction (Nussenzveig et al., 1991).
Spermine can enhance strychnine-resistant glycine
binding by increasing th drawn that the actions of glutamate and glycine sit
ligands appear to be quite distinct and to show littl
interaction (Nussenzveig et al., 1991).
Spermine can enhance strychnine-resistant glycin
binding by increasing the a

ligands appear to be quite distinct and to show little
interaction (Nussenzveig et al., 1991).
Spermine can enhance strychnine-resistant glycine
binding by increasing the affinity for glycine at its bind-
ing site (Sacaan interaction (Nussenzveig et al., 1991).
Spermine can enhance strychnine-resistant glycine
binding by increasing the affinity for glycine at its bind-
ing site (Sacaan and Johnson, 1989). Because this phe-
nomenon is still Spermine can enhance strychnine-resistant glycine
binding by increasing the affinity for glycine at its bind-
ing site (Sacaan and Johnson, 1989). Because this phe-
nomenon is still apparent even in the presence of 2AP5
an binding by increasing the affinity for glycine at its bind-
ing site (Sacaan and Johnson, 1989). Because this phe-
nomenon is still apparent even in the presence of 2AP5
and kynurenate, the conclusion was drawn that the po ing site (Sacaan and Johnson, 1989). Because this phe-
nomenon is still apparent even in the presence of 2AP5
and kynurenate, the conclusion was drawn that the po-
lyamine site was distinct from the agonist and antagonist
 nomenon is still apparent even in the presence of 2AP5
and kynurenate, the conclusion was drawn that the po-
lyamine site was distinct from the agonist and antagonist
sites already established. Another result in support of and kynurenate, the conclusion was drawn that the po-
lyamine site was distinct from the agonist and antagonist
sites already established. Another result in support of
this was that the action of spermine was not shared by lyamine site was distinct from the agonist and antagonist
sites already established. Another result in support of
this was that the action of spermine was not shared by
spermidine, a fact that distinguishes this site from sites already estal
this was that the
spermidine, a fact
polyamine site a
(Ransom, 1991).
It is difficult t is was that the action of spermine was not shared by
ermidine, a fact that distinguishes this site from the
lyamine site associated with the NMDA receptor
ansom, 1991).
It is difficult to escape the conclusion from these
i spermidine, a fact that distinguishes this site from the polyamine site associated with the NMDA receptor (Ransom, 1991).
It is difficult to escape the conclusion from these studies that glycine is able to act at a kynuren

PHARMACOLOGICAL REVIEWS

PHARMACOLOGICAL REVIEW

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quinolation to the site associated directly with
the NMDA receptor. Such a conclusion was also drawn QUINOLINIC AND KYN
sitive site in addition to the site associated directly with
the NMDA receptor. Such a conclusion was also drawn
by Danysz et al. (1989b), who reported that 7-chlorokyn-QUINOLINIC
sitive site in addition to the site associated directly
the NMDA receptor. Such a conclusion was also d
by Danysz et al. (1989b), who reported that 7-chloro
urenate or HA966 would displace labeled glycine sitive site in addition to the site associated directly with
the NMDA receptor. Such a conclusion was also drawn
by Danysz et al. (1989b), who reported that 7-chlorokyn-
urenate or HA966 would displace labeled glycine or D sitive site in addition to the site associated directly with
the NMDA receptor. Such a conclusion was also drawn
by Danysz et al. (1989b), who reported that 7-chlorokyn-
urenate or HA966 would displace labeled glycine or D the NMDA receptor. Such a conclusion was also drawn
by Danysz et al. (1989b), who reported that 7-chlorokyn-
urenate or HA966 would displace labeled glycine or D-
serine from binding sites in the rat forebrain, whereas
onl by Danysz et al. (1989b), who reported that 7-chlorok
urenate or HA966 would displace labeled glycine of
serine from binding sites in the rat forebrain, wher
only HA966 was effective in preparations of pons
spinal cord. Th urenate or HA966 would displace labeled glycine or p-
serine from binding sites in the rat forebrain, whereas
only HA966 was effective in preparations of pons and
spinal cord. This would imply the existence of kynuren-
ate serine from binding sites in the rat forebrain, whereas
only HA966 was effective in preparations of pons and
spinal cord. This would imply the existence of kynuren-
ate-insensitive, strychnine-resistant glycine sites. It
w only HA966 was effective in prepa
spinal cord. This would imply the e
ate-insensitive, strychnine-resistar
would be fascinating to establish v
connection between the two ideas.
Paradoxically, binding studies in inal cord. This would imply the existence of kynuren
e-insensitive, strychnine-resistant glycine sites. I
puld be fascinating to establish whether there is any
mection between the two ideas.
Paradoxically, binding studies

ate-insensitive, strychnine-resistant glycine sites. It
would be fascinating to establish whether there is any
connection between the two ideas.
Paradoxically, binding studies in rat neocortex indi-
cate that kynurenic ac would be fascinating to establish whether there is any
connection between the two ideas.
Paradoxically, binding studies in rat neocortex indi-
cate that kynurenic acid has a poorer ability to displace
kainate binding (IC connection between the two ideas.

Paradoxically, binding studies in rat neocortex indicate that kynurenic acid has a poorer ability to displace

kainate binding (IC₅₀ 2082 μ M) than either glutamate

binding at NMDA Paradoxically, binding studies in rat neocortex indicate that kynurenic acid has a poorer ability to displace kainate binding (IC₅₀ 2082 μ M) than either glutamate binding at NMDA receptors (IC₅₀ 184 μ M) or AMPA cate that kynurenic acid has a poorer ability to displace
kainate binding (IC₅₀ 2082 μ M) than either glutamate
binding at NMDA receptors (IC₅₀ 184 μ M) or AMPA
binding (IC₅₀ 101 μ M) (Kemp et al., 1988). Sinc kainate binding (IC₅₀ 2082 μ M) than either glutamate
binding at NMDA receptors (IC₅₀ 184 μ M) or AMPA
binding (IC₅₀ 101 μ M) (Kemp et al., 1988). Since the
same researchers were able to confirm kynurenate's a binding $(IC_{50} 101 \mu M)$ (Kemp et al., 1988). Since the same researchers were able to confirm kynurenate's ability to block electrophysiological responses to kainate, it seems that kynurenate may antagonise this compound binding $(IC_{50} 101 \mu M)$ (Kemp et al., 1988). Since the same researchers were able to confirm kynurenate's ability to block electrophysiological responses to kainate, seems that kynurenate may antagonise this compound by me researchers were able to confirm kynurenate's abil-
 A to block electrophysiological responses to kainate, it

rems that kynurenate may antagonise this compound

acting at a site other than the ligand-binding site.

ity to block electrophysiological responses to kainate, it
seems that kynurenate may antagonise this compound
by acting at a site other than the ligand-binding site.
7. Activity of kynurenate analogues. The first studies
o seems that kynurenate may antagonise this compound
by acting at a site other than the ligand-binding site.
7. Activity of kynurenate analogues. The first studies
of compounds related to kynurenic acid were of other
compon by acting at a site other than the ligand-binding site.

7. Activity of kynurenate analogues. The first studies

of compounds related to kynurenic acid were of other

components of the kynurenine metabolic pathway from

t 7. Activity of kynurenate analogues. The first studies
of compounds related to kynurenic acid were of other
components of the kynurenine metabolic pathway from
tryptophan. Although picolinic, 4-hydroxypicolinic, and
quina components of the kynurenine metabolic pathway from
tryptophan. Although picolinic, 4-hydroxypicolinic, and
quinaldic acids were able to suppress synaptically evoked
field potentials in the hippocampal slice, all of these
 components of the kynurenine metabolic pathway fro
tryptophan. Although picolinic, 4-hydroxypicolinic, an
quinaldic acids were able to suppress synaptically evok
field potentials in the hippocampal slice, all of the
substa tryptophan. Although picolinic, 4-hydroxypicolinic, and
quinaldic acids were able to suppress synaptically evoked
field potentials in the hippocampal slice, all of these
substances had only a fraction of the potency of kyn substances had only a fraction of the potency of kynuactivity. mic acid: all were at least 15 times less active (Perl
hd Stone, 1984; Robinson et al., 1985). Loss of the
rboxy grouping in 4-hydroxyquinoline also diminis
tivity.
The phenyl ring appears to be important to kynure's poten and Stone, 1984; Robinson et al., 1985). Loss of the 2-

carboxy grouping in 4-hydroxyquinoline also diminishes

activity.

The phenyl ring appears to be important to kynuren-

ate's potency in view of the relative inacti

carboxy grouping in 4-hydroxyquinoline also diminishe
activity.
The phenyl ring appears to be important to kynuren
ate's potency in view of the relative inactivity of 4
hydroxypicolinic acid. Paradoxically, perhaps, the ad activity.

The phenyl ring appears to be important to kynurentiate's potency in view of the relative inactivity of 4-

hydroxypicolinic acid. Paradoxically, perhaps, the addi-

this ring, as in

xanthurenic acid, complete The phenyl ring appears to be important to kynurenate's potency in view of the relative inactivity of 4-
hydroxypicolinic acid. Paradoxically, perhaps, the addi-
tion of an 8-hydroxy functionality in this ring, as in
xanth hydroxypicolinic acid. Paradoxically, perhaps, the addition of an 8-hydroxy functionality in this ring, as in xanthurenic acid, completely eliminates any activity. The dicarboxylic compound acridinic acid (quinoline-2,3-dicarboxylic acid) has activity comparable with that xanthurenic acid, completely eliminates any activity.
The dicarboxylic compound acridinic acid (quinoline-
2,3-dicarboxylic acid) has activity comparable with that
of kynurenic acid (Curry et al., 1986).
Noting that the pK nthurenic acid, completely eliminates any activit
he dicarboxylic compound acridinic acid (quinolin
3-dicarboxylic acid) has activity comparable with the
kynurenic acid (Curry et al., 1986).
Noting that the pKa of the 4-hy

The dicarboxylic compound acridinic acid (quinoline-
2,3-dicarboxylic acid) has activity comparable with that
of kynurenic acid (Curry et al., 1986).
Noting that the pKa of the 4-hydroxy and ring nitro-
gen groupings were 2,3-dicarboxylic acid) has activity comparable with that
of kynurenic acid (Curry et al., 1986).
Noting that the pKa of the 4-hydroxy and ring nitro-
gen groupings were 10.5 and 3.5, respectively, Robinson
et al. (1985) e of kynurenic acid (Curry et al., 1986).
Noting that the pKa of the 4-hydroxy and ring nitro-
gen groupings were 10.5 and 3.5, respectively, Robinson
et al. (1985) emphasised that at physiological pH both of
these groups wi Noting that the pKa of the 4-hydroxy and ring nitro-
gen groupings were 10.5 and 3.5, respectively, Robinson
et al. (1985) emphasised that at physiological pH both of
these groups will normally be almost 100% unionised.
H gen groupings were 10.5 and 3.5, respectively, Robinson
et al. (1985) emphasised that at physiological pH both of
these groups will normally be almost 100% unionised.
However, the role of the 4-hydroxy grouping has been
pu et al. (1985) emphasised that at physiological pH both of these groups will normally be almost 100% unionised. provever, the role of the 4-hydroxy grouping has been pursued more recently by Leeson et al. (1991) who prepar these groups will normally be almost 100% unionised. potency However, the role of the 4-hydroxy grouping has been it pursued more recently by Leeson et al. (1991) who prepared the oxanilide compound 1 (fig. 3) and noted a However, the role of the 4-hydroxy grouping has been it
pursued more recently by Leeson et al. (1991) who pre-
pared the oxanilide compound 1 (fig. 3) and noted a 10-
fold greater potency against NMDA or glycine binding
c pursued more recently by Leeson et al. (1991) who pre-
pared the oxanilide compound 1 (fig. 3) and noted a 10-
fold greater potency against NMDA or glycine binding
ompared with compound 2 (fig. 3). This led to the
aci
prop pared the oxanilide compound 1 (fig. 3) and noted a 10-
fold greater potency against NMDA or glycine binding on
compared with compound 2 (fig. 3). This led to the aci
proposal that the keto group of compound 1 (fig. 3) ma fold greater potency against NMDA or glycine binding on the compared with compound 2 (fig. 3). This led to the acid no proposal that the keto group of compound 1 (fig. 3) may concluse important for receptor affinity and t compared with compound 2 (fig. 3). T
proposal that the keto group of compound
be important for receptor affinity and the
equivalent to the 4-keto grouping of the ta
of kynurenic acid (compound 3, fig. 3).
Interestingly, re Supposed that the keto group of compound 1 (fig. 3) in important for receptor affinity and that it might
quivalent to the 4-keto grouping of the tautomeric for
kynurenic acid (compound 3, fig. 3).
Interestingly, replaceme be important for receptor affinity and that it might be
equivalent to the 4-keto grouping of the tautomeric form
of kynurenic acid (compound 3, fig. 3).
Interestingly, replacement of the 4-hydroxy function-
ality by a thio

equivalent to the 4-keto grouping of the tautomeric form
of kynurenic acid (compound 3, fig. 3).
Interestingly, replacement of the 4-hydroxy function-
ality by a thiol group yielded compounds with about
twice the potency o of kynurenic acid (compound 3, fig. 3).
Interestingly, replacement of the 4-hydroxy funct
ality by a thiol group yielded compounds with al
twice the potency of kynurenate and its halogens
derivatives. Moroni et al. (1991c) Interestingly, replacement of the 4-hydroxy function-
ality by a thiol group yielded compounds with about var
twice the potency of kynurenate and its halogenated fec
derivatives. Moroni et al. (1991c) tested the 4-thioqui-

FIG. 3. Structural formulae of kynurenic acid analogues.

field potentials in the hippocampal slice, all of these
substances had only a fraction of the potency of kynu-
renic acid-induced depolarisation of cortical or myen-
renic acid: all were at least 15 times less active (Per (5)
FIG. 3. Structural formulae of kynurenic acid analogues.
(N-1-(2-thienyl)cyclohexyl)piperidine binding and
amino acid-induced depolarisation of cortical or myen-FIG. 3. Structural formulae of kynurenic acid analogues.

(N-1-(2-thienyl)cyclohexyl)piperidine binding a

amino acid-induced depolarisation of cortical or mye

teric neurones. As with the 4-hydroxy series, 5-, 7-, FIG. 3. Structural formulae of kynurenic acid analogues.

(N-1-(2-thienyl)cyclohexyl)piperidine binding and

amino acid-induced depolarisation of cortical or myen-

teric neurones. As with the 4-hydroxy series, 5-, 7-, or
 $(N-1-(2-thienyl)cyclohexyl) piperidine binding amimo acid-induced depolarisation of cortical or myen teric neurones. As with the 4-hydroxy series, 5-, 7-, 05,7-halogen substitution produced active compounds whereas 6- or 8-halogen substitution yielded agents with$ $(N-1-(2-thienyl)cyclohexyl) piperidine binding and amino acid-induced depolarisation of cortical or myenteric neurones. As with the 4-hydroxy series, 5-, 7-, or 5,7-halogen substitution produced active compounds, whereas 6- or 8-halogen substitution yielded agents with little activity. However, significant differences were$ amino acid-induced depolarisation of cortical or myen-
teric neurones. As with the 4-hydroxy series, 5-, 7-, or
5,7-halogen substitution produced active compounds,
whereas 6- or 8-halogen substitution yielded agents with
l teric neurones. As with the 4-hydroxy series, 5-, 7-, or
5,7-halogen substitution produced active compounds
whereas 6- or 8-halogen substitution yielded agents with
little activity. However, significant differences were
no 5,7-halogen substitution produced active compounds,
whereas 6- or 8-halogen substitution yielded agents with
little activity. However, significant differences were
noted in the actions of the 7-trifluoromethyl analogues,
t whereas 6- or 8-halogen substitution yielded agents with
little activity. However, significant differences were
noted in the actions of the 7-trifluoromethyl analogues,
the 4-thio compound being almost 8-fold weaker than
t little activity. However, significant differences were
noted in the actions of the 7-trifluoromethyl analogues,
the 4-thio compound being almost 8-fold weaker than
the 4-hydroxy compound. The authors pointed out that
this noted in the actions of
the 4-thio compound
the 4-hydroxy compour
this may be a mechan
of further investigation
Leeson et al. (1991) e 4-thio compound being almost 8-fold weaker than
e 4-hydroxy compound. The authors pointed out that
is may be a mechanistically important finding worthy
further investigation.
Leeson et al. (1991) proceeded to synthesise

the 4-hydroxy compound. The authors pointed out that
this may be a mechanistically important finding worthy
of further investigation.
Leeson et al. (1991) proceeded to synthesise a cyclised
form of the oxanilide (compound this may be a mechanistically important finding worthy
of further investigation.
Leeson et al. (1991) proceeded to synthesise a cyclised
form of the oxanilide (compound 1, fig. 3), as the 2-
carboxybenzimidazole (compound of further investigation.
Leeson et al. (1991) proceeded to synthesise a cyc
form of the oxanilide (compound 1, fig. 3), as the
carboxybenzimidazole (compound 4). This compo
had greater activity than was claimed for the Leeson et al. (1991) proceeded to synthesise a cyclised
form of the oxanilide (compound 1, fig. 3), as the 2-
carboxybenzimidazole (compound 4). This compound
had greater activity than was claimed for the correspond-
ing carboxybenzimidazole (compound 4). This compound
had greater activity than was claimed for the correspond-
ing indole (compound 5, fig. 3), leading the authors to
conclude that the 3-imino grouping of compound 4 was
funct had greater activity than was claimed for the corresponding indole (compound 5, fig. 3), leading the authors to conclude that the 3-imino grouping of compound 4 was functionally equivalent to the 4-keto grouping of compound 3 and, by extension, leading to the conclusion that i ing indole (compound 5, fig. 3), leading the authors to conclude that the 3-imino grouping of compound 4 was functionally equivalent to the 4-keto grouping of compound 3 and, by extension, leading to the conclusion that i conclude that the 3-imino grouping of compour
functionally equivalent to the 4-keto grouping
pound 3 and, by extension, leading to the conclu
it is the 4-keto tautomer (compound 3) of ky
that is the form active at amino ac nctionally equivalent to the 4-keto grouping of com-
und 3 and, by extension, leading to the conclusion that
is the 4-keto tautomer (compound 3) of kynurenate
at is the form active at amino acid receptors.
Although this co pound 3 and, by extension, leading to the conclusion that
it is the 4-keto tautomer (compound 3) of kynurenate
that is the form active at amino acid receptors.
Although this conclusion cannot be dismissed solely
on the bas

it is the 4-keto tautomer (compound 3) of kynurenate
that is the form active at amino acid receptors.
Although this conclusion cannot be dismissed solely
on the basis of the low expected ionisation of kynurenic
acid noted that is the form active at amino acid receptors.
Although this conclusion cannot be dismissed solely
on the basis of the low expected ionisation of kynurenic
acid noted above, it is perhaps premature to accept the
conclusi Although this conclusion cannot be dismissed solely
on the basis of the low expected ionisation of kynurenic
acid noted above, it is perhaps premature to accept the
conclusion fully without further work. It will be appare on the basis of the low expected ionisation of kynure
acid noted above, it is perhaps premature to accept
conclusion fully without further work. It will be appar
that compounds 4 and 5 (fig. 3) are far from be
equivalent acid noted above, it is perhaps premature to accept the conclusion fully without further work. It will be apparent that compounds 4 and 5 (fig. 3) are far from being equivalent molecules because the 6- or 7-chloro substit conclusion fully without further work. It will be apparent that compounds 4 and 5 (fig. 3) are far from being equivalent molecules because the 6- or 7-chloro substituents have very different effects on potency (see below) that compounds 4 and 5 (fig. 3) are far from being
equivalent molecules because the 6- or 7-chloro substit-
uents have very different effects on potency (see below).
Furthermore, it is quite possible that the activity of equivalent molecules because the 6- or 7-chloro substituents have very different effects on potency (see below
Furthermore, it is quite possible that the activity of the various novel and flexible compounds in figure 3 is uents have very different effects of
Furthermore, it is quite possible various novel and flexible compo
fected by steric considerations thence of the keto/imino groupings.
The study of simple analogues urthermore, it is quite possible that the activity of the
prious novel and flexible compounds in figure 3 is af-
cted by steric considerations that dominate any influ-
ce of the keto/imino groupings.
The study of simple an

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quinolinic acid was taken up by Erez et a!. (1985). Their STONI
quinolinic acid was taken up by Erez et al. (1985). Their
report confirmed the absence of significant agonist or
antagonist properties of several quinolinate analogues
g sro

antagonist acid was taken up by Erez et al. (1985). Their

report confirmed the absence of significant agonist or

antagonist properties of several quinolinate analogues

reported previously by Birley et al. (1982) an quinolinic acid was taken up by Erez et al. (1985). Their the report confirmed the absence of significant agonist or contagonist properties of several quinolinate analogues gly reported previously by Birley et al. (1982) a quinolinic acid was taken up by Erez et al. (1985). The
port confirmed the absence of significant agonist
antagonist properties of several quinolinate analog
reported previously by Birley et al. (1982) and the la
of antago report confirmed the absence of significant agonist or
antagonist properties of several quinolinate analogues
reported previously by Birley et al. (1982) and the lack
of antagonism shown by xanthurenic acid. The impor-
tan antagonist properties of several quinolinate analogues gleported previously by Birley et al. (1982) and the lack for antagonism shown by xanthurenic acid. The impor-
of antagonism shown by xanthurenic acid. The impor-
dant reported previously by Birley et al. (1982) and the lack fold of antagonism shown by xanthurenic acid. The important observation was made, however, that 3-hydroxy-2- The quinoxaline carboxylic acid (compound 6, fig. 4) was of antagonism shown by xanthurenic acid. The important observation was made, however, that 3-hydroxy-2-
quinoxaline carboxylic acid (compound 6, fig. 4) was critic
almost as active as kynurenic acid as an amino acid ant g tant observation was made, however, that 3-hydroxy-2-
quinoxaline carboxylic acid (compound 6, fig. 4) was cri
almost as active as kynurenic acid as an amino acid an
antagonist, with some preference shown for the NMDA
popu quinoxaline carboxylic acid (compound 6, fig. 4) v
almost as active as kynurenic acid as an amino a
antagonist, with some preference shown for the NMI
population of receptors. The results were obtained usi
both the sodium almost as active as kynurenic
antagonist, with some preference
population of receptors. The rest
both the sodium efflux assay in
tion against picrotoxin seizures.
This discovery, in turn, resul tagonist, with some preference shown for the NMDA
pulation of receptors. The results were obtained using kth the sodium efflux assay in brain slices and protec-
on against picrotoxin seizures.
This discovery, in turn, resu

population of receptors. The results were obtained using
both the sodium efflux assay in brain slices and protec-
tion against picrotoxin seizures.
This discovery, in turn, resulted in the synthesis of
other quinoxaline co both the sodium efflux assay in brain slices and protection against picrotoxin seizures.

This discovery, in turn, resulted in the synthesis of sother quinoxaline compounds and led to the production of a series of quinoxa tion against picrotoxin seizures.

This discovery, in turn, resulted in the synthesis of

other quinoxaline compounds and led to the production

of a series of quinoxalinedione compounds, including 6,7-

dinitroquinoxalin This discovery, in turn, resulted in the synthesis of sidence of a series of quinoxalinedione compounds, including 6,7-edinitroquinoxaline-2,3-dione) (compound 7, fig. 4). These substances generated early excitement becau other quinoxaline compounds and led to the production
of a series of quinoxalinedione compounds, including 6,7-
dinitroquinoxaline-2,3-dione) (compound 7, fig. 4).
These substances generated early excitement because of
ph of a series of quinoxalinedione compounds, including 6,7-
dinitroquinoxaline-2,3-dione) (compound 7, fig. 4).
These substances generated early excitement because of
pictor (hainate and AMPA receptors), although it has
beco dinitroquinoxaline-2,3-dione) (compound 7, fig. 4). y
These substances generated early excitement because of p
their apparent selectivity for non-NMDA populations of 5
receptor (kainate and AMPA receptors), although it ha These substances generated early excitement because of part
their apparent selectivity for non-NMDA populations of 5-io
receptor (kainate and AMPA receptors), although it has of 4
become clear that they also show activity their apparent selectivity for non-NMDA populations of 5
receptor (kainate and AMPA receptors), although it has
become clear that they also show activity at the glycine
site of the NMDA receptor complex, as reflected in
b receptor (kainate and AMPA receptors), although it has become clear that they also show activity at the glycine site of the NMDA receptor complex, as reflected in binding studies and the reversal of antagonism by glycine o

binding studies and the reversal of antagonism by glycine
or D-serine (Birch et al., 1988c; Honore et al., 1988).
a. HALOGENATION. One difficulty in interpreting re-
sults obtained with kynurenic acid is that it is a mixe or D-serine (Birch et al., 1988c; Honore et al., 1988).

a. HALOGENATION. One difficulty in interpreting re-

sults obtained with kynurenic acid is that it is a mixed

contagonist, showing activity both at the recognition a. HALOGENATION. One difficulty in interpreting results obtained with kynurenic acid is that it is a mixed antagonist, showing activity both at the recognition sites for NMDA, kainate, and AMPA and at the glycine site of t

therefore, was the synthesis of 7-chlorokynurenic acid, a NE
therefore, was the synthesis of 7-chlorokynurenic acid, a
compound with almost 100-fold higher affinity for the
glycine site compared with kynurenic acid itself and 20-WE
therefore, was the synthesis of 7-chlorokynurenic acid, a
compound with almost 100-fold higher affinity for the
glycine site compared with kynurenic acid itself and 20-
fold more activity as an antagonist of NMDA-induce therefore, was the synthesis of 7-chlorokynurenic acid, a compound with almost 100-fold higher affinity for the glycine site compared with kynurenic acid itself and 20-fold more activity as an antagonist of NMDA-induced de therefore, was the synthesis of 7-chlorokynurenic acid, a compound with almost 100-fold higher affinity for the glycine site compared with kynurenic acid itself and 20-fold more activity as an antagonist of NMDA-induced de compound with almost 100-fold higher affinity for the glycine site compared with kynurenic acid itself and 20-fold more activity as an antagonist of NMDA-induced depolarisations (Kemp et al., 1988; Leeson et al., 1991). Th glycine site compared with kynurenic acid itself a fold more activity as an antagonist of NMDA-idepolarisations (Kemp et al., 1988; Leeson et al., The greater selectivity of 7-chlorokynurenate has critical in determining t fold more activity as an antagonist depolarisations (Kemp et al., 1988; L.
The greater selectivity of 7-chloroky
critical in determining the role of the
ant glycine site in receptor activation
Leeson et al. (1991) reported polarisations (Kemp et al., 1988; Leeson et al., 1991).
he greater selectivity of 7-chlorokynurenate has been
itical in determining the role of the strychnine-resist-
it glycine site in receptor activation.
Leeson et al. (

site of the NMDA receptor complex, as reflected in binding sites, this agent had IC_{50} values of $>100 \mu$ M. For binding studies and the reversal of antagonism by glycine practical reasons, the 5,7-dichloro analogue of k The greater selectivity of 7-chlorokynurenate has bearitical in determining the role of the strychnine-res ant glycine site in receptor activation.
Leeson et al. (1991) reported a large number of other substitutional divid critical in determining the role of the strychnine-resist-
ant glycine site in receptor activation.
Leeson et al. (1991) reported a large number of other
kynurenate analogues bearing halogen and other substit-
uents on the ant glycine site in receptor activation.
Leeson et al. (1991) reported a large number of other
kynurenate analogues bearing halogen and other substit-
uents on the C5 and C7 positions. Alkyl, hydroxyl, cyano,
or methoxy gr Leeson et al. (1991) reported a large number of other
kynurenate analogues bearing halogen and other substit-
uents on the C5 and C7 positions. Alkyl, hydroxyl, cyano,
or methoxy groupings at C5 resulted in compounds with
 kynurenate analogues bearing halogen and other substituents on the C5 and C7 positions. Alkyl, hydroxyl, cyano, or methoxy groupings at C5 resulted in compounds with significantly less activity against NMDA depolarisation uents on the C5 and C7 positions. Alkyl, hydroxyl, cyano, or methoxy groupings at C5 resulted in compounds with significantly less activity against NMDA depolarisation or glycine binding. Various combinations of methyl, et or methoxy groupings at C5 resulted in compounds with
significantly less activity against NMDA depolarisation
or glycine binding. Various combinations of methyl,
ethyl, or halo substituents on C5 and C7, however,
yielded m significantly less activity against NMDA depolarisation
or glycine binding. Various combinations of methyl,
ethyl, or halo substituents on C5 and C7, however,
yielded molecules at least 10-fold more active than the
parent or glycine binding. Various combinations of methyl,
ethyl, or halo substituents on C5 and C7, however,
yielded molecules at least 10-fold more active than the
parent kynurenate. The most potent substance was the
5-iodo,7ethyl, or halo substituents on C5 and C7, however,
yielded molecules at least 10-fold more active than the
parent kynurenate. The most potent substance was the
5-iodo,7-chloro derivative (compound 8, fig. 4) with a K_b
o yielded molecules at least 10-fold more active than th
parent kynurenate. The most potent substance was th
5-iodo,7-chloro derivative (compound 8, fig. 4) with a K
of 410 nM against NMDA responses and an IC₅₀ of onl
32 parent kynurenate. The most potent substance was the 5-iodo,7-chloro derivative (compound 8, fig. 4) with a K_b of 410 nM against NMDA responses and an IC₅₀ of only 32 nM against glycine binding. Against other amino ac 5-iodo,7-chloro derivative (compound 8, fig. 4) with ε of 410 nM against NMDA responses and an IC₅₀ of 32 nM against glycine binding. Against other amino a binding sites, this agent had IC₅₀ values of $>100 \mu$ M. of 410 nM against NMDA responses and an IC₅₀ of only 32 nM against glycine binding. Against other amino acid-
binding sites, this agent had IC₅₀ values of >100 μ M. For
practical reasons, the 5,7-dichloro analogue o 32 nM against glycine binding. Against other amino acid-
binding sites, this agent had IC_{50} values of $>100 \mu$ M. For
practical reasons, the 5,7-dichloro analogue of kynuren-
ate has become the glycine site antagonist o binding sites, this agent had IC_{50} values of $>100 \mu$ M. For
practical reasons, the 5,7-dichloro analogue of kynuren-
ate has become the glycine site antagonist of choice
(McNamara et al., 1990; Hurt and Baron, 1991). T practical reasons, the 5,7-dichloro analogue of kynurenate has become the glycine site antagonist of choice (McNamara et al., 1990; Hurt and Baron, 1991). This compound shows a K_i of 79 nM against glycine binding and gl ate has become the glycine site antagonist of choice (McNamara et al., 1990; Hurt and Baron, 1991). This compound shows a K_i of 79 nM against glycine binding and glycine reversible antagonism of NMDA stimulation of N-1-(McNamara et al., 1990; Hurt and Baron, 1991). This
compound shows a K_i of 79 nM against glycine binding
and glycine reversible antagonism of NMDA stimulation
of N-1-(2-thienyl)cyclohexyl)piperidine binding. As ex-
pect compound shows a K_i of 79 nM against glycine binding
and glycine reversible antagonism of NMDA stimulation
of N-1-(2-thienyl)cyclohexyl)piperidine binding. As ex-
pected, it prevents physiological and biochemical effect and glycine reversible antagonism of NMDA stimulation
of N-1-(2-thienyl)cyclohexyl)piperidine binding. As ex-
pected, it prevents physiological and biochemical effects
of NMDA in several paradigms, including long-term
pot of N-1-(2-thienyl)cyclohexyl)piperidine binding. As expected, it prevents physiological and biochemical effects of NMDA in several paradigms, including long-term potentiation and seizures (Baron et al., 1990). Its own bin pected, it prevents physiologies
of NMDA in several parad
potentiation and seizures (B
binding to rat brain membrar
69 nM) (Baron et al., 1991).
In contrast to the high spe NMDA in several paradigms, including long-term
tentiation and seizures (Baron et al., 1990). Its own
nding to rat brain membranes is with high affinity (K_c
nM) (Baron et al., 1991).
In contrast to the high specificity o binding to rat brain membranes is with high affinity $(K_d$
69 nM) (Baron et al., 1991).
In contrast to the high specificity of these analogues,
substitution of halo, alkyl, nitro, methoxy, or trifluoro-

binding to rat brain membranes is with high affinity $(K_d$
69 nM) (Baron et al., 1991).
In contrast to the high specificity of these analogues,
substitution of halo, alkyl, nitro, methoxy, or trifluoro-
methyl groupings at 69 nM) (Baron et al., 1991).
In contrast to the high specificity of these analogues,
substitution of halo, alkyl, nitro, methoxy, or trifluoro-
methyl groupings at the C6 position resulted in a loss of
any selectivity for In contrast to the high specificity of these analogy substitution of halo, alkyl, nitro, methoxy, or triflucemently groupings at the C6 position resulted in a loss any selectivity for the NMDA receptor, antagonist tency no substitution of halo, alkyl, nitro, methomethyl groupings at the C6 position result any selectivity for the NMDA receptor, tency now being greater against quisqual mediated depolarisation of brain slices.
Halogenation also ethyl groupings at the C6 position resulted in a lost sy selectivity for the NMDA receptor, antagonist
ncy now being greater against quisqualate- or kain
ediated depolarisation of brain slices.
Halogenation also enhances t

any selectivity for the NMDA receptor, antagonist po-
tency now being greater against quisqualate- or kainate-
mediated depolarisation of brain slices.
Halogenation also enhances the potency of 3-hydroxy-
2-quinolinecarbox tency now being greater against quisqualate- or kainate-
mediated depolarisation of brain slices.
Halogenation also enhances the potency of 3-hydroxy-
2-quinolinecarboxylic acid, the 6,7-dichloro analogue (9)
being approx mediated depolarisation of brain slices.

Halogenation also enhances the potency of 3-hydroxy-

2-quinolinecarboxylic acid, the 6,7-dichloro analogue (9)

being approximately 10 times more active as an NMDA

antagonist. Wh Halogenation also enhances the potency of 3-hydroxy-
2-quinolinecarboxylic acid, the 6,7-dichloro analogue (9)
being approximately 10 times more active as an NMDA
antagonist. When blocking responses to NMDA on frog
spinal 2-quinolinecarboxylic acid, the 6,7-dichloro analogue (9)
being approximately 10 times more active as an NMDA
antagonist. When blocking responses to NMDA on frog
spinal cord or the sodium efflux assay in rat brain, 3-
hyd being approximately 10 times more active as an NMDA
antagonist. When blocking responses to NMDA on frog
spinal cord or the sodium efflux assay in rat brain, 3-
hydroxy-2-quinolinecarboxylic acid is similar in potency
to 2 antagonist. When blocking responses to NMDA on frog
spinal cord or the sodium efflux assay in rat brain, 3-
hydroxy-2-quinolinecarboxylic acid is similar in potency
to 2AP7, with a pA₂ of 5.8 or 5.6, respectively (Frey spinal cord or the sodium efflux assay in rat brain, 3-
hydroxy-2-quinolinecarboxylic acid is similar in potency
to 2AP7, with a pA₂ of 5.8 or 5.6, respectively (Frey et
al., 1988). It is also active as an antagonist of to 2AP7, with a pA_2 of 5.8 or 5.6, respectively (Frey et al., 1988). It is also active as an antagonist of kainate (pA_2 5.4). The greater potency of the dichlorinated substance would be consistent with its acting at to 2AP7, with a pA₂ of 5.8 or 5.6, respectively (Frey et al., 1988). It is also active as an antagonist of kainate (pA₂ 5.4). The greater potency of the dichlorinated substance would be consistent with its acting at t al., 1988). It is also active as an antagonist of kainate $(pA_2 5.4)$. The greater potency of the dichlorinated substance would be consistent with its acting at the kynurenic acid site, a view that is supported by the rep (pA_2 5.4). The greater potency of the dichlorinated substance would be consistent with its acting at the kynurenic acid site, a view that is supported by the report that its antagonistic activity can be prevented by Dstance would be consistent with its acting at the
renic acid site, a view that is supported by the
that its antagonistic activity can be prevented
serine (Birch et al., 1989). There remain, howev
triguing differences in th that its antagonistic activity can be prevented by p-
serine (Birch et al., 1989). There remain, however, in-
triguing differences in the activity of 6,7-dichloro-3-hy-
droxy-2-quinolinecarboxylic acid in different prepara that its antagonistic activity can be prevented by p-
serine (Birch et al., 1989). There remain, however, in-
triguing differences in the activity of 6,7-dichloro-3-hy-
droxy-2-quinolinecarboxylic acid in different prepara serine (Birch et al., 1989). There remain, however, in-
triguing differences in the activity of 6,7-dichloro-3-hy-
droxy-2-quinolinecarboxylic acid in different prepara-
tions. It appears to distinguish between kainate and triguing differences in the activity of 6,7-dichloro-3-hy-
droxy-2-quinolinecarboxylic acid in different prepara-
tions. It appears to distinguish between kainate and
quisqualate effects on adult rat brain slices, blocking

spet

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QUINOLINIC AND KYN
discriminate these agonists in neonatal rat spinal cord ma
(Birch et al., 1989). This discrepancy may be partly due lor QUINOLINIC AND KYN

discriminate these agonists in neonatal rat spinal cord ma

(Birch et al., 1989). This discrepancy may be partly due lon

to the different tissues used, but tests also show that 6,7 19 QUINOLINIC AND KYNU
discriminate these agonists in neonatal rat spinal cord mat
(Birch et al., 1989). This discrepancy may be partly due lord
to the different tissues used, but tests also show that 6,7 199
dichloro-3-hydro discriminate these agonists in neonatal rat spinal cord (Birch et al., 1989). This discrepancy may be partly due to the different tissues used, but tests also show that 6,7 dichloro-3-hydroxy-2-quinolinecarboxylic acid doe discriminate these agonists in neonatal rat spinal cord (Birch et al., 1989). This discrepancy may be partly due
to the different tissues used, but tests also show that 6,7
dichloro-3-hydroxy-2-quinolinecarboxylic acid doe (Birch et al., 1989). This discrepancy may be partly contract to the different tissues used, but tests also show that dichloro-3-hydroxy-2-quinolinecarboxylic acid does in discriminate kainate and quisqualate responses on to the different tissues used, but tests also show that $\ddot{\text{d}}$ dichloro-3-hydroxy-2-quinolinecarboxylic acid does n
discriminate kainate and quisqualate responses on ad
rat neocortex (P. L. Herrling, personal communic dichloro-3-hydroxy-2-quinolinecarboxylic acid does not at discriminate kainate and quisqualate responses on adult pot rat neocortex (P. L. Herrling, personal communication). gly It is likely, therefore, that the lack of qu discriminate kainate and quisqualate responses on adult port rat neocortex (P. L. Herrling, personal communication). gly
It is likely, therefore, that the lack of quisqualate antag-
onism is a feature of the sodium efflux It is likely, therefore, that the lack of quisqualate antagonism is a feature of the sodium efflux assay. There ma
be other technical or biological considerations to be take
into account, however, because Frey et al. (1988 onism is a feature of the sodium efflux assay. There may pot
be other technical or biological considerations to be taken mainto account, however, because Frey et al. (1988) also liga
reported a parallel displacement of th be other technical or biological considerations to be t
into account, however, because Frey et al. (1988)
reported a parallel displacement of the "agonist" corresponse curves, whereas Birch et al. (1989) observed
nonparal to account, however, because Frey et al. (1988) also ported a parallel displacement of the "agonist" dose-
sponse curves, whereas Birch et al. (1989) observed a mparallel shift at high concentrations ($>30 \mu$ M).
By using

reported a parallel displacement of the "agonist" dose-
response curves, whereas Birch et al. (1989) observed a
nonparallel shift at high concentrations (>30 μ M).
By using *Xenopus* oocytes to express amino acid re-
st response curves, whereas Birch et al. (1989) observed a an anonparallel shift at high concentrations $(>30 \mu M)$. P
By using *Xenopus* oocytes to express amino acid reseptors transcribed from rat brain mRNA, Kleckner and nonparallel shift at high concentrations (>3
By using *Xenopus* oocytes to express am
ceptors transcribed from rat brain mRNA, K
Dingledine (1989) confirmed the greater p
chlorokynurenate and 6,7-dichloro-3-hydrox
necarbox By using *Xenopus* oocytes to express amino acid receptors transcribed from rat brain mRNA, Kleckner and Dingledine (1989) confirmed the greater potency of 7 chlorokynurenate and 6,7-dichloro-3-hydroxy-2-quinoli necarboxyl ceptors transcribed from rat brain mRNA, Kleckner and ve
Dingledine (1989) confirmed the greater potency of 7-
chlorokynurenate and 6,7-dichloro-3-hydroxy-2-quinoli-
necarboxylic acid compared with the parent compounds.
Bo Dingledine (1989) confirmed the greater potency of
chlorokynurenate and 6,7-dichloro-3-hydroxy-2-quinol
necarboxylic acid compared with the parent compound
Both produced parallel shifts of the dose-response cur-
for glycin chlorokynurenate and 6,7-dichloro-3-hydroxy-2-quinolinecarboxylic acid compared with the parent compounds
Both produced parallel shifts of the dose-response curv
for glycine in tests of glycine/NMDA combinations
Schild slo necarboxylic acid compared with the parent compounds.
Both produced parallel shifts of the dose-response curve
for glycine in tests of glycine/NMDA combinations.
Schild slopes of unity confirmed competitive antagonism.
Bot Both produced parallel shifts of the dose-response curv
for glycine in tests of glycine/NMDA combinations
Schild slopes of unity confirmed competitive antagonism
Both compounds were active, although less potent
against res for glycine in tests of glycine/NMDA combinations.
Schild slopes of unity confirmed competitive antagonism.
Both compounds were active, although less potent,
against responses to kainate. Indeed, 7-chlorokynurenate
was 40 Schild slopes of unity confirmed competitive antagonism.
Both compounds were active, although less potent,
against responses to kainate. Indeed, 7-chlorokynurenate
was 40 times less effective against kainate and was not
co Both compounds were active, although less potent, against responses to kainate. Indeed, 7-chlorokynurenate was 40 times less effective against kainate and was not competitive (Schild slope 0.72). Interestingly, these autho against responses to kainate. Indeed, 7-chlorokyn
was 40 times less effective against kainate and v
competitive (Schild slope 0.72). Interestingly, th
thors also noted that 6,7-halogenation increased
tency of quinoxalinedi as 40 times less effective against kainate and was not ¹
mpetitive (Schild slope 0.72). Interestingly, these au-
ors also noted that 6,7-halogenation increased the po-
ncy of quinoxalinediones for the glycine site.
Seve

competitive (Schild slope 0.72). Interestingly, these au
thors also noted that 6,7-halogenation increased the po
tency of quinoxalinediones for the glycine site.
Several studies have now been reported of extending
the kynu thors also noted that 6,7-halogenation increased the po-
tency of quinoxalinediones for the glycine site.
Several studies have now been reported of extending
the kynurenate molecule with additional groupings. Har-
rison e tency of quinoxalinediones for the glycine site.
Several studies have now been reported of extend
the kynurenate molecule with additional groupings. F
rison et al. (1990) synthesised compounds with exten
C4-position moieti Several studies have now been reported of extending
the kynurenate molecule with additional groupings. Har-
rison et al. (1990) synthesised compounds with extended
C4-position moieties including 4-(carboxymethyloxy)-
5,7-d the kynurenate molecule with additional
rison et al. (1990) synthesised compound
C4-position moieties including 4-(carboxylic acid
5,7-dichloroquinoline-2-carboxylic acid
fig. 4) and 4-(carboxymethylamino)-5,
line-2-carbox rison et al. (1990) synthesised compounds with extended C4-position moieties including 4-(carboxymethyloxy)-
5,7-dichloroquinoline-2-carboxylic acid (compound 10,
fig. 4) and 4-(carboxymethylamino)-5,7-dichloroquino-
line-5,7-dichloroquinoline-2-carboxylic acid (compound 10, fig. 4) and 4-(carboxymethylamino)-5,7-dichloroquino-
line-2-carboxylic acid (compound 11). Compound 10 retained the potency of kynurenic acid but was approxi-
mately fig. 4) and $4-(carboxymethylamino)-5,7-dichloroquino$ line-2-carboxylic acid (compound 11). Compound 10 retained the potency of kynurenic acid but was approximately 25 times more selective for the glycine site compared with the NMDA recognition site (CPP binding). The amino c line-2-carboxylic acid (compound 11). Compound 10 retained the potency of kynurenic acid but was approximately 25 times more selective for the glycine site compared with the NMDA recognition site (CPP binding). The amino tained the potency of kynurenic acid but was approximately 25 times more selective for the glycine site compared with the NMDA recognition site (CPP binding). The amino compound 11, on the other hand, was substantially mo mately 25 times more selective for the glycine si
pared with the NMDA recognition site (CPP b
The amino compound 11, on the other hand, w
stantially more potent, having an IC_{50} of 70 nM
glycine binding (comparable with pared with the NMDA recognition site (CPP binding).
The amino compound 11, on the other hand, was substantially more potent, having an IC_{60} of 70 nM against glycine binding (comparable with 5,7-dichlorokynurenate) and The amino compound
stantially more poten
glycine binding (com
ate) and was 1400-f
(Baron et al., 1992).
The added carboxyl antially more potent, having an IC_{50} of 70 nM against
ycine binding (comparable with 5,7-dichlorokynuren-
e) and was 1400-fold selective for the glycine site
aron et al., 1992).
The added carboxyl group is clearly cruc glycine binding (comparable with 5,7-dichlorokynurenate) and was 1400 -fold selective for the glycine site (Baron et al., 1992).
The added carboxyl group is clearly crucial to this high

ate) and was 1400-fold selective for the glycine site
(Baron et al., 1992).
The added carboxyl group is clearly crucial to this high
potency and selectivity because neither 4-amino nor 4-
methoxy analogues of kynurenic aci (Baron et al., 1992).
The added carboxyl group is clearly crucial to this high
potency and selectivity because neither 4-amino nor 4-
methoxy analogues of kynurenic acid have appreciable
antagonist activity. In attempting The added carboxyl group is clearly crucial to this high
potency and selectivity because neither 4-amino nor 4-
methoxy analogues of kynurenic acid have appreciable
antagonist activity. In attempting to explain the activit methoxy analogues of kynurenic acid have appreciable
antagonist activity. In attempting to explain the activity
of compound 11 (fig. 4), the authors note that calculation
of energy states suggests that kynurenic acid and i methoxy analogues of kynurenic acid have appreciable
antagonist activity. In attempting to explain the activity
of compound 11 (fig. 4), the authors note that calculation
of energy states suggests that kynurenic acid and i antagonist activity. In attempting to explain the activity
of compound 11 (fig. 4), the authors note that calculation
of energy states suggests that kynurenic acid and its
analogues prefer to exist in the quinolone tautom of compound 11 (fig. 4), the authors note that calculation
of energy states suggests that kynurenic acid and its
analogues prefer to exist in the quinolone tautomeric
form (compound 12), a possibility that was discussed
a of energy states suggests that kynurenic acid and its
analogues prefer to exist in the quinolone tautomeric
form (compound 12), a possibility that was discussed
above. The ability of compound 11 to form such a tau-
tomer (form (compound 12), a possibility that was discussed
above. The ability of compound 11 to form such a tau-
tomer (compound 13) readily may account for its high
potency (fig. 4). rm (compound 12), a possibility that was discuss
ove. The ability of compound 11 to form such a ta
mer (compound 13) readily may account for its hi
tency (fig. 4).
In related studies, analogues of 5,7-dichlorokynurenat
we above. The ability of compound 11 to form such a tau-
tomer (compound 13) readily may account for its high
potency (fig. 4).
In related studies, analogues of 5,7-dichlorokynurenate
have been described in which the carboxyl

fully may account for its hypotency (fig. 4).

In related studies, analogues of 5,7-dichloro computed in the carboxylated ring

fully saturated. The 5,7-dichloro compound is approximated.

rat neocortex (P. L. Herrling, personal communication). glycine site. Of several analogues reported, the 4-pheny-
It is likely, therefore, that the lack of quisqualate antag-
lurea derivative (compound 14, fig. 5) was the YNURENIC ACIDS
mately 10-fold less active than the unsaturated 5,7-di
lorokynurenate (Leeson et al., 1991, 1992; Foster et SUNURENIC ACIDS

1943

mately 10-fold less active than the unsaturated 5,7-dich-

lorokynurenate (Leeson et al., 1991, 1992; Foster et al.,

1992). Compounds bearing *trans*-oriented substituents 343

mately 10-fold less active than the unsaturated 5,7-dich-

lorokynurenate (Leeson et al., 1991, 1992; Foster et al.,

1992). Compounds bearing *trans*-oriented substituents

at the 2-(carboxy) and C4- positions proved mately 10-fold less active than the unsaturated 5,7-dich-
lorokynurenate (Leeson et al., 1991, 1992; Foster et al.,
1992). Compounds bearing *trans*-oriented substituents
at the 2-(carboxy) and C4- positions proved to have lorokynurenate (Leeson et al., 1991, 1992; Foster et al., 1992). Compounds bearing *trans*-oriented substituents at the 2-(carboxy) and C4- positions proved to have potent antagonist properties at the NMDA-associated lorokynurenate (Leeson et al., 1991, 1992; Foster et 1992). Compounds bearing *trans*-oriented substitue at the 2-(carboxy) and C4- positions proved to h potent antagonist properties at the NMDA-associal glycine site. Of s 1992). Compounds bearing *trans*-oriented substituents
at the 2-(carboxy) and C4- positions proved to have
potent antagonist properties at the NMDA-associated
glycine site. Of several analogues reported, the 4-pheny-
lure at the 2-(carboxy) and C4- positions proved to have
potent antagonist properties at the NMDA-associated
glycine site. Of several analogues reported, the 4-pheny-
lurea derivative (compound 14, fig. 5) was the most
potent, potent antagonist properties at the NMDA-associated
glycine site. Of several analogues reported, the 4-pheny-
lurea derivative (compound 14, fig. 5) was the most
potent, having an IC_{60} against glycine binding of 7.8 nM glycine site. Of several analogues reported, the 4-pheny-
lurea derivative (compound 14, fig. 5) was the most
potent, having an IC_{50} against glycine binding of 7.8 nM,
making this the most potent glycine site antagonis potent, having an IC₅₀ against glycine binding of 7.8 nm
making this the most potent glycine site antagoni
ligand described to date. The importance of the *tran*
configuration was emphasised by a comparison of the *c*
an making this the most potent glycine site antagonist
ligand described to date. The importance of the *trans*
configuration was emphasised by a comparison of the *cis*
and *trans* forms of 4-benzoylamide substituents (com-
p ligand described to date. The importance of the *tra* configuration was emphasised by a comparison of the α and *trans* forms of 4-benzoylamide substituents (con pounds 15 and 16) and has been established also in study configuration was emphasised by a comparison of the *cis* and *trans* forms of 4-benzoylamide substituents (compounds 15 and 16) and has been established also in a study of 4-amido-2-carboxy-tetrahydroquinolines (Stevenson and *trans* forms of 4-benzoylamide substituent
pounds 15 and 16) and has been established a
study of 4-amido-2-carboxy-tetrahydroquinolin
venson et al., 1992) Here, the *trans*-isomers (co
17) again possess the greater bi unds 15 and 16) and has been established also in a
udy of 4-amido-2-carboxy-tetrahydroquinolines (Ste-
nson et al., 1992) Here, the *trans*-isomers (compound
) again possess the greater biological activity.
b. INDOLE COMPO

study of 4-amido-2-carboxy-tetrahydroquinolines (Stevenson et al., 1992) Here, the *trans*-isomers (compound 17) again possess the greater biological activity.

b. INDOLE COMPOUNDS. In 1989, Huettner described a series of venson et al., 1992) Here, the *trans*-isomers (compound 17) again possess the greater biological activity.
b. INDOLE COMPOUNDS. In 1989, Huettner described a series of indole-2-carboylates with weak but clear activity at 17) again possess the greater biological activity.

b. INDOLE COMPOUNDS. In 1989, Huettner described a

series of indole-2-carboylates with weak but clear activity

at the glycine site. This finding was extended by Gray et b. INDOLE COMPOUNDS. In 1989, Huettner described a
series of indole-2-carboylates with weak but clear activity
at the glycine site. This finding was extended by Gray et
al. (1991) who synthesised a number of more complex
d series of indole-2-carboylates with weak but clear activity
at the glycine site. This finding was extended by Gray et
al. (1991) who synthesised a number of more complex
derivatives, several of which interact competitively at the glycine site. This finding was extended by Gray et al. (1991) who synthesised a number of more complex derivatives, several of which interact competitively with the glycine site in a range of experimental paradigms al. (1991) who synthesised a number of more complex
derivatives, several of which interact competitively with
the glycine site in a range of experimental paradigms
(Hood et al., 1992). The structural homology between
indo derivatives, several of which interact competitively with
the glycine site in a range of experimental paradigms
(Hood et al., 1992). The structural homology between
indole carboxylates and kynurenate was emphasised by
the the glycine site in a range of experimental paradigms (Hood et al., 1992). The structural homology between indole carboxylates and kynurenate was emphasised by the effect of inserting a chloro group onto the C6 position ((Hood et al., 1992). The structural homology between
indole carboxylates and kynurenate was emphasised by
the effect of inserting a chloro group onto the C6 position
(compound 18, fig. 6) which greatly enhanced potency as indole carboxylates and kynurenate was emphasised by
the effect of inserting a chloro group onto the C6 position
(compound 18, fig. 6) which greatly enhanced potency as
a displacer of glycine binding $(K_i 10 \mu M)$. The addi the effect of inserting a chloro group onto the C6 position
(compound 18, fig. 6) which greatly enhanced potency as
a displacer of glycine binding $(K_i 10 \mu M)$. The addition
of an acetic acid functionality at C3 (compound (compound 18, fig. 6) which greatly enhanced potency as
a displacer of glycine binding $(K_i 10 \mu M)$. The addition
of an acetic acid functionality at C3 (compound 19) then
further improved affinity at this site $(K_i 1.6 \mu M)$ a displacer of glycine binding $(K_i 10 \mu M)$. The addition
of an acetic acid functionality at C3 (compound 19) then
further improved affinity at this site $(K_i 1.6 \mu M)$, a
finding that may be taken to compare with the increa of an acetic acid functionality at C3 (compound 19) then
further improved affinity at this site $(K_i \ 1.6 \ \mu M)$, a
finding that may be taken to compare with the increased
potency of kynurenate analogues such as compounds 1 further improved affinity at t
finding that may be taken to con
potency of kynurenate analogue
and 11. The effect of C3 acidic :
on a range of indole compounds
To define some general prope potency of kynurenate analogues such as compounds 10
and 11. The effect of C3 acidic groupings was consistent
on a range of indole compounds.
To define some general properties of the indole pharpotency of kynurenate analogues such as compounds 10
and 11. The effect of C3 acidic groupings was consistent
on a range of indole compounds.
To define some general properties of the indole phar-
macophore, Gray et al. (19

and 11. The effect of C3 acidic groupings was consistent
on a range of indole compounds.
To define some general properties of the indole phar-
macophore, Gray et al. (1991) attempted to reconcile the
structural features of

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FIG. 7. Superimposed **structural formulae** of 7-chlorokynurenic acid (thin **lines) and** 2-(6,7-dichloro-2-carboxyindol-3-yl) acetic acid (thick **CI**
FIG. 7. Superimposed structural formula
(thin lines) and 2-(6,7-dichloro-2-carboxyin
lines) in two positions (Gray et al., 1991). THE STREET COLLET THE TREAT THE TREAT THE TREAT (thin lines) and 2-(6,7-dichloro-2-carboxyindol-3-yl) acetic acid (thick lines) in two positions (Gray et al., 1991).
T-chlorokynurenate. If the molecules are superimposed su

FIG. 7. Superimposed structural formulae of 7-chlorokynurenic acid

(thin lines) and 2-(6,7-dichloro-2-carboxyindol-3-yl) acetic acid (thick

lines) in two positions (Gray et al., 1991).

7-chlorokynurenate. If the molecul (thin lines) and 2-(6,7-dichloro-2-carboxyindol-3-yl) acetic acid (thick 100
lines) in two positions (Gray et al., 1991).
7-chlorokynurenate. If the molecules are superimposed wit
such that the ring nitrogen atoms and the The Theory is the positions (or ay et al., 1991).
The independent at C7 of the indole would enhance in activity (fig. 7A). However, this was found not to be the 7-chlorokynurenate. If the molecules are superimposed wisuch that the ring nitrogen atoms and the carboxyl the groups coincide, then the overlay would imply that a rechloro substituent at C7 of the indole would enhance ul such that the ring nitrogen atoms and the carboxyl the groups coincide, then the overlay would imply that a relation consisting a $C7$ of the indole would enhance underlivity (fig. 7A). However, this was found not to be t groups coincide, then the overlay would imply that a req
chloro substituent at C7 of the indole would enhance ula
activity (fig. 7A). However, this was found not to be the for
case, the relevant agent having a K_i agains

NE
that the chlorinated aromatic rings interact with the
receptor in a comparable way in these series of com-NE
that the chlorinated aromatic rings interact with the
receptor in a comparable way in these series of com-
pounds (fig. 7B). NE
that the chlorinat
receptor in a com
pounds (fig. 7B).
The loss of pote at the chlorinated aromatic rings interact with the
ceptor in a comparable way in these series of con
unds (fig. 7B).
The loss of potency seen in the C7-substituted mole-
le is then consistent with the effect of C8 substit

that the chlorinated aromatic rings interact with the receptor in a comparable way in these series of compounds (fig. 7B).
The loss of potency seen in the C7-substituted molecule is then consistent with the effect of C8 su receptor in a comparable way in these series of compounds (fig. 7B).

The loss of potency seen in the C7-substituted mole-

cule is then consistent with the effect of C8 substitution

in the kynurenate molecule which, as n pounds (fig. 7B).
The loss of potency seen in the C7-substituted mole-
cule is then consistent with the effect of C8 substitution
in the kynurenate molecule which, as noted earlier, re-
sults in a loss of activity. This co The loss of potency seen in the C7-substituted mole-
cule is then consistent with the effect of C8 substitution
in the kynurenate molecule which, as noted earlier, re-
sults in a loss of activity. This correspondence furth cule is then consistent with the effect of C8 substitution
in the kynurenate molecule which, as noted earlier, re-
sults in a loss of activity. This correspondence further
emphasises the correspondence in the manner of bin in the kynurenate molecule which, as noted earlier, results in a loss of activity. This correspondence furtheen
phasises the correspondence in the manner of binding
of kynurenate and indole carboxylates. Also consistent
wi sults in a loss of activity. This correspondence further
emphasises the correspondence in the manner of binding
of kynurenate and indole carboxylates. Also consistent
with this picture is the finding that the C4-hydroxyl
g emphasises the correspondence in the manner of binding
of kynurenate and indole carboxylates. Also consistent
with this picture is the finding that the C4-hydroxyl
grouping does not enhance, but rather decreases, glycine
r of kynurenate and indole carboxylates. Also consistent
with this picture is the finding that the C4-hydroxyl
grouping does not enhance, but rather decreases, glycine
receptor affinity. The importance of 4-hydroxyl group of with this picture is the finding that the C4-hydroxyl grouping does not enhance, but rather decreases, glycine receptor affinity. The importance of 4-hydroxyl group of kynurenate for binding, supports the binding coinciden ouping does not enhance, but rather decreases, glycine
ceptor affinity. The importance of 4-hydroxyl group of
murenate for binding, supports the binding coincidence
mmarised by figure 7.
Information concerning the need for

receptor affinity. The importance of 4-hydroxyl group of
kynurenate for binding, supports the binding coincidence
summarised by figure 7.
Information concerning the need for hydrogen bonding
and the tautomeric form of indo kynurenate for binding, supports the binding coincidence
summarised by figure 7.
Information concerning the need for hydrogen bonding
and the tautomeric form of indole derivatives was de-
duced from a series of esterified summarised by figure 7.
Information concerning the need for hydrogen bonding
and the tautomeric form of indole derivatives was de-
duced from a series of esterified compounds. Loss of both
acidic groupings as in compound Information concerning the need for hydrogen bonding
and the tautomeric form of indole derivatives was de-
duced from a series of esterified compounds. Loss of both
acidic groupings as in compound 20 (fig. 6) substantiall and the tautomeric form of indole derivatives was de
duced from a series of esterified compounds. Loss of bot
acidic groupings as in compound 20 (fig. 6) substantiall
diminished glycine site affinity $(K_i > 100 \mu M)$. Severa duced from a series of esterified compounds. Loss of bot
acidic groupings as in compound 20 (fig. 6) substantiall
diminished glycine site affinity $(K_i > 100 \mu M)$. Severa
amide C3 monoesters, on the other hand, including co acidic groupings as in compound 20 (fig. 6) substantially
diminished glycine site affinity $(K_i > 100 \mu M)$. Several
amide C3 monoesters, on the other hand, including com-
pound 21, were quite potent at this receptor, the il amide C3 monoesters, on the other hand, including compound 21, were quite potent at this receptor, the illustrated compound (21) having a K_i of only 470 nm. The amide C3 monoesters, on the other hand, including compound 21, were quite potent at this receptor, the illustrated compound (21) having a K_i of only 470 nm. The conclusion was drawn from these compounds that hydrogen bo pound 21, were quite potent at this receptor, the illus-
trated compound (21) having a K_i of only 470 nM. The
conclusion was drawn from these compounds that hydro-
gen bonding between the esterified nitrogen atom and
th conclusion was drawn from these compounds that hydrogen bonding between the esterified nitrogen atom and the receptor may be important for affinity. Because replacement of the ring nitrogen by oxygen, as in compound 22, re conclusion was drawn from these compounds that hydrogen bonding between the esterified nitrogen atom and the receptor may be important for affinity. Because replacement of the ring nitrogen by oxygen, as in compound 22, re gen bonding between the esterified nitrogen atom and
the receptor may be important for affinity. Because
replacement of the ring nitrogen by oxygen, as in com-
pound 22, resulted in a loss of activity, it is probable that
 the receptor may be important for affinity. Because
replacement of the ring nitrogen by oxygen, as in com-
pound 22, resulted in a loss of activity, it is probable that
hydrogen bonding is also important between the recept replacement of the ring nitrogen by oxygen, as in compound 22, resulted in a loss of activity, it is probable that hydrogen bonding is also important between the receptor and ring nitrogen. Replacement of the C3 acidic gro pound 22, resulted in a loss of activity, it is probable that
hydrogen bonding is also important between the receptor
and ring nitrogen. Replacement of the C3 acidic groups
by aliphatic alcohol moieties reduced receptor a Information concerning the need for hydrogen bonding
and the tautomeric form of indole derivatives was de-
duced from a series of esterified compounds. Loss of both
acidic groupings as in compound 20 (fig. 6) substantiall and ring nitrogen. Replacement of the C3 acidic groups
by aliphatic alcohol moieties reduced receptor affinity,
whereas an aldehyde or ketone grouping maintained
affinity, compound 23 having a K_i of 11 μ M. This may
i binding. hereas an aldehyde or ketone grouping maintained
finity, compound 23 having a K_i of 11 μ M. This may
ply that a carbonyl grouping is important for recepto:
nding.
The two approaches of using indole analogues of kyn
en affinity, compound 23 having a K_i of 11 μ M. This n
imply that a carbonyl grouping is important for recep
binding.
The two approaches of using indole analogues of k
urenic acid and compounds with extended C4 subs
uent

The two approaches of using indole analogues of kyn-
urenic acid and compounds with extended C4 substit-
uents were combined in investigations by Salituro et al.
(1990, 1992). The presence of a proprionic acid moiety binding.
The two approaches of using indole analogues of kyn-
urenic acid and compounds with extended C4 substit-
uents were combined in investigations by Salituro et al.
(1990, 1992). The presence of a proprionic acid moi The two approaches of using indole analogues of kyn-
urenic acid and compounds with extended C4 substit-
uents were combined in investigations by Salituro et al.
(1990, 1992). The presence of a proprionic acid moiety
at C3 urenic acid and compounds with extended C4 substit-
uents were combined in investigations by Salituro et al.
(1990, 1992). The presence of a proprionic acid moiety
at C3 of the indole nucleus maintains high affinity at the uents were combined in investigations by Salituro et al. (1990, 1992). The presence of a proprionic acid moiety at C3 of the indole nucleus maintains high affinity at the glycine site. The analogy with the parent kynurenic (1990, 1992). The presence of a proprionic acid moie at C3 of the indole nucleus maintains high affinity at t glycine site. The analogy with the parent kynurenic as is again emphasised by the substantial increase in prenc at C3 of the indole nucleus maintains high affinity at the glycine site. The analogy with the parent kynurenic acid
is again emphasised by the substantial increase in po-
tency obtained by halogen substitution: the 4,6-di glycine site. The analogy with the parent kynurenic acid
is again emphasised by the substantial increase in po-
tency obtained by halogen substitution: the 4,6-di-
chloro,3-propionic acid analogue, for example, displaces
 is again emphasised by the substantial increase in po-
tency obtained by halogen substitution: the 4,6-di-
chloro,3-propionic acid analogue, for example, displaces
glycine with an IC_{50} of 170 nM. This series of derivat tency obtained by halogen substitution: the 4,6-di-
chloro,3-propionic acid analogue, for example, displaces
glycine with an IC_{60} of 170 nM. This series of derivatives
culminated with the synthesis of the sulphur-conta glycine with an IC_{50} of 170 nM. This series of derivatives culminated with the synthesis of the sulphur-containing compound 24 (fig. 8), which remains one of the most potent indolic glycine site ligands tested to date culminated with the synthesis of the sulphur-containing
compound 24 (fig. 8), which remains one of the most
potent indolic glycine site ligands tested to date (IC_{60}
 100 nM) (Salituro et al., 1990, 1992).
The synth lminated with the synthesis of the sulphur-containing
mpound 24 (fig. 8), which remains one of the most
tent indolic glycine site ligands tested to date $(IC_{50}$
0 nM) (Salituro et al., 1990, 1992).
The synthesis of benza

compound 24 (fig. 8), which remains one of the most
potent indolic glycine site ligands tested to date $(IC_{50}$
100 nM) (Salituro et al., 1990, 1992).
The synthesis of benzamide analogues comparable
with compound 15, howe potent indolic glycine site ligands tested to date $(IC_{50}$
100 nM) (Salituro et al., 1990, 1992).
The synthesis of benzamide analogues comparable
with compound 15, however, resulted in complex data
that were used to deve 100 nM) (Salituro et al., 1990, 1992).
The synthesis of benzamide analogues compara
with compound 15, however, resulted in complex d
that were used to develop an impression of recep
requirement for binding (Salituro et al. The synthesis of benzamide analogues comparable
with compound 15, however, resulted in complex data
that were used to develop an impression of receptor
requirement for binding (Salituro et al., 1991). In partic-
ular, com with compound 15, however, resulted in complex that were used to develop an impression of rece requirement for binding (Salituro et al., 1991). In pa ular, compound 25 (fig. 8) showed relatively poor afficient for the gly that were used to develop an impression of receptor
requirement for binding (Salituro et al., 1991). In partic-
ular, compound 25 (fig. 8) showed relatively poor affinity
for the glycine site (IC₅₀ 17 μ M), whereas th requirement for binding (Salituro et al., 1991). In partic-
ular, compound 25 (fig. 8) showed relatively poor affinity
for the glycine site (IC₅₀ 17 μ M), whereas the N-methyl-
ated derivative (compound 26) was about

HARMACOLOGI

FIG. 8. Structural formulae of kynurenic acid analogues.

7-chloro compounds. Conversely, however, methylatic

of the nitrogen atom in the oxalic acid analogue (con-

pound 27) led to a compound with 50 times less activit FIG. 8. Structural formulae of kynurenic acid analogues. on

7-chloro compounds. Conversely, however, methylation

of the nitrogen atom in the oxalic acid analogue (com-

pound 27) led to a compound with 50 times less act 7-chloro compounds. Conversely, how
of the nitrogen atom in the oxalic ac
pound 27) led to a compound with 50
 $(IC_{50} 170 \mu M)$ and 9.5 μM , respectively)
To resolve these observations, low chloro compounds. Conversely, however, methylat the nitrogen atom in the oxalic acid analogue (c und 27) led to a compound with 50 times less actions, $\sum_{50} 170 \mu M$ and 9.5 μM , respectively). To resolve these observa

of the nitrogen atom in the oxalic acid analogue (com-
pound 27) led to a compound with 50 times less activity
(IC_{50} 170 μ M and 9.5 μ M, respectively).
To resolve these observations, low-energy conforma-
tions wer pound 27) led to a compound with 50 times less activity

(IC₅₀ 170 μ M and 9.5 μ M, respectively).

To resolve these observations, low-energy conformaind

tions were sought by calculation, a procedure that re-

veal (IC₅₀ 170 μ M and 9.5 μ M, respectively).
To resolve these observations, low-energy conformations were sought by calculation, a procedure that revealed that the tertiary compound (26, fig. 8) preferred *i cis* ori To resolve these observations, low-energy conformations were sought by calculation, a procedure that revealed that the tertiary compound (26, fig. 8) preferred cis orientation of the amide grouping (as illustrated whereas tions were sought by calculation, a procedure that revealed that the tertiary compound (26, fig. 8) preferred a cis orientation of the amide grouping (as illustrated), whereas the less active secondary compound (25) prefer vealed that the tertiary compound $(26, fig. 8)$ preferred a
cis orientation of the amide grouping (as illustrated), han
whereas the less active secondary compound (25) pre-
ferred the *trans* conformation (as illustrated) cis orientation of the amide grouping (as illustrated), $\frac{1}{2}$ make whereas the less active secondary compound (25) pre-
ferred the *trans* conformation (as illustrated). Similar time
preferences were noted for other b whereas the less active secondary compound (25) pre-
ferred the *trans* conformation (as illustrated). Similar
preferences were noted for other benzamides, leading to
the conclusion that the receptor has a sufficiently siz ferred the *trans* conformation (as illustrated). Similar preferences were noted for other benzamides, leading to the conclusion that the receptor has a sufficiently sized ky lipophilic pocket to accommodate the phenyl gr preferences were noted for other ben
the conclusion that the receptor has
lipophilic pocket to accommodate th
cated in proximity to the 4-chlorine
primary plane of the indole nucleus. cated in proximity to the 4-chlorine atom but above the
primary plane of the indole nucleus.
V. Behaviour
A. Motor Activity
The behavioural effects of kynurenines are not

V. Behaviour

Imary plane of the muole hucleus.

V. Behaviour

Motor Activity

The behavioural effects of kynurenines are not

arked. Early reports from Lapin's group (Lapin, 1989) V. Behaviour

A. Motor Activity

The behavioural effects of kynurenines are not

marked. Early reports from Lapin's group (Lapin, 1989)

noted merely a reduction in exploratory behaviour and A. Motor Activity

The behavioural effects of kynurenines are not

marked. Early reports from Lapin's group (Lapin, 1989)

noted merely a reduction in exploratory behaviour and

locomotion in both rats and mice. This decr A. Motor Activity
The behavioural effects of kynurenines are no
marked. Early reports from Lapin's group (Lapin, 1989
noted merely a reduction in exploratory behaviour an
locomotion in both rats and mice. This decrease of The behavioural effects of kynurenines are n
marked. Early reports from Lapin's group (Lapin, 198
noted merely a reduction in exploratory behaviour are
locomotion in both rats and mice. This decrease of acti
ity was seen p marked. Early reports from Lapin's group (Lapin, 1989)
noted merely a reduction in exploratory behaviour and
locomotion in both rats and mice. This decrease of activ-
ity was seen primarily in a reduction of vertical move noted merely a reduction in exploratory behaviour an locomotion in both rats and mice. This decrease of activity was seen primarily in a reduction of vertical movement (rearings) rather than horizontal movement any was not locomotion in both rats and mice. This decrease of activity was seen primarily in a reduction of vertical movement (rearings) rather than horizontal movement and was not associated with any change of body temperature.
Foll ity was seen primarily in a reduction of vertical movement (rearings) rather than horizontal movement and was not associated with any change of body temperature.
Following injection into the cerebral ventricles, both quino ment (rearings) rather than horizontal movement and
was not associated with any change of body temperature.
Following injection into the cerebral ventricles, both
quinolinate and L-kynurenine produced the opposite ef-
fect was not associated with any change of body temperature.
Following injection into the cerebral ventricles, both
quinolinate and L-kynurenine produced the opposite ef-
fects of increasing locomotor activity, with running be-Following injection into the cerebral ventricles, both
quinolinate and L-kynurenine produced the opposite ef-
fects of increasing locomotor activity, with running be-
maxiour and barrel-like rotations seen in some animals quinolinate and L-kynurenine produced the opposite effects of increasing locomotor activity, with running be-
haviour and barrel-like rotations seen in some animals
(Lapin et al., 1982). The latter motor abnormality is
pro fects of increasing locomotor activity, with running be-
haviour and barrel-like rotations seen in some animals
(Lapin et al., 1982). The latter motor abnormality is
probably due to the striatal effects of quinolinate beca haviour and barrel-like rotations seen in some
(Lapin et al., 1982). The latter motor abnors
probably due to the striatal effects of quinolinate
it can be reproduced by quinolinate injected dire
the striatum (Marranes and apin et al., 1982). The latter motor abnormality is seen be the striatal effects of quinolinate because discan be reproduced by quinolinate injected directly into de striatum (Marranes and Wauquier, 1988). Investigative th probably due to the striatal effects of quinolinate because
it can be reproduced by quinolinate injected directly into
the striatum (Marranes and Wauquier, 1988).
These effects of kynurenines on motor activity were
not mod

it can be reproduced by quinolinate injected directly into
the striatum (Marranes and Wauquier, 1988).
These effects of kynurenines on motor activity were
not modified by pretreatment with agents affecting
monoamines, incl

^{CO₂H} picolinic acid, and amphetamine-induced stereotypies, ⁽²⁶⁾ (27) eotypies by 3-hydroxyanthranilic acid and anthranilic

FIG. 8. Structural formulae of kynurenic acid analogues.

T-chloro compounds. Conversely, however, methylation of homovanillic acid in the striatum. Inter YNURENIC ACIDS
and reserpine. Nevertheless the kynurenines are able to
antagonise some aspects of the 5HT behavioural syn-345
and reserpine. Nevertheless the kynurenines are able to
antagonise some aspects of the 5HT behavioural syn-
drome in mice and rats (Green and Curzon, 1970). This 345
and reserpine. Nevertheless the kynurenines are able to
antagonise some aspects of the 5HT behavioural syn-
drome in mice and rats (Green and Curzon, 1970). This
includes the 5-hydroxytryptophan-induced head twitches and reserpine. Nevertheless the kynurenines are able to antagonise some aspects of the 5HT behavioural syn-
drome in mice and rats (Green and Curzon, 1970). This
includes the 5-hydroxytryptophan-induced head twitches
which and reserpine. Nevertheless the kynurenines are able to
antagonise some aspects of the 5HT behavioural syn-
drome in mice and rats (Green and Curzon, 1970). This
includes the 5-hydroxytryptophan-induced head twitches
which antagonise some aspects of the 5HT behavioural syn
drome in mice and rats (Green and Curzon, 1970). This
includes the 5-hydroxytryptophan-induced head twitches
which can be enhanced or suppressed at low and high
doses of L drome in mice and rats (Green and Curzon, 1970). I
includes the 5-hydroxytryptophan-induced head twitc
which can be enhanced or suppressed at low and h
doses of L-kynurenine, respectively (Handley and N
kin, 1977; Gould an which can be enhanced or suppressed at low and high doses of L-kynurenine, respectively (Handley and Miskin, 1977; Gould and Handley, 1978). Several kynurenines are also able to potentiate the effects of agents kin, 1977; Gould and Handley, 1978). Several kynurenines are also able to potentiate the effects of agents enhancing catecholamine function, including noradren-
aline itself, whose hyperthermic effect is potentiated by doses of L-kynurenine, respectively (Handley and Mis-
kin, 1977; Gould and Handley, 1978). Several kynuren-
ines are also able to potentiate the effects of agents
enhancing catecholamine function, including noradren-
aline kin, 1977; Gould and Handley, 1978). Several kynurenines are also able to potentiate the effects of agents
enhancing catecholamine function, including noradren-
aline itself, whose hyperthermic effect is potentiated by
L-k enhancing catecholamine function, including noradrenaline itself, whose hyperthermic effect is potentiated by L-kynurenine, 3-hydroxyanthranilic acid, anthranilic, or picolinic acid, and amphetamine-induced stereotypies, w enhancing catecholamine function, including noradren-
aline itself, whose hyperthermic effect is potentiated by
L-kynurenine, 3-hydroxyanthranilic acid, anthranilic, or
picolinic acid, and amphetamine-induced stereotypies, aline itself, whose hyperthermic effect is potentiated by
L-kynurenine, 3-hydroxyanthranilic acid, anthranilic, or
picolinic acid, and amphetamine-induced stereotypies,
which are prolonged by these same kynurenines (Lapin, L-kynurenine, 3-hydroxyanthranilic acid, anthranilic, or
picolinic acid, and amphetamine-induced stereotypies,
which are prolonged by these same kynurenines (Lapin,
1989). Amphetamine-induced locomotion can also be
enhance picolinic acid, and amphetamine-induced stereotypie
which are prolonged by these same kynurenines (Lapi
1989). Amphetamine-induced locomotion can also lenhanced by anthranilic acid and quinolinic acid in son
cases. The enh which are prolonged by these same kynurenines (Lapin, 1989). Amphetamine-induced locomotion can also be enhanced by anthranilic acid and quinolinic acid in some cases. The enhancement of amphetamine-induced stereotypies by 1989). Amphetamine-induced locomotion can also be
enhanced by anthranilic acid and quinolinic acid in some
cases. The enhancement of amphetamine-induced ster-
eotypies by 3-hydroxyanthranilic acid and anthranilic
acid is a enhanced by anthranilic acid and quinolinic acid in some
cases. The enhancement of amphetamine-induced ster-
eotypies by 3-hydroxyanthranilic acid and anthranilic
acid is associated with an increase in the concentration
of cases. The enhancement of amphetamine-induced ster-
eotypies by 3-hydroxyanthranilic acid and anthranilic
acid is associated with an increase in the concentration
of homovanillic acid in the striatum. Interestingly, the
ic eotypies by 3-hydroxyanthranilic acid and anthranilic acid is associated with an increase in the concentration of homovanillic acid in the striatum. Interestingly, the icv injection of kynurenate, but not L-kynurenine, is 1990a). homovanillic acid in the striatum. Interestingly, the

injection of kynurenate, but not L-kynurenine, is able

induce stereotyped behaviour in rats (Vecsei and Beal,

90a).

Some interaction has been observed with choline

icv injection of kynurenate, but not L-kynurenine, is able
to induce stereotyped behaviour in rats (Vecsei and Beal,
1990a).
Some interaction has been observed with cholinergic
systems in the rat brain in that the latency to induce stereotyped behaviour in rats (Vecsei and
1990a).
Some interaction has been observed with cholin
systems in the rat brain in that the latency of tr
induced by oxotremorine was reduced by 3-hydrox
thranilic and pi 1990a).
Some interaction has been observed with cholinergic
systems in the rat brain in that the latency of tremor
induced by oxotremorine was reduced by 3-hydroxyan-
thranilic and picolinic acids. There was also some en-
 Some interaction has been observed with cholinergic
systems in the rat brain in that the latency of tremor
induced by oxotremorine was reduced by 3-hydroxyan-
thranilic and picolinic acids. There was also some en-
hancemen systems in the rat brain in that the latency of tremo
induced by oxotremorine was reduced by 3-hydroxyan
thranilic and picolinic acids. There was also some en
hancement and prolongation of the hypothermic effec
of nicotine thranilic and picolinic acids. There was also some enhancement and prolongation of the hypothermic effect of nicotine by L-L-L-kynurenine, quinolinic, and nicotinic acids (Lapin, 1972, 1989). In one of the few studies in w ranilic and picolinic acids. There was also some en-
ncement and prolongation of the hypothermic effect
nicotine by L-L-L-kynurenine, quinolinic, and nico-
nic acids (Lapin, 1972, 1989).
In one of the few studies in which

hancement and prolongation of the hypothermic effector of nicotine by L-L-L-kynurenine, quinolinic, and nico
tinic acids (Lapin, 1972, 1989).
In one of the few studies in which the activity of
kynurenate in specific motor of nicotine by L-L-L-kynurenine, quinolinic, and nicotinic acids (Lapin, 1972, 1989).
In one of the few studies in which the activity of
kynurenate in specific motor nuclei were examined, Rob-
ertson et al. (1989) administ tinic acids (Lapin, 1972, 1989).
In one of the few studies in which the activity of
kynurenate in specific motor nuclei were examined, Rob-
ertson et al. (1989) administered the compound into the
medial segment of the monk In one of the few studies in which the activity of
kynurenate in specific motor nuclei were examined, Rob-
ertson et al. (1989) administered the compound into the
medial segment of the monkey globus pallidus. This
resulted kynurenate in specific motor nuclei were examined, Robertson et al. (1989) administered the compound into the medial segment of the monkey globus pallidus. This resulted in contralateral limb dyskinesias which bore some fe ertson et al. (1989) administered the compound into the medial segment of the monkey globus pallidus. This resulted in contralateral limb dyskinesias which bore some features of hemiballismus in humans or monkeys following medial segment of the monkey globus pallidus. This
resulted in contralateral limb dyskinesias which bore
some features of hemiballismus in humans or monkeys
following lesions of the subthalamic nucleus. Although
several in resulted in contralateral limb dyskinesias which bore
some features of hemiballismus in humans or monkeys
following lesions of the subthalamic nucleus. Although
several interpretations of the data are plausible, the
favour some features of hemiballismus in humans or monkeys following lesions of the subthalamic nucleus. Although several interpretations of the data are plausible, the favoured one was of blockade of excitatory amino acid neurot following lesions
several interpre
favoured one wi
neurotransmissi
to the pallidum. Frequency a mino acid
 B. Sex and Behavioural Recovery

Although there is no apparent difference between male

urotransmission in the pathway from the subthalamus
the pallidum.
Sex and Behavioural Recovery
Although there is no apparent difference between male
d female rats in their sensitivity to the neurotoxic to the pallidum.

B. Sex and Behavioural Recovery

Although there is no apparent difference between male

and female rats in their sensitivity to the neurotoxic

effects of quinolinate, female animals do show greater B. Sex and Behavioural Recovery
Although there is no apparent difference between male
and female rats in their sensitivity to the neurotoxic
effects of quinolinate, female animals do show greater
locomotor activity after s B. Sex and Bendotoural necovery
Although there is no apparent difference between male
and female rats in their sensitivity to the neurotoxic
effects of quinolinate, female animals do show greater
locomotor activity after s Although there is no apparent difference between male
and female rats in their sensitivity to the neurotoxic
effects of quinolinate, female animals do show greater
locomotor activity after striatal quinolinate lesions than effects of quinolinate, female animals do show greater locomotor activity after striatal quinolinate lesions than male rats (Emerich et al., 1991). Conversely, females are less inclined to show the decrease in body weight effects of quinolinate, female animals do show greater locomotor activity after striatal quinolinate lesions than male rats (Emerich et al., 1991). Conversely, females are less inclined to show the decrease in body weight locomotor activity after striatal quinolinate lesions than
male rats (Emerich et al., 1991). Conversely, females are
less inclined to show the decrease in body weight ob-
served in male animals (Zubrycki et al., 1990). The male rats (Emerich et al., 1991). Conversely, females are
less inclined to show the decrease in body weight ob-
served in male animals (Zubrycki et al., 1990). These
differences imply a role for sex-specific factors in the less inclined to show the decrease in body weight observed in male animals (Zubrycki et al., 1990). These differences imply a role for sex-specific factors in the determination of behavioural recovery following such lesion differences imply a role for sex-specific factors in the determination of behavioural recovery following such lesions, although there is as yet no indication of whether these behaviours, or their sex dependence, are charac these behaviours, or their sex dependence, are characterprocedure.

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C. *Learning and Memory*

STOM
 Learning and Memory

Whereas the NMDA receptor ligands or dizocilpine

pair performance in a passive avoidance task at doses 346

C. Learning and Memory

Whereas the NMDA receptor ligands or dizocilpine

impair performance in a passive avoidance task at doses

comparable to those protecting against seizures, the kyn-C. Learning and Memory
Whereas the NMDA receptor ligands or dizocilpine
impair performance in a passive avoidance task at doses
comparable to those protecting against seizures, the kyn-
urenate compounds have no activity i U. Learning and memory

Whereas the NMDA receptor ligands or dizocilpine

impair performance in a passive avoidance task at doses

comparable to those protecting against seizures, the kyn-

urenate compounds have no activ Whereas the NMDA receptor ligands or dizocily
impair performance in a passive avoidance task at do
comparable to those protecting against seizures, the k
urenate compounds have no activity in this paradigm
doses approxima impair performance in a passive avoidance task at doses
comparable to those protecting against seizures, the kyn-
urenate compounds have no activity in this paradigm at
doses approximately 30 times higher than their antic comparable to those protecting against seizures, the kynurenate compounds have no activity in this paradigm at doses approximately 30 times higher than their anticonvulsant ED_{50} values (Chiamulera et al., 1990). These urenate compounds have no activity in this paradigm at doses approximately 30 times higher than their anticon-
vulsant ED_{50} values (Chiamulera et al., 1990). These
findings imply that kynurenate-derived agents might
in doses approximately 30 times higher than their anticon-
vulsant ED_{50} values (Chiamulera et al., 1990). These this a
findings imply that kynurenate-derived agents might (Koel
induce fewer unwanted behavioural disturbanc findings imply that kynurenate-derived agents might
induce fewer unwanted behavioural disturbances at ef-
fective anticonvulsant doses than do the classical NMDA
receptor antagonists.
Watanabe et al. (1992) have now shown ndings imply that kynurenate-derived agents miguice fewer unwanted behavioural disturbances at exive anticonvulsant doses than do the classical NMI ceptor antagonists.
Watanabe et al. (1992) have now shown that 7-chlo-
kyn

induce fewer unwanted behavioural disturbances at effective anticonvulsant doses than do the classical NMDA receptor antagonists.
Watanabe et al. (1992) have now shown that 7-chlo-rokynurenate can diminish learning ability fective anticonvulsant doses than do the classical NMDA receptor antagonists.

Watanabe et al. (1992) have now shown that 7-chlo-

rokynurenate can diminish learning ability in a spatial 1984

memory task (the water maze) receptor antagonists.

Watanabe et al. (1992) have now shown that 7-chlo-

rokynurenate can diminish learning ability in a spatial

memory task (the water maze) if the drug is given icv

before each trial session. These do Watanabe et al. (1992) have now shown that 7-chlo-rokynurenate can diminish learning ability in a spatial memory task (the water maze) if the drug is given icy before each trial session. These doses of antagonist did not a rokynurenate can diminish learning ability in a spatial
memory task (the water maze) if the drug is given icv
before each trial session. These doses of antagonist did
not affect swimming speed, which presumably indicates
 memory task (the water maze) if the drug is given icv
before each trial session. These doses of antagonist did ky
not affect swimming speed, which presumably indicates $2 \tcdot 1$
no change of overall locomotor competence. I before each trial session. These doses of antagonist did
not affect swimming speed, which presumably indicates
no change of overall locomotor competence. In the same
study, it was confirmed that 7-chlorokynurenate would
pr not affect swimming speed, which presumably indicates
no change of overall locomotor competence. In the same
study, it was confirmed that 7-chlorokynurenate would
prevent the induction of LTP in both the Schaffer col-
late no change of overall locomotor competence. In the same
study, it was confirmed that 7-chlorokynurenate would
prevent the induction of LTP in both the Schaffer col-
lateral/commissural pathway in CA1 and the perforant
path/ prevent the induction of LTP in both the Schaffer collateral/commissural pathway in CA1 and the perforant path/dentate gyrus pathway in hippocampal slices, suggesting that LTP and behavioural learning are closely related. lateral/commissural pathway in CA1 and the perforant act
path/dentate gyrus pathway in hippocampal slices, sug-
gesting that LTP and behavioural learning are closely averained. Presumably by preventing neuronal loss, (19
7 path/dentate gyrus pathway in hippocampal s
gesting that LTP and behavioural learning a
related. Presumably by preventing neuron-
7-chlorokynurenate reduces the learning de-
after cerebral ischaemia (Wood et al., 1993). *Pelated.* Pres
P-chlorokynum
D. Sleep
D. Sleep
Two report

PHARMACOLOGICAL REVIEWS

chlorokynurenate reduces the learning deficits seen
ter cerebral ischaemia (Wood et al., 1993).
 $\begin{array}{c} \text{Reep} \\ \text{Two reports have appeared concerning the effects of} \\ \text{inolinic acid on sleeping behaviour. In the first, icv} \end{array}$ after cerebral ischaemia (wood et al., 1993).

D. Sleep

Two reports have appeared concerning the effects of $\begin{array}{c} \text{Ir} \\ \text{quindionic acid on sleeping behaviour.} \text{In the first,} \\ \text{injections of quinoline into rabbits at doses of 90 and} \end{array}$ *E.* I
Two reports have appeared concerning the effects of I
quinolinic acid on sleeping behaviour. In the first, icv am
injections of quinolinate into rabbits at doses of 90 and $\frac{\text{mis}}{\text{En}}$
180 nmol were able to induc Two reports have appeared concerning the effects of
quinolinic acid on sleeping behaviour. In the first, icv
injections of quinolinate into rabbits at doses of 90 and
 $\frac{180 \text{ nmol} \text{ were able to induce a profound decrease in the}}{180 \text{ mmol} \text{ were sleep and to abolish any evidence}}$ Two reports have appeared concerning the effects of quinolinic acid on sleeping behaviour. In the first, icv $\frac{8}{180}$ injections of quinolinate into rabbits at doses of 90 and $\frac{180}{180}$ nmol were able to induce a p quinolinic acid on sleeping behaviour. In the first, icv
injections of quinolinate into rabbits at doses of 90 and
180 nmol were able to induce a profound decrease in the
amount of slow-wave sleep and to abolish any eviden injections of quinolinate into rabbits at doses of 90 a 180 nmol were able to induce a profound decrease in tamount of slow-wave sleep and to abolish any evider of paradoxical sleep (Milasius et al., 1990). In a second rep amount of slow-wave sleep and to abolish any evidence
of paradoxical sleep (Milasius et al., 1990). In a second
report, the effects of icv injections of NMDA or quinoli-
nate were examined on the ethanol sensitivity of lon amount of slow-wave sleep and to abolish any evidence
of paradoxical sleep (Milasius et al., 1990). In a second
report, the effects of icv injections of NMDA or quinoli-
nate were examined on the ethanol sensitivity of lon of paradoxical sleep (Milasius et al., 1990). In a second
report, the effects of icv injections of NMDA or quinoli-
nate were examined on the ethanol sensitivity of long-
sleep and short-sleep mice. The NMDA agonists de-
c report, the effects of icv injections of NMDA or quinoli-
nate were examined on the ethanol sensitivity of long-
sleep and short-sleep mice. The NMDA agonists de-
intrac
creased sensitivity to ethanol, although the short-s nate were examined on the ethanol sensitivity of long-
sleep and short-sleep mice. The NMDA agonists de-
creased sensitivity to ethanol, although the short-sleep
mice proved to be the more sensitive. Conversely, NMDA b
ant sleep and short-sleep mice. The NMDA agonists decreased sensitivity to ethanol, although the short-sleep mice proved to be the more sensitive. Conversely, NMDA antagonists, including 2AP5 and dizocilpine, increased sensiti mice proved to be the more sensitive. Conversely, NMDA
antagonists, including 2AP5 and dizocilpine, increased
sensitivity to ethanol; 2AP5 also could prevent the de-
crease in sensitivity to ethanol induced by quinolinate
 mice proved to be the more sensitive. Conversely, NMDA
antagonists, including 2AP5 and dizocilpine, increased
sensitivity to ethanol; 2AP5 also could prevent the de-
crease in sensitivity to ethanol induced by quinolinate
 antagonists, including 2AP5 and dizocilpine, increase
sensitivity to ethanol; 2AP5 also could prevent the c
crease in sensitivity to ethanol induced by quinoline
(Wilson et al., 1990). These data support the hypothee
that sensitivity to ethanol; 2AP5 also could prevent the decrease in sensitivity to ethanol induced by quinolinate (Wilson et al., 1990). These data support the hypothesis to that the effects of ethanol on sleep involved the mo crease in sensitivity to ethanol induced by quinolinate T
(Wilson et al., 1990). These data support the hypothesis to m
that the effects of ethanol on sleep involved the modu-
may
lation of NMDA sensitivity. Intraperitone (Wilson et al., 1990). These data support the hypothesis to that the effects of ethanol on sleep involved the modulation of NMDA sensitivity. Intraperitoneal injections of constant active also reported to suppress active that the effects of ethanol on sleep involved the modulation of NMDA sensitivity. Intraperitoneal injections of kynurenic acid at a dose of 300 mg/kg in young rats (2 to 3 weeks of age) were also reported to suppress activ lation of NMDA sensitivity. In

kynurenic acid at a dose of 3

to 3 weeks of age) were also r

sleep and to increase the dur.

(Loikas and Hilakivi, 1989). *E. A* weeks of sleep and to i
E. Anxiety
E. Anxiety
Lapin's gro

ep and to increase the duration of waking behaviou
oikas and Hilakivi, 1989).
Anxiety
Lapin's group noted that L-kynurenine had an anxi-
enic action in the mouse social interaction test and is (Loikas and Hilakivi, 1989). late

E. Anxiety

ants

Lapin's group noted that L-kynurenine had an anxi-

ogenic action in the mouse social interaction test and in inpu

a light/dark box conflict paradigm (Lapin, 1989). Con E. Anxiety
Lapin's group noted that L-kynurenine had an anxiogenic action in the mouse social interaction test and is
a light/dark box conflict paradigm (Lapin, 1989). Con-
versely, 7-chlorokynurenate, like other antagonis E. Anxiety

Lapin's group noted that L-kynurenine had an anxi-

ogenic action in the mouse social interaction test and in

ing light/dark box conflict paradigm (Lapin, 1989). Con-

versely, 7-chlorokynurenate, like other a Lapin's group noted that L-kynurenine had an anxi-
ogenic action in the mouse social interaction test and in
a light/dark box conflict paradigm (Lapin, 1989). Con-
enversely, 7-chlorokynurenate, like other antagonists at t ogenic action in the mouse social interaction test and
a light/dark box conflict paradigm (Lapin, 1989). Coversely, 7-chlorokynurenate, like other antagonists at t
NMDA/glycine site, showed anxiolytic activity in bothe ele

NE
ation tests (Trullas et al., 1989; Winslow et al., 1990;
Kehne et al., 1991) even after systemic administration. Kehne et al., 1989; Winslow et al., 1989; Winslow et al., 1991) even after systemic administration.
Kehne et al., 1991) even after systemic administration.
Although the anxiolytic profile is shared by a number WE
ation tests (Trullas et al., 1989; Winslow et al., 1990;
Kehne et al., 1991) even after systemic administration.
Although the anxiolytic profile is shared by a number of
other amino acid antagonists, including the compe ation tests (Trullas et al., 1989; Winslow et al., 1990;
Kehne et al., 1991) even after systemic administration.
Although the anxiolytic profile is shared by a number of
other amino acid antagonists, including the competit ation tests (Trullas et al., 1989; Winslow et al., 1990
Kehne et al., 1991) even after systemic administration
Although the anxiolytic profile is shared by a number of
other amino acid antagonists, including the competitiv Kehne et al., 1991) even after systemic administration.
Although the anxiolytic profile is shared by a number of
other amino acid antagonists, including the competitive
NMDA antagonist 2AP5 and the channel blocker dizo-
ci Although the anxiolytic profile is shared by a number of
other amino acid antagonists, including the competitive
NMDA antagonist 2AP5 and the channel blocker dizo-
cilpine, 5,7-dichlorokynurenate was the only member of
thi other amino acid antagonists, including the competity NMDA antagonist 2AP5 and the channel blocker delipine, 5,7-dichlorokynurenate was the only member this group not to show marked muscle relaxant active. (Koek and Colpae this group not to show marked muscle relaxant activity (Koek and Colpaert, 1990; Kehne et al., 1991). Interestingly, the glycine site partial agonist 1-aminocyclopro-
panecarboxylic acid shows both the anxiolytic activity cilpine, 5,7-dichlorokynurenate was the only member of
this group not to show marked muscle relaxant activity
(Koek and Colpaert, 1990; Kehne et al., 1991). Interest-
ingly, the glycine site partial agonist 1-aminocyclopro this group not to show marked muscle relaxant activity
(Koek and Colpaert, 1990; Kehne et al., 1991). Interest-
ingly, the glycine site partial agonist 1-aminocyclopro-
panecarboxylic acid shows both the anxiolytic activit (Koek and Colpaert, 1990; Kehne et al., 1991). Interestingly, the glycine site partial agonist 1-aminocyclopro-
panecarboxylic acid shows both the anxiolytic activity of
the kynurenate analogues and the relative absence of 1989). necarboxylic acid shows both the anxiolytic activity of
e kynurenate analogues and the relative absence of
otor disturbances (Winslow et al., 1990; Trullas et al.,
89).
The daily administration of 100 to 200 mg/kg of L-
nu

prevent the induction of LTP in both the Schaffer col-
lateral/commissural pathway in CA1 and the perforant activity in this model, without affecting learning in a
path/dentate gyrus pathway in hippocampal slices, sug-
ge the kynurenate analogues and the relative absence of
motor disturbances (Winslow et al., 1990; Trullas et al.,
1989).
The daily administration of 100 to 200 mg/kg of L-
kynurenine to rats produced a decrease of rearing act motor disturbances (Winslow et al., 1990; Trullas et al., 1989).

2 The daily administration of 100 to 200 mg/kg of L-

2 hours later and also had a decrease of rearing activity

2 hours later and also had a depressant eff 1989).
The daily administration of 100 to 200 mg/kg of L-
kynurenine to rats produced a decrease of rearing activity
2 hours later and also had a depressant effect on general
exploratory and locomotor activity as reflected The daily administration of 100 to 200 mg/kg of L-
kynurenine to rats produced a decrease of rearing activity
2 hours later and also had a depressant effect on general
exploratory and locomotor activity as reflected in dekynurenine to rats produced a decrease of rearing activity
2 hours later and also had a depressant effect on general
exploratory and locomotor activity as reflected in de-
creased total arm entries in the elevated plus-maz 2 hours later and also had a depressant effect on general
exploratory and locomotor activity as reflected in de-
creased total arm entries in the elevated plus-maze. After
4 days of treatment the amine also produced anxio exploratory and locomotor activity as reflected in decreased total arm entries in the elevated plus-maze. After 4 days of treatment the amine also produced anxiogenic activity in this model, without affecting learning in a activity in this model, without affecting learning in a passive avoidance paradigm or extinction of an active levels at the time of peak anxiety.
F. Nociception and Opioid Interactions (1991) induced anxiety by administering caffeine at a

kynurenine to rats produced a decrease of rearing activity
2 hours later and also had a depressant effect on general
exploratory and locomotor activity as reflected in de-
creased total arm entries in the elevated plus-ma In view of a large amount of evidence that excitatory devels at the time of peak anxiety.

F. Nociception and Opioid Interactions

In view of a large amount of evidence that excitato

amino acids may be involved in primary afferent tran

mission to nociceptive neurones in the F. Nociception and Opioid Interactions

In view of a large amount of evidence that excitatory

amino acids may be involved in primary afferent trans-

mission to nociceptive neurones in the CNS, Hajos and

Engberg (1990) c Englement of evidence that excitatory

In view of a large amount of evidence that excitatory

amino acids may be involved in primary afferent trans-

mission to nociceptive neurones in the CNS, Hajos and

Engberg (1990) c In view of a large amount of evidence that excitatory
amino acids may be involved in primary afferent trans-
mission to nociceptive neurones in the CNS, Hajos and
Engberg (1990) compared the efficacy of dizocilpine and
kyn amino acids may be involved in primary afferent trans-
mission to nociceptive neurones in the CNS, Hajos and
Engberg (1990) compared the efficacy of dizocilpine and
kynurenic acid in preventing the eye-wiping behaviour
of mission to nociceptive neurones in the CNS, Hajos and
Engberg (1990) compared the efficacy of dizocilpine and
kynurenic acid in preventing the eye-wiping behaviour
of rats subjected to corneal irritation with mild capsaici Engberg (1990) compared the efficacy of dizocilpine and
kynurenic acid in preventing the eye-wiping behaviour
of rats subjected to corneal irritation with mild capsaicin
solutions. The intravenous administration of dizocil kynurenic acid in preventing the eye-wiping behaviour of rats subjected to corneal irritation with mild capsaicin solutions. The intravenous administration of dizocilpine failed to affect the capsaicin-induced irritation, of rats subjected to corneal irritation with mild capsaicin solutions. The intravenous administration of dizocilpine failed to affect the capsaicin-induced irritation, whereas intracisternally injected kynurenic acid was a solutions. The intravenous administration of dizocilpine
failed to affect the capsaicin-induced irritation, whereas
intracisternally injected kynurenic acid was able to sup-
press, and in higher doses to abolish, the eye-w failed to affect the capsaicin-induced irritation, whereas
intracisternally injected kynurenic acid was able to sup-
press, and in higher doses to abolish, the eye-wiping
behaviour. The data were interpreted to imply an in response. press, and in higher doses to abolish, the eye-wiping
behaviour. The data were interpreted to imply an in-
volvement of non-NMDA-type receptors in a nociceptive
response.
The injection of amino acid antagonists intrathecal

behaviour. The data were interpreted to imply an in-
volvement of non-NMDA-type receptors in a nociceptive
response.
The injection of amino acid antagonists intrathecally
to mice also induces biting and scratching activity volvement of non-NMDA-type receptors in a nociceptive
response.
The injection of amino acid antagonists intrathecally
to mice also induces biting and scratching activity which
may reflect activation of nociceptive neurones response.
The injection of amino acid antagonists intrathecally
to mice also induces biting and scratching activity which
may reflect activation of nociceptive neurones and which
can be prevented by amino acid antagonists. The injection of amino acid antagonists intrathecally
to mice also induces biting and scratching activity which
may reflect activation of nociceptive neurones and which
can be prevented by amino acid antagonists. Kynurenat to mice also induces biting and scratching activity which
may reflect activation of nociceptive neurones and which
can be prevented by amino acid antagonists. Kynurenate
is effective in this model, although its use reveals may reflect activation of nociceptive neurones and whican be prevented by amino acid antagonists. Kynurena
is effective in this model, although its use reveals to
possible components of NMDA sensitivity that mig
correlate can be prevented by amino acid antagonists. Kyr
is effective in this model, although its use reve
possible components of NMDA sensitivity the
correlate with the presence of two receptors, a
lated elsewhere (Urca and Raigor possible components of NMDA sensitivity that might
correlate with the presence of two receptors, as postu-
lated elsewhere (Urca and Raigorodsky, 1988).
Electrophysiological data show that NMDA receptor
antagonists, includ

possible components of NMDA sensitivity that might
correlate with the presence of two receptors, as postu-
lated elsewhere (Urca and Raigorodsky, 1988).
Electrophysiological data show that NMDA receptor
antagonists, includ lated elsewhere (Urca and Raigorodsky, 1988).
Electrophysiological data show that NMDA recepantagonists, including 2AP5 and 7-chlorokynurenate,
unable to affect early responses to nociceptive synap
input but can prevent th Electrophysiological data show that NMDA receptor
antagonists, including 2AP5 and 7-chlorokynurenate, are
unable to affect early responses to nociceptive synaptic
input but can prevent the so-called "wind-up" phenom-
enon. antagonists, including 2AP5 and 7-chlorokynurenate, are
unable to affect early responses to nociceptive synaptic
input but can prevent the so-called "wind-up" phenom-
enon. Using anaesthetised rats, Chapman and Dickenson
(unable to affect early responses to nociceptive synaptic
input but can prevent the so-called "wind-up" phenom-
enon. Using anaesthetised rats, Chapman and Dickenson
(1992) showed that 7-chlorokynurenate would prevent
windinput but can prevent the so-called "wind-up" phenom-
enon. Using anaesthetised rats, Chapman and Dickenson
(1992) showed that 7-chlorokynurenate would prevent
wind-up in response to C fibre afferent stimulation. This
bloc

QUINOLINIC AND KN
Dickenson (1992) subsequently attempted to examine (the effects of combinations of 7-chlorokynurenate with QUINOLINIC AND KYN
Dickenson (1992) subsequently attempted to examine G.
the effects of combinations of 7-chlorokynurenate with
the known analgesic morphine, which has been claimed kyp quinolinic and KYI
Dickenson (1992) subsequently attempted to examine G .
the effects of combinations of 7-chlorokynurenate with
the known analgesic morphine, which has been claimed
to exhibit the converse specificity, b Dickenson (1992) subsequently attempted to examine
the effects of combinations of 7-chlorokynurenate with
the known analgesic morphine, which has been claimed
to exhibit the converse specificity, blocking initial syn-
apti Dickenson (1992) subsequently attempted to examined the effects of combinations of 7-chlorokynurenate with the known analgesic morphine, which has been claimed to exhibit the converse specificity, blocking initial syngtic the effects of combinations of 7-chlorokynurenate with
the known analgesic morphine, which has been claimed
to exhibit the converse specificity, blocking initial syn
aptic responsiveness with less effect on secondary wind the known analgesic morphine, which has been clain
to exhibit the converse specificity, blocking initial s
aptic responsiveness with less effect on secondary wi
up. As expected, the combination of low doses of m
phine (5 to exhibit the converse specificity, blocking initial syn-
aptic responsiveness with less effect on secondary wind-
up. As expected, the combination of low doses of mor-
phine $(5 \mu g)$ and 7-chlorokynurenate $(2.5 \mu g)$ ad up. As expected, the combina
phine $(5 \mu g)$ and 7-chlorokyn
tered intrathecally to rats tot
components of dorsal horn ne
of C-fibre afferent stimulation
Interestingly, Godefroy et al ine $(5 \mu g)$ and 7-chlorokynurenate $(2.5 \mu g)$ adminis-
red intrathecally to rats totally abolished the various death
mponents of dorsal horn neurone responses to trains tested
C-fibre afferent stimulation.
Interestingly,

tered intrathecally to rats totally abolished the various decomponents of dorsal horn neurone responses to trains the of C-fibre afferent stimulation. The effection of the attend toward an increased L-kynurenine content in components of dorsal horn neurone responses to trains the dot C-fibre afferent stimulation. The effection of arthritic rats, although it is as a trend toward an increased L-kynurenine content in the fearthritic rats, altho of C-fibre afferent stimulation.
Interestingly, Godefroy et al. (1990) were able to show
a trend toward an increased L-kynurenine content in the
spinal cord dorsal horn of arthritic rats, although it is a
yet impossible to Interestingly, Godefroy et al. (1990) were able to show
a trend toward an increased L-kynurenine content in the
spinal cord dorsal horn of arthritic rats, although it is as
yet impossible to know whether this is able to co a trend toward an increased L-kynurenine content in t
spinal cord dorsal horn of arthritic rats, although it is
yet impossible to know whether this is able to contribu
directly or indirectly, to heightened NMDA recept
acti spinal cord dorsal horn of arthritic rats, although it is as
yet impossible to know whether this is able to contribute, to
directly or indirectly, to heightened NMDA receptor cre
activity via quinolinate or whether it ref yet impossible to know whether this is able to contribut
directly or indirectly, to heightened NMDA recept
activity via quinolinate or whether it reflects a con-
quence of abnormal sensory neurone activity. It wo
seem impo directly or indirectly, to heightened NMDA reactivity via quinolinate or whether it reflects a quence of abnormal sensory neurone activity. It seem important to distinguish between these by ing the work after blocking quin tivity via quinolinate or whether it reflects a conse-
ence of abnormal sensory neurone activity. It would 30
em important to distinguish between these by repeat-
g the work after blocking quinolinate synthesis. of
The re

quence of abnormal sensory neurone activity. It would 30
seem important to distinguish between these by repeat-
ing the work after blocking quinolinate synthesis. of
The relationship between opioid actions and amino
aci seem important to distinguish between these by repeat
ing the work after blocking quinolinate synthesis.
The relationship between opioid actions and amin
acids is very complex but may be of relevance not only
to antinocice ing the work after blocking quinolinate synthesis.

The relationship between opioid actions and amino dues acids is very complex but may be of relevance not only to antinociception but also to tolerance and dependence.

T The relationship between opioid actions and amino
acids is very complex but may be of relevance not only
to antinociception but also to tolerance and dependence.
The analgesic effects of morphine, for example, injected
dir acids is very complex but may be of relevance not only
to antinociception but also to tolerance and dependence.
The analgesic effects of morphine, for example, injected
directly in the periaqueductal gray matter can be pre to antinociception but also to tolerance and dependence.

The analgesic effects of morphine, for example, injected

directly in the periaqueductal gray matter can be pre-

vented by 2AP7, implying the involvement of NMDA
 The analgesic effects of morphine, for example, injected
directly in the periaqueductal gray matter can be pre-
vented by 2AP7, implying the involvement of NMDA
receptors in morphine's effects. Equally, there is evidence
f directly in the periaqueductal gray matter can be pre-
vented by 2AP7, implying the involvement of NMDA
receptors in morphine's effects. Equally, there is evidence
for a pathway from the periaqueductal gray to the nucleus vented by 2AP7, implying the involvement of NMDA
receptors in morphine's effects. Equally, there is evidence
for a pathway from the periaqueductal gray to the nucleus
raphe magnus because amino acid antagonists injected
i receptors in morphine's effects. Equally, there is even for a pathway from the periaqueductal gray to the raphe magnus because amino acid antagonists into the latter site can prevent the analgesic effency morphine applied r a pathway from the periaqueductal gray to the nucleus
phe magnus because amino acid antagonists injected
to the latter site can prevent the analgesic effects of
prophine applied into the periaqueductal gray.
Marek et al

raphe magnus because amino acid antagonists injected
into the latter site can prevent the analgesic effects of
morphine applied into the periaqueductal gray.
Marek et al. (1991) extended this possible linkage
between amin morphine applied into the periaqueductal gray.

Marek et al. (1991) extended this possible linkage

between amino acids and opiates to demonstrate that the

administration of either kynurenic acid (150 mg/kg) or

dizocilp Marek et al. (1991) extended this possible linkage
between amino acids and opiates to demonstrate that the
administration of either kynurenic acid (150 mg/kg) or
dizocilpine (0.05 mg/kg) daily for 4 days together with
mor between amino acids and opiates to demonstrate that the
administration of either kynurenic acid (150 mg/kg) or
dizocilpine (0.05 mg/kg) daily for 4 days together with
morphine were able to prevent the development of tol-
 administration of either kynurenic acid (150 mg/kg) or $(110 \text{ dizocilpine} (0.05 \text{ mg/kg})$ daily for 4 days together with by morphine were able to prevent the development of tolerance to the analgesic effects of the opioid. Neith dizocilpine (0.05 mg/kg) daily for 4 days together with
morphine were able to prevent the development of tol-
erance to the analgesic effects of the opioid. Neither of
the amino-acid antagonists had any effect on acutely
m erance to the analgesic effects of the opioid. Neither of the amino acid antagonists had any effect on acutely measured analgesic effects of morphine. Similarly nonsedative doses of kynurenate were able to prevent witherance to the analgesic effects of the opioid. Neither of by
the amino acid antagonists had any effect on acutely the
measured analgesic effects of morphine. Similarly non-
sedative doses of kynurenate were able to preven the amino acid antagonists had any effect on acutely
measured analgesic effects of morphine. Similarly non-
sedative doses of kynurenate were able to prevent with-
drawal signs seen in morphine-dependent rats treated
with measured analgesic effects of morphine. Similarly non-
sedative doses of kynurenate were able to prevent with-
drawal signs seen in morphine-dependent rats treated
with naltrexone (Rasmussen et al., 1991). Different as-
pe sedative doses of kynurenate were able to prevent with-
drawal signs seen in morphine-dependent rats treated
with naltrexone (Rasmussen et al., 1991). Different as-
pects of the withdrawal behaviour were prevented, de-
tip drawal signs seen in morphine-dependent rats treated
with naltrexone (Rasmussen et al., 1991). Different as-
pects of the withdrawal behaviour were prevented, de-
pending on whether kynurenate was administered icv or
subcu with naltrexone (Rasmussen et al., 1991). Different aspects of the withdrawal behaviour were prevented, depending on whether kynurenate was administered icv or subcutaneously. Only the former was able to suppress the withd pects of the withdrawal behaviour were prevented, depending on whether kynurenate was administered icv or subcutaneously. Only the former was able to suppress the withdrawal-induced activation of locus coeruleus cells, imp pending on whether kynurenate was administered icv or
subcutaneously. Only the former was able to suppress me-
the withdrawal-induced activation of locus coeruleus obs
cells, implying that those aspects of withdrawal pre-
 subcutaneously. Only the former was able to subter withdrawal-induced activation of locus coordination, include the aspects of withdraw vented by systemic kynurenate (ptosis, writhin weight loss) are themselves of peripher e withdrawal-induced activation of locus coeruleus oblis, implying that those aspects of withdrawal pre-
nted by systemic kynurenate (ptosis, writhing, and duight loss) are themselves of peripheral origin.
7-Chlorokynurena

cells, implying that those aspects of withdrawal prevented by systemic kynurenate (ptosis, writhing, and veright loss) are themselves of peripheral origin.

7-Chlorokynurenate has been shown to mimic the abilities of other wented by systemic kynurenate (ptosis, writhing, and duct weight loss) are themselves of peripheral origin.
T-Chlorokynurenate has been shown to mimic the tero
abilities of other amino acid antagonists in preventing
the ne weight loss) are themselves of peripheral origin. The interaction of the contrathecal administration of the opioid of the intrathecal administration of the opioid peptide dynorphin (Bakshi and Faden, 1990). The effi-7-Chlorokynurenate has been shown to mimic the
abilities of other amino acid antagonists in preventing
the neurological disturbances and tissue damage seen in
response to the intrathecal administration of the opioid
peptid abilities of other amino acid antagonists in prevent
the neurological disturbances and tissue damage seer
response to the intrathecal administration of the opi
peptide dynorphin (Bakshi and Faden, 1990). The e
cacy of 7-ch the neurological disturbances and tissue damage so
response to the intrathecal administration of the epeptide dynorphin (Bakshi and Faden, 1990). The
cacy of 7-chlorokynurenate was interpreted as imp
ing the NMDA receptor

G. *Miscellaneous Behaviours*

up. As expected, the combination of low doses of mor-
phine $(5 \mu g)$ and 7-chlorokynurenate $(2.5 \mu g)$ adminis-
tered intrathecally to rats totally abolished the various
components of dorsal horn neurone responses to trai QUINOLINIC AND KYNURENIC ACIDS

pted to examine G. Miscellaneous Behaviours

okynurenate with Even delivered directly icv at subconvulsant doses, L-

has been claimed kynurenine had little effect on learning abilities or o x

K. Miscellaneous Behaviours

Even delivered directly icv at subconvulsant doses, I

kynurenine had little effect on learning abilities or over-

all motor activity. Kynurenate was found to produce onl G. Miscellaneous Behaviours
Even delivered directly icv at subconvulsant doses, L-
kynurenine had little effect on learning abilities or over-
all motor activity. Kynurenate was found to produce only
a limited decrease of Even delivered directly icv at subconvulsant doses, L-
kynurenine had little effect on learning abilities or over-
all motor activity. Kynurenate was found to produce only
a limited decrease of general locomotion measured Even delivered directly icv at subconvulsant doses, L-
kynurenine had little effect on learning abilities or over-
all motor activity. Kynurenate was found to produce only
a limited decrease of general locomotion measured a limited decrease of general locomotion measured 60 tested (Vecsei and Beal, 1990a,b, 1991). Some of these a limited decrease of general locomotion measured 60
minutes after injection, although stereotyped behaviour,
sleeping, and ataxia were seen at shorter latencies with
death from respiratory depression at the highest doses
 minutes after injection, although stereotyped behaviour,
sleeping, and ataxia were seen at shorter latencies with
death from respiratory depression at the highest doses
tested (Vecsei and Beal, 1990a,b, 1991). Some of thes sleeping, and ataxia were seen at shorter latencies with
death from respiratory depression at the highest doses
tested (Vecsei and Beal, 1990a,b, 1991). Some of these
effects could be prevented by D-serine, implying a role death from respiratory depress
tested (Vecsei and Beal, 1990a
effects could be prevented by D-
the NMDA receptor-associated
fects (Vecsei and Beal, 1991).
Administration of 7-chloroky sted (Vecsei and Beal, 1990a,b, 1991). Some of these
fects could be prevented by D-serine, implying a role of
e NMDA receptor-associated glycine site in these ef-
ts (Vecsei and Beal, 1991).
Administration of 7-chlorokynur

effects could be prevented by D-serine, implying a role of
the NMDA receptor-associated glycine site in these ef-
fects (Vecsei and Beal, 1991).
Administration of 7-chlorokynurenate by icv injection
to rats has been report the NMDA receptor-associated glycine site in these effects (Vecsei and Beal, 1991).

Administration of 7-chlorokynurenate by icv injection

to rats has been reported to induce a dose-related in-

crease of feeding. The ef fects (Vecsei and Beal, 1991).

Administration of 7-chlorokynurenate by icv injection

to rats has been reported to induce a dose-related in-

crease of feeding. The effect was substantial, with a dose

of 30 μ g induci Administration of 7-chlorokynurenate by icv injection
to rats has been reported to induce a dose-related in
crease of feeding. The effect was substantial, with a dos
of 30 μ g inducing a 25-fold increase of food intake to rats has been reported to induce a dose-related in-
crease of feeding. The effect was substantial, with a dose
of 30μ g inducing a 25-fold increase of food intake within
 30 minutes. At the same doses, 7-chlorokynur crease of feeding. The effect was substantial, with a dose
of 30 μ g inducing a 25-fold increase of food intake within
30 minutes. At the same doses, 7-chlorokynurenate in-
duced no stereotyped activity and no significa of 30 μ g inducing a 25-fold increase of food intake within
30 minutes. At the same doses, 7-chlorokynurenate in-
duced no stereotyped activity and no significant changes
of locomotor behaviour (Sorrels and Bostock, 199 30 minutes. At the same doses, 7-chlorokynurenate in-
duced no stereotyped activity and no significant changes
of locomotor behaviour (Sorrels and Bostock, 1992);
drinking activity was normal. The coadministration of
D-ser duced no stereotyped activity and no significant cheof of locomotor behaviour (Sorrels and Bostock, 1 drinking activity was normal. The coadministration-
D-serine yielded a dose-dependent antagonism of the chlorokynurenate of locomotor behaviour (Sorrels and Bostock, 1992);
drinking activity was normal. The coadministration of
D-serine yielded a dose-dependent antagonism of the 7-
chlorokynurenate feeding, implicating the NMDA-asso-
ciated g drinking activity was normal. The coadministration of D-serine yielded a dose-dependent antagonism of the 7-chlorokynurenate feeding, implicating the NMDA-associated glycine site. It is not yet clear how, if at all, this r D-serine yielded a dose-dependent antagonism of the 7-chlorokynurenate feeding, implicating the NMDA-asso-ciated glycine site. It is not yet clear how, if at all, this relates to the discovery that kynurenate can reduce ba chlorokynurenate feeding, implicating the NMDA-associated glycine site. It is not yet clear how, if at all, this relates to the discovery that kynurenate can reduce basal acid secretion in the rat stomach (Glavin and Pinsk relates to the discovery that kynurenate can reduce basal
acid secretion in the rat stomach (Glavin and Pinsky,
1989) because it might be expected that this would di-
minish food intake. This action does reduce the forma-
 acid secretion in the rat stomach (Glavin and Pinsky, acid secretion in the rat stomach (Glavin and Pinsk
1989) because it might be expected that this would d
minish food intake. This action does reduce the form
tion of gastric ulcers in stressed animals, a feature th
might b 1989) because it in
minish food intaktion of gastric ulc
might be a useful
atives in humans.
The involvement inish food intake. This action does reduce the formation of gastric ulcers in stressed animals, a feature that ight be a useful secondary action of kynurenate deriv-
ves in humans.
The involvement of excitatory amino acid

morphine applied into the periaqueductal gray.

Marek et al. (1991) extended this possible linkage

between amino acids and opiates to demonstrate that the

administration of either kynurenic acid (150 mg/kg) or

discrimi tion of gastric ulcers in stressed animals, a feature that
might be a useful secondary action of kynurenate deriv-
atives in humans.
The involvement of excitatory amino acid receptors,
although not specifically for NMDA, w The involvement of excitatory amino acid receptors, although not specifically for NMDA, was also proposed atives in humans.

The involvement of excitatory amino acid receptors,

although not specifically for NMDA, was also proposed

for discriminatory avoidance behaviour by Ericson et al.

(1990). The performance of a visual d The involvement of excitatory amino acid receptors,
although not specifically for NMDA, was also proposed
for discriminatory avoidance behaviour by Ericson et al.
(1990). The performance of a visual discrimination task
by although not specifically for NMDA, was also proposed
for discriminatory avoidance behaviour by Ericson et al.
(1990). The performance of a visual discrimination task
by rats was impaired by kynurenic acid injected directl for discriminatory avoidance behaviour by Ericson et al. (1990). The performance of a visual discrimination task
by rats was impaired by kynurenic acid injected directly
into the nucleus accumbens. This was not accompanied (1990). The performance of a visual discrimination task
by rats was impaired by kynurenic acid injected directly
into the nucleus accumbens. This was not accompanied
by any change of open field locomotor behaviour, al-
tho into the nucleus accumbens. This was not accompanied
by any change of open field locomotor behaviour, al-
though, paradoxically, an increase of motor activity was
seen in the discrimination apparatus itself, an effect that into the nucleus accumbens. This was not accompanied
by any change of open field locomotor behaviour, al-
though, paradoxically, an increase of motor activity was
seen in the discrimination apparatus itself, an effect that by any change of open field locomotor behaviour, although, paradoxically, an increase of motor activity was seen in the discrimination apparatus itself, an effect that clearly may have interfered with the performance of th though, paradoxically, an increase of motor activity
seen in the discrimination apparatus itself, an effect
clearly may have interfered with the performance of
task. Nevertheless, the results suggested a possible
volvement seen in the disc
clearly may ha
task. Neverthe
volvement of a
tion behaviour.
Although ne early may have interfered with the performance of the sk. Nevertheless, the results suggested a possible in-
lvement of amino acid receptors in visual discrimina-
in behaviour.
Although neither the physiogical significance task. Nevertheless, the results suggested a possible in-
volvement of amino acid receptors in visual discrimina-
tion behaviour.
Although neither the physiogical significance nor the
mechanism is yet understood, Mendelson

volvement of amino acid receptors in visual discrimination behaviour.

Although neither the physiogical significance nor the

mechanism is yet understood, Mendelson et al. (1987)

observed that icv injections of kynurenat tion behaviour.

Although neither the physiogical significance nor the

mechanism is yet understood, Mendelson et al. (1987)

observed that icv injections of kynurenate (2 to 32 μ g) to

ovariectomised, oestrogen-primed Although neither the physiogical significance nor the mechanism is yet understood, Mendelson et al. (1987) observed that icv injections of kynurenate (2 to 32 μ g) to variectomised, oestrogen-primed female rats would ir mechanism is yet understood, Mendelson et al. (198
observed that icv injections of kynurenate (2 to 32 μ g)
ovariectomised, oestrogen-primed female rats would
duce lordosis. The effect was not secondary to the lib
ation ovariectomised, oestrogen-primed female rats would in-
duce lordosis. The effect was not secondary to the liber-
ation of steroids because it was not prevented by proges-
terone antagonists.
VI. Pathological States Note of the effect was not secondary to
The effect was not secondary to
ists.
VI. Pathological States
y fair to say that the clinical

It is probably fair to say that the clinical significance
It is probably fair to say that the clinical significance
the kynurenine pathway in the CNS is far from being of the kynurenine pathway in the clinical significance
of the kynurenine pathway in the CNS is far from being
fully appreciated. Much of the excitement that has sur-VI. Pathological States
It is probably fair to say that the clinical significance
of the kynurenine pathway in the CNS is far from being
fully appreciated. Much of the excitement that has sur-
rounded the development of wo VI. Pathological states
It is probably fair to say that the clinical significance
of the kynurenine pathway in the CNS is far from being
fully appreciated. Much of the excitement that has sur-
rounded the development of wo

PHARMACOLOGICAL REVIEWS

STONE
the past 12 years can be attributed to the possibility of
relevance to major disorders such as epilepsy, neurode-q 348
the past 12 years can be attributed to the possibility
relevance to major disorders such as epilepsy, neuro
generative diseases, and cerebral ischaemia. It is lik src
the past 12 years can be attributed to the possibility of
relevance to major disorders such as epilepsy, neurode-
generative diseases, and cerebral ischaemia. It is likely,
however, that other disease states may be fou the past 12 years can be attributed to the possibility of relevance to major disorders such as epilepsy, neurode-
generative diseases, and cerebral ischaemia. It is likely, however, that other disease states may be found t the past 12 years can be attributed to the possibility of
relevance to major disorders such as epilepsy, neurode-
generative diseases, and cerebral ischaemia. It is likely,
however, that other disease states may be found relevance to major disorders such as epilepsy, neurode-
generative diseases, and cerebral ischaemia. It is likely,
however, that other disease states may be found to de-
pend on kynurenine metabolism, including some forms
 generative diseases, and cerebral ischaemia. It is likely however, that other disease states may be found to depend on kynurenine metabolism, including some form of idiopathic mental retardation such as Hartnup's disease, however, that other disease states may be found to de-
pend on kynurenine metabolism, including some forms
of idiopathic mental retardation such as Hartnup's dis-
ease, a hereditary disorder involving mental retardation, t pend on kynurenine metabolism, including some forms of idiopathic mental retardation such as Hartnup's disease, a hereditary disorder involving mental retardation, attributable to the lack of tryptophan absorption and meta **Ease, a hereditary

attributable to the metabolism (Stan
** *A. Neurotoxicity***

The early inter**

Example to the lack of tryptophan absorption and $\frac{1}{2}$ and $\frac{1}{2}$ and $\frac{1}{2}$ and $\frac{1}{2}$ early interest in the neurotoxic effects of amino $\frac{1}{2}$ exids and related substances has been summarised in metabolism (Stanbury et al., 1972).

A. Neurotoxicity

The early interest in the neurotoxic effects of amino

acids and related substances has been summarised in

reviews by Schwarcz et al. (1984a) and El-Defrawy et al. A. Neurotoxicity
The early interest in the neurotoxic effects of amino
acids and related substances has been summarised in
reviews by Schwarcz et al. (1984a) and El-Defrawy et al.
(1986a). By 1980, it had become clear that The early interest in the neurotoxic effects of amino
acids and related substances has been summarised in
reviews by Schwarcz et al. (1984a) and El-Defrawy et al.
(1986a). By 1980, it had become clear that kainic acid
and The early interest in the neurotoxic effects of amino
acids and related substances has been summarised in
reviews by Schwarcz et al. (1984a) and El-Defrawy et al.
(1986a). By 1980, it had become clear that kainic acid
and reviews by Schwarcz et al. (1984a) and El-Defrawy et al. (1986a). By 1980, it had become clear that kainic acid and NMDA were among the most potent agents able to produce a combination of neuronal excitation and sub-sequen reviews by Schwarcz et al. (1984a) and El-Defrawy et al.

(1986a). By 1980, it had become clear that kainic acid

and NMDA were among the most potent agents able to

produce a combination of neuronal excitation and sub-
 (1986a). By 1980, it had become clear that kainiand NMDA were among the most potent agents a produce a combination of neuronal excitation and sequent neurodegeneration, a combination referred excitotoxicity. The initiating and NMDA were among the most potent agents able to
produce a combination of neuronal excitation and sub-
sequent neurodegeneration, a combination referred to as
excitotoxicity. The initiating factor for neurodegenera-
tion produce a combination of neuronal excitation and sub-
sequent neurodegeneration, a combination referred to as
excitotoxicity. The initiating factor for neurodegenera-
tion, in most cases, is the accumulation of intracellul sequent neurodegeneration, a combination referred to as
excitotoxicity. The initiating factor for neurodegenera-
tion, in most cases, is the accumulation of intracellular
calcium, which activates proteases and phospholipas excitotoxicity. The initiating factor for neurodegeneration, in most cases, is the accumulation of intracellular calcium, which activates proteases and phospholipases and initiates a chain of phenomena involving lipid pero tion, in most cases, is the accumulation of intracellular calcium, which activates proteases and phospholipases
and initiates a chain of phenomena involving lipid per-
oxidation and free radical generation; the latter even calcium, which activates proteases and phospholipases
and initiates a chain of phenomena involving lipid per-
oxidation and free radical generation; the latter event
may be responsible for the neuronal death (Farber, 1981; and initiates a chain of phenomena involving lipid per-

oxidation and free radical generation; the latter event

may be responsible for the neuronal death (Farber, 1981;

Garthwaite and Garthwaite, 1986; Siesjo and Wielo oxidation and free radical generation; the latter event

may be responsible for the neuronal death (Farber, 1981;

Garthwaite and Garthwaite, 1986; Siesjo and Wieloch,

1985; Verity, 1992; Stone, 1993). Both kainic acid a may be responsible for the neuronal death (Farber, 1981; Garthwaite and Garthwaite, 1986; Siesjo and Wieloch, 1985; Verity, 1992; Stone, 1993). Both kainic acid and NMDA induce increases of intracellular calcium, the forme Garthwaite and Garthwaite, 1986; Siesjo and Wieloch, 1985; Verity, 1992; Stone, 1993). Both kainic acid and NMDA induce increases of intracellular calcium, the former by triggering the intracellular calcium-mediated releas 1985; Verity, 1992; Stone, 1993). Both kainic acid and NMDA induce increases of intracellular calcium, the former by triggering the intracellular calcium-mediated release of calcium from intracellular stores and the latter NMDA induce increases of intracellular calcium, the
former by triggering the intracellular calcium-mediated
release of calcium from intracellular stores and the latter
by activating ionic channels through which sodium, poformer by triggering the intracellular calcium-mediated
release of calcium from intracellular stores and the latter
by activating ionic channels through which sodium, po-
tassium, and calcium can pass in significant quant release of calcium from intracellular stores and the latter
by activating ionic channels through which sodium, po-
tassium, and calcium can pass in significant quantities
(MacDermott et al., 1986). Quinolinic acid is simil by activating ionic channels through which sodium, potassium, and calcium can pass in significant quantities (MacDermott et al., 1986). Quinolinic acid is similarly able to increase intracellular calcium (Tsuzuki et al., 1 tassium, and calcium can pass in significant quant (MacDermott et al., 1986). Quinolinic acid is similable to increase intracellular calcium (Tsuzuki et 1989b; Lu et al. 1991). It is also probable that membidepolarisation (MacDermott et al., 1986). Quinolinic acid is similarly
able to increase intracellular calcium (Tsuzuki et al.,
1989b; Lu et al. 1991). It is also probable that membrane
depolarisation results in the activation of voltageable to increase intracellular calcium (Tsuzuki et al., follow
1989b; Lu et al. 1991). It is also probable that membrane due be
depolarisation results in the activation of voltage-de-
to the
pendent calcium channels which 1989b; Lu et al. 1991). It is also probable that membrane depolarisation results in the activation of voltage-de-
pendent calcium channels which may admit sufficient of calcium to contribute to neuronal damage; the calciu depolarisation results in the activation of voltage-dependent calcium channels which may admit sufficient calcium to contribute to neuronal damage; the calcium channel blocker nifedipine prevents damage of cultured neurone pendent calciu
calcium to conchannel block
neurones by c
et al., 1990).
Based on th lcium to contribute to neuronal damage; the calciun
annel blocker nifedipine prevents damage of culture
urones by quinolinate and other excitotoxins (Weis
al., 1990).
Based on the assumption that the link between exci
tion

channel blocker nifedipine prevents damage of culture
neurones by quinolinate and other excitotoxins (Weis
et al., 1990).
Based on the assumption that the link between exc
tation and toxicity is real, the demonstration tha neurones by quinolinate and other excitotoxins (Weiss
et al., 1990).
Based on the assumption that the link between exci-
tation and toxicity is real, the demonstration that quin-
olinic acid could excite central neurones et al., 1990).
Based on the assumption that the link between excitation and toxicity is real, the demonstration that quin-
olinic acid could excite central neurones by activation of
the NMDA population of receptors (Stone Based on the assumption that the link between excitation and toxicity is real, the demonstration that quin olinic acid could excite central neurones by activation of the NMDA population of receptors (Stone and Perkins 1981 tation and toxicity is real, the demonstration that quire olinic acid could excite central neurones by activation of the NMDA population of receptors (Stone and Perkini 1981) led naturally and rapidly to its testing as an olinic acid could excite central neurones by activation of the NMDA population of receptors (Stone and Perkins, neuron and approximent and rapidly to its testing as an excitotoxin. When administered directly into the rat s the NMDA population of receptors (Stone and Perkins, $\frac{1981}{}$ led naturally and rapidly to its testing as an excitotoxin. When administered directly into the rat striatum, quinolinate produced "axon-sparing" lesions, w 1981) led naturally and rapidly to its testing as an excitotoxin. When administered directly into the rat striatum, quinolinate produced "axon-sparing" lesions, with few marked swelling of dendrites, vacuolation, and loss tum, quinolinate produced "axon-sparing" lesions, with marked swelling of dendrites, vacuolation, and loss of cell structure in postsynaptic sites but generally good (Schwarcz et al., 1983; McGeer and Singh, 1984). arked swelling of dendrites, vacuolation, and loss of $\frac{1}{2}$
Il structure in postsynaptic sites but generally good
eservation of axons and presynaptic terminals
chwarcz et al., 1983; McGeer and Singh, 1984).
It is rema

cell structure in postsynaptic sites but generally good
preservation of axons and presynaptic terminals
(Schwarcz et al., 1983; McGeer and Singh, 1984).
It is remarkable that the areas of brain most sensitive
to this neuro preservation of axons and presynaptic terminals ferminals (Schwarcz et al., 1983; McGeer and Singh, 1984).

It is remarkable that the areas of brain most sensitive

to this neurotoxicity are the hippocampus and striatum, (Schwarcz et al., 1983; McGeer and Singh, 1984).
It is remarkable that the areas of brain most sensitive
to this neurotoxicity are the hippocampus and striatum,
which are among the areas most clearly sensitive to the
excit It is remarkable that the areas of brain most sensitive
to this neurotoxicity are the hippocampus and striatum,
which are among the areas most clearly sensitive to the
excitatory effects of quinolinic acid. Some other regi

NE
nigra, and olfactory bulb, are somewhat resistant to
quinolinate toxicity, at least in the rat brain (Schwarcz NE
nigra, and olfactory bulb, are somewhat resistant to
quinolinate toxicity, at least in the rat brain (Schwarcz
and Kohler, 1983). It has also become clear that even WE
nigra, and olfactory bulb, are somewhat resistant to
quinolinate toxicity, at least in the rat brain (Schwarcz
and Kohler, 1983). It has also become clear that even
within individual brain areas there is some differenti migra, and olfactory bulb, are somewhat resistant to quinolinate toxicity, at least in the rat brain (Schwarcz and Kohler, 1983). It has also become clear that even within individual brain areas there is some differential nigra, and olfactory bulb, are somewhat resistant to quinolinate toxicity, at least in the rat brain (Schwarcz and Kohler, 1983). It has also become clear that even within individual brain areas there is some differential quinolinate toxicity, at least in the rat brain (Schwarcz
and Kohler, 1983). It has also become clear that even
within individual brain areas there is some differential
sensitivity of neuronal cell types. Within the striat and Kohler, 1983). It has also become clear that even
within individual brain areas there is some differential
sensitivity of neuronal cell types. Within the striatum,
for example, the population of large, spiny cells appe within individual brain areas there is some differential sensitivity of neuronal cell types. Within the striatum, for example, the population of large, spiny cells appears to be relatively resistant to quinolinate toxicity sensitivity of neuronal cell types. Within the striatum,
for example, the population of large, spiny cells appears
to be relatively resistant to quinolinate toxicity, and in
the hippocampal formation pyramidal cells in the for example, the population of large, spiny cells appears
to be relatively resistant to quinolinate toxicity, and in
the hippocampal formation pyramidal cells in the CA1
and CA3-CA4 areas are significantly more sensitive t to be relatively resistant to quinolinate toxicity, and i
the hippocampal formation pyramidal cells in the CA
and CA3-CA4 areas are significantly more sensitive tha
neurones in the CA2 region or granule cells in the denta
 the hippocampal formation pyramidal cells in the CA1
and CA3-CA4 areas are significantly more sensitive than
neurones in the CA2 region or granule cells in the dentate
gyrus (Schwarcz et al., 1983, 1984a). Again, it is int and CA3-CA4 areas are significantly more sensitive than
neurones in the CA2 region or granule cells in the dentate
gyrus (Schwarcz et al., 1983, 1984a). Again, it is inter-
esting to note the parallel here between toxicity neurones in the CA2 region or granule cells in the dentate
gyrus (Schwarcz et al., 1983, 1984a). Again, it is inter-
esting to note the parallel here between toxicity and
excitation: Stone (1985b) was able to demonstrate a gyrus (Schwarcz et al., 1983, 1984a). Again, it is interesting to note the parallel here between toxicity and excitation: Stone (1985b) was able to demonstrate aprofile of neuronal excitatory sensitivity to quinolinate in esting to note the parallel here between toxicity and
excitation: Stone (1985b) was able to demonstrate a
profile of neuronal excitatory sensitivity to quinolinate
in the hippocampus that paralleled this toxic variability. excitation: Stone (1985b) was able to demonstrate a
profile of neuronal excitatory sensitivity to quinolinate
in the hippocampus that paralleled this toxic variability.
In contrast, NMDA itself appears to differentiate far profile of neuronal excitatory sensitivity to quinolinate
in the hippocampus that paralleled this toxic variability.
In contrast, NMDA itself appears to differentiate far less
between the different neuronal populations of in the hippocampus that paralleled this toxic variability.

In contrast, NMDA itself appears to differentiate far less

between the different neuronal populations of the hip-

pocampus either with respect to excitation or In contrast, NMDA itself appears to differentiate far less
between the different neuronal populations of the hip-
pocampus either with respect to excitation or toxicity
(Nadler et al., 1981; Foster et al., 1983). Indeed, between the different neuronal populations of the hip
pocampus either with respect to excitation or toxicity
(Nadler et al., 1981; Foster et al., 1983). Indeed, it was are
arly paradox that, despite the selective sensitivi (Nadler et al., 1981; Foster et al., 1983). Indeed, it was an early paradox that, despite the selective sensitivity to NMDA antagonists of quinolinate-induced excitation, the toxic profile of quinolinic acid more closely r (Nadler et al., 1981; Foster et al., 1983). Indeed, it was an early paradox that, despite the selective sensitivity to NMDA antagonists of quinolinate-induced excitation, the toxic profile of quinolinic acid more closely r early paradox that, despite the selective sensitivity NMDA antagonists of quinolinate-induced excitation
the toxic profile of quinolinic acid more closely resembles
that of kainic acid which also induces a different
degene NMDA antagonists of quinolini
the toxic profile of quinolinic acid
that of kainic acid which also
degeneration of neuronal popular
campus (Schwarcz et al., 1983).
Following quinolinic acid adm e toxic profile of quinolinic acid more closely resembled
at of kainic acid which also induces a differential
generation of neuronal populations within the hippo-
mpus (Schwarcz et al., 1983).
Following quinolinic acid adm

that of kainic acid which also induces a differential
degeneration of neuronal populations within the hippocampus (Schwarcz et al., 1983).
Following quinolinic acid administration into either
the striatum or hippocampus, degeneration of neuronal populations within the hippo-
campus (Schwarcz et al., 1983).
Following quinolinic acid administration into either
the striatum or hippocampus, there is an increase of 5HT
turnover as reflected in campus (Schwarcz et al., 1983).
Following quinolinic acid administration into either
the striatum or hippocampus, there is an increase of 5HT
turnover as reflected in the concentration of the primary
metabolite, 5-hydroxyi Following quinolinic acid administration into either
the striatum or hippocampus, there is an increase of 5HT
turnover as reflected in the concentration of the primary
metabolite, 5-hydroxyindoleacetic acid (Aldinio et al. the striatum or hippocampus, there is an increase of 5HT
turnover as reflected in the concentration of the primary
metabolite, 5-hydroxyindoleacetic acid (Aldinio et al.,
1985a). This is probably a reflection of the increa turnover as reflected in the concentration of the primary
metabolite, 5-hydroxyindoleacetic acid (Aldinio et al.,
1985a). This is probably a reflection of the increased
activity of serotonergic afferents in response to th metabolite, 5-hydroxyindoleacetic acid (Aldinio et al., 1985a). This is probably a reflection of the increased activity of serotonergic afferents in response to the loss of postsynaptic tissue. A similar increase of activ 1985a). This is probably a reflection of the increased
activity of serotonergic afferents in response to the loss
of postsynaptic tissue. A similar increase of activity in
dopaminergic nerve terminals occurs in the striatu activity of serotonergic afferents in response to the loss
of postsynaptic tissue. A similar increase of activity in
dopaminergic nerve terminals occurs in the striatum
following quinolinic acid administration and probably of postsynaptic tissue. A similar increase of activity in dopaminergic nerve terminals occurs in the striatum following quinolinic acid administration and probably due both to the loss of postsynaptic inhibitory feedback t dopaminergic nerve terminals occurs in the striatum
following quinolinic acid administration and probably
due both to the loss of postsynaptic inhibitory feedback
to the presynaptic nigtostriatal terminals and to the loss
 following quinolinic acid administration and probable due both to the loss of postsynaptic inhibitory feedbacto the presynaptic nigtostriatal terminals and to the los
of strionigral inhibitory projections (Mazzari et al. 1 due both to the loss of postsynaptic inhibitory feedback
to the presynaptic nigtostriatal terminals and to the loss
of strionigral inhibitory projections (Mazzari et al.,
1986). This finding has been noted as of particular to the presynaptic nigtostriatal terminals and to the lof strionigral inhibitory projections (Mazzari et 1986). This finding has been noted as of particular intest in relation to Huntington's disease, as there is dence tha of strionigral inhibitory projections
1986). This finding has been noted as
est in relation to Huntington's disea
dence that in this disorder there may
satory increase of dopamine activity.
Enzymes related to dopaminergic 1986). This finding has been noted as of particular interest in relation to Huntington's disease, as there is evidence that in this disorder there may also be a compensatory increase of dopamine activity.
Enzymes related t

dence that in this disorder there may also be a compensatory increase of dopamine activity.
Enzymes related to dopaminergic and 5HTergic neurones are unchanged after quinolinate administration, presumably because such mark dence that in this disorder there may also be a compensatory increase of dopamine activity.

Enzymes related to dopaminergic and 5HTergic neurones are unchanged after quinolinate administration,

presumably because such ma satory increase of dopamine activity.

Enzymes related to dopaminergic and 5HTergic neurones are unchanged after quinolinate administration,

presumably because such markers are confined to the

nerve terminals or afferen Enzymes related to dopaminergic and 5HTergic neurones are unchanged after quinolinate administration, presumably because such markers are confined to the nerve terminals or afferent projections to the striatum and are, the rones are unchanged after quinolinate administration,
presumably because such markers are confined to the
nerve terminals or afferent projections to the striatum
and are, therefore, not affected by the toxin. Similarly,
wh presumably because such markers are confined to the nerve terminals or afferent projections to the striatum and are, therefore, not affected by the toxin. Similarly, when injected into the hippocampus, which possesses chol merve terminals or afferent projections to the striand are, therefore, not affected by the toxin. Simil when injected into the hippocampus, which possed
cholinergic nerve terminals arriving from the septun
few, if any, cho and are, therefore, not affected by the toxin. Similarly when injected into the hippocampus, which possesse cholinergic nerve terminals arriving from the septum bufew, if any, cholinergic cell bodies, choline acetyltrana f when injected into the hippocampus, which poss
cholinergic nerve terminals arriving from the septure
few, if any, cholinergic cell bodies, choline acetylt:
ferase activity is quite unaffected, indicating that
olinate does cholinergic nerve terminals arriving from the septum but
few, if any, cholinergic cell bodies, choline acetyltrans-
ferase activity is quite unaffected, indicating that quin-
olinate does not directly inactivate or modify ferase activity is quite unaffected, indicating that quin-
olinate does not directly inactivate or modify acetyltrans-
ferase activity in a manner that would make it invisible
to neurochemical probes.

B. Mechanism of Neurotoxicity

In reporting that pyridine-2,6-dicarboxylic acid (dipi-
colinic acid) was as active as quinolinate in a neurochemto neurochemical probes.

B. Mechanism of Neurotoxicity

In reporting that pyridine-2,6-dicarboxylic acid (

colinic acid) was as active as quinolinate in a neurocl

ical assay of acetylcholine release from the stria B. Mechanism of Neurotoxicity
In reporting that pyridine-2,6-dicarboxylic acid (dipi-
colinic acid) was as active as quinolinate in a neurochem-
ical assay of acetylcholine release from the striatum,

PHARMACOLOGICAL REVIEW!

PHARMACOLOGICAL REVIEWS

aspet

QUINOLINIC AND KYN
Lehmann et al. (1985) concluded that this activity could
be clearly distinguished from the neurotoxic property of QUINOLINIC AND KYI
Lehmann et al. (1985) concluded that this activity could fit
be clearly distinguished from the neurotoxic property of ir
dipicolinic acid which was essentially absent. However, the QUINOLINIC AND
Lehmann et al. (1985) concluded that this activity could
be clearly distinguished from the neurotoxic property of
dipicolinic acid which was essentially absent. However,
this work has not yet been satisfacto Lehmann et al. (1985) concluded that this activity could fus
be clearly distinguished from the neurotoxic property of invertion incident which was essentially absent. However, the
this work has not yet been satisfactorily Lehmann et al. (1985) concluded that this activity could
be clearly distinguished from the neurotoxic property of
dipicolinic acid which was essentially absent. However,
this work has not yet been satisfactorily repeated a be clearly distinguished from the neurotoxic property of dipicolinic acid which was essentially absent. However, this work has not yet been satisfactorily repeated and there is evidence from other studies that the excitant dipicolinic acid which was essentially absent. However, the this work has not yet been satisfactorily repeated and and there is evidence from other studies that the excitant not activity of dipicolinic acid, measured direc this work has not yet been satisfactorily repeated a
there is evidence from other studies that the excite
activity of dipicolinic acid, measured directly on neuro
firing rates, is weaker even than that of quinolinic a
(Bir there is evidence from other studies that the excientivity of dipicolinic acid, measured directly on neurofiring rates, is weaker even than that of quinolinic (Birley et al., 1982). In other neurotoxic studies, dipinic aci firing rates, is weaker even than that of quinolinic acid (Birley et al., 1982). In other neurotoxic studies, dipicolinic acid does have some, albeit still weak, neurodegenerative activity (Foster et al., 1983). The possib inic acid does have some, albeit still weak, neurodegen-(Birley et al., 1982). In other neurotoxic studies, dipicol-
inic acid does have some, albeit still weak, neurodegen-
erative activity (Foster et al., 1983). The possible disso-
aciation of excitation and toxicity for thes inic acid does have some, albeit still weak, neurodegen-
erative activity (Foster et al., 1983). The possible disso-
ciation of excitation and toxicity for these compounds,
therefore, remains an open question, although it erative activity (Foster et al., 1983). The possible disso-
ciation of excitation and toxicity for these compounds,
therefore, remains an open question, although it should
be emphasised that at the low levels of excitation ciation of excitation and toxicity for these compounds,
therefore, remains an open question, although it should clemphasised that at the low levels of excitation and reported toxicity involved only a small amount of contam disparities. emphasised that at the low levels of excitation and revertively involved only a small amount of contamination take a more potent agent could account for the reported his parities.
 1. Presynaptic receptors. The neurotoxi

toxicity involved only a small amount of contamination tail
by a more potent agent could account for the reported had
disparities. qu
1. Presynaptic receptors. The neurotoxic effects of ref
NMDA are mediated primarily vi by a more potent agent could account for the reported disparities.

1. Presynaptic receptors. The neurotoxic effects of NMDA are mediated primarily via receptors on the postsynaptic cell surface, because changes to the aff disparities. que all the neurotoxic effects of the neurotoxic effects of the NMDA are mediated primarily via receptors on the players postynaptic cell surface, because changes to the afferent mipopulations of neurones seem 1. Presynaptic receptors. The neurotoxic effects of reflect NMDA are mediated primarily via receptors on the ple, opostsynaptic cell surface, because changes to the afferent mRN populations of neurones seem to have no effe NMDA are mediated primarily via receptors on the ple
postsynaptic cell surface, because changes to the afferent ml
populations of neurones seem to have no effect on the rat
potency of NMDA as a neurotoxin. Similarly, NMDA postsynaptic cell surface, because changes to the afferent ml
populations of neurones seem to have no effect on the
potency of NMDA as a neurotoxin. Similarly, NMDA con
can produce neuronal degeneration even in the brain t populations of neurones seem to have no effect on the raptionary of NMDA as a neurotoxin. Similarly, NMDA comproduce neuronal degeneration even in the brain the areas of rat pups before about 10 days of age when the main p potency of NMDA as a neurotoxin. Similarly, NMDA co
can produce neuronal degeneration even in the brain the
areas of rat pups before about 10 days of age when the
main projection pathways are as yet undeveloped. These c-j
 can produce neuronal degeneration even in the brain
areas of rat pups before about 10 days of age when the
main projection pathways are as yet undeveloped. These
limitations do not apply to quinolinic acid which is able
to areas of rat pups before about 10 days of age when th
main projection pathways are as yet undeveloped. Thes
limitations do not apply to quinolinic acid which is able
to produce neurotoxicity only in the presence of afferen main projection pathways are as yet undeveloped. These c -*j* limitations do not apply to quinolinic acid which is able tion produce neurotoxicity only in the presence of afferent repribres to the area of investigation. limitations do not apply to quinolinic acid which is able
to produce neurotoxicity only in the presence of afferent
fibres to the area of investigation. In the striatum, quin-
olinic acid is thus ineffective as a neurotox to produce neurotoxicity only in the presence of afferent refibres to the area of investigation. In the striatum, quin-
olinic acid is thus ineffective as a neurotoxin before the of
development of the corticostriatal pathw fibres to the area of investigation. In the striatum, quin-
olinic acid is thus ineffective as a neurotoxin before the
development of the corticostriatal pathway and is unable
to produce detectable damage in the striatum olinic acid is thus ineffective as a neurotoxin before the of
development of the corticostriatal pathway and is unable
to produce detectable damage in the striatum following in
previous destruction of the overlying cerebra development of the corticostriatal pathway and is unable
to produce detectable damage in the striatum following
previous destruction of the overlying cerebral cortex
(Foster et al., 1983) or in the hippocampus following
tr to produce detectable damage in the striatum following in
previous destruction of the overlying cerebral cortex tha
(Foster et al., 1983) or in the hippocampus following cre
transection of the perforant path (Keilhoff et a previous destruction of the overlying cerebral conference (Foster et al., 1983) or in the hippocampus follow transection of the perforant path (Keilhoff et al., 1995) Both of these pathways are believed to utilise amino a (Foster et al., 1983) or in the hippocampus followint ransection of the perforant path (Keilhoff et al., 1990
Both of these pathways are believed to utilise amino ac
neurotransmitters, raising the possibility of a particul transection of the
Both of these path
neurotransmitters,
larly critical role fe
hoff et al., 1991).
Similar observat of these pathways are believed to utilise amino acid (1
urotransmitters, raising the possibility of a particu-
high critical role for these in quinolinate toxicity (Keil-
off et al., 1991).
Similar observations have been m

neurotransmitters, raising the possibility of a particularly critical role for these in quinolinate toxicity (Keilhoff et al., 1991).

Similar observations have been made using isolated

neurones and cell cultures. Thus, i larly critical role for these in quinolinate toxicity (Ke
hoff et al., 1991).
Similar observations have been made using isolat
neurones and cell cultures. Thus, in cultures of stria
neurones, quinolinic acid is only able t door the al., 1991). definition is a set of counterparameters in the presence of striatal presence of cocultures of striatal presence of cocultured explants of all cerebral cortex (Whetsell and Schwarcz, 1983, 1989; Gal-Similar observations have been made using isolated
neurones and cell cultures. Thus, in cultures of striatal
neurones, quinolinic acid is only able to produce neuro-
toxic changes in the presence of cocultured explants of
 neurones, quinolinic acid is only able to produce neuro-
toxic changes in the presence of cocultured explants of
cerebral cortex (Whetsell and Schwarcz, 1983, 1989; Gal-
arraga et al., 1990). These findings strongly sugges neurones, quinolinic acid is only able to produce neuro-
toxic changes in the presence of cocultured explants of alt
cerebral cortex (Whetsell and Schwarcz, 1983, 1989; Gal-
arraga et al., 1990). These findings strongly su toxic changes in the presence of cocultured explants
cerebral cortex (Whetsell and Schwarcz, 1983, 1989; G.
arraga et al., 1990). These findings strongly suggest th
presynaptic terminals may be an essential feature of t
ne cerebral cortex (Whetsell and Schwarcz, 1983, 1989; G.
arraga et al., 1990). These findings strongly suggest the
presynaptic terminals may be an essential feature of t
neurotoxic activity of quinolinic acid, i.e., either q arraga et al., 1990). These findings strongly suggest that
presynaptic terminals may be an essential feature of the
neurotoxic activity of quinolinic acid, i.e., either quino-
linic acid may promote the release of secondar presynaptic terminals may be an essential feature of the
neurotoxic activity of quinolinic acid, i.e., either quino-
linic acid may promote the release of secondary neuro-
toxic agents from nerve terminals or the postsynap neurotoxic activity of quinolinic acid, i.e., either quino-
linic acid may promote the release of secondary neuro-
toxic agents from nerve terminals or the postsynaptic
effects of quinolinic acid are dependent on the permi terminals. xic agents from nerve terminals or the postsynaptic rects of quinolinic acid are dependent on the permissive renhancing effects of factors released from presynaptic a minals.
It was noted above that quinolinic acid appears

effects of quinolinic acid are dependent on the permissive
or enhancing effects of factors released from presynaptic
seterminals.
It was noted above that quinolinic acid appears unable
2,6
to release excitatory amino acids or enhancing effects of factors released from presynaptic aterminals. provided above that quinolinic acid appears unable 2
to release excitatory amino acids, such as glutamate and aspartate, from brain preparations in vitr terminals.
It was noted above that quinolinic acid appears unable
to release excitatory amino acids, such as glutamate an
aspartate, from brain preparations in vitro and, although
it has been reported to enhance their rele It was noted above that quinolinic acid appears unable
to release excitatory amino acids, such as glutamate and
aspartate, from brain preparations in vitro and, although
it has been reported to enhance their release from c aspartate, from brain preparations in vitro and, although
it has been reported to enhance their release from cere-
bral cortical surface in vivo (Connick and Stone, 1988b),
this has not been demonstrated using microdialysi

fusion of the rat hippocampus in vivo. In the latter INURENIC ACIDS

investigation, quinolinic acid administration directly to

the hippocampus at doses that produced both seizures

investigation, quinolinic acid administration directly to 349
fusion of the rat hippocampus in vivo. In the latter
investigation, quinolinic acid administration directly to
the hippocampus at doses that produced both seizures
and neuronal damage did not raise the efflux of endoge fusion of the rat hippocampus in vivo. In the lat
investigation, quinolinic acid administration directly
the hippocampus at doses that produced both seizu
and neuronal damage did not raise the efflux of endo
nous glutamate fusion of the rat hippocampus in vivo. In the latter
investigation, quinolinic acid administration directly to
the hippocampus at doses that produced both seizures
and neuronal damage did not raise the efflux of endoge-
no investigation, quinolinic acid administration directly to
the hippocampus at doses that produced both seizures
and neuronal damage did not raise the efflux of endoge-
nous glutamate or aspartate. It will be interesting to
 the hippocampus at doses that produced both seizures
and neuronal damage did not raise the efflux of endoge-
nous glutamate or aspartate. It will be interesting to
determine whether quinolinic acid can promote the re-
leas and neuronal damage did not raise the efflux of endogenous glutamate or aspartate. It will be interesting to determine whether quinolinic acid can promote the release of other excitatory agents acting at amino acid recepto nous glutamate or aspartate. It will be interesting to determine whether quinolinic acid can promote the release of other excitatory agents acting at amino acid receptors such as the sulphur-containing excitatory amino aci acid.ase of other excitatory agents acting at amino acid ceptors such as the sulphur-containing excitatory nino acids, homocysteic acid, and cysteine sulphinic id.
2. *Transcription factors*. Although a role has been aimed for

receptors such as the sulphur-containing excitatory
amino acids, homocysteic acid, and cysteine sulphinic
acid.
2. Transcription factors. Although a role has been
claimed for increased intracellular calcium in the neu-
rot amino acids, homocysteic acid, and cysteine sulphinic
acid.
2. Transcription factors. Although a role has been
claimed for increased intracellular calcium in the neu-
rotoxic activity of quinolinate, as noted earlier, the acid.

2. Transcription factors. Although a role has been

claimed for increased intracellular calcium in the neu-

rotoxic activity of quinolinate, as noted earlier, the de-

tails of subsequent stages remain unknown. Rec 2. Transcription factors. Although a role has been
claimed for increased intracellular calcium in the neu-
rotoxic activity of quinolinate, as noted earlier, the de-
tails of subsequent stages remain unknown. Recent work
h claimed for increased intracellular calcium in the neu-
rotoxic activity of quinolinate, as noted earlier, the de-
tails of subsequent stages remain unknown. Recent work
has begun to reveal isolated changes in response to
 rotoxic activity of quinolinate, as noted earlier, the d
tails of subsequent stages remain unknown. Recent wo
has begun to reveal isolated changes in response
quinolinate that may contribute to, or be a meaning
reflection tails of subsequent stages remain unknown. Recent work
has begun to reveal isolated changes in response to
quinolinate that may contribute to, or be a meaningful
reflection of, the neurodegenerative process. For exam-
ple, has begun to reveal isolated changes in response to
quinolinate that may contribute to, or be a meaningful
reflection of, the neurodegenerative process. For exam-
ple, quinolinate, like NMDA, can increase the level of
mRNA quinolinate that may contribute to, or be a meaningful
reflection of, the neurodegenerative process. For exam-
ple, quinolinate, like NMDA, can increase the level of
mRNA for the c-fos gene as well as the c-Fos product in
 reflection of, the neurodegenerative process. For example, quinolinate, like NMDA, can increase the level of mRNA for the c-fos gene as well as the c-Fos product in rat striatum (Aronin et al., 1991), hippocampus, and cort ple, quinolinate, like NMDA, can increase the level of mRNA for the c-fos gene as well as the c-Fos product in rat striatum (Aronin et al., 1991), hippocampus, and cortex (Massieu et al., 1992). The striatal expression of mRNA for the c-fos gene as well as the c-Fos product in rat striatum (Aronin et al., 1991), hippocampus, and cortex (Massieu et al., 1992). The striatal expression of these molecules was largely restricted to medium spiny rat striatum (Aronin et al., 1991), hippocampus,
cortex (Massieu et al., 1992). The striatal expression
these molecules was largely restricted to medium sp
neurones, with little evidence in large neurones. Becc
c-*fos* enc cortex (Massieu et al., 1992). The striatal expression of these molecules was largely restricted to medium spiny neurones, with little evidence in large neurones. Because c-fos encodes nuclear proteins that function as tra these molecules was largely restricted to medium spiny
neurones, with little evidence in large neurones. Because
c-*fos* encodes nuclear proteins that function as transcrip-
tion factors to modulate further gene transcript neurones, with little evidence in large neurones. Because
c-fos encodes nuclear proteins that function as transcrip-
tion factors to modulate further gene transcription (or
repression), this work indicates that NMDA recept c-fos encodes nuclear proteins that function as transcription factors to modulate further gene transcription (or repression), this work indicates that NMDA receptor activation could indirectly bring about profound changes tion factors to modulate further gene transcription (or repression), this work indicates that NMDA receptor activation could indirectly bring about profound changes of cell function at the genetic level. Related data indic activation could indirectly bring about profound changes
of cell function at the genetic level. Related data indicate
that NMDA or quinolinate can induce c-fos expression
in the neocortex (Sharp et al., 1990) and, converse that NMDA or quinolinate can induce c -*fos* expression
in the neocortex (Sharp et al., 1990) and, conversely,
that blockade of NMDA receptors can prevent the in-
crease of c -*fos* seen in response to cortical damage. of cell function at the genetic level. Related data indicate
that NMDA or quinolinate can induce c-fos expression
in the neocortex (Sharp et al., 1990) and, conversely,
that blockade of NMDA receptors can prevent the in-
c

in the neocortex (Sharp et al., 1990) and, conversely,
that blockade of NMDA receptors can prevent the in-
crease of c-*fos* seen in response to cortical damage.
3. Apoptosis. In a different approach, Ignatowicz et al.
(1 that blockade of NMDA receptors can prevent the increase of c-fos seen in response to cortical damage.

3. Apoptosis. In a different approach, Ignatowicz et al.

(1991) showed that the injection of quinolinate into rat

h crease of c-fos seen in response to cortical damage.
3. Apoptosis. In a different approach, Ignatowicz et al.
(1991) showed that the injection of quinolinate into rat
hippocampus does not induce the disruption of DNA
molec 3. Apoptosis. In a different approach, Ignatowicz et (1991) showed that the injection of quinolinate into hippocampus does not induce the disruption of D molecules characteristic of apoptosis ("programmed death"), indicat hippocampus does not induce the disruption of DNA molecules characteristic of apoptosis ("programmed cell death"), indicating the induction of a different neurode-
generative sequence by the kynurenine. The results also molecules characteristic of apoptosis ("programmed cell molecules characteristic of apoptosis ("programmed cell death"), indicating the induction of a different neurode-
generative sequence by the kynurenine. The results also
presumably imply that quinolinate is not likely to b death"), indicating the induction of a different neurode-
generative sequence by the kynurenine. The results also
presumably imply that quinolinate is not likely to be an
endogenous agent involved in the initiation of apop generative sequence by the kynurenine. The results also
presumably imply that quinolinate is not likely to be an
endogenous agent involved in the initiation of apoptosis,
although it should perhaps be considered that cell endogenous agent involved in the initiation of apoptosis, although it should perhaps be considered that cellular machinery in the adult brain will be rather different from that in the gestational or postnatal animal when n endogenous agent involved if
although it should perhaps
machinery in the adult brain
that in the gestational or por
apoptosis primarily occurs.
4. Cytoskeletal disruption. though it should perhaps be considered that cellula
achinery in the adult brain will be rather different from
at in the gestational or postnatal animal when nature
optosis primarily occurs.
4. Cytoskeletal disruption. The

machinery in the adult brain will be rather different from
that in the gestational or postnatal animal when natural
apoptosis primarily occurs.
4. Cytoskeletal disruption. The specificity of the quin-
olinate molecule for that in the gestational or postnatal animal when natura
apoptosis primarily occurs.
4. Cytoskeletal disruption. The specificity of the quin-
olinate molecule for NMDA receptors is reflected by the
relatively strict structu apoptosis primarily occurs.
4. Cytoskeletal disruption. The specificity of the quin-
olinate molecule for NMDA receptors is reflected by the
relatively strict structural requirements for both neu-
ronal excitation (Birley 4. Cytoskeletal disruption. The specificity of the quolinate molecule for NMDA receptors is reflected by t relatively strict structural requirements for both noronal excitation (Birley et al., 1982) and neurotoxic assesse olinate molecule for NMDA receptors is reflected by the relatively strict structural requirements for both neuronal excitation (Birley et al., 1982) and neurotoxicity assessed neurochemically (Foster et al., 1983) or elect relatively strict structural requirements for both neu-
ronal excitation (Birley et al., 1982) and neurotoxicity
assessed neurochemically (Foster et al., 1983) or electro-
physiologically (Schurr et al., 1991, 1992). The 2 ronal excitation (Birley et al., 1982) and neurotoxicials assessed neurochemically (Foster et al., 1983) or electrophysiologically (Schurr et al., 1991, 1992). The 2,5-
2,6-, and 3,4-pyridine dicarboxylates have some activ assessed neurochemically (Foster et al., 1983) or electry
physiologically (Schurr et al., 1991, 1992). The 2,5
2,6-, and 3,4-pyridine dicarboxylates have some activit
although less than quinolinate itself (2,3-pyridine dic physiologically (Schurr et al., 1991, 1992). The 2, 2,6-, and 3,4-pyridine dicarboxylates have some activity although less than quinolinate itself (2,3-pyridine dicarboxylic acid), whereas those analogues that have met or 3-, and 3,4-pyridine dicarboxylates have some activity, though less than quinolinate itself (2,3-pyridine dicar-
xylic acid), whereas those analogues that have meta-
para-placed carboxyl groups are generally inactive.
Inte although less than quinolinate itself (2,3-pyridine dicar-
boxylic acid), whereas those analogues that have meta-
or para-placed carboxyl groups are generally inactive.
Interestingly, a very similar structure-activity prof

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proteins by quinolinate and its analogues (Nonneman et
al., 1988). Quinolinate, in particular, induces significant t st
1988). The setting by quinolinate and its analogues (Nonneman et
1., 1988). Quinolinate, in particular, induces significant
1. Changes of physicochemical membrane properties of husre
proteins by quinolinate and its analogues (Nonneman et
al., 1988). Quinolinate, in particular, induces significant
changes of physicochemical membrane properties of hu-
man erythrocytes, assessed using electron spin re proteins by quinolinate and its analogues (Nonneman et al., 1988). Quinolinate, in particular, induces significant changes of physicochemical membrane properties of human erythrocytes, assessed using electron spin resonanc proteins by quinolinate and its analogues (Nonneman et
al., 1988). Quinolinate, in particular, induces significant the
changes of physicochemical membrane properties of hu-
man erythrocytes, assessed using electron spin re al., 1988). Quinolinate, in particular, induces significant the changes of physicochemical membrane properties of human erythrocytes, assessed using electron spin resonance as of markers attached to the cytoskeletal protei changes of physicochemical membrane properties of human erythrocytes, assessed using electron spin resonance
of markers attached to the cytoskeletal protein spectrin
(Farmer and Butterfield, 1984; Farmer et al., 1984). Thi man erythrocytes, assessed using electron spin resonance of markers attached to the cytoskeletal protein spectri
(Farmer and Butterfield, 1984; Farmer et al., 1984). The
protein is almost identical with fodrin and is a maj

(Farmer and Butterfield, 1984; Farmer et al., 1984). T
protein is almost identical with fodrin and is a ma
component of the neuronal cytoskeleton in the CNS.
The similarities in the structural requirements for su
physicoch protein is almost identical with fodrin and is a major accomponent of the neuronal cytoskeleton in the CNS. The similarities in the structural requirements for such resphysicochemical actions and neurotoxicity raises intri component of the neuronal cytoskeleton in the CNS.

The similarities in the structural requirements for such

physicochemical actions and neurotoxicity raises intrigu-

ling questions about the mechanisms of toxicity. It The similarities in the structural requirements for such
physicochemical actions and neurotoxicity raises intrigu-
ing questions about the mechanisms of toxicity. It is
conceivable, for example, that it is an initial disr ing questions about the mechanisms of toxicity. It is kyronceivable, for example, that it is an initial disruption incording of the cytoskeleton that leads to the efflux of amino acids An and thus begins the usually accept conceivable, for example, that it is an initial disrupt
of the cytoskeleton that leads to the efflux of amino ac
and thus begins the usually accepted cascade of eve
leading to death. The loss of cytoskeletal rigidity n
als of the cytoskeleton that leads to the efflux of a
and thus begins the usually accepted cascade
leading to death. The loss of cytoskeletal riq
also contribute to the release of calcium fron
lular pools, further exacerbating d thus begins the usually accepted cascade of events ending to death. The loss of cytoskeletal rigidity may the so contribute to the release of calcium from intracel-
so contribute to the release of calcium from intracel-

leading to death. The loss of cytoskeletal rigidity may
also contribute to the release of calcium from intracel-
lular pools, further exacerbating the damage.
5. Lipid peroxidation. Another interesting discovery
was report also contribute to the release of calcium from intracel-
lular pools, further exacerbating the damage.
5. Lipid peroxidation. Another interesting discovery
was reported by Rios and Santamaria (1991), who ex-
amined the for lular pools, further exacerbating the damage.
5. Lipid peroxidation. Another interesting discovers was reported by Rios and Santamaria (1991), who amined the formation of thiobarbituric acid derivation in rat brain homogen 5. Lipid peroxidation. Another interesting discovery volt was reported by Rios and Santamaria (1991), who ex-
amined the formation of thiobarbituric acid derivatives veal
as a measure of lipid peroxidation in rat brain ho was reported by Rios and Santamaria (1991), who ϵ amined the formation of thiobarbituric acid derivatives a measure of lipid peroxidation in rat brain homogenetes. Quinolinate, at concentrations of only 20 to μ M, in amined the formation of thiobarbituric acid derivations as a measure of lipid peroxidation in rat brain homonates. Quinolinate, at concentrations of only 20 to μ M, increased the amount of lipid peroxidation signerally c as a measure of lipid peroxidation in rat brain homogenates. Quinolinate, at concentrations of only 20 to 80 μ M, increased the amount of lipid peroxidation significantly compared with controls. Because lipid peroxidati mates. Quinolinate, at concentrations of only 20 to 80 qui μ M, increased the amount of lipid peroxidation significantly compared with controls. Because lipid peroxidation is believed to be intimately related to free ra μ M, increased the amount of lipid peroxidation significantly compared with controls. Because lipid peroxidation is believed to be intimately related to free radical so formation and, thus, with cellular damage, this ma cantly compared with controls. Because lipid peroxidation is believed to be intimately related to free radical formation and, thus, with cellular damage, this may suggest that quinolinate toxicity could be mediated partly tion is believed to be intimately related to free radical formation and, thus, with cellular damage, this may suggest that quinolinate toxicity could be mediated partly by this route. However, the observation that is most formation and, thus, with cellular damage, this may suggest that quinolinate toxicity could be mediated partly by this route. However, the observation that is most intriguing was that the presence of kynurenic acid prevent suggest that quinolinate toxicity could be mediated partly
by this route. However, the observation that is mos
intriguing was that the presence of kynurenic acid pre
vented the action of quinolinate, implying possibly tha
 by this route. However, the observation that is most intriguing was that the presence of kynurenic acid prevented the action of quinolinate, implying possibly that the changes were receptor mediated. Furthermore, L kynuren intriguing was that the presence of kynurenic acid prevented the action of quinolinate, implying possibly that
the changes were receptor mediated. Furthermore, L-
kynurenine actually *decreased* lipid peroxidation com-
par vented the action of quinolinate, implying possibly that
the changes were receptor mediated. Furthermore, L-
kynurenine actually *decreased* lipid peroxidation com-
pared with controls. It would be interesting to determine the changes were receptor mediated. Furthermore, L-
kynurenine actually *decreased* lipid peroxidation com-
pared with controls. It would be interesting to determine
the effect of more selective NMDA antagonists on basal
a pared with controls. It would be interesting to determine
the effect of more selective NMDA antagonists on basal
and quinolinate-induced peroxidation.
Quinolinate toxicity can be potentiated by tetrahy-
droaminoacridine (Z pared with controls. It would be interesting to determine
the effect of more selective NMDA antagonists on basal
and quinolinate-induced peroxidation.
droaminoacridine (Zhu et al., 1988). Potentiation was
of seen at a dose

the effect of more selective NMDA antagonists on basal muand quinolinate-induced peroxidation. the quinolinate toxicity can be potentiated by tetrahy-
droaminoacridine (Zhu et al., 1988). Potentiation was of seen at a dose and quinolinate-induced peroxidation.

Quinolinate toxicity can be potentiated by tetrahy-

droaminoacridine (Zhu et al., 1988). Potentiation was

seen at a dose of 5 mg/kg, but not 10 mg/kg, and the

authors considered th Quinolinate toxicity can be potentiated by tetrahy-
droaminoacridine (Zhu et al., 1988). Potentiation was
seen at a dose of 5 mg/kg, but not 10 mg/kg, and the
authors considered that this effect was sufficiently con-
siste droaminoacridine (Zhu et al., 1988). Potentiation was
seen at a dose of 5 mg/kg, but not 10 mg/kg, and the
authors considered that this effect was sufficiently con-
sistent with the previously demonstrated partial agonist
 seen at a dose of 5 mg/kg, but not 10 mg/kg, and the authors considered that this effect was sufficiently consistent with the previously demonstrated partial agonist activity of tetrahydroaminoacridine at the phencyclidine authors considered that this effect was sufficiently consistent with the previously demonstrated partial agonist yieldictivity of tetrahydroaminoacridine at the phencyclidine asite of the NMDA channel and that the phencycl sistent with the previously demonstrated partial
activity of tetrahydroaminoacridine at the phenc
site of the NMDA channel and that the phenc
location probably represented the main site of a
tetrahydroaminoacridine. Howeve activity of tetrahydroaminoacridine at the phencycle idea of the NMDA channel and that the phencyclocation probably represented the main site of active tetrahydroaminoacridine. However, tetrahydroaminity ridine is an effec site of the NMDA channel and that the phencyclidine quicketion probably represented the main site of action of the tetrahydroaminoacridine. However, tetrahydroaminoaccidine is an effective inhibitor of cerebral acetylcholi tetrahydroaminoacridine. However, tetrahydroaminoac-
ridine is an effective inhibitor of cerebral acetylcholin-
sterase and is now known to block a number of ionic
channels, including those for potassium and the nicotinic ridine is an effective inhibitor of cerebral acetylcholin-
esterase and is now known to block a number of ionic
channels. including those for potassium and the nicotinic in the basal ganglia of patients with Pa
receptor-a ridine is an effective inhibitor of cerebral acetylcholiesterase and is now known to block a number of ion channels, including those for potassium and the nicotine receptor-associated channels. The mechanism of action tetr esterase and is
channels, inclu
receptor-associ
of tetrahydroa:
ered unproven.
Aminooxyac annels, including those for potassium and the nicotinic irceptor-associated channels. The mechanism of action (tetrahydroaminoacridine must, therefore, be consided unproven.
Aminooxyacetic acid was recently shown to induc

receptor-associated channels. The mechanism of action
of tetrahydroaminoacridine must, therefore, be consid-
ered unproven.
Aminooxyacetic acid was recently shown to induce
seizures and neuronal damage (Beal et al., 1991a; of tetrahydroaminoacridine must, therefore, be considered unproven.

Aminooxyacetic acid was recently shown to induce

seizures and neuronal damage (Beal et al., 1991a; Turski

et al., 1992; McMaster et al., 1991). These p ered unproven.

Aminooxyacetic acid was recently shown to induce

seizures and neuronal damage (Beal et al., 1991a; Turski neuronal

et al., 1992; McMaster et al., 1991). These phenomena with

were attributed to the indire Aminooxyacetic acid was recently shown to induce
seizures and neuronal damage (Beal et al., 1991a; Turski neu
et al., 1992; McMaster et al., 1991). These phenomena wit
were attributed to the indirect activation of NMDA Th
 seizures and neuronal damage (Beal et al., 1991a; Turski
et al., 1992; McMaster et al., 1991). These phenomena
were attributed to the indirect activation of NMDA
receptors, partly based on the use of antagonists and
partly

(Farmer and Butterfield, 1984; Farmer et al., 1984). This nism of NMDA receptor activation. However, aminooxy-
protein is almost identical with fodrin and is a major acetate is a very effective inhibitor of a range of tran ing questions about the mechanisms of toxicity. It is kynurenine metabolism to kynurenate may lead to an conceivable, for example, that it is an initial disruption increased flux along the pathway to quinolinic acid itself NE
pocampal pathology observed in these experiments and
that produced by quinolinic acid. It is possible that these NE
pocampal pathology observed in these experiments and
that produced by quinolinic acid. It is possible that these
effects could be due to the inhibition of kynurenine WE
pocampal pathology observed in these experiments and
that produced by quinolinic acid. It is possible that these
effects could be due to the inhibition of kynurenine
aminotransferase by aminooxyacetate, leading to a depocampal pathology observed in these experiments and
that produced by quinolinic acid. It is possible that these
effects could be due to the inhibition of kynurenine
aminotransferase by aminooxyacetate, leading to a de-
cl pocampal pathology observed in these experiments at that produced by quinolinic acid. It is possible that the
ffects could be due to the inhibition of kynuren
aminotransferase by aminooxyacetate, leading to a
cline of extr that produced by quinolinic acid. It is possible that the effects could be due to the inhibition of kynure
aminotransferase by aminooxyacetate, leading to a
cline of extracellular kynurenate and, thus, less ant
nism of NMD effects could be due to the inhibition of kynurenii
aminotransferase by aminooxyacetate, leading to a d
cline of extracellular kynurenate and, thus, less antag
nism of NMDA receptor activation. However, aminoox
acetate is aminotransferase by aminooxyacetate, leading to a decline of extracellular kynurenate and, thus, less antagonism of NMDA receptor activation. However, aminooxy-
acetate is a very effective inhibitor of a range of transamin cline of extracellular kynurenate and, thus, less antagonism of NMDA receptor activation. However, aminooxy-
acetate is a very effective inhibitor of a range of trans-
aminase enzymes, and caution should be exercised in
re nism of NMDA receptor activation. However, aminooxy-
acetate is a very effective inhibitor of a range of trans-
aminase enzymes, and caution should be exercised in
restricting interpretation only to the inhibition of the
k acetate is a very effective inhibitor of a range of trans-
aminase enzymes, and caution should be exercised in
restricting interpretation only to the inhibition of the
kynurenine-related enzyme. In addition, a decrease of
 aminase enzymes, and caution should be exercised in
restricting interpretation only to the inhibition of the
kynurenine-related enzyme. In addition, a decrease of
kynurenine metabolism to kynurenate may lead to an
increase restricting interpretation only to the inhibition of
kynurenine-related enzyme. In addition, a decreas
kynurenine metabolism to kynurenate may lead t
increased flux along the pathway to quinolinic acid is
Any of these effe kynurenine metabolism to kynurenate may lead to an kynurenine metabolism to kynurenate may lead to are increased flux along the pathway to quinolinic acid itself Any of these effects may contribute to the aminooxyac etate neurotoxicity, although it should be emphasised tha increased flux along the pathway to quinolinic acid itself.
Any of these effects may contribute to the aminooxyac-
etate neurotoxicity, although it should be emphasised
that this compound has a high propensity to cause non Any of these effects may contribute to the aminooxyactate neurotoxicity, although it should be emphasised that this compound has a high propensity to cause non-
selective cell toxicity; any such agent may induce some
loss etate neurotoxicity, although it should be emphasise
that this compound has a high propensity to cause nor
selective cell toxicity; any such agent may induce som
loss of membrane potential that will tend to relieve th
volt that this compound has a high propensity to cause non-
selective cell toxicity; any such agent may induce some
loss of membrane potential that will tend to relieve the
voltage-dependent blockade by magnesium of ionic chanloss of membrane potential that will tend to relieve the voltage-dependent blockade by magnesium of ionic channels associated with the NMDA receptor and, thus, reveal an *apparent* NMDA-mediated effect.

peared (Rieke, 1992) suggesting that a compound referred to throughout as "L-kynurenic acid" may cause veal an *apparent* NMDA-mediated effect.
6. Other kynurenines. Several kynurenines other than
quinolinate may also be neurotoxic. One report has ap-
peared (Rieke, 1992) suggesting that a compound re-
ferred to throughout 6. Other kynurenines. Several kynurenines other than quinolinate may also be neurotoxic. One report has appeared (Rieke, 1992) suggesting that a compound referred to throughout as "L-kynurenic acid" may cause some neurotox quinolinate may also be neurotoxic. One report has appeared (Rieke, 1992) suggesting that a compound referred to throughout as "L-kynurenic acid" may cause some neurotoxicity. Since kynurenic acid does not exist in isomeri peared (Rieke, 1992) suggesting that a compound referred to throughout as "L-kynurenic acid" may cause some neurotoxicity. Since kynurenic acid does not exist in isomeric forms, and high concentrations have been used by ma ferred to throughout as "L-kynurenic acid" may casome neurotoxicity. Since kynurenic acid does not e
in isomeric forms, and high concentrations have b
used by many other groups with no evidence of neuro
damage (Foster et a some neurotoxicity. Since kynurenic acid does not exist
in isomeric forms, and high concentrations have been
used by many other groups with no evidence of neuronal
damage (Foster et al., 1984b; Winn et al., 1991; Jhaman-
d in isomeric forms, and high coused by many other groups with damage (Foster et al., 1984b; Widas et al., 1990), the identity of used is something of a mystery.
Rather more certain is that ed by many other groups with no evidence of neuronal
mage (Foster et al., 1984b; Winn et al., 1991; Jhaman-
s et al., 1990), the identity of the compound actually
ed is something of a mystery.
Rather more certain is that 3

that this compound has a high propensity to cause non-
selective cell totricity; any such agent may induce some
selective cell torelieve the
loos of membrane potential that will tend to relieve the
voltage-dependent blocka das et al., 1990), the identity of the compound actually
used is something of a mystery.
Rather more certain is that 3-hydroxykynurenine is
toxic to neurones (Eastman and Guilarte, 1989), an
action that may be mediated by toxic to neurones (Eastman and Guilarte, 1989), an action that may be mediated by the intracellular accu-
mulation of hydrogen peroxide or free radicals following used is something of a mystery.

Rather more certain is that 3-hydroxykynurenine is

toxic to neurones (Eastman and Guilarte, 1989), an

action that may be mediated by the intracellular accu-

mulation of hydrogen peroxide Rather more certain is that 3-hydroxykynurenine
toxic to neurones (Eastman and Guilarte, 1989), a
action that may be mediated by the intracellular acc
mulation of hydrogen peroxide or free radicals followin
the iron-cataly toxic to neurones (Eastman and Guilarte, 1989), an
action that may be mediated by the intracellular accu-
mulation of hydrogen peroxide or free radicals following
the iron-catalysed autoxidation of the kynurenine (East-
ma action that may be mediated by the intracellular accumulation of hydrogen peroxide or free radicals following
the iron-catalysed autoxidation of the kynurenine (East-
man and Guilarte, 1990). It should be recalled that lev mulation of hydrogen peroxide or free radicals following
the iron-catalysed autoxidation of the kynurenine (East-
man and Guilarte, 1990). It should be recalled that levels
of 3-hydroxykynurenine are elevated in patients w the iron-catalysed autoxidation of the kynurenine (E man and Guilarte, 1990). It should be recalled that level of 3-hydroxykynurenine are elevated in patients v
Huntington's disease (Pearson and Reynolds, 1992).'
metabolic man and Guilarte, 1990). It should be recalled that levels
of 3-hydroxykynurenine are elevated in patients with
Huntington's disease (Pearson and Reynolds, 1992). The
metabolic product of 3-hydroxykynurenine, 3-hydrox
yant of 3-hydroxykynurenine are elevated in patients with
Huntington's disease (Pearson and Reynolds, 1992). The
metabolic product of 3-hydroxykynurenine, 3-hydrox-
yanthranilic acid, has also been shown to be neurotoxic,
and a Huntington's disease (Pearson and Reynolds, 1992). The
metabolic product of 3-hydroxykynurenine, 3-hydrox-
yanthranilic acid, has also been shown to be neurotoxic,
and although this is at least 4-fold less active than
quin metabolic product of 3-hydroxykynurenine, 3-hydroxyanthranilic acid, has also been shown to be neurotoxiend although this is at least 4-fold less active the quinolinate (Jhamandas et al., 1990), it is still possibilitied t yanthranilic acid, has also been shown to be net
and although this is at least 4-fold less acti
quinolinate (Jhamandas et al., 1990), it is still
that some toxicity attributed to 3-hydroxykyr
could be due to its conversion d although this is at least 4-fold less active t
inolinate (Jhamandas et al., 1990), it is still pose
at some toxicity attributed to 3-hydroxy-synures
uld be due to its conversion to this metabolite.
As noted again in sect could be due to its conversion to this metabolite.

quinolinate (Jhamandas et al., 1990), it is still possible
that some toxicity attributed to 3-hydroxykynurenine
could be due to its conversion to this metabolite.
As noted again in section E10, the ratio of 3-hydroxy-
kynu As noted again in section E10, the ratio of 3-hydroxyin the basal ganglia of patients with Parkinson's disease

the basal ganglia of patients with Parkinson's disease
gawa et al., 1992).
Neuroprotection against Quinolinate
A variety of agents has been found to modify the
urotoxic effects of quinolinate, most being consistent (Ogawa et al., 1992).
C. Neuroprotection against Quinolinate
A variety of agents has been found to modify the
neurotoxic effects of quinolinate, most being consistent
with the mediation of that toxicity by NMDA receptors. C. Neuroprotection against Quinolinate
A variety of agents has been found to modify the
neurotoxic effects of quinolinate, most being consistent
with the mediation of that toxicity by NMDA receptors.
Thus, competitive NMD C. *Neuroprotection against Quinounate*
A variety of agents has been found to modify the
neurotoxic effects of quinolinate, most being consistent
with the mediation of that toxicity by NMDA receptors.
Thus, competitive NM A variety of agents has been found ω_{\bullet} modify the
urotoxic effects of quinolinate, most being consiste
with the mediation of that toxicity by NMDA receptor
Thus, competitive NMDA antagonists such as $2AP5$ a
 $2AP7$ (Sc neurotoxic effects of quinolinate, most being consistent
with the mediation of that toxicity by NMDA receptors.
Thus, competitive NMDA antagonists such as 2AP5 and
2AP7 (Schwarcz et al., 1984a,b; Garthwaite and Garth-
wait

PHARMACOLOGICAL REVIEWS

QUINOLINIC AND KYNURENIC ACIDS 351

quinolinic AND K
cilpine (Beal et al., 1988a; Engber and Chase, 1988;
Vezzani et al., 1989a; Keilhoff et al., 1991), ketamine QUINOLINIC AND K

eilpine (Beal et al., 1988a; Engber and Chase, 1988;

Vezzani et al., 1989a; Keilhoff et al., 1991), ketamine

(Lees, 1987), zinc (Kida and Matja, 1990), and even qUINOLINIC AND KYN

cilpine (Beal et al., 1988a; Engber and Chase, 1988; al.,

Vezzani et al., 1989a; Keilhoff et al., 1991), ketamine En

(Lees, 1987), zinc (Kida and Matja, 1990), and even ma

systemically administered m cilpine (Beal et al., 1988a; Engber and Chase, 1988;
Vezzani et al., 1989a; Keilhoff et al., 1991), ketamine
(Lees, 1987), zinc (Kida and Matja, 1990), and even
systemically administered magnesium (Wolf et al., 1990),
are Vezzani et al., 1989a; Keilhoff et al., 1991), ketamine (Lees, 1987), zinc (Kida and Matja, 1990), and even systemically administered magnesium (Wolf et al., 1990), are effective. It should be noted, however, that the effi Vezzani et al., 1989a; Keilhoff et al., 1991), ketamine (Lees, 1987), zinc (Kida and Matja, 1990), and even systemically administered magnesium (Wolf et al., 1990), are effective. It should be noted, however, that the effi (Lees, 1987), zinc (Kida and Matja, 1990), and even masystemically administered magnesium (Wolf et al., 1990), in are effective. It should be noted, however, that the effi-
cacy of magnesium may be related more to its gene systemically administered magnesium (Wolf et al., 1990), ing
are effective. It should be noted, however, that the effi-
cacy of magnesium may be related more to its general tive
depressant effect on neuronal excitability, are effective. It should be noted, however, that the efficacy of magnesium may be related more to its general
depressant effect on neuronal excitability, or on the
release of necessary presynaptic factors, than to any
sele cacy of magnesium may be related more to its ge
depressant effect on neuronal excitability, or or
release of necessary presynaptic factors, than to
selective suppression of NMDA receptor opera
Quinolinate toxicity, at leas depressant effect on neuronal excitability, or on the
release of necessary presynaptic factors, than to any
selective suppression of NMDA receptor operation.
Quinolinate toxicity, at least of GABA and acetylcholine-
contai release of necessary presynaptic factors, than to a
selective suppression of NMDA receptor operatic
Quinolinate toxicity, at least of GABA and acetylcholin
containing neurones in the striatum, can also be pi
vented by syst selective suppression of NMDA receptor operation. ir
Quinolinate toxicity, at least of GABA and acetylcholine-
containing neurones in the striatum, can also be pre-
vented by systemically applied monosialogangliosides be
(Quinolinate toxicity, at least of GABA and acetylcholine-
containing neurones in the striatum, can also be pre-
vented by systemically applied monosialogangliosides
(Lombardi et al., 1989) and by the prior implantation of
 containing neurones in the striatum, can also be prevented by systemically applied monosialogangliosides (Lombardi et al., 1989) and by the prior implantation of foetal striatal tissue (Pearlman et al., 1991). An intact ni vented by systemically applied monosialogangliosides been
(Lombardi et al., 1989) and by the prior implantation of syst
foetal striatal tissue (Pearlman et al., 1991). An intact tage
nigrostriatal pathway in adult animals (Lombardi et al., 1989) and by the prior implantation
foetal striatal tissue (Pearlman et al., 1991). An inti
nigrostriatal pathway in adult animals is itself protect
(Buisson et al., 1991). The mechanism of protection
the foetal striatal tissue (Pearlman et al., 1991). An intact
nigrostriatal pathway in adult animals is itself protective
(Buisson et al., 1991). The mechanism of protection in
these latter cases remains uncertain, but because nigrostriatal pathway in adult animals is itself protective (Buisson et al., 1991). The mechanism of protection in these latter cases remains uncertain, but because protection is also afforded against other types of cerebr (Buisson et al., 1991). The mechanism of protection in these latter cases remains uncertain, but because protection is also afforded against other types of cerebral insult, it is not likely that there is any selective acti these latter cases remains uncertain, but because protec-
tion is also afforded against other types of cerebral insult,
it is not likely that there is any selective activity against
quinolinate. Since some protection is se tion is also afforded against other types of cerebral insult,
it is not likely that there is any selective activity against
quinolinate. Since some protection is seen even in corti-
costriatal cultures with no apparent req it is not likely that there is any selective activity against
quinolinate. Since some protection is seen even in corti-
costriatal cultures with no apparent requirement for the
formation of synaptic connections between the quinolinate. Since some protection is seen even in cortical constriated cultures with no apparent requirement for the tin formation of synaptic connections between the established tissue and the newly added tissue, it is costriatal cultures with no appare
formation of synaptic connection
lished tissue and the newly adder
that humoral factors such as trinvolved (Whetsell et al., 1989).
The protective ability of agents mation of synaptic connections between the estab-
hed tissue and the newly added tissue, it is probable teen
at humoral factors such as trophic factors may be μ g
volved (Whetsell et al., 1989).
The protective ability o

lished tissue and the newly added tissue, it is probat
that humoral factors such as trophic factors may
involved (Whetsell et al., 1989).
The protective ability of agents such as dizocilpine
not entirely understood because that humoral factors such as trophic factors may be μ
involved (Whetsell et al., 1989). The protective ability of agents such as dizocilpine is lift
not entirely understood because the drug can be admin-
istered up to involved (Whetsell et al., 1989).
The protective ability of agents such as dizocilpine
not entirely understood because the drug can be admi
istered up to 5 hours after an intrahippocampal injectio
of quinolinate, whereas q The protective ability of agents such as dizocilpine is line
not entirely understood because the drug can be admin-
istered up to 5 hours after an intrahippocampal injection tox
of quinolinate, whereas quinolinate has enti not entirely understood because the drug can be admin-
istered up to 5 hours after an intrahippocampal injection to
of quinolinate, whereas quinolinate has entirely disap-
olpeared from the injection site by 2 hours (Bakke istered up to 5 hours after an intrahippocampal injection
of quinolinate, whereas quinolinate has entirely disap-
peared from the injection site by 2 hours (Bakker and
Foster, 1991). This may indicate that the activation o of quinolinate, whereas quinolinate has entirely disap-
peared from the injection site by 2 hours (Bakker and adr
Foster, 1991). This may indicate that the activation of the
NMDA receptors serves merely as a preliminary ev Foster, 1991). This may indicate that the activation of NMDA receptors serves merely as a preliminary event to initiate longer term cycles of endogenous amino acid Foster, 1991). This may indicate that the activation of the NMDA receptors serves merely as a preliminary event row initiate longer term cycles of endogenous amino acid release or a developing increase of NMDA receptor sen NMDA receptors serves merely as
to initiate longer term cycles of end
release or a developing increase of N
sitivity that reaches a critical thre
cell damage only some hours later.
In terms of understanding the me initiate longer term cycles of endogenous amino a
lease or a developing increase of NMDA receptor se
ivity that reaches a critical threshold for triggeri
ll damage only some hours later.
In terms of understanding the mecha

release or a developing increase of NMDA receptor sen-
sitivity that reaches a critical threshold for triggering with
cell damage only some hours later. freq
In terms of understanding the mechanisms of excito-
syst
toxicit sitivity that reaches a critical threshold for triggering
cell damage only some hours later.
In terms of understanding the mechanisms of excito
toxicity and its prevention, it would also be valuable to
have a resolution of cell damage only some hours later. Frequence in terms of understanding the mechanisms of excito-
toxicity and its prevention, it would also be valuable to have a resolution of conflicting results obtained by Eng-
her and C In terms of understanding the mechanisms of excito toxicity and its prevention, it would also be valuable to have a resolution of conflicting results obtained by Eng ber and Chase (1988) and Choi and Visekul (1988). The la toxicity and its prevention, it would also be valuable to
have a resolution of conflicting results obtained by Eng-
ber and Chase (1988) and Choi and Visekul (1988). The
latter group reported that a number of opioid compou have a resolution of conflicting results obtained by Eng-
ber and Chase (1988) and Choi and Visekul (1988). The
latter group reported that a number of opioid compounds
as well as their nonopioid enantiomers, would prevent
 ber and Chase (1988) and Choi and Visekul (1988). The
latter group reported that a number of opioid compounds,
as well as their nonopioid enantiomers, would prevent
quinolinate toxicity on cultures of mouse cortical neu-
r latter group reported that a number of opioid compounds,
as well as their nonopioid enantiomers, would prevent
quinolinate toxicity on cultures of mouse cortical neu-
rones. Engber and Chase (1988) could not see any pro-
t as well as their nonopioid enantiomers, would propulate toxicity on cultures of mouse cortical
rones. Engber and Chase (1988) could not see any
tection in vivo against quinolinate injected into the
striatum by systemically quinolinate toxicity on cultures of mouse cortical nerones. Engber and Chase (1988) could not see any p
tection in vivo against quinolinate injected into the
striatum by systemically administered dextrometh
phan, a finding nes. Engber and Chase (1988) could not see any pro-
ction in vivo against quinolinate injected into the rat
riatum by systemically administered dextromethor-
an, a finding later confirmed by Zhu et al. (1989).
Clearly, the

tection in vivo against quinolinate injected into the intertaintum by systemically administered dextromethophan, a finding later confirmed by Zhu et al. (1989).
Clearly, there may be a regional or species different to expl striatum by systemically administered dextromethor
phan, a finding later confirmed by Zhu et al. (1989).
Clearly, there may be a regional or species difference
to explain this difference which may also reflect impor-
tant phan, a finding later confirmed by Zhu et al. (1989).
Clearly, there may be a regional or species different
to explain this difference which may also reflect imp
tant distinctions between in vivo and culture technique
incl Clearly, there may be a regional or species difference
to explain this difference which may also reflect impor-
tant distinctions between in vivo and culture techniques,
including the uncertainty that must attend the physi tant distinctions between in vivo and culture techniques, (Filloux et al., 1991).
including the uncertainty that must attend the physio-
logical status of cultures. In this particular comparison, prevent striated toxicity tant distinctions between in vivo and culture technique including the uncertainty that must attend the physiological status of cultures. In this particular comparis however, the amounts of quinolinate administered in verse including the uncertainty that must attend the physio-
logical status of cultures. In this particular comparison, prev
however, the amounts of quinolinate administered in vivo dans
were relatively high (150 to 300 nmol), w logical status of cultures. In this particular comparison,
however, the amounts of quinolinate administered in vivo
were relatively high (150 to 300 nmol), whereas substan-
tial lesions can be produced in adult rat striatu

YNURENIC ACIDS
al., 1983; Waldvogel et al., 1991). The doses used by
Engber and Chase (1988) may, therefore, have been YNURENIC ACIDS
al., 1983; Waldvogel et al., 1991). The doses used by
Engber and Chase (1988) may, therefore, have been
maximal for inducing toxicity and appear correspond-YNURENIC ACIDS
al., 1983; Waldvogel et al., 1991). The doses use
Engber and Chase (1988) may, therefore, have
maximal for inducing toxicity and appear corresp
ingly less amenable to antagonism. On the other h al., 1983; Waldvogel et al., 1991). The doses used by Engber and Chase (1988) may, therefore, have been maximal for inducing toxicity and appear correspondingly less amenable to antagonism. On the other hand, the mouse cor Engber and Chase (1988) may, therefore, have been maximal for inducing toxicity and appear correspondingly less amenable to antagonism. On the other hand, the mouse cortex cultures seem to be relatively insensi-Engber and Chase (1988) may, therefore, have been
maximal for inducing toxicity and appear correspond-
ingly less amenable to antagonism. On the other hand,
the mouse cortex cultures seem to be relatively insensi-
tive to maximal for inducing toxicity and appear correspondingly less amenable to antagonism. On the other hand, the mouse cortex cultures seem to be relatively insensitive to quinolinate-induced damage (Kim and Choi, 1987), raisi ingly less amenable to antagonism. On the other hand, the mouse cortex cultures seem to be relatively insensitive to quinolinate-induced damage (Kim and Choi, 1987), raising the possibility of subtle differences in the str the mouse cortex cult
tive to quinolinate-in
1987), raising the poss
structure-activity rela
in vitro and in vivo.
Insofar as quinolina 1987), raising the possibility of subtle differences in the structure-activity relationships of the NMDA receptors in vitro and in vivo.
Insofar as quinolinate may prove to be an important endogenous excitotoxin, it is unf

1987), raising the possibility of subtle differences in the structure-activity relationships of the NMDA receptors in vitro and in vivo.
Insofar as quinolinate may prove to be an important endogenous excitotoxin, it is unf structure-activity relationships of the NMDA receptors
in vitro and in vivo.
Insofar as quinolinate may prove to be an important
endogenous excitotoxin, it is unfortunate that there have
been relatively few reports of agen in vitro and in vivo.
Insofar as quinolinate may prove to be an important
endogenous excitotoxin, it is unfortunate that there have
been relatively few reports of agents that can be applied
systemically to provide protecti Insofar as quinolinate may prove to be an important
endogenous excitotoxin, it is unfortunate that there have
been relatively few reports of agents that can be applied
systemically to provide protection. Most competitive a endogenous excitotoxin, it is unfortunate that there have
been relatively few reports of agents that can be applie
systemically to provide protection. Most competitive are
tagonists, including 2AP5 and 2AP7 as well as bacl been relatively few reports of agents that can be applied
systemically to provide protection. Most competitive an-
tagonists, including 2AP5 and 2AP7 as well as baclofen,
nimodipine, and ketamine, were said to have little systemically to provide protection. Most competitive antagonists, including 2AP5 and 2AP7 as well as baclofen,
nimodipine, and ketamine, were said to have little activ-
ity in this respect (Beal et al., 1988a). Indeed, the tagonists, including 2AP5 and 2AP7 as well as baclofen
nimodipine, and ketamine, were said to have little activ
ity in this respect (Beal et al., 1988a). Indeed, the only
agents that seem to afford consistent protection ag nimodipine, and ketamine, were said to have little activity in this respect (Beal et al., 1988a). Indeed, the only agents that seem to afford consistent protection against quinolinate are dizocilpine (Beal et al., 1988a) a agents that seem to afford consistent protection against quinolinate are dizocilpine (Beal et al., 1988a) and kynurenic acid (Germano et al., 1987), although a recent report claims protection by orally administered meman-
 agents that seem to afford consisting
quinolinate are dizocilpine (Beal
urenic acid (Germano et al., 19
report claims protection by orall
tine (Kielhoff and Wolf, 1992).
Purines, such as phenylisopro inolinate are dizocilpine (Beal et al., 1988a) and kynenic acid (Germano et al., 1987), although a recent
port claims protection by orally administered meman-
ne (Kielhoff and Wolf, 1992).
Purines, such as phenylisopropyla

urenic acid (Germano et al., 1987), although a recent
report claims protection by orally administered meman-
tine (Kielhoff and Wolf, 1992).
Purines, such as phenylisopropyladenosine, will pro-
tect against kainate toxicit report claims protection by orally administered memantine (Kielhoff and Wolf, 1992).

Purines, such as phenylisopropyladenosine, will protect against kainate toxicity even at doses as low as 10
 μ g/kg (MacGregor and St tine (Kielhoff and Wolf, 1992).

Purines, such as phenylisopropyladenosine, will prect against kainate toxicity even at doses as low as
 μ g/kg (MacGregor and Stone, 1992; 1993a,b) but he

no effect against intrahippoca Purines, such as phenylisopropyladenosine, will protect against kainate toxicity even at doses as low as 10 μ g/kg (MacGregor and Stone, 1992; 1993a,b) but have no effect against intrahippocampal injections of quinolina tect against kainate toxicity even at doses as low as 10 μ g/kg (MacGregor and Stone, 1992; 1993a,b) but have no effect against intrahippocampal injections of quino-
linate unless coadministered with it (Connick and Sto μ g/kg (MacGregor and Stone, 1992; 1993a,b) but have
no effect against intrahippocampal injections of quino-
linate unless coadministered with it (Connick and Stone,
1989b). Doses of 1 or 0.1 mg/kg actually enhance the
 no effect against intrahippocampal injections of quino-
linate unless coadministered with it (Connick and Stone,
1989b). Doses of 1 or 0.1 mg/kg actually enhance the
toxicity produced by submaximal concentrations of quin-
 linate unless coadministered with it (Connick and Stone,
1989b). Doses of 1 or 0.1 mg/kg actually enhance the
toxicity produced by submaximal concentrations of quin-
olinate, an effect that can be mimicked by peripherally
 1989b). Doses of 1 or 0.1 mg/kg actually enhance the toxicity produced by submaximal concentrations of quinolinate, an effect that can be mimicked by peripheral administered ganglion-blocking drugs and which matherefore, r toxicity produced by subn
olinate, an effect that ca
administered ganglion-b
therefore, reflect a period
nick and Stone, 1989b).
1. Quinolinate as an e: inate, an effect that can be mimicked by peripherally
ministered ganglion-blocking drugs and which may,
erefore, reflect a period of systemic hypotension (Con-
ck and Stone, 1989b).
1. Quinolinate as an experimental tool.

administered ganglion-blocking drugs and which may,
therefore, reflect a period of systemic hypotension (Con-
nick and Stone, 1989b).
1. Quinolinate as an experimental tool. The ability of
quinolinate, like kainate, to des therefore, reflect a period of systemic hypotension (Connick and Stone, 1989b).

1. Quinolinate as an experimental tool. The ability of

quinolinate, like kainate, to destroy neuronal somata

with little effect on synaptic nick and Stone, 1989b).

1. Quinolinate as an experimental tool. The ability of

quinolinate, like kainate, to destroy neuronal somata

with little effect on synaptic terminals has led to its

frequent use as a tool in the 1. Quinolinate as an experimental tool. The ability of quinolinate, like kainate, to destroy neuronal somata with little effect on synaptic terminals has led to its frequent use as a tool in the localisation of transmitter with little effect on synaptic terminals has led to its frequent use as a tool in the localisation of transmitter systems. Injected into the NBM, for example, quinolinate has no effect on the density of muscarinic receptor with little effect on synaptic terminals has led to its frequent use as a tool in the localisation of transmitter systems. Injected into the NBM, for example, quinolinate has no effect on the density of muscarinic receptor frequent use as a tool in the localisation of transmitter
systems. Injected into the NBM, for example, quinolinate
has no effect on the density of muscarinic receptors
linked to phosphatidylinositol turnover in the neocort systems. Injected into the NBM
has no effect on the density
linked to phosphatidylinositol t
whereas injections directly into
coupling (Scarth et al., 1989).
In the basal ganglia, quinol In the basal ganglia game in the basal ganglia and the secondary in the secondary already here as injections directly into the cortex eliminate this upling (Scarth et al., 1989).
In the basal ganglia, quinolinate injection

linked to phosphatidylinositol turnover in the neocortex,
whereas injections directly into the cortex eliminate this
coupling (Scarth et al., 1989).
In the basal ganglia, quinolinate injections into the
striatum remove dop whereas injections directly into the cortex eliminate this coupling (Scarth et al., 1989).
In the basal ganglia, quinolinate injections into the striatum remove dopamine D1 receptors both locally, indicating their presence coupling (Scarth et al., 1989).
In the basal ganglia, quinolinate injections into the
striatum remove dopamine D1 receptors both locally,
indicating their presence on intrinsic striatal cells, and
in the ipsilateral pallid In the basal ganglia, quinolinate injections into the striatum remove dopamine D1 receptors both locally, indicating their presence on intrinsic striatal cells, and in the ipsilateral pallidum and nigra, revealing their pr striatum remove dopamine D1 receptors both locally,
indicating their presence on intrinsic striatal cells, and
in the ipsilateral pallidum and nigra, revealing their
presence on projecting axon terminals (Barone et al.,
19 indicating their presence on intrinsic striatal cells, and in the ipsilateral pallidum and nigra, revealing the presence on projecting axon terminals (Barone et al. 1987). D2 receptor binding is also diminished (Masuo of a in the ipsilateral pallidum and nigra, revealing their presence on projecting axon terminals (Barone et al., 1987). D2 receptor binding is also diminished (Masuo et al., 1990). In the nucleus accumbens, quinolinate injecti presence on projecting

1987). D2 receptor bin

al., 1990). In the nucle

tions eliminate D1 rece

(Filloux et al., 1991).

Interestingly, althou 87). D2 receptor binding is also diminished (Masuo et , 1990). In the nucleus accumbens, quinolinate injections eliminate D1 receptor binding but not D2 receptors illoux et al., 1991).
Interestingly, although dizocilpine g tions eliminate D1 receptor binding but not D2 receptors

tions eliminate D1 receptor binding but not D2 receptors
(Filloux et al., 1991).
Interestingly, although dizocilpine given acutely can
prevent striatal toxicity produced by quinolinate (Gior-
dano et al., 1990), the sensit (Filloux et al., 1991).
Interestingly, although dizocilpine given acutely can
prevent striatal toxicity produced by quinolinate (Gior-
dano et al., 1990), the sensitivity of intrinsic neurones to
quinolinate is enhanced by Interestingly, although dizocilpine given acutely c
prevent striatal toxicity produced by quinolinate (Giodano et al., 1990), the sensitivity of intrinsic neurones
quinolinate is enhanced by prior chronic treatment with
th prevent striatal toxicity produced by quinolinate (Giordano et al., 1990), the sensitivity of intrinsic neurones to quinolinate is enhanced by prior chronic treatment with the antagonist (Norman et al., 1990). It may be im

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erative disorders, to know whether this reflects up-re
lation of NMDA receptors or a component of the po 8

lative disorders, to know whether this reflects up-regu

lation of NMDA receptors or a component of the post-

receptor processes involved in toxicity. 352
erative disorders, to know whether this
lation of NMDA receptors or a componenceptor processes involved in toxicity. *D. Huntington's Disease* involved in toxicity.
 D. Huntington's Disease

The demonstration that kainic acid could produce
The demonstration that kainic acid could produce for the demonstration that kainic acid could produce for the demonstration in the striatum was accompanied produce receptor processes involved in toxicity.

D. Huntington's Disease

The demonstration that kainic acid could produce

neuronal degeneration in the striatum was accompanied

by the speculation that a related agent might be r D. Huntington's Disease
The demonstration that kainic acid could produced
neuronal degeneration in the striatum was accompan
by the speculation that a related agent might be respo
sible for the neuronal damage seen in dege D. Huntington's Disease
The demonstration that kainic acid could produce
neuronal degeneration in the striatum was accompanied
by the speculation that a related agent might be respon-
sible for the neuronal damage seen in The demonstration that kainic acid could produce firm
neuronal degeneration in the striatum was accompanied pep
by the speculation that a related agent might be respon-
acible for the neuronal damage seen in degenerative d neuronal degeneration in the striatum was accompanied
by the speculation that a related agent might be respon-
sible for the neuronal damage seen in degenerative dis-
orders such as Huntington's disease (Coyle and of
Schwa by the speculation that a related agent might be responsible for the neuronal damage seen in degenerative disorders such as Huntington's disease (Coyle an Schwarcz, 1976; McGeer and McGeer, 1976; Sanberg eal., 1989; Bruyn sible for the neuronal damage seen in degenerative disorders such as Huntington's disease (Coyle and Schwarcz, 1976; McGeer and McGeer, 1976; Sanberg et al., 1989; Bruyn and Stoof, 1990). The existence of quin-
olinic acid orders such as Huntington's disease (Coyle a
Schwarcz, 1976; McGeer and McGeer, 1976; Sanberg
al., 1989; Bruyn and Stoof, 1990). The existence of qu
olinic acid as an endogenous excitotoxin, therefore, fi
nished research c Schwarcz, 1976; McGeer and McGeer, 1976; Sanberg al., 1989; Bruyn and Stoof, 1990). The existence of quire olinic acid as an endogenous excitotoxin, therefore, fulnished research concerning the aetiology of this hered tary al., 1989; Bruyn and Stoof, 1990). The existence of quin-
olinic acid as an endogenous excitotoxin, therefore, fur-
inished research concerning the aetiology of this heredi-
accumulation of quinolinate in the CNS could
dif olinic acid as an endogenous excitotoxin, therefore, fur-
nished research concerning the aetiology of this heredi-
tary disorder with a novel hypothesis: the chronic, path-
sise
ological accumulation of quinolinate in the nished research concerning the aetiology of this her
tary disorder with a novel hypothesis: the chronic, po
ological accumulation of quinolinate in the CNS co
result in an increased rate of neuronal death, leading
the sign tary disorder with a novel hypothesis: the chronic, pathological accumulation of quinolinate in the CNS could result in an increased rate of neuronal death, leading to the significant neuronal depletion observed in Hunting ological accumulation of quinolinate in the CNS could diff
result in an increased rate of neuronal death, leading to
the significant neuronal depletion observed in Hunting-regi
ton's striatum and neocortex (Schwarcz et al. result in an increased rate of neuronal death, leading to
the significant neuronal depletion observed in Hunting-
ton's striatum and neocortex (Schwarcz et al., 1984a;
Stone et al., 1987). This hypothesis was largely based the significant neuronal depletion observed in Huntington's striatum and neocortex (Schwarcz et al., 1984a;
Stone et al., 1987). This hypothesis was largely based on
speculation and the rather crude comparison of motor
and ton's striatum and neocortex (Schwarcz et al., 1984a; and
Stone et al., 1987). This hypothesis was largely based on the
speculation and the rather crude comparison of motor Boo
and behavioural changes in quinolinate-lesion Stone et al., 1987). This hypothesis w
speculation and the rather crude co
and behavioural changes in quinolina
and in patients with Huntington's d
Fibiger, 1979; Sanberg et al., 1989).
It became a much more serious con eculation and the rather crude comparison of mot
d behavioural changes in quinolinate-lesioned anima
d in patients with Huntington's disease (Mason an
biger, 1979; Sanberg et al., 1989).
It became a much more serious conte

and behavioural changes in quinolinate-lesioned animals
and in patients with Huntington's disease (Mason and
Fibiger, 1979; Sanberg et al., 1989).
It became a much more serious contender as an expla-
nation of Huntington's and in patients with Huntington's disease (Mason and
Fibiger, 1979; Sanberg et al., 1989).
It became a much more serious contender as an expla-
ination of Huntington's disease when Beal et al. (1985) or
observed that the i Fibiger, 1979; Sanberg et al., 1989). ton's
It became a much more serious contender as an expla-
ive, ination of Huntington's disease when Beal et al. (1985) of all
observed that the intrastriatal injection of kainate or o It became a much more serious contender as an expla-
nation of Huntington's disease when Beal et al. (1985) of a
observed that the intrastriatal injection of kainate or
ibotenate, which is normally regarded as an NMDA f nation of Huntington's disease when Beal et al. (1985) cobserved that the intrastriatal injection of kainate or cibotenate, which is normally regarded as an NMDA free protor agonist, produced a loss of somatostatin and the observed that the intrastriatal injection of kainate or ibotenate, which is normally regarded as an NMDA receptor agonist, produced a loss of somatostatin and neuropeptide Y immunoreactivity, whereas an increase of both of ibotenate, which is normally regarded as an NMDA functioned receptor agonist, produced a loss of somatostatin and tot neuropeptide Y immunoreactivity, whereas an increase quare of both of these peptides had been seen in Hu receptor agonist, produced a loss of somatostatin and totom
neuropeptide Y immunoreactivity, whereas an increase quino
f both of these peptides had been seen in Huntington's chole
striatum. Striatal lesions induced by quin neuropeptide Y immunoreactivity, whereas an increase of both of these peptides had been seen in Huntington's striatum. Striatal lesions induced by quinolinate, on the other hand, produce the loss of GABA and substance whic of both of these peptides had been seen in Huntington
striatum. Striatal lesions induced by quinolinate, on t
other hand, produce the loss of GABA and substance
which is characteristic of the Huntington's disease str
tum, striatum. Striatal lesions induced by quinolinate, on the other hand, produce the loss of GABA and substance P which is characteristic of the Huntington's disease striatum, with the preservation of somatostatin and neuro-p other hand, produce the loss of GABA and substance P ti
which is characteristic of the Huntington's disease stria-
tum, with the preservation of somatostatin and neuro-
peptide Y concentration. This neurochemical profile r which is characteristum, with the prese
peptide Y concentra
produces exactly the
(Beal et al., 1986).
A more extensive m, with the preservation of somatostatin and ne
ptide Y concentration. This neurochemical profile
oduces exactly the profile seen in Huntington's dis
leal et al., 1986).
A more extensive analysis of amino acid concer
ons i

peptide Y concentration. This neurochemical profile re-
produces exactly the profile seen in Huntington's disease
(Beal et al., 1986).
A more extensive analysis of amino acid concentra-
tions in quinolinate-lesioned animal produces exactly the profile seen in Huntington's disease

(Beal et al., 1986).

A more extensive analysis of amino acid concentra-

tions in quinolinate-lesioned animals and Huntington's

disease brain has supported this (Beal et al., 1986).
A more extensive analysis of amino acid concentra-
tions in quinolinate-lesioned animals and Huntington's
disease brain has supported this comparison (Ellison et
al., 1987). A subsequent reexamination A more extensive analysis of amino acid concentra-
tions in quinolinate-lesioned animals and Huntington's
produces faine has supported this comparison (Ellison et
al., 1987). A subsequent reexamination of quinolinate
biles tions in quinolinate-lesioned animals and Huntington's disease brain has supported this comparison (Ellison et al., 1987). A subsequent reexamination of quinolinate lesions failed to confirm the selectivity of the lesion (disease brain has supported this comparison (Ellison et neutrino.)
al., 1987). A subsequent reexamination of quinolinate bin
lesions failed to confirm the selectivity of the lesion bec
(Davies and Roberts, 1987); the same al., 1987). A subsequent reexamination of quinolinate lesions failed to confirm the selectivity of the lesion (Davies and Roberts, 1987); the same group later reported the loss of somatostatin and neuropeptide Y and the re lesions failed to confirm the selectivity of the lesio.
(Davies and Roberts, 1987); the same group later reported the loss of somatostatin and neuropeptide Y an
the relative preservation of a population of apparentl
cholin (Davies and Roberts, 1987); the same group later re-
ported the loss of somatostatin and neuropeptide Y and
the relative preservation of a population of apparently
cholinergic neurones staining for acetylcholinesterase
and ported the loss of somatostatin and neuropeptide Y and
the relative preservation of a population of apparently
cholinergic neurones staining for acetylcholinesterase
and choline acetylase (Davies and Roberts, 1988). These
 the relative preservation of a population of apparent cholinergic neurones staining for acetylcholinestera
and choline acetylase (Davies and Roberts, 1988). The
latter studies, in turn, received some support from even
denc cholinergic neurones staining for acetylcholinester
and choline acetylase (Davies and Roberts, 1988). Th
latter studies, in turn, received some support from ϵ
dence that cholinergic neurones were indeed more resi
ant to and choline acetylase (Davies and Roberts, 1988). These I
latter studies, in turn, received some support from evi-
dence that cholinergic neurones were indeed more resist-
ant to quinolinate than were neuropeptide Y or som latter studies, in turn, received some support from evidence that cholinergic neurones were indeed more resistant to quinolinate than were neuropeptide Y or somato-
statin-containing cells (Boegman et al., 1987a; Boegman i dence that cholinergic neurones were indeed more resistant to quinolinate than were neuropeptide Y or somato-
statin-containing cells (Boegman et al., 1987a; Boegman
and Parent, 1988). Interestingly, cells in the neocortex ant to quinolinate than were neuropeptide Y or somato-
statin-containing cells (Boegman et al., 1987a; Boegman
and Parent, 1988). Interestingly, cells in the neocortex
containing these same peptides were resistant to quino statin-containing cells (Boegman et al., 1987a; Boegman
and Parent, 1988). Interestingly, cells in the neocortex
containing these same peptides were resistant to quino-
linate, a finding that has been confirmed by Beal et

NE
due to quinolinate are not restricted to the controversia
markers discussed before, but alterations in opioid an WE
due to quinolinate are not restricted to the controversial
markers discussed before, but alterations in opioid and
neurotensin systems also ensue, at least in the nucleus NE
due to quinolinate are not restricted to the controversial
markers discussed before, but alterations in opioid and
neurotensin systems also ensue, at least in the nucleus
accumbens (Churchill et al., 1990). due to quinolinate are not restricted
markers discussed before, but altera
neurotensin systems also ensue, at laccumbens (Churchill et al., 1990).
The original results of Beal et a ie to quinolinate are not restricted to the controversiant arkers discussed before, but alterations in opioid and urotensin systems also ensue, at least in the nucleus cumbens (Churchill et al., 1990).
The original results

markers discussed before, but alterations in opioid and
neurotensin systems also ensue, at least in the nucleus
accumbens (Churchill et al., 1990).
The original results of Beal et al. (1985) were con-
firmed more recently neurotensin systems also ensue, at least in the nucleus
accumbens (Churchill et al., 1990).
The original results of Beal et al. (1985) were con-
firmed more recently in a careful quantitative study of
peptide activity in r accumbens (Churchill et al., 1990).
The original results of Beal et al. (1985) were con
firmed more recently in a careful quantitative study o
peptide activity in response to selective excitatory amin
acid agonists (Beal e The original results of Beal et al. (1985) were con-
firmed more recently in a careful quantitative study of
peptide activity in response to selective excitatory amino
acid agonists (Beal et al., 1989). Whereas kainate, qu firmed more recently in a careful quantitative study of
peptide activity in response to selective excitatory amino
acid agonists (Beal et al., 1989). Whereas kainate, quis-
qualate, and AMPA all induced a dose-related decr peptide activity in response to selective excitatory amino
acid agonists (Beal et al., 1989). Whereas kainate, quis-
qualate, and AMPA all induced a dose-related decrease
of substance P, GABA, neuropeptide Y, and somatosta acid agonists (Beal et al., 1989). Whereas kainate, quis-
qualate, and AMPA all induced a dose-related decrease
of substance P, GABA, neuropeptide Y, and somatostatin
levels, doses of up to 360 nmol, were able to deplete
G qualate, and AMPA all induced a dose-related decrease
of substance P, GABA, neuropeptide Y, and somatostatin
levels, doses of up to 360 nmol, were able to deplete
GABA and substance P with no significant changes of
the oth of substance P, GABA, neuropeptide Y, and somatosta
levels, doses of up to 360 nmol, were able to depl
GABA and substance P with no significant changes
the other peptides. The relative resistance of chol
acetylase-containi levels, doses of up to 360 nmol, were able to deplete GABA and substance P with no significant changes of the other peptides. The relative resistance of choline acetylase-containing cells was confirmed. It was emphasised i GABA and substance P with no significant changes of
the other peptides. The relative resistance of choline
acetylase-containing cells was confirmed. It was empha-
sised in this study that the relative susceptibilities of
 the other peptides. The relative resistance of choline acetylase-containing cells was confirmed. It was emphasised in this study that the relative susceptibilities of different neurone populations could only be observed in acetylase-containing cells was confirmed. It was emphasised in this study that the relative susceptibilities of different neurone populations could only be observed in peripheral regions of the lesion area and not in the c sised in this study that the relative susceptibilities of different neurone populations could only be observed in peripheral regions of the lesion area and not in the core region where quinolinate concentration would be hi different neurone populations could only be observed in
peripheral regions of the lesion area and not in the core
region where quinolinate concentration would be highest
and where all neurones were killed. It was proposed peripheral regions of the lesion area and not in the core region where quinolinate concentration would be highest and where all neurones were killed. It was proposed that the disputed results of Davies and Roberts (1987) a region where quinolinate concentration
and where all neurones were killed. Ithe disputed results of Davies and
Boegman et al. (1987a) may have
examining the core of their lesions.
Beal et al. (1988b) emphasised th d where all neurones were killed. It was proposed that education is and Roberts (1987) begman et al. (1987a) may have been due to that even in Hunting the core of their lesions.
Beal et al. (1988b) emphasised that even in

Boegman et al. (1987a) may have been due to their examining the core of their lesions.
Beal et al. (1988b) emphasised that even in Hunting-
ton's disease the sparing of some neurones is only rela-
tive, and in more severe Boegman et al. (1987a) may have been due to their
examining the core of their lesions.
Beal et al. (1988b) emphasised that even in Hunting-
ton's disease the sparing of some neurones is only rela-
tive, and in more severe examining the core of their lesions.
Beal et al. (1988b) emphasised that even in Hunti
ton's disease the sparing of some neurones is only r
tive, and in more severe pathological cases, there is a
of all neurone types. The Beal et al. (1988b) emphasised that even in Hunting
ton's disease the sparing of some neurones is only relative, and in more severe pathological cases, there is a loo
of all neurone types. The neurochemical profile through ton's disease the sparing of some neurones is only relative, and in more severe pathological cases, there is a los
of all neurone types. The neurochemical profile through
out quinolinate lesions is then, perhaps paradoxica tive, and in more severe pathological cases, there is a loss
of all neurone types. The neurochemical profile through-
out quinolinate lesions is then, perhaps paradoxically,
further supportive of a role for a quinolinate-l of all neurone types. The neurochemical profile through-
out quinolinate lesions is then, perhaps paradoxically,
further supportive of a role for a quinolinate-like exci-
totoxin in Huntington's disease degeneration. Since out quinolinate lesions is then, perhaps paradoxically,
further supportive of a role for a quinolinate-like exci-
totoxin in Huntington's disease degeneration. Since
quinolinate lesions can result in an increase of striata totoxin in Huntington's disease degeneration. Since quinolinate lesions can result in an increase of striatal cholecystokinin (Takita and Kato, 1989), it would be interesting to see how this compares with Huntington's tissue. sised in this study that the relative susceptibilities of different neurone populations could only be observed in represipent region where a peripheral region where a peripheral exponentiation would be highest and where a

cholecystokinin (Takita and Kato, 1989), it would be
interesting to see how this compares with Huntington's
tissue.
The sparing of cholinergic neurones in the striatum
has now been confirmed (Norman et al., 1991) with the
 interesting to see how this compares with Huntington's
tissue.
The sparing of cholinergic neurones in the striatum
has now been confirmed (Norman et al., 1991) with the
additional observations that glutamate binding to
NM tissue.
The sparing of cholinergic neurones in the striatum
has now been confirmed (Norman et al., 1991) with the
additional observations that glutamate binding to
NMDA receptors and D1 dopamine receptor binding
were sever The sparing of cholinergic neurones in the striatum
has now been confirmed (Norman et al., 1991) with the
additional observations that glutamate binding to
NMDA receptors and D1 dopamine receptor binding
were severely dimi has now been confirmed (Norman et al., 1991) with the additional observations that glutamate binding to NMDA receptors and D1 dopamine receptor binding were severely diminished by quinolinate lesions. The latter observatio additional observations that glutamate binding to
NMDA receptors and D1 dopamine receptor binding
were severely diminished by quinolinate lesions. The
latter observation would be entirely consistent with the
predominant lo NMDA receptors and D1 dopamine receptor binding
were severely diminished by quinolinate lesions. The
latter observation would be entirely consistent with the
predominant localisation of D1 receptors to intrinsic
neurones w were severely diminished by quinolinate lesions. The latter observation would be entirely consistent with the predominant localisation of D1 receptors to intrinsic neurones within the striatum. The decrease of glutamate bi latter observation would be entirely consistent with the
predominant localisation of D1 receptors to intrinsic
neurones within the striatum. The decrease of glutamate
binding, although interesting, remains to be explained predominant localisation of D1 receptors to intrinsic
neurones within the striatum. The decrease of glutamate
binding, although interesting, remains to be explained,
because the binding of dizocilpine, normally assumed to
 neurones within the str
binding, although inter
because the binding of
bind to the NMDA-a
sensitive to quinolinate
At this point, it is im nding, although interesting, remains to be explained, cause the binding of dizocilpine, normally assumed to nd to the NMDA-associated ion channel, was less nsitive to quinolinate.
At this point, it is important to mention

because the binding of dizocilpine, normally assumed to
bind to the NMDA-associated ion channel, was less
sensitive to quinolinate.
At this point, it is important to mention an additiona
marker of some neuronal groups, NAD bind to the NMDA-associated ion channel, was less
sensitive to quinolinate.
At this point, it is important to mention an additional
marker of some neuronal groups, NADPH diaphorase.
This enzyme has been demonstrated histoc sensitive to quinolinate.

At this point, it is important to mention an additional

marker of some neuronal groups, NADPH diaphorase.

This enzyme has been demonstrated histochemically in

the CNS by a large number of grou At this point, it is important to mention an additional
marker of some neuronal groups, NADPH diaphorase.
This enzyme has been demonstrated histochemically in
the CNS by a large number of groups since the first
reports of marker of some neuronal groups, NADPH diaphorase.
This enzyme has been demonstrated histochemically in
the CNS by a large number of groups since the first
reports of its presence by (Thomas and Pearse, 1964).
Its significa This enzyme has been demonstrated histochemically in
the CNS by a large number of groups since the first
reports of its presence by (Thomas and Pearse, 1964).
Its significance lies in the fact that neurones containing
it a the CNS by a large number of groups since the first
reports of its presence by (Thomas and Pearse, 1964).
Its significance lies in the fact that neurones containing
it appear to be relatively preserved in Huntington's disreports of its presence by (Thomas and Pearse, 196
Its significance lies in the fact that neurones containi
it appear to be relatively preserved in Huntington's d
ease striatum (Ferrante et al., 1984) and that it f
quently Its significance lies in the fact that neurones containing
it appear to be relatively preserved in Huntington's dis-
ease striatum (Ferrante et al., 1984) and that it fre-
quently occurs colocalised with somatostatin or ne it appear to be relatively preserved in Huntington's dis-
ease striatum (Ferrante et al., 1984) and that it fre-
quently occurs colocalised with somatostatin or neuro-
peptide Y (Vincent et al., 1983). Koh et al. (1986) we

QUINOLINIC AND
neurones showing resistance to quinolinate toxicity dis-
played the presence of NADPH diaphorase. Resistance QUINOLINIC AND K
neurones showing resistance to quinolinate toxicity dis-
played the presence of NADPH diaphorase. Resistance
was also shown to NMDA itself but not to glutamate, QUINOLINIC AND
neurones showing resistance to quinolinate toxicity dis-
played the presence of NADPH diaphorase. Resistance
was also shown to NMDA itself but not to glutamate
kainate, or quisqualate; indeed, the latter two neurones showing resistance to quinolinate toxicity dis-
played the presence of NADPH diaphorase. Resistance
was also shown to NMDA itself but not to glutamate, or
kainate, or quisqualate; indeed, the latter two agents
pro neurones showing resistance to quinolinate toxicity dis-
played the presence of NADPH diaphorase. Resistance
was also shown to NMDA itself but not to glutamate,
kainate, or quisqualate; indeed, the latter two agents
produc ayed the presence of NADPH diaphorase. Resistance
is also shown to NMDA itself but not to glutamate,
inate, or quisqualate; indeed, the latter two agents
oduced a preferential loss of NADPH diaphorase cells.
This work is i

was also shown to NMDA itself but not to glutamate, or kainate, or quisqualate; indeed, the latter two agents is
produced a preferential loss of NADPH diaphorase cells. see This work is important for two reasons. First, it kainate, or quisqualate; indeed, the latter two agents produced a preferential loss of NADPH diaphorase cells.
This work is important for two reasons. First, it im-
mediately raises the question of whether the presence of
 produced a preferential loss of NADPH diaphorase cells. seen
This work is important for two reasons. First, it im-
madiately raises the question of whether the presence of
NADPH diaphorase is itself neuroprotective against This work is important for two reasons. First, it im-
mediately raises the question of whether the presence of
NADPH diaphorase is itself neuroprotective against
NMDA receptor activation. This view has taken on
greater sig mediately raises the question of whether the presence of
NADPH diaphorase is itself neuroprotective against tin
NMDA receptor activation. This view has taken on
greater significance in recent years with the realisation be
 NADPH diaphorase is itself neuroprotective against
NMDA receptor activation. This view has taken on
greater significance in recent years with the realisation
that NADPH diaphorase is, in fact, a form of nitric oxide
syntha NMDA receptor activation. This view has taken
greater significance in recent years with the realisat
that NADPH diaphorase is, in fact, a form of nitric ox
synthase, a cytosolic calmodulin-dependent enzyme
tivated by, amon greater significance in recent years with the realisation
that NADPH diaphorase is, in fact, a form of nitric oxide
synthase, a cytosolic calmodulin-dependent enzyme ac-
tivated by, among other things, an increase of intra that NADPH diaphorase is, in fact, a form of nitric oxide al.
synthase, a cytosolic calmodulin-dependent enzyme ac-
tivated by, among other things, an increase of intracel-
ace
lular calcium levels and which is ultimately synthase, a cytosolic calmodulin-dependent enzyme ac-
tivated by, among other things, an increase of intracel-
lular calcium levels and which is ultimately responsible NA
for the release of nitric oxide from L-arginine. Th tivated by, among other things, an increase of intracel-
lular calcium levels and which is ultimately responsible
for the release of nitric oxide from L-arginine. There is a
paradox here because the nitric oxide produced b lular calcium levels and which is ultimately responsible NA
for the release of nitric oxide from L-arginine. There is a tra
paradox here because the nitric oxide produced by T
NMDA receptor stimulation may mediate at least for the release of nitric oxide from L-arginine. There is a paradox here because the nitric oxide produced by NMDA receptor stimulation may mediate at least part of the neurotoxicity (Dawson et al., 1992; Loiacono and Bear paradox here because the nitric oxide produced by
NMDA receptor stimulation may mediate at least part
of the neurotoxicity (Dawson et al., 1992; Loiacono and the
Beart, 1992), possibly by activating guanylate cyclase, in
a NMDA receptor stimulation may mediate at least part
of the neurotoxicity (Dawson et al., 1992; Loiacono and
Beart, 1992), possibly by activating guanylate cyclase,
although the precise mechanistic relationship between
nitr of the neurotoxicity (Dawson et al., 1992; Loiacono and tum
Beart, 1992), possibly by activating guanylate cyclase, indi
although the precise mechanistic relationship between diap
nitric oxide, cyclic GMP, and neurotoxicit Beart, 1992), possibly by activating guanylate cyclase, in although the precise mechanistic relationship between durinc oxide, cyclic GMP, and neurotoxicity remains unclear. Similarly, the explanation for the resistance to tric oxide, cyclic GMP, and neurotoxicity remains un-

ear. Similarly, the explanation for the resistance to an

mage of NADPH diaphorase-positive neurones re-

hains obscure.

It has also been pointed out that, since quin

clear. Similarly, the explanation for the resistance
damage of NADPH diaphorase-positive neurones
mains obscure.
It has also been pointed out that, since quinolinate
normally metabolised to nicotinamide adenine dinuc
otide damage of NADPH diaphorase-positive neurones remains obscure.
It has also been pointed out that, since quinolinate is
normally metabolised to nicotinamide adenine dinucle-
otide, cells bearing the enzyme may have a greater mains obscure.
It has also been pointed out that, since quinolinate is es
normally metabolised to nicotinamide adenine dinucle-
otide, cells bearing the enzyme may have a greater re-
quirement for quinolinate and, thus, ma It has also been pointed out that, since quinolinate is
normally metabolised to nicotinamide adenine dinucle-
otide, cells bearing the enzyme may have a greater re-
quirement for quinolinate and, thus, may remove it more
r rmally metabolised to nicotinamide adenine dinucle-
ide, cells bearing the enzyme may have a greater re-
irement for quinolinate and, thus, may remove it more
pidly from the extracellular space (Beal et al., 1986).
Second,

otide, cells bearing the enzyme may have a greater re-
quirement for quinolinate and, thus, may remove it more
rapidly from the extracellular space (Beal et al., 1986).
Second, the work of Koh et al. (1986) indirectly lend quirement for quinolinate and, thus, may remove it more
rapidly from the extracellular space (Beal et al., 1986).
Second, the work of Koh et al. (1986) indirectly lends
support to the neurochemical data of Beal et al. (198 rapidly from the extracellular space (Beal et al., 1986).
Second, the work of Koh et al. (1986) indirectly lensupport to the neurochemical data of Beal et al. (198
1989), because the preservation of NADPH diaphora
cells im Second, the work of Koh et al. (1986) indirectly lends
support to the neurochemical data of Beal et al. (1985,
1989), because the preservation of NADPH diaphorase
cells implies the preservation of a population of soma-
tos support to the neurochemical data of Beal et al. (1985, be a potent neurotoxin. Such contamination might then 1989), because the preservation of NADPH diaphorase account for the nonselective cell damage seen by some cells 1989), because the preservation of NADPH diaphorase
cells implies the preservation of a population of soma-
tostatin-/neuropeptide Y-containing neurones. Indeed,
Koh and Choi (1988) confirmed that the same pattern
of excit cells implies the preservation of a population of soma-
tostatin-/neuropeptide Y-containing neurones. Indeed, qui
Koh and Choi (1988) confirmed that the same pattern Cho
of excitotoxicity, i.e., sensitivity of NADPH diapho tostatin-/neuropeptide Y-containing neurones. Indeed,
Koh and Choi (1988) confirmed that the same pattern
of excitotoxicity, i.e., sensitivity of NADPH diaphorase
neurones to kainate and resistance to quinolinate, can
also Koh and Choi (1988) confirmed that the same patt
of excitotoxicity, i.e., sensitivity of NADPH diaphor-
neurones to kainate and resistance to quinolinate, compla-
also be demonstrated in cultures of striatal neuron-
Unfort of excitotoxicity, i.e., sensitivity of NADPH diaphorase
neurones to kainate and resistance to quinolinate, can
also be demonstrated in cultures of striatal neurones.
Unfortunately, there is still no opportunity for compla neurones to kainate and resistance to quinolinate, can
also be demonstrated in cultures of striatal neurones. los
Unfortunately, there is still no opportunity for compla-
incency with this picture. Ferriero et al. (1990) s also be demonstrated in cultures of striatal neurones.
Unfortunately, there is still no opportunity for compla-
cency with this picture. Ferriero et al. (1990) stated that,
in adult rat striatum, they could find no evidenc cency with this picture. Ferriero et al. (1990) stated that, produce chemical alterations to quinolinate or any con-
in adult rat striatum, they could find no evidence for the taminants. Such changes may then yield nonsele in adult rat striatum, they could find no evidence for the in adult rat striatum, they could find no evidence for the resistance to quinolinate of NADPH diaphorase cells; only in neonatal animals before 7 days of age could such a resistance by demonstrated. This again raises doubt resistance to quinolinate of NADPH diaphorase cells;
only in neonatal animals before 7 days of age could such
a resistance by demonstrated. This again raises doubts
as to the reliability of the selectivity data, because cu only in neonatal animals before 7 days of age could such as c
a resistance by demonstrated. This again raises doubts dam
as to the reliability of the selectivity data, because cul-
tured neurones may be more sensitive to q as to the reliability of the selectivity data, because cultured neurones may be more sensitive to quinolinate because they dedifferentiate to a state equivalent to immature neurones in vivo.
Most recently, two groups have to the reliability of the selectivity data, because cul-
red neurones may be more sensitive to quinolinate to
cause they dedifferentiate to a state equivalent to q
mature neurones in vivo.
Most recently, two groups have at

tured neurones may be more sensitive to quinolinate to because they dedifferentiate to a state equivalent to quimature neurones in vivo.

Most recently, two groups have attempted to resolve the noted discrepancies by study because they dedifferentiate to a state equivalent to quin
immature neurones in vivo.
Most recently, two groups have attempted to resolve that
the noted discrepancies by studying the time courses of for the
quinolinate les immature neurones in vivo.

Most recently, two groups have attempted to resolve

the noted discrepancies by studying the time courses of

following the intrastriatal injection

months and 1 year following the intrastriatal Most recently, two groups have attempted to resolve
the noted discrepancies by studying the time courses of
quinolinate lesions. Beal et al. (1991c) found that, at 6
months and 1 year following the intrastriatal injection
 the noted discrepancies by studying the time courses of quinolinate lesions. Beal et al. (1991c) found that, at 6 months and 1 year following the intrastriatal injection of quinolinate, there was a decrease of GABA and sub quinolinate lesions. Beal et al. (1991c) found that, a
months and 1 year following the intrastriatal inject
of quinolinate, there was a decrease of GABA and s
stance P levels with sparing of NADPH diaphorase
tivity and an months and 1 year following the intrastriatal injection cof quinolinate, there was a decrease of GABA and substance P levels with sparing of NADPH diaphorase activity and an increase of neuropeptide Y and somato-
statin im

finding, which was considered to reflect the preservation YNURENIC ACIDS

finding, which was considered to reflect the preservation

of peptide-containing neurones in the face of a shrinkage

of total striatal volume, was considered especially signif-3

SIMURENIC ACIDS

finding, which was considered to reflect the preservation

of peptide-containing neurones in the face of a shrinka

of total striatal volume, was considered especially sign

icant because it mirrors the finding, which was considered to reflect the preservation
of peptide-containing neurones in the face of a shrinkage
of total striatal volume, was considered especially signif-
icant because it mirrors the increase in these of peptide-containing neurones in the face of a shrinkage
of total striatal volume, was considered especially signif-
icant because it mirrors the increase in these peptides
seen in Huntington's disease striatum. The autho of peptide-containing neurones in the face of a shrinkage
of total striatal volume, was considered especially signif-
icant because it mirrors the increase in these peptides
seen in Huntington's disease striatum. The autho of total striatal volume, was considered especially signi-
icant because it mirrors the increase in these peptide
seen in Huntington's disease striatum. The authors thu
maintain their assertion that the neurochemical profi icant because it mirrors the increase in these peptides
seen in Huntington's disease striatum. The authors thus
maintain their assertion that the neurochemical profile
produced by quinolinate resembles closely that of Hunseen in Huntington's disease striatum. The authors thus
maintain their assertion that the neurochemical profile
produced by quinolinate resembles closely that of Hun-
tington's striatum, a view supported by the loss of
NMD maintain their assertion that the neurochemical profile
produced by quinolinate resembles closely that of Hun-
tington's striatum, a view supported by the loss of
NMDA receptors relative to non-NMDA receptors in
both situa produced by quinolinate resembles closely that of Huntington's striatum, a view supported by the loss of NMDA receptors relative to non-NMDA receptors in both situations (Greenamyre and Young, 1989). Susel et al. (1991) no tington's striatum, a view supported by the loss of NMDA receptors relative to non-NMDA receptors in both situations (Greenamyre and Young, 1989). Susel et al. (1991) noted that low doses of chronically infused quinolinate NMDA receptors relative to non-NMDA receptors in
both situations (Greenamyre and Young, 1989). Susel et
al. (1991) noted that low doses of chronically infused
quinolinate (90 nmol/day) depleted striatum of choline
acetylas both situations (Greenamyre and Young, 1989). Suse
al. (1991) noted that low doses of chronically infur
quinolinate (90 nmol/day) depleted striatum of chol
acetylase and glutamate decarboxylase without affect
NADPH diaphor al. (1991) noted that low doses of chron
quinolinate (90 nmol/day) depleted striat
acetylase and glutamate decarboxylase wit
NADPH diaphorase, but it was only at h
trations that the latter enzyme was lost.
The second "chro inolinate (90 nmol/day) depleted striatum of choline
etylase and glutamate decarboxylase without affecting
ADPH diaphorase, but it was only at higher concen-
ations that the latter enzyme was lost.
The second "chronic: inv

acetylase and glutamate decarboxylase without affectin
NADPH diaphorase, but it was only at higher concer
trations that the latter enzyme was lost.
The second "chronic: investigation involved infusin
quinolinate from osmot NADPH diaphorase, but it was only at higher concentrations that the latter enzyme was lost.
The second "chronic: investigation involved infusing
quinolinate from osmotic minipumps into the rat stria-
tum for 1 to 2 weeks (trations that the latter enzyme was lost.

The second "chronic: investigation involved infusing

quinolinate from osmotic minipumps into the rat stria-

tum for 1 to 2 weeks (Forloni et al., 1992). Analyses

indicated no The second "chronic: investigation involved infusing
quinolinate from osmotic minipumps into the rat stria-
tum for 1 to 2 weeks (Forloni et al., 1992). Analyses
indicated no preservation of somatostatin- or NADPH
diaphora quinolinate from osmotic minipumps into the rat stria-
tum for 1 to 2 weeks (Forloni et al., 1992). Analyses
indicated no preservation of somatostatin- or NADPH
diaphorase-containing neurones, but the concentrations
attain tum for 1 to 2 weeks (Forloni et al., 1992). Analyses
indicated no preservation of somatostatin- or NADPH
diaphorase-containing neurones, but the concentrations
attained during the experimental period remains unclear,
and indicated no preservation of somatostatin- or l
diaphorase-containing neurones, but the concentationed during the experimental period remains
and thus uncertainty remains as to whether th
have been sufficient to inflict ma aphorase-containing neurones, but the concentrations
tained during the experimental period remains unclear,
d thus uncertainty remains as to whether they may
we been sufficient to inflict maximal damage.
The possible role attained during the experimental period remains unclear,
and thus uncertainty remains as to whether they may
have been sufficient to inflict maximal damage.
The possible role of quinolinate in Huntington's dis-
ease is cle

and thus uncertainty remains as to whether they may
have been sufficient to inflict maximal damage.
The possible role of quinolinate in Huntington's dis-
ease is clearly a major issue, and yet there is no final
resolution have been sufficient to inflict maximal damage.
The possible role of quinolinate in Huntington's dis-
ease is clearly a major issue, and yet there is no final
resolution of the conflict of results between different
laborat The possible role of quinolinate in Huntington's dis-
ease is clearly a major issue, and yet there is no final
resolution of the conflict of results between different
laboratories. Neither is there any obvious way forward
 ease is clearly a major issue, and yet there is no final
resolution of the conflict of results between different
laboratories. Neither is there any obvious way forward
to achieve a resolution. Our own results indicate that trations that the latter enzyme was lost.
The second "chronic: investigation involved infusing
quinolinate from osmotic: minipumps into the rat stria-
tum for 1 to 2 weeks (Forloni et al., 1992). Analyses
indicated no pre laboratories. Neither is there any obvious way forward
to achieve a resolution. Our own results indicate that
samples of quinolinate may sometimes be contaminated
by small amounts of quinoline, which we have found to
be a to achieve a resolution. Our own results indicate that
samples of quinolinate may sometimes be contaminated
by small amounts of quinoline, which we have found to
be a potent neurotoxin. Such contamination might then
accoun samples of quinolinate may sometimes be contaminated
by small amounts of quinoline, which we have found to
be a potent neurotoxin. Such contamination might then
account for the nonselective cell damage seen by some
groups, by small amounts of quinoline, which we have found to
be a potent neurotoxin. Such contamination might then
account for the nonselective cell damage seen by some
groups, although most laboratories seem to obtain their
quin be a potent neurotoxin. Such contamination might then account for the nonselective cell damage seen by some groups, although most laboratories seem to obtain their quinolinate from the same commercial source (Sigma Chemica account for the nonselective cell damage seen by some
groups, although most laboratories seem to obtain their
quinolinate from the same commercial source (Sigma
Chemical Co.), and major variations in quality would not
be groups, although most laboratories seem to obtain their
quinolinate from the same commercial source (Sigma
Chemical Co.), and major variations in quality would not
be expected. Nevertheless, this may be one avenue to
explo quinolinate from the same commercial source (Sigm
Chemical Co.), and major variations in quality would no
be expected. Nevertheless, this may be one avenue t
explore because storage conditions, the routine use of
long-term Chemical Co.), and major variations in quality would not
be expected. Nevertheless, this may be one avenue to
explore because storage conditions, the routine use of
long-term stock solutions, or the precise manner of makbe expected. Nevertheless, this may be one avenue to explore because storage conditions, the routine use of long-term stock solutions, or the precise manner of making solutions and adjusting the pH may conspire to produce explore because storage conditions, the routine use of long-term stock solutions, or the precise manner of making solutions and adjusting the pH may conspire to produce chemical alterations to quinolinate or any contaminan long-term stock solutions, or the precise manner of making solutions and adjusting the pH may conspire to produce chemical alterations to quinolinate or any contaminants. Such changes may then yield nonselective cell toxic produce chemical alterations to quinolinate or any condamage. minants. Such changes may then yield nonselective
Il toxicity that could mask what is currently accepted
only a relative resistance of neurones to quinolinate
mage.
Two recent papers have added elements of confusion
the st

cell toxicity that could mask what is currently accepte
as only a relative resistance of neurones to quinolinat
damage.
Two recent papers have added elements of confusio
to the story. Qin et al. (1992) showed that intrastr as only a relative resistance of neurones to quinolinate
damage.
Two recent papers have added elements of confusion
to the story. Qin et al. (1992) showed that intrastriatal
quinolinate depletes glutamate decarboxylase act damage.
Two recent papers have added elements of confusion
to the story. Qin et al. (1992) showed that intrastriatal
quinolinate depletes glutamate decarboxylase activity, as
has been seen in previous studies. The GABA neu Two recent papers have added elements of confusion
to the story. Qin et al. (1992) showed that intrastriatal
quinolinate depletes glutamate decarboxylase activity, as
has been seen in previous studies. The GABA neurones
th to the story. Qin et al. (1992) showed that intrastriatal quinolinate depletes glutamate decarboxylase activity, as has been seen in previous studies. The GABA neurones that were resistant to quinolinate also exhibited sta quinolinate depletes glutamate decarboxylase activity, thas been seen in previous studies. The GABA neuron
that were resistant to quinolinate also exhibited stainin
for the calcium-binding protein parvalbumin, althoug
it i has been seen in previous studies. The GABA neurones
that were resistant to quinolinate also exhibited staining
for the calcium-binding protein parvalbumin, although
it is not clear whether some of the quinolinate-sensitiv for the calcium-binding protein parvalbumin, although
it is not clear whether some of the quinolinate-sensitive
cells also contained this protein; Waldvogel et al. (1991)
found a parallel decline of parvalbumin and calbind imuno-staining after intrastriatal quinolinate. is not clear whether some of the quinolinate-sensitive
lls also contained this protein; Waldvogel et al. (1991)
und a parallel decline of parvalbumin and calbindin
uno-staining after intrastriatal quinolinate.
Qin et al. (cells also contained this protein; Waldvogel et al. (1991)
found a parallel decline of parvalbumin and calbindin
imuno-staining after intrastriatal quinolinate.
Qin et al. (1992) also reported that quinolinate killed
all c

PHARMACOLOGICAL REVIEWS

S54
would run counter to the claim described earlier. The signed and reason for confusion is that the lesion site still contained m strom
would run counter to the claim described earlier. The
reason for confusion is that the lesion site still contained
rells containing NADPH diaphorase. 354
would run counter to the claim desp
reason for confusion is that the lesion
cells containing NADPH diaphorase.
In a second paper, Manfridi et In a second paper, Manfridi et al. (1991) reported subsom for confusion is that the lesion site still contained in this containing NADPH diaphorase.
In a second paper, Manfridi et al. (1991) reported sults of the experimen

would run counter to the claim described earlier. The reason for confusion is that the lesion site still contained cells containing NADPH diaphorase.
In a second paper, Manfridi et al. (1991) reported results of the experi reason for confusion is that the lesion site still contained m
cells containing NADPH diaphorase.
In a second paper, Manfridi et al. (1991) reported
results of the experiment in which kainate or quinolinate v
was injected cells containing NADPH diaphorase.
In a second paper, Manfridi et al. (1991) reported
results of the experiment in which kainate or quinolinate
was injected into the hippocampus of freely moving rats
and somatostatin was m In a second paper, Manfridi et al. (1991) reported
results of the experiment in which kainate or quinolinate
was injected into the hippocampus of freely moving rats
and somatostatin was measured. Whereas quinolinate
induce results of the experiment in which kainate or quinolinate volwas injected into the hippocampus of freely moving rats is and somatostatin was measured. Whereas quinolinate dainduced a 5-fold increase of extracellular somato was injected into the hippocampus of freely moving r and somatostatin was measured. Whereas quinolin
induced a 5-fold increase of extracellular somatosts
concentration, kainate-induced increases were m
more modest. The eff and somatostatin was measured. Whereas quinol
induced a 5-fold increase of extracellular somator
concentration, kainate-induced increases were
more modest. The effect of quinolinate could, pre
ably, be the result of depola induced a 5-fold increase of extracellular somatostatin vi
concentration, kainate-induced increases were much
more modest. The effect of quinolinate could, presum-
si
ably, be the result of depolarisation of somatostatin-
 concentration, kainate-induced increases were munder more modest. The effect of quinolinate could, presuably, be the result of depolarisation of somatostat containing neurones, although it has also been claim that quinolin more modest. The effect of quinolinate could, presumably, be the result of depolarisation of somatostatin-containing neurones, although it has also been claimed that quinolinate will increase the expression of preprosomato ably, be the result of depolarisation of somatostatin-
containing neurones, although it has also been claimed
that quinolinate will increase the expression of prepro-
somatostatin mRNA (Patel et al. 1991) and may thus,
lik containing neurones, although it has also been claimed
that quinolinate will increase the expression of prepro-
somatostatin mRNA (Patel et al. 1991) and may thus,
like NMDA itself (Williams et al., 1991), directly en-
han that quinolinate will increase the expression of prepro-
somatostatin mRNA (Patel et al. 1991) and may thus,
like NMDA itself (Williams et al., 1991), directly en-
hance somatostatin synthesis and release. After 3 days,
th somatostatin mRNA (Patel et al. 1991) and may thus,
like NMDA itself (Williams et al., 1991), directly en-
hance somatostatin synthesis and release. After 3 days,
the authors then observed that quinolinate had destroyed
al like NMDA itself (Williams et al., 1991), directly enhance somatostatin synthesis and release. After 3 days, the authors then observed that quinolinate had destroyed all neurones in the hippocampus, including those expecte hance somatostatin synthesis and release. After 3 days
the authors then observed that quinolinate had destroyed
all neurones in the hippocampus, including those ex-
pected to stain for somatostatin, whereas kainate did not the authors then observed that quinolinate had destroyed
all neurones in the hippocampus, including those ex-
pected to stain for somatostatin, whereas kainate did not
affect somatostatin-containing cells. This is clearly all neurones in the hippocampus, including those ex-
pected to stain for somatostatin, whereas kainate did not
affect somatostatin-containing cells. This is clearly con-
trary to the finding reported by Beal's group, unles pected to stain for somatostatin, whereas kainate did not
affect somatostatin-containing cells. This is clearly con-
trary to the finding reported by Beal's group, unless dif
somatostatin-containing neurones in the striatu affect somatostatin-containing cells. This is clearly con-
trary to the finding reported by Beal's group, unless dif
somatostatin-containing neurones in the striatum and Ch
hippocampus react differently to excitotoxins. On trary to the finding reported by Beal's group, unless diffeomatostatin-containing neurones in the striatum and Ch
hippocampus react differently to excitotoxins. On the der
other hand, Susel et al. (1991) found that only th somatostatin-containing neurones in the striatum and
hippocampus react differently to excitotoxins. On the
other hand, Susel et al. (1991) found that only the
infusion of higher concentrations of quinolinate (270 and
540 n hippocampus react differently to excitotoxins. On the other hand, Susel et al. (1991) found that only thinfusion of higher concentrations of quinolinate (270 an 540 nmol/day) caused a change of striatal somatostat concentr other hand, Sus
infusion of higher
540 nmol/day) cr
concentration, alterm experiment:
Although the e fusion of higher concentrations of quinolinate (270 and 0 nmol/day) caused a change of striatal somatostatin ncentration, although this was decreased after short-
rm experiments.
Although the experimental emphasis has been

540 nmol/day) caused a change of striatal somatostatin
concentration, although this was decreased after short-
term experiments.
Although the experimental emphasis has been on so-
matostatin and neuropeptide Y because of concentration, although this was decreased after show term experiments.

Although the experimental emphasis has been on a matostatin and neuropeptide Y because of the relevant to Huntington's disease, there is little doubt term experiments.

Although the experimental emphasis has been on so-

matostatin and neuropeptide Y because of the relevance

to Huntington's disease, there is little doubt that quino-

linate does change the expression o Although the experimental emphasis has been on a matostatin and neuropeptide Y because of the relevant to Huntington's disease, there is little doubt that quino-
linate does change the expression of other neuroactic peptid matostatin and neuropeptide Y because of the relevance
to Huntington's disease, there is little doubt that quino-
linate does change the expression of other neuroactive
peptides. In the nucleus accumbens, for example, quin to Huntington's disease, there is little doubt
linate does change the expression of other peptides. In the nucleus accumbens, for exam
linate produces changes of muscimol, quinucl
zoate, neurotensin, and Tyr-D-Ala-Gly-N-M
 linate does change the expression of other neuroactive
peptides. In the nucleus accumbens, for example, quino-
linate produces changes of muscimol, quinuclidinyl ben-
zoate, neurotensin, and Tyr-D-Ala-Gly-N-MePhe-Gly-
OH-b peptides. In the nucleus accumbens, for example, quino-
linate produces changes of muscimol, quinuclidinyl ben-
zoate, neurotensin, and Tyr-D-Ala-Gly-N-MePhe-Gly-
OH-binding sites, although the nature of the changes
differ linate produces changes of muscimol, quinuclidinyl ben-
zoate, neurotensin, and Tyr-D-Ala-Gly-N-MePhe-Gly-
OH-binding sites, although the nature of the changes
differed in different regions of the nucleus. Neurotensin
bind zoate, neurotensin, and Tyr-D-Ala-Gly-N-MePhe-Gly-

OH-binding sites, although the nature of the changes

differed in different regions of the nucleus. Neurotensin

binding was decreased in the lateral accumbens but not

s OH-binding sites, although the nature of the changes differed in different regions of the nucleus. Neurotensin binding was decreased in the lateral accumbens but not medial areas. Following quinolinate administration into differed in different regions of the nucleus. Neurotensin
binding was decreased in the lateral accumbens but not
medial areas. Following quinolinate administration into
the rat striatum, levels of neurotensin peptide were binding was decreased in the lateral accumbens but not som
medial areas. Following quinolinate administration into sitis
the rat striatum, levels of neurotensin peptide were in-
creased, although the density of binding sit medial areas. Following quinolinate administration into sit
the rat striatum, levels of neurotensin peptide were in-
creased, although the density of binding sites was de-
ereased (Masuo et al., 1990). This result was take creased, although the density of binding sites was decreased (Masuo et al., 1990). This result was taken to indicate that the expression of neurotensin within the striatum was partly under the control of intrinsic neu-
ron creased (Masuo et al., 1990). This result was taken to andicate that the expression of neurotensin within the astriatum was partly under the control of intrinsic neurones.

A similar interpretation may explain the increase

indicate that the expression of neurotensin within the striatum was partly under the control of intrinsic neurones.
A similar interpretation may explain the increase of met-enkephalin levels in rat striatum and globus pall striatum was partly under the control of intrinsic neu
rones.
A similar interpretation may explain the increase of
met-enkephalin levels in rat striatum and globus pallidu
that were induced by four excitotoxins: kainate, q rones.
A similar interpretation may explain the increase met-enkephalin levels in rat striatum and globus palli
that were induced by four excitotoxins: kainate, q
qualate, quinolinate, and NMDA (Ruzicka and Jham
das, 1990) A similar interpretation may explain the increase of remet-enkephalin levels in rat striatum and globus pallidus that were induced by four excitotoxins: kainate, quisqualate, quinolinate, and NMDA (Ruzicka and Jhaman-vidas met-enkephalin levels in rat striatum and globus pallidus
that were induced by four excitotoxins: kainate, quis
qualate, quinolinate, and NMDA (Ruzicka and Jhaman
das, 1990). Wherease kainate was the most potent o
these, q that were induced by four excitotoxins: kainate, quis-
qualate, quinolinate, and NMDA (Ruzicka and Jhaman-vidas, 1990). Wherease kainate was the most potent of 1.
these, quinolinate induced the greatest increase of met-
en qualate, quinolinate, and NMDA (Ruzicka and Jhaman-vivelas, 1990). Wherease kainate was the most potent of 1.2 these, quinolinate induced the greatest increase of metaphelin immunoreactivity even though the effect was The das, 1990). Wherease kainate was the most potent of 1.
these, quinolinate induced the greatest increase of met-
enkephalin immunoreactivity even though the effect was T
mediated entirely through NMDA receptors and could m
 these, quinolinate induced the greatest increase of met-
enkephalin immunoreactivity even though the effect was
mediated entirely through NMDA receptors and could
be blocked by CPP or kynurenate. The mechanism of
the incre enkephalin immunoreactivity even though the effect was The
mediated entirely through NMDA receptors and could mill
be blocked by CPP or kynurenate. The mechanism of no
the increase remains obscure because quinolinate halve

NE
significant alteration in the release of enkephalin im-
munoreactivity from lesioned striata (Ruzicka et al., WE
significant alteration in the release of enkephalin im-
munoreactivity from lesioned striata (Ruzicka et al.,
1991). 1991). gnificant alteration in the release of enkephalin im-
unoreactivity from lesioned striata (Ruzicka et al.,
91).
The argument most frequently raised against an in-
lvement of quinolinate in neurodegenerative diseases

significant alteration in the release of enkephalin im-
munoreactivity from lesioned striata (Ruzicka et al.,
1991).
The argument most frequently raised against an in-
volvement of quinolinate in neurodegenerative diseases munoreactivity from lesioned striata (Ruzicka et al., 1991).

The argument most frequently raised against an in-

volvement of quinolinate in neurodegenerative diseases

is that the concentrations needed to induce neuronal 1991).
The argument most frequently raised against an in-
volvement of quinolinate in neurodegenerative diseases
is that the concentrations needed to induce neuronal
damage are far higher than can be achieved in vivo. This The argument most frequently raised against are volvement of quinolinate in neurodegenerative dise
is that the concentrations needed to induce neur
damage are far higher than can be achieved in vivo.
view partly arises ou volvement of quinolinate in neurodegenerative diseases
is that the concentrations needed to induce neuronal
damage are far higher than can be achieved in vivo. This
view partly arises out of work indicating that concentra is that the concentrations needed to induce neuronal damage are far higher than can be achieved in vivo. This view partly arises out of work indicating that concentrations of 250 to 400 μ M quinolinate were needed to in damage are far higher than can be achieved in viv
view partly arises out of work indicating that con
tions of 250 to 400 μ M quinolinate were needed to
signs of damage in neocortical cultures, even wl
posed for up to 96 Eventy arises out of work indicating that concentra-
ons of 250 to 400 μ M quinolinate were needed to induce
gns of damage in neocortical cultures, even when ex-
sed for up to 96 hours (Kim and Choi, 1987).
This argumen

tions of 250 to 400 μ M quinolinate were needed to induce
signs of damage in neocortical cultures, even when ex-
posed for up to 96 hours (Kim and Choi, 1987).
This argument must now be recognised as fallacious
for at l posed for up to 96 hours (Kim and Choi, 1987).
This argument must now be recognised as fallacious for at least two reasons. First, it has been noted that in some disorders the concentrations of quinolinate in brain of qui posed for up to 96 hours (Kim and Choi, 1987).
This argument must now be recognised as fallacious
for at least two reasons. First, it has been noted that in
some disorders the concentrations of quinolinate in brain
or CSF This argument must now be recognised as fallacious
for at least two reasons. First, it has been noted that in
some disorders the concentrations of quinolinate in brain
or CSF can increase to low micromolar levels. Second,
 for at least two reasons. First, it has been noted that in
some disorders the concentrations of quinolinate in brain
or CSF can increase to low micromolar levels. Second,
quinolinate concentrations as low as 100 nM can cau some disorders the concentrations of quinolinate in brain
or CSF can increase to low micromolar levels. Second,
quinolinate concentrations as low as 100 nM can cause
signs of damage to spinal neurones in culture after as
l or CSF can increase to low micromolar levels. Second,
quinolinate concentrations as low as 100 nM can cause
signs of damage to spinal neurones in culture after as
little as 24 hours of exposure (Giulian et al., 1990) or
de quinolinate concentrations as low as 100 nM can cause
signs of damage to spinal neurones in culture after as
little as 24 hours of exposure (Giulian et al., 1990) or
degeneration of striatal neurones after several weeks
(W signs of damage to spinal neurones in culture after as
little as 24 hours of exposure (Giulian et al., 1990) or
degeneration of striatal neurones after several weeks
(Whetsell and Schwarcz, 1989). The reasons for the
diffe little as 24 hours of exposure (Giulian et al., 1990)
degeneration of striatal neurones after several wee
(Whetsell and Schwarcz, 1989). The reasons for t
different results compared with the studies of Kim a
Choi (1987) is degeneration of striatal neurones after several weeks

(Whetsell and Schwarcz, 1989). The reasons for the

different results compared with the studies of Kim and

Choi (1987) is not clear, but it was noted that the mousedifferent results compared with the studies of Kim and Choi (1987) is not clear, but it was noted that the mouse-
derived cultures used by this group were also different in insensitive to quinolinate.
One possibility is that the mouse neurones are insufnoi (1987) is not clear, but it was noted that the mous
rived cultures used by this group were also different
eir behaviour with dextromethorphan and relative
sensitive to quinolinate.
One possibility is that the mouse neu

derived cultures used by this group were also different in their behaviour with dextromethorphan and relatively insensitive to quinolinate.
One possibility is that the mouse neurones are insufficiently mature compared with ficiently mature compared with those of the rat since,
even in the latter species, cultured neurones require at
least 7 days of establishment before developing sensitivity to excitotoxins (Keilhoff and Erdo, 1991). It is also One possibility is that the mouse neurones are insuf-
ficiently mature compared with those of the rat since,
even in the latter species, cultured neurones require at
least 7 days of establishment before developing sensitiv ficiently mature compared with those of the rat since,
even in the latter species, cultured neurones require at
least 7 days of establishment before developing sensitiv-
ity to excitotoxins (Keilhoff and Erdo, 1991). It is even in the latter species, cultured neurones require at least 7 days of establishment before developing sensitivity to excitotoxins (Keilhoff and Erdo, 1991). It is also possible that the development of neurotoxicity is s least 7 days of establishment before developing sensitivity to excitotoxins (Keilhoff and Erdo, 1991). It is also possible that the development of neurotoxicity is slower in the mouse. The neurotoxic effect of quinolinate ity to excitotoxins (Keilhoff and Erdo, 1991). It is als possible that the development of neurotoxicity is slowe
in the mouse. The neurotoxic effect of quinolinate in rat
does not appear for some hours after it has been cl possible that the development of neurotoxicity is slower
in the mouse. The neurotoxic effect of quinolinate in rats
does not appear for some hours after it has been cleared
from the brain and can be prevented by neuroprote in the mouse. The n
does not appear for
from the brain and c
given several hours
and Foster, 1991).
One further facto es not appear for some hours after it has been cleared

om the brain and can be prevented by neuroprotectants

ven several hours later (Keilhoff et al., 1991; Bakker

d Foster, 1991).

One further factor that may need to

from the brain and can be prevented by neuroprotectar
given several hours later (Keilhoff et al., 1991; Bakk
and Foster, 1991).
One further factor that may need to be considered
some of this work is the presence of sensiti given several hours later (Keilhoff et al., 1991; Bakker
and Foster, 1991).
One further factor that may need to be considered in
some of this work is the presence of sensitising or desen-
sitising agents in culture media. and Foster, 1991).

One further factor that may need to be considered in

some of this work is the presence of sensitising or desen-

sitising agents in culture media. A particularly striking

example may be quinolinate it One further factor that may need to be considered in
some of this work is the presence of sensitising or desensitising agents in culture media. A particularly striking
example may be quinolinate itself. Heyes (1992) recen some of this work is the presence of sensitising or desensitising agents in culture media. A particularly striking example may be quinolinate itself. Heyes (1992) recently $\frac{100}{100}$ emphasised that the levels of quino sitising agents in culture media. A particularly striking
example may be quinolinate itself. Heyes (1992) recently
emphasised that the levels of quinolinate present in
animal serum used in some culture media may be as low
 example may be quinolinate itself. Heyes (1992) recently
emphasised that the levels of quinolinate present in
animal serum used in some culture media may be as low
as 92 nM or may reach 3000 nM. Such variation in
quinolina emphasised that the levels of quinolinate present in
animal serum used in some culture media may be as low
as 92 nM or may reach 3000 nM. Such variation in
quinolinate content, if present for extended periods
could well ac animal serum used in some culture meas 92 nM or may reach 3000 nM.
quinolinate content, if present for
could well account for the reported d
ronal viability in different laboratories.
It has now been demonstrated that 92 nM or may reach 3000 nM. Such variation in
inolinate content, if present for extended periods,
uld well account for the reported differences in neu-
nal viability in different laboratories.
It has now been demonstrated

quinolinate content, if present for extended periods,
could well account for the reported differences in neu-
ronal viability in different laboratories.
It has now been demonstrated that the slow infusion
of quinolinate in could well account for the reported differences in neu-
ronal viability in different laboratories.
It has now been demonstrated that the slow infusion
of quinolinate into the rat hippocampus or striatum in
vivo can also in ronal viability in different laboratories.

It has now been demonstrated that the slow infusion

of quinolinate into the rat hippocampus or striatum is

vivo can also induce neuronal damage. At rates as low a

1.2 nmol/hou It has now been demonstrated that the slow infusion
of quinolinate into the rat hippocampus or striatum in
vivo can also induce neuronal damage. At rates as low as
1.2 nmol/hour, quinolinate produced hippocampal dam-
age a of quinolinate into the rat hippocampus or striatum in
vivo can also induce neuronal damage. At rates as low as
1.2 nmol/hour, quinolinate produced hippocampal dam-
age after 1 week (Vezzani et al., 1991b; Susel et al., 19 vivo can also induce neuronal damage. At rates as low as 1.2 nmol/hour, quinolinate produced hippocampal damage after 1 week (Vezzani et al., 1991b; Susel et al., 1991). These experiments still involve the administration o 1.2 nmol/hour, quinolinate produced hippocampal dam-
age after 1 week (Vezzani et al., 1991b; Susel et al., 1991).
These experiments still involve the administration of
millimolar solutions of quinolinate, but at the rates age after 1 week (Vezzani et al., 1991b; Susel et al., 1991)
These experiments still involve the administration of
millimolar solutions of quinolinate, but at the rates used
no accumulation of quinolinate could be detected These experiments still involve the administration of
millimolar solutions of quinolinate, but at the rates used
no accumulation of quinolinate could be detected near
the injection sites. It is likely, therefore, that loca

aspet

QUINOLINIC AN
thus supporting the contention that, if chronically main-
tained, very low levels of quinolinate can be neurotox QUINOLINIC AND K
thus supporting the contention that, if chronically main-
tained, very low levels of quinolinate can be neurotoxic
in vivo. thus supporting
tained, very low
in vivo.
1. Kynurenine

1. Kynurening the contention that, if chronically maintained, very low levels of quinolinate can be neurotoxic in vivo.
 1. Kynurenine concentrations in Huntington's disease.

Efforts to demonstrate changes of quinolin in vivo.

I. Kynurenine concentrations in Huntington's disease.

Efforts to demonstrate changes of quinolinate concen-

Efforts to demonstrate changes of quinolinate concen-

The results suggest that a defect of kynurenate in vivo.

1. Kynurenine concentrations in Huntington's disease

Efforts to demonstrate changes of quinolinate concentration, however, have not been consistent with the

simple concept that increased levels contribute to Hu 1. Kynurenine concentrations in Huntington's disease. deflorts to demonstrate changes of quinolinate concentration, however, have not been consistent with the maimple concept that increased levels contribute to Huntington' Efforts to demonstrate changes of quinolinate concentration, however, have not been consistent with the main simple concept that increased levels contribute to Hun-
Tington's pathology. Neither the urinary excretion of of
 tration, however, have not been consistent with the
simple concept that increased levels contribute to Hun-
tington's pathology. Neither the urinary excretion of
quinolinate (Heyes et al., 1985) nor the activity of its
cat simple concept that increased levels contribute to Hun-

tington's pathology. Neither the urinary excretion of of

quinolinate (Heyes et al., 1985) nor the activity of its

sancetabolic enzyme QPRT in blood (primarily plat tington's pathology. Neither the urinary excretion of of t
quinolinate (Heyes et al., 1985) nor the activity of its same
catabolic enzyme QPRT in blood (primarily platelets) and
(Foster and Schwarcz, 1985) is abnormal in p quinolinate (Heyes et al., 1985) nor the activity of its
catabolic enzyme QPRT in blood (primarily platelets)
(Foster and Schwarcz, 1985) is abnormal in patients with
Huntington's disease. Similarly, quinolinate in the CSF catabolic enzyme QPRT in blood (primarily platelets)
(Foster and Schwarcz, 1985) is abnormal in patients with
Huntington's disease. Similarly, quinolinate in the CSF
of subjects with Huntington's disease is apparently nor-(Foster and Schwarcz, 1985) is abnormal in patients with
Huntington's disease. Similarly, quinolinate in the CSF
of subjects with Huntington's disease is apparently nor-
mal (Schwarcz et al., 1988b), and Reynolds et al. (1 Huntington's disease. Similarly, quinolinate in the CSF of subjects with Huntington's disease is apparently normal (Schwarcz et al., 1988b), and Reynolds et al. (1988) tem could demonstrate no significant difference betwee of subjects with Huntington's disease is apparently n
mal (Schwarcz et al., 1988b), and Reynolds et al. (19
could demonstrate no significant difference between
putamen or frontal cortex from patients with disease a
contro mal (Schwarcz et al., 1988b), and Reynolds et al. (1988) ter
could demonstrate no significant difference between the in
putamen or frontal cortex from patients with disease and 19
control subjects, although the reported l could demonstrate no significant difference between the putamen or frontal cortex from patients with disease and control subjects, although the reported level of approximately 100 ng/g (about 0.7 μ M) is about 10 times putamen or frontal cortex from patients with disease and
control subjects, although the reported level of approxi-
mately 100 ng/g (about 0.7 μ M) is about 10 times the
plevel seen by other groups (Schwarcz et al., 1988b control subjects, although the reported level of approximately 100 ng/g (about 0.7μ M) is about 10 times the level seen by other groups (Schwarcz et al., 1988b; Moroni et al., 1986c ; Heyes and Lackner, 1990; Heyes mately 100 ng/g (about 0.7 μ M) is about 10 times the plevel seen by other groups (Schwarcz et al., 1988b; Mo-
roni et al., 1986c ; Heyes and Lackner, 1990; Heyes et the same, 1991a; Turski et al., 1988). Similarly, qui level seen by other groups (Schwarcz et al., 1988b; Moroni et al., 1986c ; Heyes and Lackner, 1990; Heyes et al., 1991a; Turski et al., 1988). Similarly, quinolinate levels in brain or CSF were found to be the same, or low roni et al., 1986c ; Heyes and Lackner, 1990; Heyes et al., 1991a; Turski et al., 1988). Similarly, quinolinate levels in brain or CSF were found to be the same, or lower than, those in control subjects (Heyes et al., 1991 al., 1991a; Turski et al., 1988). Similarly, quinolinate levels in brain or CSF were found to be the same, or lower than, those in control subjects (Heyes et al., 1991a, 1992a). There are, nevertheless, strong suspicions t levels in brain or CSF were found to be the same, or ky lower than, those in control subjects (Heyes et al., 1991a, 1992a). There are, nevertheless, strong suspicions that pithe kynurenine pathway is hyperactive in Hunting lower than, those in control subjects (Heyes et al., 1992a). There are, nevertheless, strong suspicions the kynurenine pathway is hyperactive in Huntingto
the kynurenine pathway is hyperactive in Huntingto
disease since si 1992a). There are, nevertheless, strong suspicions the the kynurenine pathway is hyperactive in Huntington'
disease since significant increases in the activity of 3HAO have been demonstrated in postmortem Hunting
ton's bra the kynurenine pathway is hyperactive in Huntington's chieses since significant increases in the activity of 1
3HAO have been demonstrated in postmortem Huntington's brain, the greatest abnormality being in the striatum (S disease since significant increases in the activity of IV
3HAO have been demonstrated in postmortem Hunting-ele
ton's brain, the greatest abnormality being in the stria-
situm (Schwarcz et al., 1988a). Although it is proba 3HAO have been demonstrated in postmortem Hunting-
ton's brain, the greatest abnormality being in the stria-
tum (Schwarcz et al., 1988a). Although it is probable
that this hyperactivity is largely due to the increased gli ton's brain, the greatest abnormality being in the st
tum (Schwarcz et al., 1988a). Although it is prob-
that this hyperactivity is largely due to the increased
to neurone ratio in degenerating tissue, it is impor-
not to tum (Schwarcz et al., 1988a).

that this hyperactivity is largely

to neurone ratio in degeneratin

mot to exclude it as a factor in m

ing the progress of the disease.

It should be recalled, however at this hyperactivity is largely due to the increased glia
neurone ratio in degenerating tissue, it is important
t to exclude it as a factor in maintaining or exacerbat-
g the progress of the disease.
It should be recalled

to neurone ratio in degenerating tissue, it is important for the exclude it as a factor in maintaining or exacerbat-
ing the progress of the disease. The primary substrate of the substrate of 3-hydroxyanthranilic acid, the not to exclude it as a factor in maintaining or exacerbat-
ing the progress of the disease. In
It should be recalled, however, that the administration
of 3-hydroxyanthranilic acid, the primary substrate of ti
3HAO, substan ing the progress of the disease.
It should be recalled, however, that the administration
of 3-hydroxyanthranilic acid, the primary substrate of
3HAO, substantially increases the cerebral synthesis of
quinolinate (Speciale It should be recalled, however, that the administration disof 3-hydroxyanthranilic acid, the primary substrate of ting 3HAO, substantially increases the cerebral synthesis of vierguinolinate (Speciale et al., 1989a). This $3HAO$, substantially increases the cerebral synthesis of view of the unchanged quinolinate concentration in post-
quinolinate (Speciale et al., 1989a). This indicates that mortem brain, and alternative views of the data m $3HAO$, substantially increases the cerebral synthesis of quinolinate (Speciale et al., 1989a). This indicates that the enzyme is not normally saturated with substrate, and an increased activity of $3HAO$ per se is not like quinolinate (Speciale et al., 1989a). This indicates
the enzyme is not normally saturated with substrate,
an increased activity of 3HAO per se is not likely to
increased quinolinate unless accompanied by other :
abolic abn e enzyme is not normally saturated with substrate, and
increased activity of 3HAO per se is not likely to yield
thereased quinolinate unless accompanied by other met-
olic abnormalities or increased substrate supply.
Atten

an increased activity of 3HAO per se is not likely to yield the increased quinolinate unless accompanied by other metabolic abnormalities or increased substrate supply. be Attention has now been redirected to the analysis increased quinolinate unless accompanied by other met-
abolic abnormalities or increased substrate supply. belc
Attention has now been redirected to the analysis of T
other kynurenines. The first report of this type showed abolic abnormalities or increased substrate supply.
Attention has now been redirected to the analysis of
other kynurenines. The first report of this type showed
the presence of kynurenic acid in human brain, but no
change Attention has now been redirected to the analysis cother kynurenines. The first report of this type showe the presence of kynurenic acid in human brain, but n change of kynurenate concentration in the caudate nucleus, pall other kynurenines. The first report of this type showed step presence of kynurenic acid in human brain, but no
change of kynurenate concentration in the caudate nu-
cleus, pallidum, or prefrontal cortex (area 10) of Hun-
t the presence of kynurenic acid in human brain, but no
change of kynurenate concentration in the caudate nu-
cleus, pallidum, or prefrontal cortex (area 10) of Hun-
tington's disease brains were detected; but a doubling of
 change of kynurenate concentration in the caudate nucleus, pallidum, or prefrontal cortex (area 10) of Huntington's disease brains were detected; but a doubling of concentration in the primary motor cortex (area 4) was fou cleus, pallidum, or prefrontal cortex (area 10) of Hun-
tington's disease brains were detected; but a doubling of
concentration in the primary motor cortex (area 4) was of s
found (Connick et al., 1989). The number of samp tington's disease brains were detected; but a doubling of that ky
concentration in the primary motor cortex (area 4) was of stim
found (Connick et al., 1989). The number of samples excitatively
studied was, however, relati concentration in the primary motor cortex (area 4) was of st
found (Connick et al., 1989). The number of samples exci
studied was, however, relatively small (five patients), and et a
in a subsequent analysis of 30 Huntingt found (Connick et al., 1989). The number of samples executied was, however, relatively small (five patients), and et in a subsequent analysis of 30 Huntington's brains from protients of comparable age and with similar post studied was, however, relatively small (five patients), and et
in a subsequent analysis of 30 Huntington's brains from pre
patients of comparable age and with similar postmortem in
delays, Beal et al. (1990) observed a dec in a subsequent analysis of 30 Huntington's brains from
patients of comparable age and with similar postmortem
indelays, Beal et al. (1990) observed a decrease in the
information of kynurenic acid from L-kynurenine in the
 patients of comparable age and with similar postmortem ind
delays, Beal et al. (1990) observed a decrease in the int
formation of kynurenic acid from L-kynurenine in the tim
striatum (putamen) with a significantly lower am

XNURENIC ACIDS
Huntington's disease. The overall concentration of kyn-
urenate was 40% less in the diseased samples. These vnurenate Acips

Huntington's disease. The overall concentration of kyn-

urenate was 40% less in the diseased samples. These

changes did not seem to relate to patient age, cause of 355
Huntington's disease. The overall concentration of kyn-
urenate was 40% less in the diseased samples. These
changes did not seem to relate to patient age, cause of
death, or medication. Huntington's disease
urenate was 40% le
changes did not seer
death, or medication
The results sugger untington's disease. The overall concentration of kynemate was 40% less in the diseased samples. These anges did not seem to relate to patient age, cause of ath, or medication.
The results suggest that a defect of kynurena

urenate was 40% less in the diseased samples. These
changes did not seem to relate to patient age, cause of
death, or medication.
The results suggest that a defect of kynurenate for-
mation may occur in patients with Hunti changes did not seem to relate to patient age, cause of death, or medication.
The results suggest that a defect of kynurenate for-
mation may occur in patients with Huntington's disease.
This is supported by the observatio death, or medication.
The results suggest that a defect of kynurenate for-
mation may occur in patients with Huntington's disease.
This is supported by the observation that no disturbance
of tyrosine metabolism could be de mation may occur in patients with Huntington's disease.
This is supported by the observation that no disturbance
of tyrosine metabolism could be demonstrated in the
same samples, based on an analysis of catecholamines
and mation may occur in patients with Huntington's disease.
This is supported by the observation that no disturbance
of tyrosine metabolism could be demonstrated in the
same samples, based on an analysis of catecholamines
and This is supported by the observation th
of tyrosine metabolism could be dem
same samples, based on an analysis o
and their metabolites, or of tryptophe
5HT and 5-hydroxyindoleacetic acid.
In a subsequent study, the same gr tyrosine metabolism could be demonstrated in the
me samples, based on an analysis of catecholamines
d their metabolites, or of tryptophan metabolism to
IT and 5-hydroxyindoleacetic acid.
In a subsequent study, the same gro

same samples, based on an analysis of catecholamines
and their metabolites, or of tryptophan metabolism to
5HT and 5-hydroxyindoleacetic acid.
In a subsequent study, the same group reported re-
duced amounts of kynurenate and their metabolites, or of tryptophan metabolism to 5HT and 5-hydroxyindoleacetic acid.
In a subsequent study, the same group reported reduced amounts of kynurenate in inferior and middle
temporal cortex and significant 5HT and 5-hydroxyindoleacetic acid.

In a subsequent study, the same group reported re-

duced amounts of kynurenate in inferior and middle

temporal cortex and significant reductions of kynurenate

in five of six neocorti In a subsequent study, the same group reported re-
duced amounts of kynurenate in inferior and middle
temporal cortex and significant reductions of kynurenate
in five of six neocortical regions examined (Beal et al.,
1992b duced amounts of kynurenate in inferior and middle
temporal cortex and significant reductions of kynurenate
in five of six neocortical regions examined (Beal et al.,
1992b). The extent of the loss of kynurenate was sub-
st temporal cortex and significant reductions of kynurenate
in five of six neocortical regions examined (Beal et al.,
1992b). The extent of the loss of kynurenate was sub-
stantial with the precentral gyrus and inferior and s in five of six neocortical regions examined (Beal et al., 1992b). The extent of the loss of kynurenate was substantial with the precentral gyrus and inferior and superior temporal gyri possessing only about 23% of control 1992b). The extent of the loss of kynurenate was substantial with the precentral gyrus and inferior and superior temporal gyri possessing only about 23% of control kynurenate levels. Of particular importance in this study, stantial with the precentral gyrus and inferior and superior temporal gyri possessing only about 23% of control
kynurenate levels. Of particular importance in this study,
the brains of patients with Parkinson's disease or perior temporal gyri possessing only aboutly survey as a symulation of patients with Parkinson's heimer's disease exhibited no significantly survey in the marked similarities between the marked similarities between the mar the brains of patients with Parkinson's disease or Alz-
heimer's disease exhibited no significant changes of L-
kynurenine or kynurenate concentrations.
The marked similarities between the neurochemical
profile of Huntingt

the brains of patients with Parkinson's disease or Alz-
heimer's disease exhibited no significant changes of L-
kynurenine or kynurenate concentrations.
The marked similarities between the neurochemical
profile of Huntingt heimer's disease exhibited no significant changes of L-
kynurenine or kynurenate concentrations.
The marked similarities between the neurochemical
profile of Huntington's disease striatum and the effects
of quinolinate in kynurenine or kynurenate concentrations.

The marked similarities between the neurochemical

profile of Huntington's disease striatum and the effects

of quinolinate in animals were discussed above (section

IV.D). Recent The marked similarities between the neuroche
profile of Huntington's disease striatum and the e
of quinolinate in animals were discussed above (se
IV.D). Recent work has also revealed similarities i
electrophysiological ch profile of Huntington's disease striatum and the effects
of quinolinate in animals were discussed above (section
IV.D). Recent work has also revealed similarities in the
electrophysiological characteristics of quinolinateof quinolinate in animals were discussed above (section IV.D). Recent work has also revealed similarities in the electrophysiological characteristics of quinolinate-lesioned rats and patients with Huntington's disease with IV.D). Recent work has also revealed similarities in the electrophysiological characteristics of quinolinate-le-
sioned rats and patients with Huntington's disease with
respect to sensory-evoked potentials (Schwarz et al., electrophysiological characteristics of quinolinate-le
sioned rats and patients with Huntington's disease wit
respect to sensory-evoked potentials (Schwarz et al
1992), which further supports a link. Those similaritie
form sioned rats and patients with Huntington's disease with respect to sensory-evoked potentials (Schwarz et al., 1992), which further supports a link. Those similarities form a powerful argument for the involvement of quinoli respect to sensory-evoked potentials (Schwarz et al., 1992), which further supports a link. Those similarities form a powerful argument for the involvement of quinolinate, or a closely related but as yet unidentified agent 1992), which further supports a link. Those similaritieform a powerful argument for the involvement of quinolinate, or a closely related but as yet unidentified agen in the characteristic neurodegeneration of Huntington di form a powerful argument for the involvement of quin-
olinate, or a closely related but as yet unidentified agent,
in the characteristic neurodegeneration of Huntington's
disease. Any relationship between quinolinate and olinate, or a closely related but as yet unidentified agent
in the characteristic neurodegeneration of Huntington'
disease. Any relationship between quinolinate and Hun
tington's disease cannot be a simple one, however, i: in the characteristic neurodegeneration of Huntington's
disease. Any relationship between quinolinate and Hun-
tington's disease cannot be a simple one, however, in
view of the unchanged quinolinate concentration in postdisease. Any relationship between quinolinate and Huntington's disease cannot be a simple one, however, in view of the unchanged quinolinate concentration in post-
mortem brain, and alternative views of the data must be co tington's disease cannot be a simple one, however, in
view of the unchanged quinolinate concentration in post-
mortem brain, and alternative views of the data must be
considered. One possible compromise position may be
tha view of the unchanged quinolinate concentration in post-
mortem brain, and alternative views of the data must be
considered. One possible compromise position may be
that neurones experiencing metabolic distress are more
se below). more intered. One possible compromise position may be at neurones experiencing metabolic distress are more nesitive to normal levels of quinolinic acid (see section low).
The decrease of kynurenate levels would invite the

that neurones experiencing metabolic distress are more
sensitive to normal levels of quinolinic acid (see section
below).
The decrease of kynurenate levels would invite the
speculation that the balance between these agoni sensitive to normal levels of quinolinic acid (see section
below).
The decrease of kynurenate levels would invite the
speculation that the balance between these agonist and
antagonist compounds is changed such that quinoli below).
The decrease of kynurenate levels would invite the
speculation that the balance between these agonist and
antagonist compounds is changed such that quinolinate
has, overall, a greater influence on neuronal viabilit The decrease of kynurenate levels would invite the speculation that the balance between these agonist and antagonist compounds is changed such that quinolinate has, overall, a greater influence on neuronal viability than i speculation that the balance between these agonist and
antagonist compounds is changed such that quinolinate
has, overall, a greater influence on neuronal viability
than in control tissue. It is implicit in this hypothesis antagonist compounds is changed such that quinolinate
has, overall, a greater influence on neuronal viability
than in control tissue. It is implicit in this hypothesis
that kynurenate is able to prevent the neurotoxic resu has, overall, a greater influence on neuronal viability
than in control tissue. It is implicit in this hypothesis
that kynurenate is able to prevent the neurotoxic result
of stimulating NMDA receptors as well as the neuron than in control tissue. It is implicit in this hypothesis
that kynurenate is able to prevent the neurotoxic result
of stimulating NMDA receptors as well as the neuronal
excitation. This was first shown to be the case by Fo that kynurenate is able to prevent the neurotoxic r
of stimulating NMDA receptors as well as the neuro
excitation. This was first shown to be the case by F_0
et al. (1984b), who reported that equimolar kynure
produced a of stimulating NMDA receptors as well as the neuronal excitation. This was first shown to be the case by Foster et al. (1984b), who reported that equimolar kynurenate produced an 80% protection against the quinolinate-indu excitation. This was first shown to be the case by Foster
et al. (1984b), who reported that equimolar kynurenate
produced an 80% protection against the quinolinate-
induced loss of choline acetylase in rat striatum. Of gre et al. (1984b), who reported that equimolar kynurenate
produced an 80% protection against the quinolinate-
induced loss of choline acetylase in rat striatum. Of great
interest was the observation that kynurenate was 6 to 7 produced an 80% protection against the quinolinate-
induced loss of choline acetylase in rat striatum. Of great
interest was the observation that kynurenate was 6 to 7
times more effective as an antagonist of quinolinate t interest was the observation that kynurenate was 6 to 7 times more effective as an antagonist of quinolinate than of NMDA. The blockade of quinolinate toxicity has been confirmed by other groups in the hippocampus (Lekieff

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et al., 1990; Vornov and Coyle, 1991), nucleus basalis
et al., 1990; Vornov and Coyle, 1991), nucleus basalis
(Boegman et al., 1985; Beninger et al., 1986; Winn et al., 856
et al., 1990; Vornov and Coyle, 1991), nucleus basalis
(Boegman et al., 1985; Beninger et al., 1986; Winn et al.,
1991), striatum (Uckele et al., 1989; Patel et al., 1990), strom
1990; Vornov and Coyle, 1991), nucleus basalis
1992, Seninger et al., 1986; Winn et al., 1991), striatum (Uckele et al., 1989; Patel et al., 1990),
1991), striatum (Uckele et al., 1989; Patel et al., 1990),
1987). Pr et al., 1990; Vornov and Coyle, 1991), nucleus basalis in set (Boegman et al., 1985; Beninger et al., 1986; Winn et al., enoiting 1991), striatum (Uckele et al., 1989; Patel et al., 1990), hyperpart of the crebellum (Lehma et al., 1990; Vornov and Coyle, 1991), nucleus basalis (Boegman et al., 1985; Beninger et al., 1986; Winn et al., 1991), striatum (Uckele et al., 1989; Patel et al., 1990), and cerebellum (Lehmann, 1987). Protection appear (Boegman et al., 1985; Beninger et al., 1986; Winn et al., 1991), striatum (Uckele et al., 1989; Patel et al., 1990
and cerebellum (Lehmann, 1987). Protection appears to
occur proximal to any change of calcium concentratio 1991), striatum (Uckele et al., 1989; Patel et al., 199
and cerebellum (Lehmann, 1987). Protection appears
occur proximal to any change of calcium concentratio
because kynurenate also prevents the increase of intr
cellular and cerebellum (Lehmann, 1987). Protection appears
occur proximal to any change of calcium concentrat
because kynurenate also prevents the increase of int
cellular calcium in response to NMDA receptor stin
lation in hippoc cur proximal to any change of calcium concentration
cause kynurenate also prevents the increase of intra-
llular calcium in response to NMDA receptor stimu-
ion in hippocampal cultures (Oliver et al., 1990).
As predicted,

because kynurenate also prevents the increase of intra-
cellular calcium in response to NMDA receptor stimu-
lation in hippocampal cultures (Oliver et al., 1990).
As predicted, if endogenous amino acids are involved,
the n cellular calcium in response to NMDA receptor stimu-
lation in hippocampal cultures (Oliver et al., 1990). rena
As predicted, if endogenous amino acids are involved, han
the neuronal damage induced by cerebral insults, hylation in hippocampal cultures (Oliver et al., 1990).
As predicted, if endogenous amino acids are involved,
the neuronal damage induced by cerebral insults, hy-
poxia, hypoglycaemia, or ischaemia can be reduced by
kynurena As predicted, if endogenous amino acids are involved,
the neuronal damage induced by cerebral insults, hy-
poxia, hypoglycaemia, or ischaemia can be reduced by
kynurenate (Germano et al., 1987; Priestley et al., 1990;
Kata the neuronal damage induced by cerebral insults, hypoxia, hypoglycaemia, or ischaemia can be reduced by kynurenate (Germano et al., 1987; Priestley et al., 1990; Katayama et al., 1992). The protection against ischaemia is poxia, hypoglycaemia, or ischaemia can be reduced by
kynurenate (Germano et al., 1987; Priestley et al., 1990;
Katayama et al., 1992). The protection against ischaemia
is somewhat controversial, however. Germano et al.
(19 kynurenate (Germano et al., 1987; Priestley et al., 1990
Katayama et al., 1992). The protection against ischaemis
is somewhat controversial, however. Germano et al
(1987) obtained an approximately 40% reduction of in
farct Katayama et al., 1992). The protection against ischaemia
is somewhat controversial, however. Germano et al.
(1987) obtained an approximately 40% reduction of in-
farct size in an adult rat ischaemia model (middle cere-
bra is somewhat controversial, however. Germano et al. of (1987) obtained an approximately 40% reduction of infarct size in an adult rat ischaemia model (middle cerebral artery occlusion) when kynurenate was administered i (1987) obtained an approximately 40% reduction of in-
farct size in an adult rat ischaemia model (middle cerebral
artery occlusion) when kynurenate was administered Intraperitoneally in high doses of 300 mg/kg repeat farct size in an adult rat ischaemia model (middle cere-
bral artery occlusion) when kynurenate was administered
intraperitoneally in high doses of 300 mg/kg repeated
three times. Similar results were reported by Nozaki an bral artery occlusion) when kynurenate was administered Intraperitoneally in high doses of 300 mg/kg repeated and three times. Similar results were reported by Nozaki and Hundel (1992), who measured an approximately 6-fold intraperitoneally in high doses of 300 mg/kg repeated an three times. Similar results were reported by Nozaki and H
Beal (1992), who measured an approximately 6-fold in-
crease of brain kynurenate concentration in response three times. Similar results were reported by Nozaki and Hu
Beal (1992), who measured an approximately 6-fold in-
crease of brain kynurenate concentration in response to
this peripheral treatment. Protection was also affor crease of brain kynurenate concentration in response to
this peripheral treatment. Protection was also afforded
against the cerebral oedema (Simon et al., 1986a) and
neuronal loss (Andine et al., 1988; Nozaki and Beal,
199 crease of brain kynurenate concentration in response to
this peripheral treatment. Protection was also afforded
against the cerebral oedema (Simon et al., 1986a) and
neuronal loss (Andine et al., 1988; Nozaki and Beal,
199 this peripheral treatment. Protection was also afforded against the cerebral oedema (Simon et al., 1986a) and neuronal loss (Andine et al., 1988; Nozaki and Beal, 1992) seen in neonatal rats following carotid occlusion. Th against the cerebral oedema (Simon et al., 1986a) and because heuronal loss (Andine et al., 1988; Nozaki and Beal, exileptively expansively in meonatal rats following carotid occlusion. In The protection was increased by p neuronal loss (Andine et al., 1988; Nozaki and Beal, ex
1992) seen in neonatal rats following carotid occlusion. lir
The protection was increased by probenecid. These re-
sults are easier to understand because kynurenate w 1992) seen in neonatal rats following carotid occlusion
The protection was increased by probenecid. These results are easier to understand because kynurenate would
be expected to cross the blood-brain barrier more readilin The protection was increased by probenecid. These re-
sults are easier to understand because kynurenate would
be expected to cross the blood-brain barrier more readily
in young animals. Oddly, no protection could be dem-
o sults are eases
be expected
in young an
onstrated ir
al., 1990).
Some ar expected to cross the blood-brain barrier more readily
young animals. Oddly, no protection could be dem-
strated in spontaneously hypertensive rats (Roussel et P
1990).
Some argument has concentrated on the role of the
ang

in young animals. Oddly, no protection could be demonstrated in spontaneously hypertensive rats (Roussel et al., 1990).
Some argument has concentrated on the role of changes of body temperature in the neuroprotective effec onstrated in spontaneously hypertensive rats (Roussel et Peral., 1990).

slow-

slow-

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changes of body temperature in the neuroprotective ef-

of fects of kynurenate and other agents. However, Gill and ace

W al., 1990).
Some argument has concentrated on the role of
changes of body temperature in the neuroprotective effects of kynurenate and other agents. However, Gill and
Woodruff (1990) showed that maintenance of core tem-
pe Some argument has concentrated on the role of changes of body temperature in the neuroprotective effects of kynurenate and other agents. However, Gill and Woodruff (1990) showed that maintenance of core temperature does no changes of body temperature in the neuroprotectifiects of kynurenate and other agents. However, Gift Woodruff (1990) showed that maintenance of correpreture does not diminish the protective effect of urenate against cerebr It does remain and other agents. However, Gill and
 ϵ codruff (1990) showed that maintenance of core tem-
 ϵ rature does not diminish the protective effect of kyn-
 ϵ and a strong possibility that the protection

Woodruff (1990) showed that maintenance of core tem-
perature does not diminish the protective effect of kyn-
liurenate against cerebral ischaemia in adult rats.
It does remain a strong possibility that the protection de
p perature does not diminish the protective effect of kynternate against cerebral ischaemia in adult rats.
It does remain a strong possibility that the protect
provided by kynurenate is indirect and due to induchanges of per urenate against cerebral ischaemia in adult rats. for It does remain a strong possibility that the protection deprovided by kynurenate is indirect and due to induced the changes of peripheral kynurenine metabolism, particu It does remain a strong possibility that the protection
provided by kynurenate is indirect and due to induce
changes of peripheral kynurenine metabolism, particu
larly because tryptophan has also been claimed to affor
prot provided by kynurenate is indirect and due to induce
changes of peripheral kynurenine metabolism, particularly because tryptophan has also been claimed to affor
protection against ischaemia (Carney, 1986). The add
tional p changes of peripheral kynurenine metabolism, particularly because tryptophan has also been claimed to afford protection against ischaemia (Carney, 1986). The additional point has been made that the high doses of kynurenate larly because tryptophan has also been claimed to afford brand protection against ischaemia (Carney, 1986). The addi-
notional point has been made that the high doses of kynu-
renate needed may have substantial effects on protection against ischaemia (Carney, 1986). The addi-
tional point has been made that the high doses of kynu-
renate needed may have substantial effects on general (199
cellular metabolism (Austin, 1988). However, there i tional point has been made that the high doses of kynu-
renate needed may have substantial effects on general (199
cellular metabolism (Austin, 1988). However, there is stem
some evidence that the protection is normally du renate needed may have substantial effects on general cellular metabolism (Austin, 1988). However, there is some evidence that the protection is normally due to receptor blockade because no changes of metabolism were detec cellular metabolism (Austin, 1988). However, there is st
some evidence that the protection is normally due to
receptor blockade because no changes of metabolism an
were detected in an in vivo study using nuclear resonance some evidence that the protection is normally due to espectfor blockade because no changes of metabolism and were detected in an in vivo study using nuclear resonance and spectroscopy (Roucher et al., 1991). It is also unl receptor blockade because no changes of metabolism
were detected in an in vivo study using nuclear resonance
spectroscopy (Roucher et al., 1991). It is also unlikely
that kynurenate is acting to suppress the release of
end were detected in an in vivo study using nuclear resonance spectroscopy (Roucher et al., 1991). It is also unlikely that kynurenate is acting to suppress the release of endogenous amino acids induced by the imposed insult b spectroscopy (Rouce
that kynurenate is
endogenous amino
because it protects
(Zhu et al., 1989).
One aspect of kyn at kynurenate is acting to suppress the release of dogenous amino acids induced by the imposed insult cause it protects against directly injected quinolinate hu et al., 1989).
One aspect of kynurenate pharmacology that rem endogenous amino acids induced by the imposed insult because it protects against directly injected quinolinate (Zhu et al., 1989).

One aspect of kynurenate pharmacology that remains

to be explained is why it *potentiates*

because it protects against directly injected quinolinate (Zhu et al., 1989).

One aspect of kynurenate pharmacology that remains

to be explained is why it *potentiates* the neurotoxic effect

of ibotenate (Foster et al.,

^{NE}
in some cases, kainate (Winn et al., 1991). This pheno
enon is consistent, to a degree, with the two-recep ending we
in some cases, kainate (Winn et al., 1991). This phenom-
enon is consistent, to a degree, with the two-receptor
hypothesis of Stone and Burton (1988) in which iboten-NE
in some cases, kainate (Winn et al., 1991). This pheno
enon is consistent, to a degree, with the two-recep
hypothesis of Stone and Burton (1988) in which ibote
ate is proposed to act at only one species of NMI in some cases, kainate (Winn et al., 1991). This phenom-
enon is consistent, to a degree, with the two-receptor
hypothesis of Stone and Burton (1988) in which iboten-
ate is proposed to act at only one species of NMDA
rece in some cases, kainate (Winn et al., 1991). This phenom-
enon is consistent, to a degree, with the two-receptor
hypothesis of Stone and Burton (1988) in which iboten-
ate is proposed to act at only one species of NMDA
rece enon is consistent, to a degree, with the two-receptor hypothesis of Stone and Burton (1988) in which ibotenate is proposed to act at only one species of NMDA receptor, but this view does not fully account for the net pote hypothesis of Stone and Burton (1988) in which iboten-
ate is proposed to act at only one species of NMDA
receptor, but this view does not fully account for the net
potentiation seen. It may be necessary to postulate that
 ate is proposed to act at only one species of NMDA receptor, but this view does not fully account for the net potentiation seen. It may be necessary to postulate that the block of receptors on inhibitory neurones by kynu-
 receptor, but this view does not fully account for the net potentiation seen. It may be necessary to postulate that the block of receptors on inhibitory neurones by kynurenate results in a disinhibitory effect sufficient t potentiation seen. It may be necess
the block of receptors on inhibitor
renate results in a disinhibitory ef
hance ibotenate toxicity in the ab
blockade at its excitatory receptor.
The neuroprotective properties e block of receptors on inhibitory neurones by kynu-
nate results in a disinhibitory effect sufficient to en-
nce ibotenate toxicity in the absence of kynurenate
ockade at its excitatory receptor.
The neuroprotective prope

renate results in a disinhibitory effect sufficient to enhance ibotenate toxicity in the absence of kynurenate blockade at its excitatory receptor.
The neuroprotective properties of kynurenate have been put to good use in hance ibotenate toxicity in the absence of kynurenate
blockade at its excitatory receptor.
The neuroprotective properties of kynurenate have
been put to good use in preventing the neurotoxic effects
of the kainate-like tox blockade at its excitatory receptor.
The neuroprotective properties of kynurenate have
been put to good use in preventing the neurotoxic effects
of the kainate-like toxin, domoic acid, present in a batch
of Atlantic mussel The neuroprotective properties of kynurenate have
been put to good use in preventing the neurotoxic effects
of the kainate-like toxin, domoic acid, present in a batch
of Atlantic mussels (Pinsky et al., 1989). The efficacy been put to good use in preve
of the kainate-like toxin, don
of Atlantic mussels (Pinsky
kynurenate was enhanced by
benecid (Bose et al., 1990).
In addition to being cons. the kainate-like toxin, domoic acid, present in a batch
Atlantic mussels (Pinsky et al., 1989). The efficacy of
nurenate was enhanced by the administration of pro-
necid (Bose et al., 1990).
In addition to being consistent

of Atlantic mussels (Pinsky et al., 1989). The efficacy of
kynurenate was enhanced by the administration of pro-
benecid (Bose et al., 1990).
In addition to being consistent with the histological
and neurochemical similari kynurenate was enhanced by the administration of
benecid (Bose et al., 1990).
In addition to being consistent with the histolo
and neurochemical similarities of quinolinate lesions
Huntingtonian degeneration, the relative benecid (Bose et al., 1990).
In addition to being consistent with the histologic
and neurochemical similarities of quinolinate lesions and
Huntingtonian degeneration, the relative overstimul
tion of NMDA receptors secondar In addition to being consistent with the histological
and neurochemical similarities of quinolinate lesions and
Huntingtonian degeneration, the relative overstimula-
tion of NMDA receptors secondary to kynurenate deple-
ti and neurochemical similarities of quinolinate lesions and
Huntingtonian degeneration, the relative overstimula-
tion of NMDA receptors secondary to kynurenate deple-
tion might account for the loss (down-regulation?) of
th Huntingtonian degeneration, the relative overstimulation of NMDA receptors secondary to kynurenate depletion might account for the loss (down-regulation?) of these sites reported by Young et al. (1988). As it has been sugg tion of NMDA receptors secondary to kynurenate deption might account for the loss (down-regulation?) these sites reported by Young et al. (1988). As it holder suggested that subtypes of NMDA receptor mexist that are differ tion might account for the loss (down-regulation?) of these sites reported by Young et al. (1988). As it has been suggested that subtypes of NMDA receptor may exist that are differentially sensitive to NMDA, quinolinic aci these sites reported by Young et al. (1988). As it has been suggested that subtypes of NMDA receptor may exist that are differentially sensitive to NMDA, quino-
linic acid, and kynurenic acid (Stone and Burton, 1988), it m been suggested that subtypes of NMDA receptor
exist that are differentially sensitive to NMDA, qu
linic acid, and kynurenic acid (Stone and Burton, 19
it might also be illuminating to determine whether t
sites are differen ist that are differentially sensitive to NMDA, quino-
ic acid, and kynurenic acid (Stone and Burton, 1988)
might also be illuminating to determine whether these
es are differentially lost in Huntington's disease.
Such poss

linic acid, and kynurenic acid (Stone and Burton, 1988),
it might also be illuminating to determine whether these
sites are differentially lost in Huntington's disease.
Such possibilities leave open the question of why kyn it might also be illuminating to determine whether the
sites are differentially lost in Huntington's disease.
Such possibilities leave open the question of why ky
urenine metabolism should be defective in the first pla
Per sites are differentially lost in Huntington's disease.
Such possibilities leave open the question of why kynurenine metabolism should be defective in the first place.
Perhaps the most obvious possibility would be a dimini-Such possibilities leave open the question of why kyn-
urenine metabolism should be defective in the first place.
Perhaps the most obvious possibility would be a dimin-
ished uptake of tryptophan or L-kynurenine into cells urenine metabolism should be defective in the first
Perhaps the most obvious possibility would be a
ished uptake of tryptophan or L-kynurenine into c
the CNS. The former seems unlikely because the
of 5-hydroxytryptophan, 5 Perhaps the most obvious possibility would be a dimin-
ished uptake of tryptophan or L-kynurenine into cells of
the CNS. The former seems unlikely because the levels
of 5-hydroxytryptophan, 5HT, and 5-hydroxyindole-
acetic ished uptake of tryptophan or L-kynurenine into cells of
the CNS. The former seems unlikely because the levels
of 5-hydroxytryptophan, 5HT, and 5-hydroxyindole-
acetic acid are largely unchanged in Huntington's brains
(Bea the CNS. The former seems unlikely because the levels
of 5-hydroxytryptophan, 5HT, and 5-hydroxyindole-
acetic acid are largely unchanged in Huntington's brains
(Beal et al., 1992b); the latter explanation may be more
like of 5-hydroxytryptophan, 5HT, and 5-hydroxyindole-
acetic acid are largely unchanged in Huntington's brains
(Beal et al., 1992b); the latter explanation may be more
likely because reduced L-kynurenine concentrations were
fo acetic acid are largely unchanged in Huntington's brains
(Beal et al., 1992b); the latter explanation may be more
likely because reduced L-kynurenine concentrations were
found in two regions of the neocortex. Specific enzy (Beal et al., 1992b); the latter explanation may be more likely because reduced L-kynurenine concentrations were found in two regions of the neocortex. Specific enzyme deficiencies remain to be explored for several steps o likely because reduced L-kynurenine concentrations were
found in two regions of the neocortex. Specific enzyme
deficiencies remain to be explored for several steps of
the kynurenine pathway. There is apparently no clear
la found in two regions of the neocortex. Specific enzyme deficiencies remain to be explored for several steps of the kynurenine pathway. There is apparently no clear lack of kynurenine aminotransferase activity in several br deficiencies remain to be explored for several st
the kynurenine pathway. There is apparently no
lack of kynurenine aminotransferase activity in s
brain regions (Beal et al., 1992b), but there seem
no data concerning a pos e kynurenine pathway. There is apparently no clear
ck of kynurenine aminotransferase activity in several
ain regions (Beal et al., 1992b), but there seem to be
data concerning a possible deficiency of IDO.
A novel proposal

lack of kynurenine aminotransferase activity in several
brain regions (Beal et al., 1992b), but there seem to be
no data concerning a possible deficiency of IDO.
A novel proposal has been championed by Beal et al.
(1992b) brain regions (Beal et al., 1992b), but there seem to
no data concerning a possible deficiency of IDO.
A novel proposal has been championed by Beal et
(1992b) that Huntington's disease degeneration n
stem from a fundamenta no data concerning a possible deficiency of IDO.

A novel proposal has been championed by Beal et al.

(1992b) that Huntington's disease degeneration may

stem from a fundamental metabolic defect. This hypoth-

esis is bas A novel proposal has been championed by Beal et (1992b) that Huntington's disease degeneration n
stem from a fundamental metabolic defect. This hypo
esis is based on reports of reduced glucose metaboli
and cytochrome oxida (1992b) that Huntington's disease degeneration may
stem from a fundamental metabolic defect. This hypoth-
esis is based on reports of reduced glucose metabolism
and cytochrome oxidase activity in brain and disturb-
ances o stem from a fundamental metabolic defect. This hypo
esis is based on reports of reduced glucose metaboli
and cytochrome oxidase activity in brain and distu
ances of mitochondrial function in platelets. It was s
gested that esis is based on reports of reduced glucose metabolism
and cytochrome oxidase activity in brain and disturb-
ances of mitochondrial function in platelets. It was sug-
gested that a metabolic defect might enhance the requir and cytochrome oxidase activity in brain and disturbances of mitochondrial function in platelets. It was suggested that a metabolic defect might enhance the requirement for nicotinamide nucleotides, thus diverting L-
kynur ances of mitochondrial function in platelets. It was suggested that a metabolic defect might enhance the requirement for nicotinamide nucleotides, thus diverting I kynurenine away from kynurenate (the concentration c which gested that a metabolic defect might enhance the requirement for nicotinamide nucleotides, thus diverting L-
kynurenine away from kynurenate (the concentration of
which is decreased), through 3HAO (increased) via quin-
oli ment for nicotinamide nucleotides, thus diverting L-
kynurenine away from kynurenate (the concentration of
which is decreased), through 3HAO (increased) via quin-
olinate (decreased) into nicotinamide. This hypothesis
acco kynurenine away from kynurenate (the concentration of which is decreased), through 3HAO (increased) via quin-
olinate (decreased) into nicotinamide. This hypothesis
accounts for some of the experimental observations made
t which is decreased), through 3HAO (increased) via quin-
olinate (decreased) into nicotinamide. This hypothesis
accounts for some of the experimental observations made
to date, but in view of the relative nonspecificity of

QUINOLINIC AND KYNURENIC ACIDS
tive striatal neurone loss in Huntington's disease. It strains, or in QPRT active
carries the added attraction that several metabolic inhib- mality of cerebral 3HAO. QUINOLINIC AFT and the striatal neurone loss in Huntington's disease.
Carries the added attraction that several metabolic inhib-
itors are capable of producing neuronal damage whic QUINOLINIC AND
tive striatal neurone loss in Huntington's disease. It
carries the added attraction that several metabolic inhib-
itors are capable of producing neuronal damage which,
in some cases, bears marked similaritie tive striatal neurone loss in Huntington's disease. It carries the added attraction that several metabolic inhibitiors are capable of producing neuronal damage which, in some cases, bears marked similarities to quinolinate tive striatal neurone loss in Hicarries the added attraction that s
itors are capable of producing no
in some cases, bears marked sim
and human pathological lesions.

E. Seizures

and human pathological lesions. be te

E. Seizures

1. Kynurenine concentrations in seizures. Excitatory creas

amino acid agonists, especially those acting at NMDA Also,

receptors, can produce seizures in animals and, co E. Seizures
1. Kynurenine concentrations in seizures. Excitatory
amino acid agonists, especially those acting at NMDA
receptors, can produce seizures in animals and, con-
versely, NMDA antagonists can effectively prevent s E. Seizures
1. Kynurenine concentrations in seizures. Excitatory
amino acid agonists, especially those acting at NMDA
receptors, can produce seizures in animals and, con-
versely, NMDA antagonists can effectively prevent s 1. Kynurenine concentrations in seizures. Excitated amino acid agonists, especially those acting at NMI receptors, can produce seizures in animals and, coversely, NMDA antagonists can effectively prevent sures initiated by amino acid agonists, especially those acting at NMDA receptors, can produce seizures in animals and, conversely, NMDA antagonists can effectively prevent seizures initiated by electrical shocks, chemical convulsants, or ap receptors, can produce seizures in animals and, con-
versely, NMDA antagonists can effectively prevent sei-
tizures initiated by electrical shocks, chemical convul-
sants, or appropriate handling of genetically mutant
in a versely, NMDA antagonists can effectively prevent seizures initiated by electrical shocks, chemical convulsants, or appropriate handling of genetically mutant is animals. It is, therefore, natural to inquire whether there zures initiated by electrical shocks, chemical convulsants, or appropriate handling of genetically mutan animals. It is, therefore, natural to inquire whether ther is any change in the levels of quinolinate in epileptistat sants, or appropriate handling of genetically mutant incominals. It is, therefore, natural to inquire whether there lis any change in the levels of quinolinate in epileptic act states. Heyes et al. (1990a) found no differe animals. It is, therefore, natural to inquire whether there is any change in the levels of quinolinate in epileptic actates. Heyes et al. (1990a) found no differences in quin-
solinate concentrations in epileptic foci comp is any change in the levels of quinolinate in epileptic activity
states. Heyes et al. (1990a) found no differences in quin-
olinate concentrations in epileptic foci compared with high le
nonspiking regions of temporal neoc states. Heyes et al. (1990a) found no olinate concentrations in epileptic f
nonspiking regions of temporal neoco
time of surgery from human patie
intractable complex partial epilepsy.
A significant decrease (approximat inate concentrations in epileptic foci compared with high
nspiking regions of temporal neocortex removed at the
ne of surgery from human patients suffering from contractable complex partial epilepsy.
A significant decreas

nonspiking regions of temporal neocortex removed at the time of surgery from human patients suffering from c
intractable complex partial epilepsy. α is a significant decrease (approximately 30%) was found g
in the conc time of surgery from human patients suffering from compon
intractable complex partial epilepsy. combin
A significant decrease (approximately 30%) was found gether
in the concentration of quinolinate in epileptic compared c intractable complex partial epilepsy.

A significant decrease (approximately 30%) was found

in the concentration of quinolinate in epileptic compared

with control CSF, whether the samples were taken from

interictal or A significant decrease (approximately 30%) was fournin the concentration of quinolinate in epileptic compare with control CSF, whether the samples were taken from interictal or immediately postictal patients. The decreasin in the concentration of quinolinate in epileptic compared cent
with control CSF, whether the samples were taken from if the
interictal or immediately postictal patients. The decrease et a
in quinolinate is consistent with with control CSF, whether the samples were taken from interictal or immediately postictal patients. The decreasin quinolinate is consistent with that found in an inves tigation by Young et al. (1983) of L-kynurenine levels interictal or immediately postictal patients. The decrease et at in quinolinate is consistent with that found in an inves-
tigation by Young et al. (1983) of L-kynurenine levels in ser
the CSF of epileptic patients with o in quinolinate is consistent with that found in an inves-
tigation by Young et al. (1983) of L-kynurenine levels in
the CSF of epileptic patients with or without drug treat-
ment, in which the levels of this amine were fo the CSF of epileptic patients with or without drug treat-
ment, in which the levels of this amine were found to be
consistently decreased. The concentration in epileptic
patients not currently receiving medication was 5.2 the CSF of epileptic patients with or without drug treat-
ment, in which the levels of this amine were found to be
consistently decreased. The concentration in epileptic
patients not currently receiving medication was 5.2 ment, in which the levels of this amine were found to consistently decreased. The concentration in epilep
patients not currently receiving medication was 5.2 co
pared with 9.13 ng/ml, suggesting that the loss of
kynurenin consistently decreased. The concentration in epileptic
patients not currently receiving medication was 5.2 com-
pared with 9.13 ng/ml, suggesting that the loss of L-
kynurenine, and thus possibly of quinolinate, is a disea patients not currently recepared with 9.13 ng/ml, s
kynurenine, and thus poss
related phenomenon not s
tiepileptic drug treatment
Not only is this result

kynurenine, and thus possibly of quinolinate, is a disease-
related phenomenon not secondary to the effects of an-
tiepileptic drug treatment.
Not only is this result contrary to that expected if
quinolinate was implicated related phenomenon not secondary to the effects of an-
tiepileptic drug treatment.
Not only is this result contrary to that expected if
quinolinate was implicated in the initiation of seizures
but it is also contrary to th tiepileptic drug treatment. (
Not only is this result contrary to that expected if
quinolinate was implicated in the initiation of seizures
but it is also contrary to that predicted by an earlier
study in which Feldblum et Not only is this result contrary to that expected if c
quinolinate was implicated in the initiation of seizures the but it is also contrary to that predicted by an earlier fe
study in which Feldblum et al. (1988) claimed a quinolinate was implicated in the initiation of seizures
but it is also contrary to that predicted by an earlier
study in which Feldblum et al. (1988) claimed a decrease
in the activity of the quinolinate-metabolising enzy but it is also contrary to that predicted by an earlier
study in which Feldblum et al. (1988) claimed a decrease
in the activity of the quinolinate-metabolising enzyme
QPRT. Activity of this enzyme was significantly lower
 study in which Feldblum et al. (1988) claimed a decrease in the activity of the quinolinate-metabolising enzy
QPRT. Activity of this enzyme was significantly low
in epileptogenic zones of the brain than in nonepile
tissue in the activity of the quinolinate-metabolising enzy
QPRT. Activity of this enzyme was significantly love
in epileptogenic zones of the brain than in nonepilep
tissue taken from either the same patients or nonepile
tic sub QPRT. Activity of this enzyme was significantly lower
in epileptogenic zones of the brain than in nonepileptic
tissue taken from either the same patients or nonepilep-
tic subjects (thus eliminating any effect of drug medi in epileptogenic zones of
tissue taken from either
tic subjects (thus elimin
tion). The loss of enzyn
and temporal neocortex.
An examination of 3 sue taken from either the same patients or nonepilep-

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1992) who compared activity in epileptic mice

1992) who compared activity in epileptic mice

1992) who compared activity in epileptic mice

tic subjects (thus eliminating any effect of drug medica-
tion). The loss of enzyme was up to 90% in the frontal
and temporal neocortex.
An examination of 3HAO activity in epileptic mice
was conducted by Nakano et al. (199 tion). The loss of enzyme was up to 90% in the frontal
and temporal neocortex.
An examination of 3HAO activity in epileptic mice
was conducted by Nakano et al. (1992) who compared
the inbred E1 strain of animals, which con extinct and temporal neocortex. The air of 3HAO activity in epileptic mice I
was conducted by Nakano et al. (1992) who compared act
the inbred E1 strain of animals, which convulse after it h
being tossed into the air, with An examination of 3HAO activity in epileptic mice
was conducted by Nakano et al. (1992) who compare
the inbred E1 strain of animals, which convulse afte
being tossed into the air, with the parent ddY strain and
two unrelat was conducted by Nakano et al. (1992) who compared active interpret in the inbred E1 strain of animals, which convulse after it being tossed into the air, with the parent ddY strain and [w two unrelated strains, BALB/cA an the inbred E1 strain of animals, which convulse afted being tossed into the air, with the parent ddY strain an two unrelated strains, BALB/cA and C3H/HeN Whereas the 3HAO activity was not detectable in the brains of the la two unrelated strains, BALB/cA and C3H/HeN.
Whereas the 3HAO activity was not detectable in the
brains of the latter strains, the enzyme was clearly pres-
ent in ddY animals and was present in approximately
17-fold higher two unrelated strains, BALB/cA and C3H/HeN. 1984
Whereas the 3HAO activity was not detectable in the fluni
brains of the latter strains, the enzyme was clearly pres-
provident in ddY animals and was present in approximate Whereas the 3HAO activity was not detectable in the flur
brains of the latter strains, the enzyme was clearly pres-
ent in ddY animals and was present in approximately cep
17-fold higher activity in brains of the seizurebrains of the latter strains, the enzyme was clearly present in ddY animals and was present in approximately 17-fold higher activity in brains of the seizure-prone strain. Interestingly, no difference could be demonstrated

STRIF STRING ACIDS
Strains, or in QPRT activity, implying a specific abnor-YNURENIC ACIDS
strains, or in QPRT activi
mality of cerebral 3HAO.
The tentative conclusion

in some cases, bears marked similarities to quinolinate of quinolinate may be involved in E1 seizures needs to
and human pathological lesions.
E. Seizures
E. Seizures
1. Kynurenine concentrations in seizures. Excitat 357

Trains, or in QPRT activity, implying a specific abnor-

ality of cerebral 3HAO.

The tentative conclusion that an enhanced synthesis

quinolinate may be involved in E1 seizures needs to strains, or in QPRT activity, implying a specific abnormality of cerebral 3HAO.
The tentative conclusion that an enhanced synthesis
of quinolinate may be involved in E1 seizures needs to
be tempered by the observation that strains, or in QPRT activity, implying a specific abnormality of cerebral 3HAO.
The tentative conclusion that an enhanced synthesis
of quinolinate may be involved in E1 seizures needs to
be tempered by the observation that mality of cerebral 3HAO.
The tentative conclusion that an enhanced synthesis
of quinolinate may be involved in E1 seizures needs to
be tempered by the observation that 3HAO activity is
already high by 6 weeks of age, befor The tentative conclusion that an enhanced synthesis
of quinolinate may be involved in E1 seizures needs to
be tempered by the observation that 3HAO activity is
already high by 6 weeks of age, before the mice are
susceptibl of quinolinate may be involved in E1 seizures needs to
be tempered by the observation that 3HAO activity is
already high by 6 weeks of age, before the mice are
susceptible to seizure induction, and the activity in-
creases be tempered by the observation that 3HAO activity is already high by 6 weeks of age, before the mice are susceptible to seizure induction, and the activity increases only an additional 2-fold up to 7 months of age. Also, i already high by 6 weeks of age, before the mice
susceptible to seizure induction, and the activity
creases only an additional 2-fold up to 7 months of
Also, it is likely that 3HAO is not normally saturate
its substrates be susceptible to seizure induction, and the activity
creases only an additional 2-fold up to 7 months of :
Also, it is likely that 3HAO is not normally saturated
its substrates because, as described before, adminis
tion of 3 Also, it is likely that 3HAO is not normally saturated by
its substrates because, as described before, administra-
tion of 3-hydroxyanthranilic acid can elevate substan-
tially the brain levels of metabolically distal kynu including quinolinate (Speciale et al. 1989a,b).

tion of 3-hydroxyanthranilic acid can elevate substantially the brain levels of metabolically distal kynurenines
including quinolinate (Speciale et al. 1989a,b).
It is not clear, therefore, whether an increased 3HAO
activi tially the brain levels of metabolically distal kynurenines
including quinolinate (Speciale et al. 1989a,b).
It is not clear, therefore, whether an increased 3HAO
activity would, in fact, increase quinolinate levels, but
S including quinolinate (Speciale et al. 1989a,b).
It is not clear, therefore, whether an increased 3HAO
activity would, in fact, increase quinolinate levels, but
Suzuki and Mori (1992) have now reported abnormally
high leve It is not clear, therefore, whether an increased 3HAO
activity would, in fact, increase quinolinate levels, but
Suzuki and Mori (1992) have now reported abnormally
high levels of L-kynurenine in E1 mouse brain, raising
the activity would, in fact, increase quinolinate levels, but
Suzuki and Mori (1992) have now reported abnormally
high levels of L-kynurenine in E1 mouse brain, raising
the possibility that 3-hydroxyanthranilate or another
com Suzuki and Mori (1992) have now reported abnormally
high levels of L-kynurenine in E1 mouse brain, raising
the possibility that 3-hydroxyanthranilate or another
component of the pathway may also be elevated. The
combinatio high levels of L-kynurenine in E1 mouse brain, raising
the possibility that 3-hydroxyanthranilate or another
component of the pathway may also be elevated. The
combination of increased 3HAO and its substrate to-
gether cou the possibility that 3-hydroxyanthranilate or another component of the pathway may also be elevated. The combination of increased 3HAO and its substrate together could certainly lead to elevated quinolinate concentrations, component of the pathway may also be elevated. The

combination of increased 3HAO and its substrate to-

gether could certainly lead to elevated quinolinate con-

centrations, an effect that might be further potentiated
 combination of increased 3HAO and its substrate to-
gether could certainly lead to elevated quinolinate con-
centrations, an effect that might be further potentiated
if the dramatic loss of human QPRT seen by Feldblum
et a

centrations, an effect that might be further potentiated
if the dramatic loss of human QPRT seen by Feldblum
et al. (1988) also occurs in the mice.
2. Kynurenines and seizure induction. As well as ob-
serving correlations if the dramatic loss of humari QPRT seen by Feldblum
et al. (1988) also occurs in the mice.
2. Kynurenines and seizure induction. As well as ob-
serving correlations between changes of kynurenine me-
tabolism and seizures, et al. (1988) also occurs in the mice.
2. Kynurenines and seizure induction. As well as observing correlations between changes of kynurenine me-
tabolism and seizures, several groups have examined the
influence of kynureni 2. Kynurenines and seizure induction. As well as observing correlations between changes of kynurenine metabolism and seizures, several groups have examined the influence of kynurenines on seizure activity. Much of the earl 1989). bolism and seizures, several groups have examined the
fluence of kynurenines on seizure activity. Much of the
rly work in this area was summarised by Lapin (1981
89).
When administered to rats before the full developmen
th

kynurenine, and thus possibly of quinolinate, is a disease-
related phenomenon not secondary to the effects of an-
related phenomenon not secondary to the effects of an-
tiepileptic drug treatment.
(Lapin, 1978b, 1989). Qu activity would, in fact, increase quinolinate levels, but
Sizuki and Mori (1992) have now reported abnormally
high levels of L-kynurenine in E1 mouse brain, raising
the possibility that 3-hydroxyanthramilate or another
com influence of kynurenines on seizure activity. Much of the
early work in this area was summarised by Lapin (1981,
1989).
When administered to rats before the full development
of the blood-brain barrier, a number of kynureni early work in this area was summarised by Lapin (1981, 1989).
1989).
When administered to rats before the full development
of the blood-brain barrier, a number of kynurenines are
able to produce convulsions after systemic 1989).
When administered to rats before the full development
of the blood-brain barrier, a number of kynurenines are
able to produce convulsions after systemic injections
(Lapin, 1978b, 1989). Quinolinic acid is the most a When administered to rats before the full development of the blood-brain barrier, a number of kynurenines and able to produce convulsions after systemic injection (Lapin, 1978b, 1989). Quinolinic acid is the most active co of the blood-brain barrier, a number of kynurenines are able to produce convulsions after systemic injections (Lapin, 1978b, 1989). Quinolinic acid is the most active compound. Seizures are also produced after the icv inje able to produce convulsions after systemic injections (Lapin, 1978b, 1989). Quinolinic acid is the most active compound. Seizures are also produced after the icv injection of these compounds, quinolinate being at least 10fold more active than L-kynurenine in this respect (Lapin, 1981a; Schwarcz et al., 1984b; Vezzani et al., 1986, 1988, 1989a,b; Wu et al., 1987). Paradoxically, the compound. Seizures are also produced after the icv injection of these compounds, quinolinate being at least 10-
fold more active than L-kynurenine in this respect
(Lapin, 1981a; Schwarcz et al., 1984b; Vezzani et al.,
1986 tion of these compounds, quinolinate being at least 10-
fold more active than L-kynurenine in this respect
(Lapin, 1981a; Schwarcz et al., 1984b; Vezzani et al.,
1986, 1988, 1989a,b; Wu et al., 1987). Paradoxically, the
in fold more active than L-kynurenine in this respect (Lapin, 1981a; Schwarcz et al., 1984b; Vezzani et al., 1986, 1989, 1989a, b; Wu et al., 1987). Paradoxically, the intraperitoneal injection of quinolinate or L-kynurenine (Lapin, 1981a; Schwarcz et al., 1984b; Vezzani et al., 1986, 1988, 1989a,b; Wu et al., 1987). Paradoxically, the intraperitoneal injection of quinolinate or L-kynurenine in adult animals has anticonvulsant effects (Lapin, 1986, 1988, 1989a,b; Wu et al., 1987). Paradoxically, the interpretioneal injection of quinolinate or L-kynurenine adult animals has anticonvulsant effects (Lapin, 19
1989). There is no accepted explanation for this, altho in adult animals has anticonvulsant effects (Lapin, 1980, 1989). There is no accepted explanation for this, although it may reflect changes of peripheral kynurenine metabolism resulting in secondary changes of cerebral kyn renines. 89). There is no accepted explanation for this, although
may reflect changes of peripheral kynurenine metab-
ism resulting in secondary changes of cerebral kynu-
nines.
It is likely that the epileptogenic activity is due t

it may reflect changes of peripheral kynurenine metab-
olism resulting in secondary changes of cerebral kynu-
renines.
It is likely that the epileptogenic activity is due to the
activation of NMDA receptors by quinolinate, olism resulting in secondary changes of cerebral kynu-
renines.
It is likely that the epileptogenic activity is due to the
activation of NMDA receptors by quinolinate, although
it has also been shown that quinolinate and L renines.
It is likely that the epileptogenic activity is due to the
activation of NMDA receptors by quinolinate, although
it has also been shown that quinolinate and L-kynurenine
[which also induces seizures (Lapin, 1989; It is likely that the epileptogenic activity is due to the
activation of NMDA receptors by quinolinate, although
it has also been shown that quinolinate and L-kynurenine
[which also induces seizures (Lapin, 1989; Pinelli e activation of NMDA receptors by quinolinate, although
it has also been shown that quinolinate and L-kynurenine
[which also induces seizures (Lapin, 1989; Pinelli et al.,
1984)] can antagonise the pentobarbitone stimulation it has also been shown that quinolinate and L-kynurenine [which also induces seizures (Lapin, 1989; Pinelli et al., 1984)] can antagonise the pentobarbitone stimulation of flunitrazepam binding in rat forebrain. This effec [which also induces seizures (Lapin, 1989; Pinelli et a
1984)] can antagonise the pentobarbitone stimulation of
flunitrazepam binding in rat forebrain. This effect in
volves a reduction of affinity of the benzodiazepine r 1984)] can antagonise the pentobarbitone stimulation of flunitrazepam binding in rat forebrain. This effect involves a reduction of affinity of the benzodiazepine receptor and is apparent at relatively low concentration: flunitrazepam binding in 1
volves a reduction of affin
ceptor and is apparent at
L-kynurenine shows an IC₆
31 μ M (Zarkovsky, 1986).
Doses as little as 3 nmo lves a reduction of affinity of the benzodiazepine re-
ptor and is apparent at relatively low concentration:
kynurenine shows an IC₅₀ of 36 μ M and quinolinate of
 μ M (Zarkovsky, 1986).
Doses as little as 3 nmol qui

abled to the rat hippocampus of unanaesthetised rats and rectly into the rat hippocampus of unanaesthetised rats are were able to produce electroencephalographic signs of and 358
rectly into the rat hippocampus of unanaesthetised rats
were able to produce electroencephalographic signs of z
seizure activity (Schwarcz et al., 1984b; Foster et al., fi strom and the rat hippocampus of unanaesthetised rats
were able to produce electroencephalographic signs of
seizure activity (Schwarcz et al., 1984b; Foster et al.,
1984b; Lapin, 1989). Above this level, dose-related perectly into the rat hippocampus of unanaesthetised rats
were able to produce electroencephalographic signs of
seizure activity (Schwarcz et al., 1984b; Foster et al.,
1984b; Lapin, 1989). Above this level, dose-related perectly into the rat hippocampus of unanaesthetised rats rowere able to produce electroencephalographic signs of zseizure activity (Schwarcz et al., 1984b; Foster et al., filesting lasting between approduce of electroenceph were able to produce electroencephalographic signs
seizure activity (Schwarcz et al., 1984b; Foster et
1984b; Lapin, 1989). Above this level, dose-related
riods of electroencephalographic spiking lasting betwe
20 and 60 se seizure activity (Schwarcz et al., 1984b; Foster et al., find 1984b; Lapin, 1989). Above this level, dose-related pe-
riods of electroencephalographic spiking lasting between clou
20 and 60 seconds were noted, together wit 1984b; Lapin, 1989). Above this level, dose-related pe-
riods of electroencephalographic spiking lasting between
20 and 60 seconds were noted, together with an increas-
ing severity of overt seizure behaviour. Initial wet 20 and 60 seconds were noted, together with an increas-
ing severity of overt seizure behaviour. Initial wet dog
shakes and enhanced locomotor activity were followed
why stereotypies and, subsequently, seizures. The seizu ing severity of overt seizure behaviour. Initial wet dog d
shakes and enhanced locomotor activity were followed w
by stereotypies and, subsequently, seizures. The seizures q
induced by 120 nmol quinolinic acid, which produ by stereotypies and, subsequently, seizures. The seizures induced by 120 nmol quinolinic acid, which produced seizures without any accompanying signs of ataxia or other locomotor changes, were prevented by pretreat-ment wi induced by 120 nmol quinolinic acid, which produced
seizures without any accompanying signs of ataxia or
other locomotor changes, were prevented by pretreat-
ment with the NMDA antagonist, 2AP7, also injected
into the hipp seizures without any accompanying signs of ataxia or other locomotor changes, were prevented by pretreatment with the NMDA antagonist, 2AP7, also injected into the hippocampus. This investigation concluded that quinolinic other locomotor changes, were prevented by pretreat-
ment with the NMDA antagonist, 2AP7, also injected
into the hippocampus. This investigation concluded that
quinolinic acid is the most potent endogenous convulsant
compo ment with the NMDA antagonist, 2AP7, also injected but
into the hippocampus. This investigation concluded that bloco
quinolinic acid is the most potent endogenous convulsant or n
compound to be described. The long latency into the hippocampus. This investigation concluded that
quinolinic acid is the most potent endogenous convulsant
compound to be described. The long latency of the sei-
zures observed by Schwarcz et al. (1984b) of between 1 quinolinic acid is the most potent endogenous convulsant
compound to be described. The long latency of the sei-
zures observed by Schwarcz et al. (1984b) of between 19
and 32 minutes was felt to be explicable on the basis compound to be described. The long latency of the sei-
zures observed by Schwarcz et al. (1984b) of between 19
and 32 minutes was felt to be explicable on the basis that
an endogenous agent needs to be released by quinolin zures observed by Schwarcz et al. (1984b) of between 19 and 32 minutes was felt to be explicable on the basis that an endogenous agent needs to be released by quinolinic acid or that protective mechanisms need to be exhaus and 32 minutes was felt to be explicable on the basis that
an endogenous agent needs to be released by quinolinic
acid or that protective mechanisms need to be exhausted
before a seizure can be initiated. However, the shor an endogenous agent needs to be released by quinolinic
acid or that protective mechanisms need to be exhausted
before a seizure can be initiated. However, the short
latencies of 2 to 3 minutes after icv administration re-
 before a seizure can be initiated. However, the short the latencies of 2 to 3 minutes after icv administration re-
ported by Lapin's group argue against these possibilities mand in favour of the view that quinolinic acid n latencies of 2 to 3 minutes after icv administration reported by Lapin's group argue against these possibilities and in favour of the view that quinolinic acid needs to gain access to a local region of brain distant from t rted by Lapin's group argue against these possibilities in favour of the view that quinolinic acid needs in access to a local region of brain distant from the ppocampus, possibly the striatum, to induce seizures Whatever t and in favour of the view that quinolinic acid needs to gain access to a local region of brain distant from the hippocampus, possibly the striatum, to induce seizures.
Whatever the mechanisms, quinolinate-induced electrogr

gain access to a local region of brain distant from the hippocampus, possibly the striatum, to induce seizures.
Whatever the mechanisms, quinolinate-induced electrographic seizures can be prevented by a range of anti-convu hippocampus, possibly the striatum, to induce seizures.
Whatever the mechanisms, quinolinate-induced electrographic seizures can be prevented by a range of anti-
convulsant drugs used to treat human grand mal epilepsy,
inc Whatever the mechanisms, quinolinate-induced electrographic seizures can be prevented by a range of anti-
convulsant drugs used to treat human grand mal epilepsy,
including carbamazepine, phenobarbitone, valproate, di-
aze convulsant drugs used to treat human grand mal epilepsy,
including carbamazepine, phenobarbitone, valproate, di-
azepam, and, at high dosage, phenytoin (Vezzani et al.,
1986); none of these anticonvulsants prevented the ne including carbamazepine, phenobarbitone, valproate, di-
azepam, and, at high dosage, phenytoin (Vezzani et al.,
1986); none of these anticonvulsants prevented the neu-
rotoxic effects of quinolinate, indicating an importan including carbamazepine, phenobarbitone, valproate, di-
azepam, and, at high dosage, phenytoin (Vezzani et al.,
1986); none of these anticonvulsants prevented the neu-
rotoxic effects of quinolinate, indicating an importan azepam, and, at high dosage, phenytoin (Vezzani et al., re
1986); none of these anticonvulsants prevented the neu-
rotoxic effects of quinolinate, indicating an important enchanistic difference between seizures and toxicit 1986); none of these anticonvulsants prevented the n
rotoxic effects of quinolinate, indicating an import
mechanistic difference between seizures and toxic
Confirmation of this interesting distinction was achiev
subsequent rotoxic effects of quinolinate, indicating an import
mechanistic difference between seizures and toxic
Confirmation of this interesting distinction was achie
subsequently by measuring changes of calcium conc
tration in hip mechanistic difference between seizures and toxicity.
Confirmation of this interesting distinction was achieved
subsequently by measuring changes of calcium concen-
tration in hippocampal extracellular fluid by microdi-
al Confirmation of this interesting distinction was achies
subsequently by measuring changes of calcium con
tration in hippocampal extracellular fluid by micr
alysis (Vezzani et al., 1988). Quinolinate, at convuls
doses, indu subsequently by measuring changes of calcium concentration in hippocampal extracellular fluid by microdialysis (Vezzani et al., 1988). Quinolinate, at convulsant doses, induced a 2AP7-sensitive reduction of extracellular c tration in hippocampal extracellular fluid by microdialysis (Vezzani et al., 1988). Quinolinate, at convulsant doses, induced a 2AP7-sensitive reduction of extracellular calcium, an effect prevented by anticonvulsant drugs alysis (Vezzani et al
doses, induced a 2AI
lar calcium, an effect
As in the previous
prevent neurotoxicit
The seizure-promo ses, induced a 2AP7-sensitive reduction of extracellu-

r calcium, an effect prevented by anticonvulsant drugs. the

i in the previous study, these same drugs did not effect

event neurotoxicity.

The seizure-promoting act

lar calcium, an effect prevented by anticonvulsant drugs. the interprevent neurotoxicity. The seizure-promoting activity of quinolinic acid and the micotinic acid was indicated by their ability to diminish title latency to As in the previous study, these same drugs did no
prevent neurotoxicity.
The seizure-promoting activity of quinolinic acid an
incotinic acid was indicated by their ability to diminis
the latency to seizures induced by subc prevent neurotoxicity.
The seizure-promoting activity of quinolinic acid and
nicotinic acid was indicated by their ability to diminish
the latency to seizures induced by subcutaneous injec-
tions of nicotine. A number of a The seizure-promoting activity of quinolinic acid anicotinic acid was indicated by their ability to diminis
the latency to seizures induced by subcutaneous inje
tions of nicotine. A number of anticholinergic drug
including nicotinic acid was indicated by their ability to diminish
the latency to seizures induced by subcutaneous injec-
tions of nicotine. A number of anticholinergic drugs,
including atropine, scopolamine, benactyzine, and chlor the latency to seizures induced by subcutaneous injections of nicotine. A number of anticholinergic drugs, without including atropine, scopolamine, benactyzine, and chlor-conductyzine, were able to block seizures due to mu tions of nicotine. A number of anticholinergic dru
including atropine, scopolamine, benactyzine, and chla
actyzine, were able to block seizures due to muscarii
or nicotinic agonists without affecting seizures induc
by quin cluding atropine, scopolamine, benactyzine, and cl
tyzine, were able to block seizures due to musca
nicotinic agonists without affecting seizures ind
quinolinate or L-kynurenine (Lapin, 1972, 1989).
Catecholamines, includi

actyzine, were able to block seizures due to musca
or nicotinic agonists without affecting seizures ind
by quinolinate or L-kynurenine (Lapin, 1972, 1989)
Catecholamines, including dopamine and noradl
line injected icv, bl or nicotinic agonists without affecting seizures induced
by quinolinate or L-kynurenine (Lapin, 1972, 1989).
Catecholamines, including dopamine and noradrena-
line injected icv, block L-kynurenine- and quinolinate-
induced by quinolinate or L-kynurenine (Lapin, 1972, 1989).
Catecholamines, including dopamine and noradrer
line injected icv, block L-kynurenine- and quinolina
induced seizures in mice. Vezzani and Schwarcz (198
noted a reduction Catecholamines, including dopamine and noradrena-
line injected icv, block L-kynurenine- and quinolinate-
induced seizures in mice. Vezzani and Schwarcz (1985) (C
noted a reduction of noradrenaline levels in the hippo-
cam line injected icv, block L-kynurenine- and quinolinate-
induced seizures in mice. Vezzani and Schwarcz (1985) (C
noted a reduction of noradrenaline levels in the hippo-
campus of rats at the time of seizure and in a later

riods of electroencephalographic spiking lasting between clonidine enhanced the seizures, suggesting that α_2 -adre-
20 and 60 seconds were noted, together with an increas-
increasing severity of overt seizure behaviour seizures without any accompanying signs of ataxia or zures (Lapin, 1989). Interestingly, 5HTP and 5-meth-
other locomotor changes, were prevented by pretreat-
ment with the NMDA antagonist, 2AP7, also injected but not by q rones by 6-hydroxydopamine facilitated quinolinate sei-NE
rones by 6-hydroxydopamine facilitated quinolinate seizures (Wu et al., 1987; Lapin and Ryzov, 1990). This
finding was supported by showing that α_1 -adrenoceptor Finding by 6-hydroxydopamine facilitated quinolinate sequences (Wu et al., 1987; Lapin and Ryzov, 1990). This finding was supported by showing that α_1 -adrenoceptor agonists antagonised quinolinate seizures; low doses rones by 6-hydroxydopamine facilitated quinolinate seizures (Wu et al., 1987; Lapin and Ryzov, 1990). This finding was supported by showing that α_1 -adrenoceptor agonists antagonised quinolinate seizures; low doses of zures (Wu et al., 1987; Lapin and Ryzov, 1990). This finding was supported by showing that α_1 -adrenoceptor agonists antagonised quinolinate seizures; low doses of zures (Wu et al., 1987; Lapin and Ryzov, 1990). This
finding was supported by showing that α_1 -adrenoceptor
agonists antagonised quinolinate seizures; low doses of
clonidine enhanced the seizures, suggesting that α_2 finding was supported by showing that α_1 -adrenoceptor agonists antagonised quinolinate seizures; low doses of clonidine enhanced the seizures, suggesting that α_2 -adrenoceptors might facilitate the convulsions. The agonists antagonised quinolinate seizures; low doses of clonidine enhanced the seizures, suggesting that α_2 -adre-noceptors might facilitate the convulsions. The effect of dopamine was prevented by haloperidol which, t clonidine enhanced the seizures, suggesting that α_2 -anceptors might facilitate the convulsions. The effection and represented by haloperidol which, toget with other neuroleptics, enhanced the L-kynurenine quinolinate noceptors might facilitate the convulsions. The effect of dopamine was prevented by haloperidol which, together with other neuroleptics, enhanced the L-kynurenine and quinolinate seizures (Lapin and Ryzov, 1990). Propranol dopamine was prevented by haloperidol which, toget
with other neuroleptics, enhanced the L-kynurenine a
quinolinate seizures (Lapin and Ryzov, 1990). Propr
olol and pindolol were also effective in suppressing a
zures (Lapi with other neuroleptics, enhanced the L-kynurenine and
quinolinate seizures (Lapin and Ryzov, 1990). Propran-
olol and pindolol were also effective in suppressing sei-
zures (Lapin, 1989). Interestingly, 5HTP and 5-meth-
o quinolinate seizures (Lapin and Ryzov, 1990). Propran-
olol and pindolol were also effective in suppressing sei-
zures (Lapin, 1989). Interestingly, 5HTP and 5-meth-
oxytryptamine reduced seizures induced by L-kynurenine
b olol and pindolol were also effective in suppressing s
zures (Lapin, 1989). Interestingly, 5HTP and 5-me
oxytryptamine reduced seizures induced by L-kynuren
but not by quinolinic acid in mice. Conversely, lesions
blockade zures (Lapin, 1989). Interestingly, 5HTP and 5-metoxytryptamine reduced seizures induced by L-kynureni
but not by quinolinic acid in mice. Conversely, lesions
blockade of 5HT neurones by 5,6-dihydroxytryptami
or metergolin oxytryptamine reduced seizures induced by L-kynurent but not by quinolinic acid in mice. Conversely, le blockade of 5HT neurones by 5,6-dihydroxytry or metergoline enhanced the convulsant effect o linic acid but not L-kynu it not by quinolinic acid in mice. Conversely, lesions
ockade of 5HT neurones by 5,6-dihydroxytryptami
metergoline enhanced the convulsant effect of quir
nic acid but not L-kynurenine (Lapin, 1981a).
Seizures represent one

before a seizure can be initiated. However, the short the convulsions were not affected. Because little quino-
latencies of 2 to 3 minutes after icv administration re-
linate passes across the blood-brain barrier, this act blockade of 5HT neurones by 5,6-dihydroxytryptamine
or metergoline enhanced the convulsant effect of quino-
linic acid but not L-kynurenine (Lapin, 1981a).
Seizures represent one of the most dangerous conse-
quences of th or metergoline enhanced the convulsant effect of quino-
linic acid but not L-kynurenine (Lapin, 1981a).
Seizures represent one of the most dangerous conse-
quences of the high-pressure neurological syndrome in
divers. Both linic acid but not L-kynurenine (Lapin, 1981a).
Seizures represent one of the most dangerous consequences of the high-pressure neurological syndrome in
divers. Both quinolinate and L-kynurenine reduced the
onset pressures Seizures represent one of the most dangerous consequences of the high-pressure neurological syndrome in quences of the high-pressure neurological syndrome in divers. Both quinolinate and L-kynurenine reduced the onset pressures required for tremor initiation, although the convulsions were not affected. Because little quinoli onset pressures required for tremor initiation, although onset pressures required for tremor initiation, although
the convulsions were not affected. Because little quino-
linate passes across the blood-brain barrier, this activity
may reflect a greater peripheral action of these the convulsions were not affected. Because little quino-
linate passes across the blood-brain barrier, this activity
may reflect a greater peripheral action of these agents
on acute liver function and glycolysis than on ce linate passes across the blood-brain barrier, this activity
may reflect a greater peripheral action of these agents
on acute liver function and glycolysis than on central
excitation at the doses used (Wardley-Smith et al., may reflect a greater peripheral action of these agents
on acute liver function and glycolysis than on central
excitation at the doses used (Wardley-Smith et al., 1989).
It has been reported that the pressures needed for t on acute liver function and glycolysis than on central excitation at the doses used (Wardley-Smith et al., 1989).
It has been reported that the pressures needed for the induction of seizures in rats are increased after tre excitation at the doses used (Wardley-Smith et al., 1989).
It has been reported that the pressures needed for the
induction of seizures in rats are increased after treatment
with excitatory amino acid antagonists (Meldrum It has been reported that the pressures needed for the
induction of seizures in rats are increased after treatment
with excitatory amino acid antagonists (Meldrum et al.,
1983). Kynurenic acid, also injected peripherally a induction of seizures in rats are increased after treatment
with excitatory amino acid antagonists (Meldrum et al.,
1983). Kynurenic acid, also injected peripherally at a
dose of 100 mg/kg, was claimed to achieve a similar 1983). Kynurenic acid, also injected peripherally at a dose of 100 mg/kg , was claimed to achieve a similar reduction of high-pressure seizure sensitivity.
a. KYNURENIC ACID. Kynurenic acid is a far more effective inhibi

dose of 100 mg/kg, was claimed to achieve a similar reduction of high-pressure seizure sensitivity.
a. KYNURENIC ACID. Kynurenic acid is a far more effective inhibitor of sound-induced seizures in DBA/2 mice than of NMDLAreduction of high-pressure seizure sensitivity.

a. KYNURENIC ACID. Kynurenic acid is a far more

effective inhibitor of sound-induced seizures in DBA/2

mice than of NMDLA-induced seizures (Chiamulera et

al., 1990), the a. KYNURENIC ACID. Kynurenic acid is a far more

effective inhibitor of sound-induced seizures in DBA/2

mice than of NMDLA-induced seizures (Chiamulera et

al., 1990), the ED₅₀ of kynurenate for the former being

only effective inhibitor of sound-induced seizures in DBA/2 mice than of NMDLA-induced seizures (Chiamulera et al., 1990), the ED₅₀ of kynurenate for the former being only 3.8 μ g per mouse as against 25 μ g against NMDL mice than of NMDLA-induced seizures (Chiamulera et al., 1990), the ED₅₀ of kynurenate for the former being only 3.8 μ g per mouse as against 25 μ g against NMDLA seizures. Nevertheless, in this model, too, D-serine al., 1990), the ED₅₀ of kynurenate for the former being
only 3.8 μ g per mouse as against 25 μ g against NMDLA
seizures. Nevertheless, in this model, too, D-serine could
reverse the anticonvulsant effect of kynureni only 3.8 μ g per mouse as against 25 μ g against NMDLA
seizures. Nevertheless, in this model, too, D-serine could
reverse the anticonvulsant effect of kynurenic acid. 7-
Chlorokynurenic acid appears to be more selecti seizures. Nevertheless, in this model, too, D-serine could
reverse the anticonvulsant effect of kynurenic acid. 7-
Chlorokynurenic acid appears to be more selective for
the sound-induced seizures in DBA/2 mice, being an
e reverse the anticonvulsant effect of kynurenic acid
Chlorokynurenic acid appears to be more selective
the sound-induced seizures in DBA/2 mice, being
effective antagonist at a dose of 10μ g per animal, w
had no effect o Chlorokynurenic acid appears to be more selective for
the sound-induced seizures in DBA/2 mice, being an
effective antagonist at a dose of 10 μ g per animal, which
had no effect on NMDLA-induced seizures. Coadminis-
tra the sound-induced seizures in DBA/2 mice, being
effective antagonist at a dose of 10 μ g per animal, wh
had no effect on NMDLA-induced seizures. Coadmin
tration of D-serine at 10 to 100 μ g per mouse, i.e., 5 to
times effective antagonist at a dose of 10 μ g per animal, which
had no effect on NMDLA-induced seizures. Coadminis-
tration of D-serine at 10 to 100 μ g per mouse, i.e., 5 to 50
times the ED₅₀ of kynurenate, could revers had no effect on NMDLA-induced seizures. Coadminis
tration of D-serine at 10 to 100 μ g per mouse, i.e., 5 to 5
times the ED₅₀ of kynurenate, could reverse the anticon
vulsant activity. Supporting the specificity of t times the ED_{50} of kynurenate, could reverse the anticonvulsant activity. Supporting the specificity of this action was the finding that D-serine did not reverse the anticonvulsant action of diazepam. mes the ED_{50} of kynurenate, could reverse the anticon-
ilsant activity. Supporting the specificity of this action
as the finding that D-serine did not reverse the anti-
nvulsant action of diazepam.
The injection of 7-c

vulsant activity. Supporting the specificity of this action
was the finding that D-serine did not reverse the anti-
convulsant action of diazepam.
The injection of 7-chlorokynurenic acid through an
indwelling cannula into was the finding that D-serine did not reverse the anti-
convulsant action of diazepam.
The injection of 7-chlorokynurenic acid through an
indwelling cannula into the basolateral amygdala of rats
was found to delay substant convulsant action of diazepam.

The injection of 7-chlorokynurenic acid through an

indwelling cannula into the basolateral amygdala of rats

was found to delay substantially the development of fully

kindled seizures when The injection of 7-chlorokynurenic acid through an
indwelling cannula into the basolateral amygdala of rats
was found to delay substantially the development of fully
kindled seizures when the kynurenate was injected before indwelling cannula into the basolateral amygdala of rats
was found to delay substantially the development of fully
kindled seizures when the kynurenate was injected before
daily periods of electrical stimulation in the amy was found to delay substantially the development of fully
kindled seizures when the kynurenate was injected before
daily periods of electrical stimulation in the amygdala
(Croucher and Bradford, 1990). This antiepileptogen kindled seizures when the kynurenate was injected before
daily periods of electrical stimulation in the amygdala
(Croucher and Bradford, 1990). This antiepileptogenic
action of 7-chlorokynurenate was prevented if glycine
w daily periods of electrical stimulation in the amygdale (Croucher and Bradford, 1990). This antiepileptogenic action of 7-chlorokynurenate was prevented if glycine was coadministered simultaneously. The important point was

QUINOLINIC AND K
renate is indeed the prevention of epileptogenesis rather
than an antagonism or suppression of an underlying fully QUINOLINIC AND KYNI

renate is indeed the prevention of epileptogenesis rather fro

than an antagonism or suppression of an underlying fully or

kindled seizure, because cessation of 7-chlorokynurenate res QUINOLINIC ANI

renate is indeed the prevention of epileptogenesis rathe

than an antagonism or suppression of an underlying full

kindled seizure, because cessation of 7-chlorokynurenat

injections was followed by the dev renate is indeed the prevention of epileptogenesis rather
than an antagonism or suppression of an underlying fully
kindled seizure, because cessation of 7-chlorokynurenate
injections was followed by the development of maxi renate is indeed the prevention of epileptogenesis rather from an antagonism or suppression of an underlying fully obtindled seizure, because cessation of 7-chlorokynurenate relations was followed by the development of ma than an antagonism or suppression of an underlying fully or
kindled seizure, because cessation of 7-chlorokynurenate
injections was followed by the development of maximal ele
seizure activity during a period of a further 5 kindled seizure, because cessation of 7-chlorokynuren
injections was followed by the development of maxin
seizure activity during a period of a further 5 to 6 d
at a rate comparable to that in control animals. ⁷
point wa injections was followed by the development of maxim
seizure activity during a period of a further 5 to 6 da
at a rate comparable to that in control animals. T
point was also made that the treatment with 7-chloo
kynurenate seizure activity during a period of a further 5 to 6 days range of acidic compounds whose transport would be
at a rate comparable to that in control animals. The affected by probenecid, they must be interpreted with
point point was also made that the treatment with 7-chloro-(Croucher and Bradford, 1990). nurenate had a depressant effect, not only on behavioral evidence of seizures but also on the occurrence of plictrical afterdischarges following the kindling stimuli circucher and Bradford, 1990). production is the state o

ioural evidence of seizures but also on the occurrence of
electrical afterdischarges following the kindling stimuli
(Croucher and Bradford, 1990).
7-Chlorokynurenate was also shown to increase the
threshold for seizure pro electrical afterdischarges following the kindling stimu
(Croucher and Bradford, 1990).
7-Chlorokynurenate was also shown to increase the
threshold for seizure production in fully kindled animal
and this effect could be rev (Croucher and Bradford, 1990).
7-Chlorokynurenate was also shown to increase the
threshold for seizure production in fully kindled animals,
and this effect could be reversed by glycine. The inter-
esting finding was made t 7-Chlorokynurenate was also shown to increase t
threshold for seizure production in fully kindled anima
and this effect could be reversed by glycine. The inte
esting finding was made that, once initiated, the mot
and elect threshold for seizure production in fully kindled animals,
and this effect could be reversed by glycine. The inter-
esting finding was made that, once initiated, the motor
and electrical concomitants of the seizure were no and this effect could be reversed by glycine. The intendent esting finding was made that, once initiated, the mot and electrical concomitants of the seizure were no different following 7-chlorokyurenate than they were in c esting finding was made that, once initiated, the motor
and the strychnine-resistant glycine site associ-
and electrical concomitants of the seizure were no differ-
ated with the NMDA receptor. Certainly, kynurenate or
ent ent following 7-chlorokynurenate than they were in control animals. The actions of 7-chlorokyurenate are, therefore, specifically directed against the threshold for the initiation of seizure activity rather than its expres ent following 7-chlorokynurenate
trol animals. The actions of 7-chlo
fore, specifically directed agains
initiation of seizure activity rath
(Croucher and Bradford, 1991).
Evidence that the glycine site between and Shair and Bradford, 1991).
Evidence that the glycine site of the NMDA receptor
not fully saturated in vivo was obtained by Singh et

fore, specifically directed against the threshold for the initiation of seizure activity rather than its expression (Croucher and Bradford, 1991).

Evidence that the glycine site of the NMDA receptor is not fully saturate initiation of seizure activity rather than its expression
(Croucher and Bradford, 1991).
Evidence that the glycine site of the NMDA receptor
is not fully saturated in vivo was obtained by Singh et
al. (1990), who reported (Croucher and Bradford, 1991). volvet that the glycine site of the NMDA receptor back is not fully saturated in vivo was obtained by Singh et seized. (1990), who reported the D-serine injected icv at doses in r of 10 to 2 Evidence that the glycine site of the NMDA recep
is not fully saturated in vivo was obtained by Singh
al. (1990), who reported the D-serine injected icv at do
of 10 to 200 μ g would enhance the ability of NMDLA
induce s is not fully saturated in vivo was obtained by Singh et al. (1990) , who reported the D-serine injected icv at doses of 10 to 200 μ g would enhance the ability of NMDLA to induce seizures. The effect was marked, with a al. (1990), who reported the D-serine injected icv at doses
of 10 to 200 μ g would enhance the ability of NMDLA to
induce seizures. The effect was marked, with an approx-
imate 3-fold increase in NMDLA potency that was of 10 to 200 μ g would enhance the ability of NMDLA tinduce seizures. The effect was marked, with an approx imate 3-fold increase in NMDLA potency that was no shared by L-serine. Evidence that this effect was me diated induce seizures. The effect was marked, with an approx-
imate 3-fold increase in NMDLA potency that was not
shared by L-serine. Evidence that this effect was me-
diated by the glycine site comes from the fact that D-
serin imate 3-fold increase in NMDLA potency that was is
hared by L-serine. Evidence that this effect was not
diated by the glycine site comes from the fact that
serine would also prevent the anticonvulsant activity
kynurenic ac shared by L-serified by the gly
serine would also
kynurenic acid b
nist CPP.
It was noted a ated by the glycine site comes from the fact that D-
rine would also prevent the anticonvulsant activity of
nurenic acid but not the competitive NMDA antago-
st CPP.
It was noted above that increasing the concentration
end

serine would also prevent the anticonvulsant activity of
kynurenic acid but not the competitive NMDA antago-
nist CPP.
It was noted above that increasing the concentration
of endogenous kynurenate by the use of nicotinylal kynurenic acid but not the competitive NMDA antag
nist CPP.
It was noted above that increasing the concentratiof
endogenous kynurenate by the use of nicotinylalani
also produces protection against chemically or elect
cally mist CPP.
It was noted above that increasing the of endogenous kynurenate by the use of
also produces protection against chemically induced seizures (section II.A.1.a).
In mice D-serine, but not L-serine, was It was noted above that increasing the concentration
endogenous kynurenate by the use of nicotinylalanis
o produces protection against chemically or elect
lly induced seizures (section II.A.1.a).
In mice D-serine, but not

of endogenous kynurenate by the use of nicotinylalanine
also produces protection against chemically or electri-
cally induced seizures (section II.A.1.a).
In mice D-serine, but not L-serine, was found to poten-
tiate NMDAalso produces protection against chemically or electrically induced seizures (section II.A.1.a).

In mice D-serine, but not L-serine, was found to potentiate NMDA- or pentylenetetrazol-induced seizures after the intervinge cally induced seizures (section II.A.1.a).
In mice D-serine, but not L-serine, was found to pote
tiate NMDA- or pentylenetetrazol-induced seizures aft
icv injection (Singh et al., 1990). D-Serine also prevent
the anticonvu In mice D-serine, but not L-serine, was found to potentiate NMDA- or pentylenetetrazol-induced seizures after
icv injection (Singh et al., 1990). D-Serine also prevented
the anticonvulsant activity of kynurenate in these c tiate NMDA- or pentylenetetrazol-induced seizures after
icv injection (Singh et al., 1990). D-Serine also prevented
the anticonvulsant activity of kynurenate in these chem-
ically induced seizure models and acted as an inh icv injection (Singh et al., 1990). D-Serine also prevented the the anticonvulsant activity of kynurenate in these chemically induced seizure models and acted as an inhibitor In of sound-induced seizures in DBA/2 mice. The the anticonvulsant activity of kynurenate in these chemically induced seizure models and acted as an inhibitor
of sound-induced seizures in DBA/2 mice. The results of
suggest that convulsant activity might be sensitive to ically induced seizure models and acted as an inhibitor I
of sound-induced seizures in DBA/2 mice. The results of i
suggest that convulsant activity might be sensitive to vul
local concentrations of endogenous glycine acti of sound-induced seizures in DBA/2 mice. The results of suggest that convulsant activity might be sensitive to vulceal concentrations of endogenous glycine acting bless through its allosteric site on the NMDA receptor and suggest that convulsant activity might be sensitive to local concentrations of endogenous glycine acting through its allosteric site on the NMDA receptor and that, because this site would appear to be normally less than fu local concentrations of endogenous glycine acthrough its allosteric site on the NMDA receptor
that, because this site would appear to be normally
than fully saturated with ligand, endogenous kynure
might have important mod through its allosteric site
that, because this site wou
than fully saturated with l
might have important mo
tions attainable in vivo.
b. L-KYNURENINE. Rece at, because this site would appear to be normally less
an fully saturated with ligand, endogenous kynurenate
ight have important modulatory activity at concentra-
ons attainable in vivo.
b. L-KYNURENINE. Recent work sugges

than fully saturated with ligand, endogenous kynurenate
might have important modulatory activity at concentra-
tions attainable in vivo.
b. L-KYNURENINE. Recent work suggests that loading
animals with L-kynurenine may dela might have important modulatory activity at concentra-
tions attainable in vivo.
b. L-KYNURENINE. Recent work suggests that loading
animals with L-kynurenine may delay the onset of pen-
tylenetetrazol- or NMDA-induced seiz tions attainable in vivo.

b. L-KYNURENINE. Recent work suggests that loading

animals with L-kynurenine may delay the onset of pen-

tylenetetrazol- or NMDA-induced seizures and increase

the survival of mice (Vecsei et a b. L-KYNURENINE. Recent work suggests that loading
animals with L-kynurenine may delay the onset of pen-
tylenetetrazol- or NMDA-induced seizures and increase
the survival of mice (Vecsei et al., 1992b). The dose of L-
kyn animals with L-kynurenine may delay the onset of pen-
tylenetetrazol- or NMDA-induced seizures and increase
the survival of mice (Vecsei et al., 1992b). The dose of L-
kynurenine used would have elevated CNS kynurenate
abo tylenetetrazol- or NMDA-induced seizures and increase
the survival of mice (Vecsei et al., 1992b). The dose of L-
kynurenine used would have elevated CNS kynurenate
about 6-fold and had no effect on learning behaviour at
t

from seizures was conferred by injections of probenecid Souther a combination of this drug and L-kynurenine. The
or a combination of this drug and L-kynurenine. The
results may be consistent with a degree of protection by 359
from seizures was conferred by injections of probenecid
or a combination of this drug and L-kynurenine. The
results may be consistent with a degree of protection by
elevated central kynurenate, but in view of the wide from seizures was conferred by injections of probenecid
or a combination of this drug and L-kynurenine. The
results may be consistent with a degree of protection by
elevated central kynurenate, but in view of the wide
rang from seizures was conferred by injections of probenecid
or a combination of this drug and L-kynurenine. The
results may be consistent with a degree of protection by
elevated central kynurenate, but in view of the wide
rang or a combination of this drug and L-kynurenine. The
results may be consistent with a degree of protection by
elevated central kynurenate, but in view of the wide
range of acidic compounds whose transport would be
affected caution. Interestingly, the compounds whose transport would be interpreted by probenecid, they must be interpreted with ution.
Interestingly, the convulsant effect of strychnine ap-
led icv was enhanced by L-kynurenine in several s affected by probenecid, they must be interpreted with
caution.
Interestingly, the convulsant effect of strychnine ap-

affected by probenecid, they must be interpreted with
caution.
Interestingly, the convulsant effect of strychnine ap-
plied icv was enhanced by L-kynurenine in several spe-
cies; this effect was prevented by glycine, which caution.
Interestingly, the convulsant effect of strychnine ap-
plied icv was enhanced by L-kynurenine in several spe-
cies; this effect was prevented by glycine, which also
proved to be a particularly effective suppressan Interestingly, the convulsant effect of strychnine applied icv was enhanced by L-kynurenine in several species; this effect was prevented by glycine, which also proved to be a particularly effective suppressant of seizures plied icv was enhanced by L-kynurenine in several species; this effect was prevented by glycine, which also proved to be a particularly effective suppressant of seizures due to L-kynurenine (Lapin et al., 1982; Lapin, 1980 proved to be a particularly effective suppressant of seizures due to L-kynurenine (Lapin et al., 1982; Lapin, 1980, 1981a,b). This is an intriguing observation in view zures due to L-kynurenine (Lapin et al., 1982; Lapin, zures due to L-kynurenine (Lapin et al., 1982; Lapin, 1980, 1981a,b). This is an intriguing observation in view
of the close relationship now recognised between kynu-
renate- and the strychnine-resistant glycine site assoc 1980, 1981a,b). This is an intriguing observation in view
of the close relationship now recognised between kynu-
renate- and the strychnine-resistant glycine site associ-
ated with the NMDA receptor. Certainly, kynurenate of the close relationship now recognised between kynu-
renate- and the strychnine-resistant glycine site associ-
ated with the NMDA receptor. Certainly, kynurenate or
7-chlorokynurenate are very effective anticonvulsants
w renate- and
ated with tl
7-chlorokyr
when admin
al., 1990).
The ante 7-chlorokynurenate are very effective anticonvulsants

7-chlorokynurenate are very effective anticonvulsants
when administered icv (Chiamulera et al., 1990; Singh et
al., 1990).
The antagonism of kynurenine-induced seizures in-
volves some striking species differences. For exa when administered icv (Chiamulera et al., 1990; Singh et al., 1990).

The antagonism of kynurenine-induced seizures in-

volves some striking species differences. For example,

baclofen and sodium hydroxybutyrate potently al., 1990).
The antagonism of kynurenine-induced seizures in-
volves some striking species differences. For example,
baclofen and sodium hydroxybutyrate potently inhibit
seizures due to quinolinic acid in mice but are inef The antagonism of kynurenine-induced seizures in-
volves some striking species differences. For example,
baclofen and sodium hydroxybutyrate potently inhibit
seizures due to quinolinic acid in mice but are ineffective
in r volves some striking species differences. For examp
baclofen and sodium hydroxybutyrate potently inhi
seizures due to quinolinic acid in mice but are ineffect
in rats (Lapin, 1981a; Lapin et al., 1986). A number
anticonvul baclofen and sodium hydroxybutyrate potently inhibit
seizures due to quinolinic acid in mice but are ineffective
in rats (Lapin, 1981a; Lapin et al., 1986). A number of
anticonvulsant drugs, including phenobarbitone, pheny seizures due to quinolinic acid in mice but are ineffective
in rats (Lapin, 1981a; Lapin et al., 1986). A number of
anticonvulsant drugs, including phenobarbitone, pheny-
toin, primidone, diazepam, and trimethadione, have in rats (Lapin, 1981a; Lapin et al., 1986). A number of
anticonvulsant drugs, including phenobarbitone, pheny-
toin, primidone, diazepam, and trimethadione, have some
ability to suppress seizures induced by quinolinic acid anticonvulsant drugs, including phenobarbitone, phenytoin, primidone, diazepam, and trimethadione, have some ability to suppress seizures induced by quinolinic acid or L-kynurenine injected icv. Phenobarbitone was equally ability to suppress seizures induced by quinolinic acid or L-kynurenine injected icv. Phenobarbitone was equally active against picrotoxin-, L-kynurenine-, and quinolinic acid-induced seizures, and three kynurenines, kynur ability to suppress seizures induced by quinolinic acid or
L-kynurenine injected icv. Phenobarbitone was equally
active against picrotoxin-, L-kynurenine-, and quinolinic
acid-induced seizures, and three kynurenines, kynur L-kynurenine injected icv. Phenobarbitone was equally
active against picrotoxin-, L-kynurenine-, and quinolinic
acid-induced seizures, and three kynurenines, kynurenic
acid, picolinic acid, and xanthurenic acid, selectivel active against picrotoxin-, L-kynurenine-, and quinolinic
acid-induced seizures, and three kynurenines, kynurenic
acid, picolinic acid, and xanthurenic acid, selectively
prevented seizures induced by picrotoxin in mice (La acid-induced seizures, and three kynurenines, kynure
acid, picolinic acid, and xanthurenic acid, selectiv
prevented seizures induced by picrotoxin in mice (Lap
1989). Together with the observation that L-kynuren
and quinol acid, picolinic acid, and xanthurenic acid, selectively
prevented seizures induced by picrotoxin in mice (Lapin,
1989). Together with the observation that L-kynurenine
and quinolinate can prevent the stimulation of benzodi prevented seizures induced by picrotoxin in mice (Lapin, 1989). Together with the observation that L-kynurenine and quinolinate can prevent the stimulation of benzodi-
azepine binding by pentobarbitone (Zarkovsky, 1986), t 1989). Together with the observation that L-ky
and quinolinate can prevent the stimulation of
azepine binding by pentobarbitone (Zarkovs)
these observations may support the suggestion
is a specific involvement of the barbi and quinolinate can prevent the stimulation of benzodi-
azepine binding by pentobarbitone (Zarkovsky, 1986),
these observations may support the suggestion that there
is a specific involvement of the barbiturate-/picrotoxi azepine binding by pentobarbitone (Zarkovsky, 1986),
these observations may support the suggestion that there
is a specific involvement of the barbiturate-/picrotoxin-
binding site of the GABA receptor complex involved in
 these observations may support the suggestion that there
is a specific involvement of the barbiturate-/picrotoxin-
binding site of the GABA receptor complex involved in
the seizure and anticonvulsant activities of differen binding site of the GABA receptor complex involved in
the seizure and anticonvulsant activities of different
members of the kynurenine pathway (Lapin, 1989).
In view of the absence of direct excitatory properties
of L-kynu

binding site of the GABA receptor complex involved in
the seizure and anticonvulsant activities of different
members of the kynurenine pathway (Lapin, 1989).
In view of the absence of direct excitatory properties
of L-kynu the seizure and anticonvulsant activities of different
members of the kynurenine pathway (Lapin, 1989).
In view of the absence of direct excitatory properties
of L-kynurenine, an alternative explanation of the con-
vulsant members of the kynurenine pathway (Lapin, 1989).
In view of the absence of direct excitatory properties
of L-kynurenine, an alternative explanation of the con-
vulsant activity of kynurenines suggested that it might
block In view of the absence of direct excitatory properties
of L-kynurenine, an alternative explanation of the con-
vulsant activity of kynurenines suggested that it might
block sensitivity to inhibitory amino acids, such as
G of L-kynurenine, an alternative explanation of the con-
vulsant activity of kynurenines suggested that it might
block sensitivity to inhibitory amino acids, such as
GABA and glycine; this possibility was strengthened by
th vulsant activity of kynurenines suggested that it might block sensitivity to inhibitory amino acids, such as GABA and glycine; this possibility was strengthened by the presence of a glycine moiety in the side chain of the block sensitivity to inhibitory amino acids, su
GABA and glycine; this possibility was strengthen
the presence of a glycine moiety in the side chain
L-kynurenine molecule. When tested on inhibito
sponses to GABA or glycine GABA and glycine; this possibility was strengthened by
the presence of a glycine moiety in the side chain of the
L-kynurenine molecule. When tested on inhibitory re-
sponses to GABA or glycine, applied by microiontopho-
re the presence of a glycine moiety in the side chain of the L-kynurenine molecule. When tested on inhibitory responses to GABA or glycine, applied by microiontophoresis in vivo, neither L-kynurenine nor kynurenic acid would L-kynurenine molecule. When tested on inhibitory responses to GABA or glycine, applied by microiontopheresis in vivo, neither L-kynurenine nor kynurenic active would block these inhibitory effects (Perkins and Ston 1982). sponses to GABA or glycine, applied by microiontophoresis in vivo, neither L-kynurenine nor kynurenic acid
would block these inhibitory effects (Perkins and Stone, 1982). Pinelli et al. (1985) reported that L-kynurenine,
 resis in vivo, neither L-kynurenine nor kynurenic ac
would block these inhibitory effects (Perkins and Ston
1982). Pinelli et al. (1985) reported that L-kynurenin
the isomer active in producing convulsions in rats, cou
di would block these inhibitory effects (Perkins and Sto 1982). Pinelli et al. (1985) reported that L-kynureni
the isomer active in producing convulsions in rats, co
displace GABA binding with an IC_{60} of 10 μ M. A quati 1982). Pinelli et al. (1985) reported that L-kynurenine,
the isomer active in producing convulsions in rats, could
displace GABA binding with an IC_{60} of 10 μ M. A quan-
titative analysis of GABA activity in depressin the isomer active in producing convulsions in rats, could
displace GABA binding with an IC_{50} of 10 μ M. A quan-
titative analysis of GABA activity in depressing popula-
tion spikes in hippocampal slices, however, yie

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360
urenine in concentrations up to 500 μ M (Stone, 1986b).
It would be of great interest to see the data of Pinelli et 360
urenine in concentrations up to 500 μ M (Stone, 1986b). if
It would be of great interest to see the data of Pinelli et
al. (1985) extended to clarify the precise regions and t STONE
urenine in concentrations up to 500 μ M (Stone, 1986b). int
It would be of great interest to see the data of Pinelli et occ
al. (1985) extended to clarify the precise regions and ter-
cellular sites at which the d urenine in concentrations up to 500 μ M (Stone, 1986b).
It would be of great interest to see the data of Pinelli et al. (1985) extended to clarify the precise regions and cellular sites at which the displacement of GABA curred.

al. (1985) extended to clarify the precise regio
cellular sites at which the displacement of GA
curred.
The interesting view has been put forward that
the major kynurenine metabolites, 3-hydroxyky
ine, might be involved in cellular sites at which the displacement of GABA oc-
curred.
The interesting view has been put forward that one of
the major kynurenine metabolites, 3-hydroxykynuren-
ine, might be involved in seizure production. This hy-
 tased on the interesting view has been put forward that one of absorber the major kynurenine metabolites, 3-hydroxykynuren-
ine, might be involved in seizure production. This hypothesis is based on the observation that, wh The interesting view has been put forward that one of
the major kynurenine metabolites, 3-hydroxykynuren-
ine, might be involved in seizure production. This hy-
pothesis is based on the observation that, whereas the
levels the major kynurenine metabolites, 3-hydroxykynuren-
ine, might be involved in seizure production. This hy-
pothesis is based on the observation that, whereas the
newless of 3-hydroxykynurenine in normal rats are ap-
proxi ine, might be involved in seizure production. This hy-
pothesis is based on the observation that, whereas the
levels of 3-hydroxykynurenine in normal rats are ap-
proximately 1 nmol/g (Gal and Sherman, 1978), this can
cin pothesis is based on the observation that, whereas the levels of 3-hydroxykynurenine in normal rats are approximately 1 nmol/g (Gal and Sherman, 1978), this can increase to >200 nmol/g in neonatal animals provided with proximately 1 nmol/g (Gal and Sherman, 1978), this can increase to >200 nmol/g in neonatal animals provided with a diet deficient in vitamin B_6 (Guilarte and Wagner, 1987). In fact, recent data from more sophisticate proximately 1 nmol/g (Gal and Sherman, 1978), this can
increase to >200 nmol/g in neonatal animals provided
with a diet deficient in vitamin B_6 (Guilarte and Wagner, ration 1987). In fact, recent data from more sophist increase to >200 nmol/g in neonatal animals provided In with a diet deficient in vitamin B_6 (Guilarte and Wagner, recent 1987). In fact, recent data from more sophisticated anal-
1987). In fact, recent data from more with a diet deficient in vitamin B_6 (Guilarte and Wagner, 1987). In fact, recent data from more sophisticated anal-
yses suggest that, in normal mice or rats, the basal 3-
hydroxykynurenine concentration may be as litt 1987). In fact, recent data from more sophisticated analyses suggest that, in normal mice or rats, the basal 3-hydroxykynurenine concentration may be as little as 60 pmol/g (Heyes and Quearry, 1988). Intermediate levels o hydroxykynurenine concentration may be as little as 60 pmol/g (Heyes and Quearry, 1988). Intermediate levels of approximately 200 pmol/g in human brain were reported by Pearson and Reynolds (1991). The potential rel of approximately 200 pmol/g in human brain were re-

pmol/g (Heyes and Quearry, 1988). Intermediate levels
of approximately 200 pmol/g in human brain were re-
ported by Pearson and Reynolds (1991).
The potential relevance of an increased 3-hydroxykyn-
urenine to the occurren of approximately 200 pmol/g in human brain were re-
ported by Pearson and Reynolds (1991).
The potential relevance of an increased 3-hydroxykyn-
urenine to the occurrence of seizures in neonatal animals
was supported by t ported by Pearson and Reynolds (1991).
The potential relevance of an increased 3-hydroxy
urenine to the occurrence of seizures in neonatal an
was supported by the failure of vitamin B_s-deficient
rats to display either se The potential relevance of an increased 3-hydroxykyn-seen
urenine to the occurrence of seizures in neonatal animals bloom
was supported by the failure of vitamin B_6 -deficient adult
rats to display either seizures or el urenine to the occurrence of seizures in neonatal animations was supported by the failure of vitamin B_6 -deficient adrets to display either seizures or elevated 3-hydroxykynurenine. The relationship prompted these autho was supported by the failure of vitamin B_6 -deficient a
rats to display either seizures or elevated 3-hydroxy
urenine. The relationship prompted these author
examine the effects of 3-hydroxykynurenine on be
diazepine-bi rats to display either seizures or elevated 3-hydroxykyn-
urenine. The relationship prompted these authors to
examine the effects of 3-hydroxykynurenine on benzo-
diazepine-binding sites. Although rather high concentra-
t examine the effects of 3-hydroxykynurenine on benzo-
diazepine-binding sites. Although rather high concentra-
tions were needed (approximately 1 mM) to displace
flunitrazepam itself, concentrations comparable with
those m diazepine-binding sites. Although rather high concentra-
tions were needed (approximately 1 mM) to displace
flunitrazepam itself, concentrations comparable with
those measured in vivo were able to increase significantly
t tions were needed (approximately 1 mM) to displace sflunitrazepam itself, concentrations comparable with sthose measured in vivo were able to increase significantly μ the K_d of the GABA stimulation of flunitrazepam b

those measured in vivo were able to increase significar
the K_d of the GABA stimulation of flunitrazepam bind
(Guilarte et al., 1988).
c. VITAMIN B₆ DEFICIENCY. Quite apart from a possi
role of kynurenines in idiopathi the K_d of the GABA stimulation of flunitrazepam binding excellent (Guilarte et al., 1988).

C. VITAMIN B₆ DEFICIENCY. Quite apart from a possible wrole of kynurenines in idiopathic epilepsy, the relation-list of the p (Guilarte et al., 1988).

c. VITAMIN B₆ DEFICIENCY. Quite apart from a possible

role of kynurenines in idiopathic epilepsy, the relation-

ship between kynurenine metabolism and seizures has

long been of interest beca c. VITAMIN B₆ DEFICIENCY. Quite apart from a possible wrole of kynurenines in idiopathic epilepsy, the relation-
hip between kynurenine metabolism and seizures has (S
long been of interest because of the presence of maj ship between kynurenine metabolism and seizures has (Stone, 1988). This has raised the possibility that kynu-
long been of interest because of the presence of major renic acid may have rather complicated actions in the
sei ship between kynurenine metabolism and seizures has
long been of interest because of the presence of major
seizures in pyridoxine deficiency. Seizures can be induced
in adult animals as well as in the young (Sharma and
Kak long been of interest because of the presence of major seizures in pyridoxine deficiency. Seizures can be induced in adult animals as well as in the young (Sharma and Kakshinamurti, 1992), and a partial pyridoxine deficien seizures in pyridoxine deficiency. Seizures can be induce
in adult animals as well as in the young (Sharma an
Kakshinamurti, 1992), and a partial pyridoxine def
ciency can be induced by some common antiepilept
medications in adult animals as well as in the young (Sharma and Kakshinamurti, 1992), and a partial pyridoxine decrease seizure occur-
ciency can be induced by some common antiepilept
medications including phenytoin (Reinken, 1975); ciency can be induced by some common antiepileptic
medications including phenytoin (Reinken, 1975); treat-
ment with vitamin B_6 will then decrease seizure occur-
rence.
Pyridoxal phosphate (fig. 1) is an essential cofa

medications including phenytoin (Reinken, 1975); treatment with vitamin B_6 will then decrease seizure occurrence.
Pyridoxal phosphate (fig. 1) is an essential cofactor for several enzymes of the kynurenine pathway, and ment with vitamin B_6 will then decrease seizure occurrence.

Pyridoxal phosphate (fig. 1) is an essential cofactor

for several enzymes of the kynurenine pathway, and,

consequently, a lack of the vitamin can result in rence.

Pyridoxal phosphate (fig. 1) is an essential cofactor

for several enzymes of the kynurenine pathway, and,

consequently, a lack of the vitamin can result in a dra-

matic increase of kynurenine excretion (Yeh and Pyridoxal phosphate (fig. 1) is an essential cofactor
for several enzymes of the kynurenine pathway, and,
consequently, a lack of the vitamin can result in a dra-
matic increase of kynurenine excretion (Yeh and Brown,
1977 for several enzymes of the kynurenine pathway,
consequently, a lack of the vitamin can result in a
matic increase of kynurenine excretion (Yeh and B
1977). As an example, Takeuchi and Shibata (
recorded a more than 400-fo consequently, a lack of the vitamin can result in a dr
matic increase of kynurenine excretion (Yeh and Brow
1977). As an example, Takeuchi and Shibata (198
recorded a more than 400-fold increase of 3-hydroxyky
urenine in matic increase of kynurenine excretion (Yeh and Brown, nist
1977). As an example, Takeuchi and Shibata (1984) wit
recorded a more than 400-fold increase of 3-hydroxykyn-exh
urenine in vitamin B₆-deficient rats. Indeed, 1977). As an example, Takeuchi and Shibata (1984) wit
recorded a more than 400-fold increase of 3-hydroxykyn-exh
urenine in vitamin B₆-deficient rats. Indeed, the excre-
poution of excessive amounts of kynurenines follo recorded a more than 400-fold increase of 3-hydroxykyn
urenine in vitamin B₆-deficient rats. Indeed, the excre
tion of excessive amounts of kynurenines following
tryptophan load has been used for many years as a
diagno form activity, consisting a tryptophan load has been used for many years as a codiagnostic test for pyridoxine deficiency (Wolf, 1974). etimage of *action pyridoxine deficiency* (Wolf, 1974). Expleption activity, consistin

tryptophan load has been used for many years as a diagnostic test for pyridoxine deficiency (Wolf, 1974).
3. Electrophysiological epileptiform activity. Epileptiform activity, consisting of rhythmic bursts of action
potent

It would be of great interest to see the data of Pinelli et occurrence of these periodic depolarisations and the in-
al. (1985) extended to clarify the precise regions and terictal electrophysiological activity observed in WE
interest since the parallel was first drawn between the
occurrence of these periodic depolarisations and the in-NE
interest since the parallel was first drawn between the
occurrence of these periodic depolarisations and the in-
terictal electrophysiological activity observed in animal NE
interest since the parallel was first drawn between the
occurrence of these periodic depolarisations and the in-
terictal electrophysiological activity observed in animal
seizures and epileptic patients. The particular interest since the parallel was first drawn between to cocurrence of these periodic depolarisations and the terictal electrophysiological activity observed in anim seizures and epileptic patients. The particular importance interest since the parallel was first drawn between the occurrence of these periodic depolarisations and the interictal electrophysiological activity observed in animaseizures and epileptic patients. The particular impotan occurrence of these periodic depolarisations and the in-
terictal electrophysiological activity observed in animal
seizures and epileptic patients. The particular impor-
tance of NMDA receptors to these phenomena is prob-
 terictal electrophysiological activity observed in animal
seizures and epileptic patients. The particular impor-
tance of NMDA receptors to these phenomena is prob-
ably based on the voltage dependency of the magnesium
blo seizures and epileptic patients. The particular importance of NMDA receptors to these phenomena is probably based on the voltage dependency of the magnesium blockade of the ion channels associated with the NMD₄ receptor, ably based on the voltage dependency of the magnesium
blockade of the ion channels associated with the NMDA
receptor, because it appears to be the relief of this mag-
nesium blockade that contributes to the initiation of
p paroxysmal depolarisation and the closure of calcium
channels that causes cessation of these periods.
In a number of cases, the involvement of NMDA receptor, because it appears to be the relief of this magceptor, because it appears to be the relief of this mag-
sium blockade that contributes to the initiation of
roxysmal depolarisation and the closure of calcium
annels that causes cessation of these periods.
In a number of

receptors has been contributes to the initiation of
paroxysmal depolarisation and the closure of calcium
channels that causes cessation of these periods.
In a number of cases, the involvement of NMDA
receptors has been con paroxysmal depolarisation and the closure of calcium
channels that causes cessation of these periods.
In a number of cases, the involvement of NMDA
receptors has been confirmed by the specific blockade of
epileptiform bur channels that causes cessation of these periods.
In a number of cases, the involvement of NMDA
receptors has been confirmed by the specific blockade of
epileptiform bursts by 2AP5 or related selective NMDA
antagonists. In In a number of cases, the involvement of NMI
receptors has been confirmed by the specific blockade
epileptiform bursts by 2AP5 or related selective NMI
antagonists. In addition, kynurenic acid is able to blo
the induction receptors has been confirmed by the specific blockade of
epileptiform bursts by 2AP5 or related selective NMDA
antagonists. In addition, kynurenic acid is able to block
the induction of these bursts under a number of exper epileptiform bursts by 2AP5 or related selective NMDA
antagonists. In addition, kynurenic acid is able to block
the induction of these bursts under a number of experi-
mental conditions in the neocortex (Uchida, 1992), the the induction of these bursts under a number of experimental conditions in the neocortex (Uchida, 1992), the hippocampus (Stone, 1988; Brady and Swan, 1988), and the amygdala (Gean, 1990) where non-NMDA receptors the induction of these bursts under a number of experimental conditions in the neocortex (Uchida, 1992), the hippocampus (Stone, 1988; Brady and Swan, 1988), and the amygdala (Gean, 1990) where non-NMDA receptors seem to b mental conditions in the neocortex (Uchida, 1992), the
hippocampus (Stone, 1988; Brady and Swan, 1988), and
the amygdala (Gean, 1990) where non-NMDA receptors
seem to be primarily involved because they can be
blocked by ky seem to be primarily involved because they can be
blocked by kynurenate and CNQX to a far greater extent
than by 2AP5.
In the hippocampal preparation, bursts induced by Example amygdala (Gean, 1990) where non-NMDA receptors
 $\begin{array}{r}\n\text{em} & \text{to} & \text{be} \\
\text{em} & \text{to} & \text{be} \\
\text{or} & \text{be} & \text{primarily involved because they can be} \\
\text{or} & \text{be} & \text{be} \\
\text{or} & \text{be} & \text{be} \\
\text{an} & \text{by} & 2\text{AP5}.\n\end{array}$

urenine. The relationship prompted these authors to magnesium-free media can be blocked by 2AP5 with an examine the effects of 3-hydroxykynurenine on benzo-
 ED_{50} of 66 μ M and by kynurenate with an ED₅₀ of 110

di antagonists. In addition, kynurenic acid is able to block
the induction of these bursts under a number of experimental conditions in the necocretar (Uchida, 1998), the
hippocampus (Stone, 1988; Brady and Swan, 1988), and
 blocked by kynurenate and CNQX to a far greater extent
than by 2AP5.
In the hippocampal preparation, bursts induced by
magnesium-free media can be blocked by 2AP5 with an
ED₅₀ of 66 μ M and by kynurenate with an ED₅₀ than by 2AP5.
In the hippocampal preparation, bursts induced by magnesium-free media can be blocked by 2AP5 with an ED_{50} of 66 μ M and by kynurenate with an ED_{50} of 110 μ M. Bursts also can be induced by GABA an In the hippocampal preparation, bursts induced
magnesium-free media can be blocked by 2AP5 with
 ED_{50} of 66 μ M and by kynurenate with an ED_{50} of 1
 μ M. Bursts also can be induced by GABA antagoni
such as picroto magnesium-free media can be blocked by 2AP5 with an
 ED_{50} of 66 μ M and by kynurenate with an ED_{50} of 110
 μ M. Bursts also can be induced by GABA antagonists

such as picrotoxin, however, and, under these circu ED_{50} of 66 μ M and by kynurenate with an ED_{50} of 110 μ M. Bursts also can be induced by GABA antagonists such as picrotoxin, however, and, under these circumstances, the ED_{50} for kynurenate was increased to 1 μ M. Bursts also can be induced by GABA antagonists
such as picrotoxin, however, and, under these circum-
stances, the ED_{50} for kynurenate was increased to 132
 μ M. Kynurenate was now more potent than 2AP5. When
ex stances, the ED_{50} for kynurenate was increased to 132 μ M. Kynurenate was now more potent than 2AP5. When examined against iontophoretic applications of NMDA, quisqualate, or kainate, both 2AP5 and kynurenic acid wer stances, the ED_{50} for kynurenate was increased to 132 μ M. Kynurenate was now more potent than 2AP5. When examined against iontophoretic applications of NMDA, quisqualate, or kainate, both 2AP5 and kynurenic acid wer μ M. Kynurenate was now more potent than 2AP5. When examined against iontophoretic applications of NMDA, quisqualate, or kainate, both 2AP5 and kynurenic acid were found to be selective antagonists of NMDA with little e examined against iontophoretic applications of NMD.
quisqualate, or kainate, both 2AP5 and kynurenic ac
were found to be selective antagonists of NMDA wi
little effect on quisqualate or kainate on CA3 neuron
(Stone, 1988). quisqualate, or kainate, both 2AP5 and kynurenic acid
were found to be selective antagonists of NMDA with
little effect on quisqualate or kainate on CA3 neurones
(Stone, 1988). This has raised the possibility that kynu-
re were found t
little effect o
(Stone, 1988)
renic acid m
CA3 region.
It is possi (Stone, 1988). This has raised the possibility that kynu-

(Stone, 1988). This has raised the possibility that kynu-
renic acid may have rather complicated actions in the
CA3 region.
It is possible that the results are explicable if the
endogenous agonist at NMDA receptors in the renic acid may have rather complicated actions in CA3 region.
It is possible that the results are explicable if endogenous agonist at NMDA receptors in the C
region, probably glutamate or aspartate, has a pharma-
cological CA3 region.
It is possible that the results are explicable if the
endogenous agonist at NMDA receptors in the CA3
region, probably glutamate or aspartate, has a pharma-
cological profile on those cells responsible for init It is possible that the results are explicable if the endogenous agonist at NMDA receptors in the CA3 region, probably glutamate or aspartate, has a pharma-cological profile on those cells responsible for initiating burst endogenous agonist at NMDA receptors in the CA
region, probably glutamate or aspartate, has a pharma
cological profile on those cells responsible for initiatir
burst activity that is different from that of the exogenou
ago region, probably glutamate or aspartate, has a pharma
cological profile on those cells responsible for initiatin
burst activity that is different from that of the exogenou
agonists NMDA, quisqualate, and kainate. The phar
 cological profile on those cells responsible for initiating
burst activity that is different from that of the exogenous
agonists NMDA, quisqualate, and kainate. The phar-
macology of 2AP5 and kynurenate against those com-
 burst activity that is different from that of the exogenous agonists NMDA, quisqualate, and kainate. The pharmacology of 2AP5 and kynurenate against those compounds would then not necessarily be reflected in the results ob agonists NMDA, quisqualate, and kainate. The phar-
macology of 2AP5 and kynurenate against those com-
pounds would then not necessarily be reflected in the
results obtained with exogenously applied selective ago-
nists. Co macology of 2AP5 and kynurenate against those compounds would then not necessarily be reflected in the results obtained with exogenously applied selective agonists. Conversely, it may be that there are neurones within the pounds would then not necessarily be reflected in the results obtained with exogenously applied selective ago nists. Conversely, it may be that there are neurone within the CA3 region involved in initiating bursts that exh results obtained with exogenously applied selective
nists. Conversely, it may be that there are neu
within the CA3 region involved in initiating burst
exhibit a different sensitivity to the antagonist
pounds than they do t sts. Conversely, it may be that there are neurones
thin the CA3 region involved in initiating bursts that
hibit a different sensitivity to the antagonist com-
unds than they do to the CA3 pyramidal cells.
In an independent

diagnostic test for pyridoxine deficiency (Wolf, 1974). etic application of excitatory amino acid agonists to CA3
3. Electrophysiological epileptiform activity. Epilepti-cells was performed in the presence of a superfused
 within the CA3 region involved in initiating bursts
exhibit a different sensitivity to the antagonist c
pounds than they do to the CA3 pyramidal cells.
In an independent study by Brady and Swan (19
comparable results were exhibit a different sensitivity to the antagonist compounds than they do to the CA3 pyramidal cells.
In an independent study by Brady and Swan (1988), comparable results were obtained. First, the iontophoretic application pounds than they do to the CA3 pyramidal cells.
In an independent study by Brady and Swan (1988),
comparable results were obtained. First, the iontophor-
etic application of excitatory amino acid agonists to CA3
cells was In an independent study by Brady and Swan (1988),
comparable results were obtained. First, the iontophor-
etic application of excitatory amino acid agonists to CA3
cells was performed in the presence of a superfused
soluti comparable results were obtained. First, the iontophoretic application of excitatory amino acid agonists to CA3 cells was performed in the presence of a superfused solution of kynurenate. A selective blockade of NMDA sensi etic application of excitatory amino acid agonists to CA3
cells was performed in the presence of a superfused
solution of kynurenate. A selective blockade of NMDA
sensitivity was obtained with no significant effect on
quis

QUINOLINIC AND
that intracellular recordings revealed no change in the
current voltage relationships of CA3 cells during the
application of kynurenate at effective antagonistic con-
centrations, confirming other reports th that intracellular recordings revealed no change in the current voltage relationships of CA3 cells during the application of kynurenate at effective antagonistic concentrations, confirming other reports that kynurenate has that intracellular recordings revealed no change in th
current voltage relationships of CA3 cells during th
application of kynurenate at effective antagonistic cor
centrations, confirming other reports that kynurenat
has n current voltage relationships of CA3 cells during the rena-
application of kynurenate at effective antagonistic con-
centrations, confirming other reports that kynurenate 1990
has no direct effect on postsynaptic cell memb application of kynurenate at effective antagonistic concentrations, confirming other reports that kynurenate has no direct effect on postsynaptic cell membrane properties. When examined as inhibitors of epileptiform bursts centrations, confirming other reports that kynurenate 19
has no direct effect on postsynaptic cell membrane prop-
erties. When examined as inhibitors of epileptiform in
bursts induced by perfusion with penicillin, however, has no direct effect on postsynaptic cell membrane prop-
erties. When examined as inhibitors of epileptiform in
bursts induced by perfusion with penicillin, however, co
kynurenic acid was confirmed to be a potent inhibitor erties. When examined as inhibitors of epileptiform ine,
bursts induced by perfusion with penicillin, however, concentration and was confirmed to be a potent inhibitor of or
these potentials, whereas 2AP5 had no apparent a bursts induced by perfusion with penicillin, however, kynurenic acid was confirmed to be a potent inhibitor of these potentials, whereas 2AP5 had no apparent activity at concentrations that totally eliminated sensitivity t kynurenic acid was confirmed to b
these potentials, whereas 2AP5 ha
at concentrations that totally elinexogenous NMDA. The conclusion
parallelled those of Stone (1988).
A different interpretation was pl ese potentials, whereas 2AP5 had no apparent activity 199
concentrations that totally eliminated sensitivity to 4.
ogenous NMDA. The conclusions drawn, therefore, emp
rallelled those of Stone (1988).
A different interpret

at concentrations that totally eliminated sensitivity to exogenous NMDA. The conclusions drawn, therefore, parallelled those of Stone (1988).
A different interpretation was placed on the results by Brady and Swan in that t exogenous NMDA. The conclusions drawn, therefore,
parallelled those of Stone (1988).
A different interpretation was placed on the results by
Brady and Swan in that they remarked on the previous
finding that blocking drugs parallelled those of Stone (1988). in ce

A different interpretation was placed on the results by

Brady and Swan in that they remarked on the previous

infar

finding that blocking drugs for the NMDA-associated (wet

phen A different interpretation was placed on the results by
Brady and Swan in that they remarked on the previous
finding that blocking drugs for the NMDA-associated (
phencyclidine site were able to block not only NMDA
respons Brady and Swan in that they remarked on the previous
finding that blocking drugs for the NMDA-associated
phencyclidine site were able to block not only NMDA
responses but also epileptiform activity. Their conclusion
was th finding that blocking drugs for the NMDA-associated (we
phencyclidine site were able to block not only NMDA st
responses but also epileptiform activity. Their conclusion R
was that the NMDA recognition site of the receptor phencyclidine site were able to block not only NMDA stresponses but also epileptiform activity. Their conclusion Rives that the NMDA recognition site of the receptor to channel complex may be different in the CA3 region of responses but also epileptiform activity. Their conclusion Ri
was that the NMDA recognition site of the receptor to
channel complex may be different in the CA3 region of na
the immature rats from which their preparations w was that the NMDA recognition site of the receptor
channel complex may be different in the CA3 region of
the immature rats from which their preparations were
taken. The NMDA recognition site in these cases would
be one tha channel complex may be different in the CA3 region of
the immature rats from which their preparations were
taken. The NMDA recognition site in these cases would
be one that had a kynurenate-preferring binding site that
was the immature rats from which their preparations were pataken. The NMDA recognition site in these cases would de be one that had a kynurenate-preferring binding site that cowas able to interact with kynurenate rather than 2 taken. The NMDA recognition site in these cases would develope that had a kynurenate-preferring binding site that convas able to interact with kynurenate rather than 2AP5. Such a fundamentally different receptor profile sh be one that had a kynurenate-preferring binding site that
was able to interact with kynurenate rather than 2AP5.
Such a fundamentally different receptor profile should
be detectable in binding studies performed during earl A further study different receptor profile should
change fundamentally different receptor profile should
detectable in binding studies performed during early
velopment and restricted to the CA3 region.
A further study repl

Such a fundamentally different receptor profile should
be detectable in binding studies performed during early
development and restricted to the CA3 region.
A further study replicating the essential findings of
the above p be detectable in binding studies performed during early
development and restricted to the CA3 region.
A further study replicating the essential findings of
the above papers was reported by Cherubini et al. (1991).
This gro development and restricted to the CA3 region. sev
A further study replicating the essential findings of cul
the above papers was reported by Cherubini et al. (1991). Qu
This group recorded inward currents in CA3 neurones d A further study replicating the essential findings of cheabove papers was reported by Cherubini et al. (1991). G
This group recorded inward currents in CA3 neurones d
from rat hippocampus in the immediate postnatal and sla the above papers was reported by Cherubini et al. (1991).
This group recorded inward currents in CA3 neurones
from rat hippocampus in the immediate postnatal and
adult preparations. Bursts were induced by repeated
applicat from rat hippocampus in the immediate postnatal and adult preparations. Bursts were induced by repeated applications of potassium or potassium channel blockers, and it was found that none of the selective competitive applications of potassium or potassium channel blockers,
and it was found that none of the selective competitive
NMDA antagonists, including 2AP5 and CPP, would
prevent these periodic inward currents after they were
establ and it was found that non
NMDA antagonists, inclu
prevent these periodic investablished. They were, how
acid as well as by CNQX.
In distinction to these prevent these periodic inward currents after they were that established. They were, however, prevented by kynurenic results, in distinction to these results, Wuarin et al. (1990) hyd reported that bicuculline-induced burst

established. They were, however, prevented by kynurenic
acid as well as by CNQX.
In distinction to these results, Wuarin et al. (1990)
reported that bicuculline-induced bursts, recorded in
samples of human neocortex remove IDC
In distinction to these results, Wuarin et al. (1990) hyd
reported that bicuculline-induced bursts, recorded in four
samples of human neocortex removed for the treatment Bec
of intractable epilepsy in children, could b In distinction to these results, Wuarin et al. (1990) hydreported that bicuculline-induced bursts, recorded in four samples of human neocortex removed for the treatment Bec of intractable epilepsy in children, could be reported that bicuculline-induced bursts, recorded in four samples of human neocortex removed for the treatment Bever of intractable epilepsy in children, could be abolished by matchler and kynurenic acid. It would be inte samples of human neocortex removed for the treatment B
of intractable epilepsy in children, could be abolished by m
 $2AP5$ and kynurenic acid. It would be interesting to p
determine whether this represents (a) a pathologi of intractable epilepsy in children, could be abolished by may $2AP5$ and kynurenic acid. It would be interesting to podetermine whether this represents (a) a pathological sign created to the establishment of bursts and, 2AP5 and kynurenic acid. It would be interesting to petermine whether this represents (a) a pathological sign crelated to the establishment of bursts and, thus, epilepsy in these cases; (b) a developmental difference in determine whether this represents (a) a pathological sign creased enzyme activity (Heyes et al., 1992b).
related to the establishment of bursts and, thus, epilepsy Kynurenic acid has proved to be an effective neuro-
in related to the establishment of bursts and, thus, epile
in these cases; (b) a developmental difference in
human tissue; (c) a pharmacological difference betwe
neocortical and hippocampal tissue in other species;
(d) a diff in these cases; (b) a developmental difference in the human tissue; (c) a pharmacological difference between neocortical and hippocampal tissue in other species; or (d) a difference in the mechanism involved in bicucul-
 human tissue; (c) a pharmacological difference between sing
neocortical and hippocampal tissue in other species; or tion
 (d) a difference in the mechanism involved in bicucul-
line-induced, as opposed to picrotoxin-indu respectively and hippocampal tissue in other species;
(d) a difference in the mechanism involved in bicucu
line-induced, as opposed to picrotoxin-induced, burst
It will also be important to repeat this work using
range of (d) a difference in the mechanism involved in bicucul-
line-induced, as opposed to picrotoxin-induced, bursts. eleva
It will also be important to repeat this work using a chae-
range of kynurenate and $2AP5$ concentrations line-induced, as opposed to picrotoxin-induced, bursts. elevation of extracellular potassium levels following is-
It will also be important to repeat this work using a chaemia when administered by microdialysis locally in It will also be important to repeat this work using
range of kynurenate and 2AP5 concentrations to establish clearer comparability with the animal studies. Th
administration of daily injections of kynurenate icv (36
nmol) range of kynurenate and 2AP5 concentrations to estab-
lish clearer comparability with the animal studies. The
administration of daily injections of kynurenate icv (360 n
mmol) slowed the rate of development of amygdaloid-
 lish clearer comparability with the animal studies. The evided
administration of daily injections of kynurenate icv (360 mia in
mol) slowed the rate of development of amygdaloid-
aminkindled seizures in mature and immatur

QUINOLINIC AND KYNURENIC ACIDS
that intracellular recordings revealed no change in the of afterdischarges (Thompson et al., 1988). Both kynu-
current voltage relationships of CA3 cells during the renate and 7-chlorokynuren application of kynurenate at effective antagonistic con-
centrations, confirming other reports that kynurenate 1990) or peripheral administration in a variety of animal of afterdischarges (Thompson et al., 1988). Both kynurenate and 7-chlorokynurenate and 7-chlorokynurenate have anticonvulsant activity after central (Chiamulera et al., 1990; Singh et al., 361

of afterdischarges (Thompson et al., 1988). Both kynu-

renate and 7-chlorokynurenate have anticonvulsant ac-

tivity after central (Chiamulera et al., 1990; Singh et al.,

1990) or peripheral administration in a vari of afterdischarges (Thompson et al., 1988). Both kynu-
renate and 7-chlorokynurenate have anticonvulsant ac-
tivity after central (Chiamulera et al., 1990; Singh et al.,
1990) or peripheral administration in a variety of a of afterdischarges (Thompson et al., 1988). Both kyrenate and 7-chlorokynurenate have anticonvulsant
tivity after central (Chiamulera et al., 1990; Singh et
1990) or peripheral administration in a variety of an
models. Fur renate and 7-chlorokynurenate have anticonvulsant activity after central (Chiamulera et al., 1990; Singh et al., 1990) or peripheral administration in a variety of animal models. Furthermore, the administration of L-kynure tivity after central (Chiamulera et al., 1990; Singh et al., 1990) or peripheral administration in a variety of animal models. Furthermore, the administration of L-kynuren-
ine, which leads to an increase of brain kynurena 1990) or peripheral administration in a variety of animal models. Furthermore, the administration of L-kynurenine, which leads to an increase of brain kynurenate concentrations, is also able to reduce kainate-, NMDLA-, or models. Furthermore, the admin
ine, which leads to an increase
concentrations, is also able to red
or pentylenetetrazol-induced se
1992b; Vecsei and Beal, 1990b).
4. Ischaemia. Sourkes (1978) e, which leads to an increase of brain kynurenate
ncentrations, is also able to reduce kainate-, NMDLA-,
pentylenetetrazol-induced seizures (Vecsei et al.,
92b; Vecsei and Beal, 1990b).
4. *Ischaemia*. Sourkes (1978) was a

concentrations, is also able to reduce kainate-, NMDLA-,
or pentylenetetrazol-induced seizures (Vecsei et al.,
1992b; Vecsei and Beal, 1990b).
4. Ischaemia. Sourkes (1978) was among the first to
emphasise the abnormalities or pentylenetetrazol-induced seizures (Vecsei et al., 1992b; Vecsei and Beal, 1990b).
4. *Ischaemia*. Sourkes (1978) was among the first to emphasise the abnormalities of kynurenine metabolism
in central ischaemic disorder 1992b; Vecsei and Beal, 1990b).
4. Ischaemia. Sourkes (1978) was among the first to
emphasise the abnormalities of kynurenine metabolism
in central ischaemic disorders. The concentration of L-
kynurenine is significantly 4. Ischaemia. Sourkes (1978) was among the first to emphasise the abnormalities of kynurenine metabolism
in central ischaemic disorders. The concentration of L-
kynurenine is significantly elevated in the region of brain
 emphasise the abnormalities of kynurenine metabolism
in central ischaemic disorders. The concentration of L-
kynurenine is significantly elevated in the region of brain
infarcts, from control levels of approximately 500 n in central ischaemic disorders. The concentration of L-
kynurenine is significantly elevated in the region of brain
infarcts, from control levels of approximately 500 ng/g
(wet weight) to approximately 1500 ng/g in cortex kynurenine is significantly elevated in the region of brain infarcts, from control levels of approximately 500 ng/g (wet weight) to approximately 1500 ng/g in cortex and striatum and >2000 ng/g in the amygdala (Jellinge infarcts, from control levels of approximately 500 ng/
(wet weight) to approximately 1500 ng/g in cortex and
striatum and >2000 ng/g in the amygdala (Jellinger and
Riederer, 1981). Findings such as these led the author
to (wet weight) to approximately 1500 ng/g in cortex and
striatum and >2000 ng/g in the amygdala (Jellinger and
Riederer, 1981). Findings such as these led the authors
to make what may yet prove a prophetic statement,
namely striatum and >2000 ng/g in the amygdala (Jellinger and Riederer, 1981). Findings such as these led the authors to make what may yet prove a prophetic statement, namely, that "... disorders of cerebral metabolism ... in Riederer, 1981). Findings such as these led the authors
to make what may yet prove a prophetic statement,
namely, that "... disorders of cerebral metabolism ... in
particular indoleamine function are contributing to the
de to make what may yet
namely, that "...disorder
particular indoleamine fu
development of post-isch
complicating oedema."
With the development mely, that "... disorders of cerebral metabolism ...
rticular indoleamine function are contributing to
velopment of post-ischaemic brain damage and
mplicating oedema."
With the development of specific assays for quino
te,

adult preparations. Bursts were induced by repeated up to 3000 fmol/mg. It is intriguing that these latter applications of potassium or potassium channel blockers, regions of brain are also the regions that exhibit the and applications of potassium or potassium channel blockers, regions of brain are also the regions that exhibit the
and it was found that none of the selective competitive greatest neurological deterioration after ischaemia. I prevent these periodic inward currents after they were that the elevation of quinolinate concentration is the established. They were, however, prevented by kynurenic result of a combined increase in the enzymic activities particular indoleamine function are contributing to the development of post-ischaemic brain damage and the complicating oedema."
With the development of specific assays for quinoli-
nate, Heyes and Nowak (1990) reported th development of post-ischaemic brain damage and the complicating oedema."
With the development of specific assays for quinoli-
nate, Heyes and Nowak (1990) reported that quinolinate
levels remained normal or possibly were d complicating oedema."
With the development of specific assays for quinoli-
nate, Heyes and Nowak (1990) reported that quinolinate
levels remained normal or possibly were decreased for
several hours after the reestablishmen With the development of specific assays for quinoli-
nate, Heyes and Nowak (1990) reported that quinolinate
levels remained normal or possibly were decreased for
several hours after the reestablishment of cerebral cir-
cul nate, Heyes and Nowak (1990) reported that quinolinate
levels remained normal or possibly were decreased for
several hours after the reestablishment of cerebral cir-
culation after 5 to 15 minutes of ischaemia in gerbils. levels remained normal or possibly were decreased for
several hours after the reestablishment of cerebral cir-
culation after 5 to 15 minutes of ischaemia in gerbils.
Quinolinate did show marked increases at 2, 4, and 7
d several hours after the reestablishment of cerebral circulation after 5 to 15 minutes of ischaemia in gerbils.
Quinolinate did show marked increases at 2, 4, and 7 days postischaemia, with the hippocampus and striatum sho culation after 5 to 15 minutes of ischaemia in gerbils.
Quinolinate did show marked increases at 2, 4, and 7
days postischaemia, with the hippocampus and striatum
showing up to 60-fold changes, from approximately 50
up to Quinolinate did show marked increases at 2, 4, and 7 days postischaemia, with the hippocampus and striatum showing up to 60-fold changes, from approximately 50 up to 3000 fmol/mg. It is intriguing that these latter regions (wet weight) to approximately 1500 ng/g in cortex and
striatum and >2000 ng/g in the amygdala (Jellinger and
Riederer, 1981). Findings such as these led the authors
to make what may yet prove a prophetic statement,
name up to 3000 fmol/mg. It is intriguing that these latter regions of brain are also the regions that exhibit the regions of brain are also the regions that exhibit the greatest neurological deterioration after ischaemia. In subsequent work from the same laboratory, it appears that the elevation of quinolinate concentration is the res greatest neurological deterioration after ischaemia. In
subsequent work from the same laboratory, it appears
that the elevation of quinolinate concentration is the
result of a combined increase in the enzymic activities of that the elevation of quinolinate concentration is the that the elevation of quinolinate concentration is the result of a combined increase in the enzymic activities of IDO, kynureninase, kynurenine-3-hydroxylase, and 3-hydroxyanthranilic acid in the hippocampus, changes not f result of a combined increase in the enzymic activities of IDO, kynureninase, kynurenine-3-hydroxylase, and 3-hydroxyanthranilic acid in the hippocampus, changes not found in the undamaged cerebellum (Saito et al., 1992a). IDO, kynureninase, kynurenine-3-hydroxylase, and 3-
hydroxyanthranilic acid in the hippocampus, changes not
found in the undamaged cerebellum (Saito et al., 1992a).
Because these authors further found clear evidence for
ma hydroxyanthranilic acid in the hippocampus, changes not found in the undamaged cerebellum (Saito et al., 1992a).
Because these authors further found clear evidence for macrophage infiltration in the damaged areas, it was p found in the undamaged cerebellum (Saito et a
Because these authors further found clear evi
macrophage infiltration in the damaged area
postulated that these cells were the source of
creased enzyme activity (Heyes et al., ecause these authors further found clear evidence is
acrophage infiltration in the damaged areas, it we
stulated that these cells were the source of the is
ased enzyme activity (Heyes et al., 1992b).
Kynurenic acid has pro macrophage infiltration in the damaged areas, it was
postulated that these cells were the source of the in-
creased enzyme activity (Heyes et al., 1992b).
Kynurenic acid has proved to be an effective neuro-
protective age

postulated that these cells were the source of the
creased enzyme activity (Heyes et al., 1992b).
Kynurenic acid has proved to be an effective neu
protective agent against ischaemia-induced damage
single systemic injection creased enzyme activity (Heyes et al., 1992b).
Kynurenic acid has proved to be an effective neuro-
protective agent against ischaemia-induced damage; a
single systemic injection of 300 mg/kg gave some protec-
tion against Kynurenic acid has proved to be an effective neuro-
protective agent against ischaemia-induced damage; a
single systemic injection of 300 mg/kg gave some protec-
tion against carotid occlusion damage in 7-day-old rats
(And protective agent against ischaemia-induced damage; a
single systemic injection of 300 mg/kg gave some protec-
tion against carotid occlusion damage in 7-day-old rats
(Andine et al., 1988). Kynurenate also prevents the earl single systemic injection of 300 mg/kg gave some protection against carotid occlusion damage in 7-day-old rats
(Andine et al., 1988). Kynurenate also prevents the early
elevation of extracellular potassium levels following tion against carotid occlusion damage in 7-day-old rats
(Andine et al., 1988). Kynurenate also prevents the early
elevation of extracellular potassium levels following is-
chaemia when administered by microdialysis locally (Andine et al., 1988). Kynurenate also prevents the ea
elevation of extracellular potassium levels following
chaemia when administered by microdialysis locally in
the hippocampus (Katayama et al., 1991). This provid
eviden elevation of extracellular potassium levels following is-
chaemia when administered by microdialysis locally into
the hippocampus (Katayama et al., 1991). This provides
evidence that the increased potassium following ischa chaemia when administered by microdialysis locally into
the hippocampus (Katayama et al., 1991). This provides
evidence that the increased potassium following ischae-
mia is largely secondary to the activation of excitator evidence that the increased potassium following ischaemia is largely secondary to the activation of excitatory amino acid receptors.
5. Concussion. Brain damage due to a concussive injury seems to share a number of pharmac

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with ischaemia. For example, kynurenic acid was able to also

prevent the posttraumatic increase of cellular metabo- meta 362
with ischaemia. For example, kynurenic acid was able
prevent the posttraumatic increase of cellular meta
lism following fluid percussion injury in rats when lism following fluid percussion injury in rats when apwith ischaemia. For example, kynurenic acid was able to
prevent the posttraumatic increase of cellular metabo-
lism following fluid percussion injury in rats when ap-
plied locally (Kawamata et al., 1992). This protection with ischaemia. For example, kynurenic acid was able
prevent the posttraumatic increase of cellular metal
lism following fluid percussion injury in rats when s
plied locally (Kawamata et al., 1992). This protecti
was also prevent the posttraumatic increase of cellular metabolism following fluid percussion injury in rats when applied locally (Kawamata et al., 1992). This protection was also seen after 2AP5 and CNQX administration, supporting lism following fluid percussion injury in rats when applied locally (Kawamata et al., 1992). This protectic was also seen after 2AP5 and CNQX administration supporting the involvement of several types of recepto presumably plied locally (Kawas also seen aft
supporting the inversumably responent
mate or aspartate.
In related work In a salso seen after 2AP5 and CNQX administration
pporting the involvement of several types of receptor
esumably responding to an enhanced release of gluta
ate or aspartate.
In related work, Wrathall et al. (1992) induced

supporting the involvement of several types of receptors
presumably responding to an enhanced release of gluta-
mate or aspartate.
In related work, Wrathall et al. (1992) induced trau-
matic spinal injuries in rats and fou presumably responding to an enhanced release of gluta-

mate or aspartate.

In related work, Wrathall et al. (1992) induced trau-

In matic spinal injuries in rats and found that neither

intravenous dextromethorphan nor mate or aspartate. Lasting protection or improved trau-

In related work, Wrathall et al. (1992) induced trau-

intravenous dextromethorphan nor dizocilpine were able

into produce lasting protection or improved recovery In related work, Wrathall et al. (1992) induced trau-
matic spinal injuries in rats and found that neither L
intravenous dextromethorphan nor dizocilpine were able
to produce lasting protection or improved recovery of
fun matic spinal injuries in rats and found that neither intravenous dextromethorphan nor dizocilpine were able to produce lasting protection or improved recovery of chinesion. In contrast, kynurenic acid, at 300 mg/kg or app intravenous dextromethorphan nor dizocilpine were able
to produce lasting protection or improved recovery of
function. In contrast, kynurenic acid, at 300 mg/kg or
applied locally to the damaged cord, was able to produce
 to produce lasting protection or improved recovery of churchion. In contrast, kynurenic acid, at 300 mg/kg or applied locally to the damaged cord, was able to produce significant protection up to at least 2 months followi function. In contrast, kynurenic acid, at 300 mg/kg or of applied locally to the damaged cord, was able to produce plagarificant protection up to at least 2 months following (Figury. The antagonist profile was interpreted applied locally to the damaged cord, was able
significant protection up to at least 2 month
injury. The antagonist profile was interpreted
the involvement of non-NMDA receptors
many of the long-term neurological sequelae.
 mificant protection up to at least 2 months following
jury. The antagonist profile was interpreted to indicate
e involvement of non-NMDA receptors in causing
any of the long-term neurological sequelae.
6. *Hypoglycaemia*.

injury. The antagonist profile was interpreted to indicat
the involvement of non-NMDA receptors in causin
many of the long-term neurological sequelae.
6. Hypoglycaemia. A period of profound hypoglycaemi
produces neuronal d the involvement of non-NMDA receptors in causing
many of the long-term neurological sequelae.
6. Hypoglycaemia. A period of profound hypoglycaemia
produces neuronal damage in several brain regions, dam-
age that can be pre many of the long-term neurological sequelae.

6. Hypoglycaemia. A period of profound hypoglycaemia

produces neuronal damage in several brain regions, dam-

age that can be prevented by antagonists acting at

NMDA-sensiti 6. Hypoglycaemia. A period of profound hypoglycaemia encontrol produces neuronal damage in several brain regions, damage that can be prevented by antagonists acting at $NMDA$ -sensitive receptors (Wieloch, 1985a,b; Simon et produces neuronal damage in several brain regions, damage that can be prevented by antagonists acting at NMDA-sensitive receptors (Wieloch, 1985a,b; Simon et al., 1986b). Heyes et al. (1990b) measured quinolinate in whole age that can be prevented by antagonists acting at $NMDA$ -sensitive receptors (Wieloch, 1985a,b; Simon et al., 1986b). Heyes et al. (1990b) measured quinolinate in phole brain and extracellular fluid of animals subjected t NMDA-sensitive receptors (Wieloch, 1985a,b; Sireal, 1986b). Heyes et al. (1990b) measured quinolin
whole brain and extracellular fluid of animals subset of hypogly
caemia and reported a 6.5-fold elevat
quinolinate in plasm al., 1986b). Heyes et al. (1990b) measured quinolinate in position whole brain and extracellular fluid of animals subjected to hypoglycaemia and reported a 6.5-fold elevation of quinolinate in plasma at the onset of elect whole brain and extracellular fluid of animals subjected
to hypoglycaemia and reported a 6.5-fold elevation of
quinolinate in plasma at the onset of electroencephalo-
graphic isoelectricity. Less dramatic changes (2- to 3to hypoglycaemia and reported a 6.5-fold elevation of quinolinate in plasma at the onset of electroencephalo-
graphic isoelectricity. Less dramatic changes $(2 - t_0)$ and fold) were detected in all brain areas examined. Ne quinolinate in plasma at the onset of electroencephalo-
graphic isoelectricity. Less dramatic changes $(2 - t_0)^2$ this
fold) were detected in all brain areas examined. Neither
the time course nor the extent of the quinolin graphic isoelectricity. Less dramatic changes (2016) were detected in all brain areas examined.
the time course nor the extent of the quinolinate is
were considered appropriate to account for the
histological damage seen f Indeed, were detected in all brain areas examined. Neith e time course nor the extent of the quinolinate increasure considered appropriate to account for the rapstological damage seen following hypoglycaemia.
Indeed, when

the time course nor the extent of the quinolinate increase
were considered appropriate to account for the rapid
histological damage seen following hypoglycaemia.
Indeed, when the concentration in hippocampal extra-
cellula were considered appropriate to account for the rapide histological damage seen following hypoglycaemia.
Indeed, when the concentration in hippocampal extra cellular fluid was assessed using microdialysis, the estimated con histological damage seen following hypoglycaemia.

Indeed, when the concentration in hippocampal extra-

cellular fluid was assessed using microdialysis, the esti-

mated control level of approximately 67 nmol/litre (cor-Indeed, when the concentration in hippocampal extra-
cellular fluid was assessed using microdialysis, the est
mated control level of approximately 67 nmol/litre (co
rected for recovery) was unaffected by 40 minutes
hypogly cellular fluid was assessed using microdialysis, the esti-
mated control level of approximately 67 nmol/litre (cor-
rected for recovery) was unaffected by 40 minutes of
thypoglycaemia. Coupled with the absence of any extr mated control level of approximately 67 nmol/litre (corrected for recovery) was unaffected by 40 minutes of the hypoglycaemia. Coupled with the absence of any extractillar change of quinolinate, it was proposed that some o rected for recovery) was unaffected by 40 minutes of
hypoglycaemia. Coupled with the absence of any extra-
cellular change of quinolinate, it was proposed that some
other excitotoxic agent or process mediates this form of
 hypoglycaemia. Coupled with the absence of any extra-
cellular change of quinolinate, it was proposed that some
other excitotoxic agent or process mediates this form of
neuronal damage. The absence of changes of quinolinat cellular change of quinolinate, it was proposed that somether excitotoxic agent or process mediates this form neuronal damage. The absence of changes of quinolinatin cortex and hippocampus was confirmed by Westerbe et al. other excitotoxic agent or process mediates this form of
neuronal damage. The absence of changes of quinolinate
in cortex and hippocampus was confirmed by Westerberg
et al. (1990) using 30 minutes of insulin-induced hypogneuronal damage. The absence of changes of quinolinate of incorder in cortex and hippocampus was confirmed by Westerberg injet al. (1990) using 30 minutes of insulin-induced hypog-
that al. (1990) using 30 minutes of insul in cortex and hippocampus was confirmed by Westerberg
et al. (1990) using 30 minutes of insulin-induced hypog-
lycaemia. However, these authors were of the opinion
that the recorded changes of striatal quinolinate, up to
2 et al. (1990) using 30 minutes of i
lycaemia. However, these author
that the recorded changes of stri
2.2 times basal, could, if mainta
contribute to striatal degeneration
A comparison of studies of isch Comparison and the recorded changes of striatal quinolinate, use the recorded changes of striatal quinolinate, use times basal, could, if maintained for long perintribute to striatal degeneration.
A comparison of studies o

2.2 times basal, could, if maintained for long periods, contribute to striatal degeneration.
A comparison of studies of ischaemia and hypoglycaemia raises some important questions regarding the reasons for the different ki 2.2 times basal, could, if maintained for long periods, contribute to striatal degeneration.
A comparison of studies of ischaemia and hypoglycaemia raises some important questions regarding the reasons for the different ki contribute to striatal degeneration.
A comparison of studies of ischaemia and hypoglycaemia raises some important questions regarding the reasons for the different kinetics of quinolinate changes.
Although the retarded ele A comparison of studies of ischaemia and hypoglycae-
mia raises some important questions regarding the rea-
sons for the different kinetics of quinolinate changes. of
Although the retarded elevation of quinolinate after is mia raises some important questions regarding the rea-
sons for the different kinetics of quinolinate changes. O
Although the retarded elevation of quinolinate after is-
chaemia might be the result of neuronal death and th sons for the different kinetics of quinolinate changes. Of Although the retarded elevation of quinolinate after is-
chaemia might be the result of neuronal death and the grand-
secondary gliosis, it would seem important to Although the retarded elevation of quinolinate after is-
chaemia might be the result of neuronal death and the
greater changes may be anticipated. Despite these limi-
secondary gliosis, it would seem important to establish chaemia might be the result of neuronal death and the greate
secondary gliosis, it would seem important to establish tation
the mechanism of the rapid increase of plasma and brain defici
tissue quinolinate with hypoglycaem secondary gliosis, it would seem important to establis
the mechanism of the rapid increase of plasma and brain
tissue quinolinate with hypoglycaemia. Although tl
slow increase in quinolinate may be a consequence of ε
i tissue quinolinate with hypoglycaemia. Although the slow increase in quinolinate may be a consequence of an increased blood-brain barrier permeability with a correspondingly increased penetration of precursor, it may

NE
also reflect a more fundamental relationship between
metabolic status and kynurenine metabolism. NE
also reflect a more fundamental relationsh
metabolic status and kynurenine metabolism
7. Hepatic damage. From Riederer's labor

100 reflect a more fundamental relationship between
100 reflect damage. From Riederer's laboratory there
17. *Hepatic damage*. From Riederer's laboratory there
100 reflect data concerning the levels of kynurenines also reflect a more fundamental relationship between
metabolic status and kynurenine metabolism.
7. *Hepatic damage*. From Riederer's laboratory there
have emerged data concerning the levels of kynurenines
in liver disease also reflect a more fundamental relationship betw
metabolic status and kynurenine metabolism.
7. Hepatic damage. From Riederer's laboratory t
have emerged data concerning the levels of kynuren
in liver disease (Riederer e metabolic status and kynurenine metabolism.
7. Hepatic damage. From Riederer's laboratory there
have emerged data concerning the levels of kynurenines
in liver disease (Riederer et al., 1981). Serum L-kynuren-
ine was est 7. Hepatic damage. From Riederer's laboratory there have emerged data concerning the levels of kynurenines in liver disease (Riederer et al., 1981). Serum L-kynurenine was estimated at 2μ M in control subjects and up to have emerged data concerning the levels of kynurenines
in liver disease (Riederer et al., 1981). Serum L-kynuren-
ine was estimated at $2 \mu M$ in control subjects and up to
17.4 μ M in patients in acute coma due to hepat in liver disease (Riederer et al., 1981). Serum L-kynuren-
ine was estimated at 2 μ M in control subjects and up to
17.4 μ M in patients in acute coma due to hepatic failure.
Less marked changes of serum tryptophan we ine was estimated at 2 μ M in control subjects and up to 17.4 μ M in patients in acute coma due to hepatic failure.
Less marked changes of serum tryptophan were recorded.
In the CSF, the changes were just as great wit 17.4 μ M in patients in acute coma due to hepatic failure.
Less marked changes of serum tryptophan were recorded.
In the CSF, the changes were just as great with control
L-kynurenine at 37 ng/ml and 10 times this, 397 n Less marked changes of serum tryptophan were recorded.
In the CSF, the changes were just as great with control
L-kynurenine at 37 ng/ml and 10 times this, 397 ng/ml,
in hepatic coma. Interestingly, no change was noted in
 In the CSF, the changes were just as great with cont
L-kynurenine at 37 ng/ml and 10 times this, 397 ng/i
in hepatic coma. Interestingly, no change was noted
cases of diabetic coma (54 ng/ml). The administratiof
L-valine L-kynurenine at 37 ng/ml and 10 times this, 397 ng/ml,
in hepatic coma. Interestingly, no change was noted in
cases of diabetic coma (54 ng/ml). The administration
of L-valine rapidly restored L-kynurenine and trypto-
pha in hepatic coma. Interestingly, no change was noted in cases of diabetic coma (54 ng/ml). The administration of L-valine rapidly restored L-kynurenine and trypto-
phan levels to normal and induced rapid patient arousal (Ri cases of diabetic coma (54 ng/ml). The administration
of L-valine rapidly restored L-kynurenine and trypto-
phan levels to normal and induced rapid patient arousa
(Riederer et al., 1981). This may reflect the competition
f L-valine rapidly restored L-kynurenine and trypto-
an levels to normal and induced rapid patient arousal
iederer et al., 1981). This may reflect the competition
r tryptophan and L-kynurenine transport into brain.
Moroni et phan levels to normal and induced rapid patient arousal (Riederer et al., 1981). This may reflect the competition for tryptophan and L-kynurenine transport into brain.
Moroni et al. (1986c) later extended this work and foc

(Riederer et al., 1981). This may reflect the competition
for tryptophan and L-kynurenine transport into brain.
Moroni et al. (1986c) later extended this work and
focused greater attention on the possibility that hepatic
e for tryptophan and L-kynurenine transport into brain.
Moroni et al. (1986c) later extended this work and
focused greater attention on the possibility that hepatic
encephalopathy or the coma due to hepatic failure could
res focused greater attention on the possibility that hepatic
encephalopathy or the coma due to hepatic failure could
result from the accumulation of kynurenines in the CNS.
It was pointed out, for example, that animal models focused greater attention on the possibility that hepatic
encephalopathy or the coma due to hepatic failure could
result from the accumulation of kynurenines in the CNS.
It was pointed out, for example, that animal models encephalopathy or the coma due to hepatic failure c
result from the accumulation of kynurenines in the I
It was pointed out, for example, that animal mode
hepatic failure induce substantial increases in
plasma and brain tr result from the accumulation of kynurenines in the CNS.
It was pointed out, for example, that animal models of
hepatic failure induce substantial increases in both
plasma and brain tryptophan and that the administra-
tion It was pointed out, for example, that animal models of hepatic failure induce substantial increases in both plasma and brain tryptophan and that the administration of high doses of tryptophan could induce a comatose state hepatic failure induce substantial increases in bot
plasma and brain tryptophan and that the administre
tion of high doses of tryptophan could induce a comatos
state in animals (Rossi-Fanelli et al., 1982). Therefore
this plasma and brain tryptophan and that the administra-
tion of high doses of tryptophan could induce a comatose
state in animals (Rossi-Fanelli et al., 1982). Therefore,
this group prepared rats with chronic portacaval anastion of high doses of tryptophan could induce a comate state in animals (Rossi-Fanelli et al., 1982). Thereforthis group prepared rats with chronic portacaval an tomoses as a model of hepatic failure and analysed seral bra state in animals (Rossi-Fanelli et al., 1982). Therefore, this group prepared rats with chronic portacaval anas-
tomoses as a model of hepatic failure and analysed several brain regions for their content of a range of tryp this group prepared rats with chronic portacaval anas-
tomoses as a model of hepatic failure and analysed sev-
eral brain regions for their content of a range of trypto-
phan metabolites. In general, the concentrations of tomoses as a model of hepatic failure and analysed several brain regions for their content of a range of trypto-
phan metabolites. In general, the concentrations of 5-
hydroxyindoleacetic acid and quinolinic acid increased eral brain regions for their content of a range of try
phan metabolites. In general, the concentrations c
hydroxyindoleacetic acid and quinolinic acid incre
after 4 weeks to levels of between 65 and 185% of cont
(Moroni et phan metabolites. In general, the concentrations of 5-
hydroxyindoleacetic acid and quinolinic acid increased
after 4 weeks to levels of between 65 and 185% of controls
(Moroni et al., 1986b). Since the extracellular conce hydroxyindoleacetic acid and quinolinic acid increased
after 4 weeks to levels of between 65 and 185% of controls
(Moroni et al., 1986b). Since the extracellular concentra-
tions of quinolinate are normally rather low, it after 4 weeks to levels of between 65 and 185% of controls (Moroni et al., 1986b). Since the extracellular concentrations of quinolinate are normally rather low, it is unlikely that changes of this magnitude could exert si tions of quinolinate are normally rather low, it is unlikely
that changes of this magnitude could exert significant
acute effects on amino acid receptors. However, in the
study by Vecsei et al. (1992a,b), the early accumul tions of quinolinate are normally rather low, it is unlikely
that changes of this magnitude could exert significant
acute effects on amino acid receptors. However, in the
study by Vecsei et al. (1992a,b), the early accumul that changes of this magnitude could exert significant acute effects on amino acid receptors. However, in the study by Vecsei et al. (1992a,b), the early accumulation of central kynurenic acid following peripheral injectio Frame from the all. (1986) later extracted to increased metabolism control is and Moroni et al. (1986) later extended this work and focused greater attention on the possibility that hepatic encephalopathy or the coma due study by Vecsei et al. (1992a,b), the exported the contral kynurenic acid following peripheral tissues.

injections, an effect attributed to increase injections, an effect attributed to increase.

It is very probable that, central kynurenic acid following peripheral injection
L-kynurenine was substantially less after repeated
jections, an effect attributed to increased metabolism
L-kynurenine by peripheral tissues.
It is very probable that,

of L-kynurenine was substantially less after repeated
injections, an effect attributed to increased metabolism
of L-kynurenine by peripheral tissues.
It is very probable that, during the 4-week period of
experiments by Mor injections, an effect attributed to increased metabolism
of L-kynurenine by peripheral tissues.
It is very probable that, during the 4-week period of
experiments by Moroni et al., such a compensatory in-
crease of metaboli of L-kynurenine by peripheral tissues.
It is very probable that, during the 4-week period of
experiments by Moroni et al., such a compensatory in-
crease of metabolism by tissues, such as the kidney and
intestine, with act experiments by Moroni et al., such a compensatory increase of metabolism by tissues, such as the kidney and intestine, with active kynurenine-metabolising systems, could have reduced the impact of portacaval anastomosis. experiments by Moroni et al., such a compensatory in-
crease of metabolism by tissues, such as the kidney and
intestine, with active kynurenine-metabolising systems,
could have reduced the impact of portacaval anastomosis. crease of metabolism by tissues, such as the kidney and
intestine, with active kynurenine-metabolising systems,
could have reduced the impact of portacaval anastomosis.
In any case, it is arguable whether the very limited intestine, with active kynurenine-metabolising systems,
could have reduced the impact of portacaval anastomosis.
In any case, it is arguable whether the very limited loss
of liver function modeled by such anastomoses provi could have reduced the impact of portacaval anastomosis
In any case, it is arguable whether the very limited loss
of liver function modeled by such anastomoses provide
a realistic equivalent to severe hepatic failure wher
 In any case, it is arguable whether the very limited loss
of liver function modeled by such anastomoses provides
a realistic equivalent to severe hepatic failure when
greater changes may be anticipated. Despite these limiof liver function modeled by such anastomoses provid
a realistic equivalent to severe hepatic failure whe
greater changes may be anticipated. Despite these lim
tations, the experiment does confirm the ability of liv
defici a realistic equivalent to severe hepatic failure wh
greater changes may be anticipated. Despite these lin
tations, the experiment does confirm the ability of li-
deficits to increase cerebral quinolinate levels and ma
tain greater changes may be anticipated. Despite these limitations, the experiment does confirm the ability of liver deficits to increase cerebral quinolinate levels and maintains the possibility that even small changes of quin tations, the experiment does confirm the ability of liver
deficits to increase cerebral quinolinate levels and main-
tains the possibility that even small changes of quinoli-
nate, if persistent during a long period, could deficits to increase cerebral quinolinate levels and maintains the possibility that even small changes of quinolinate, if persistent during a long period, could have detrimental effects on neuronal survival. It would also

QUINOLINIC AND KYNURENIC ACIDS
range of tissues at much shorter time periods after the plasma levels of kynurenine. Indeed, if these various
findings are considered together, the conclusion seems range of tissues at much shorter timestablishment of the vascular shunt.
In samples of CSF taken from hum

QUINOLINIC AND KYN

In samples of the vascular shunt.

In samples of CSF taken from human subjects during

patic coma, the quinolinate concentration was 152 re range of tissues at much shorter time periods after the plasestablishment of the vascular shunt. In samples of CSF taken from human subjects during ines hepatic coma, the quinolinate concentration was 152 respression compa range of tissues at much shorter time periods after the
establishment of the vascular shunt.
In samples of CSF taken from human subjects during
hepatic coma, the quinolinate concentration was 152
compared with 22 pmol/ml i establishment of the vascular shunt. In
In samples of CSF taken from human subjects during
hepatic coma, the quinolinate concentration was 152
recompared with 22 pmol/ml in control CSF. Consistent too
with this, analysis o In samples of CSF taken from human subjects duri
hepatic coma, the quinolinate concentration was 1
compared with 22 pmol/ml in control CSF. Consiste
with this, analysis of frontal cortex from patients dyi
after episodes o hepatic coma, the quinolinate concentration was 152 r compared with 22 pmol/ml in control CSF. Consistent twith this, analysis of frontal cortex from patients dying that after episodes of hepatic encephalopathy showed qui compared with 22 pmol/ml in control CSF. Consistent to
with this, analysis of frontal cortex from patients dying the
after episodes of hepatic encephalopathy showed quino-
linate levels of 2.6 nmol/g, or 2.6 μ M, more t with this, analysis of frontal cortex from patients dying
after episodes of hepatic encephalopathy showed quino-
linate levels of 2.6 nmol/g, or 2.6 μ M, more than 3 times
those of controls. Two of the patients examined after episodes of hepatic encephalopathy showed quino-
linate levels of 2.6 nmol/g, or 2.6 μ M, more than 3 times
those of controls. Two of the patients examined showed
cerebral levels of approximately 10 μ M quinolin those of controls. Two of the patients examined showed
cerebral levels of approximately $10 \mu M$ quinolinate, con-
centrations known to be toxic to neurones if maintained
(Moroni et al., 1986b). These changes are also cons those of controls. Two of the patients examined showerebral levels of approximately 10μ M quinolinate, contrations known to be toxic to neurones if maintai (Moroni et al., 1986b). These changes are also consis with the cerebral levels of approximately 10μ M quinolinate, concentrations known to be toxic to neurones if maintaine (Moroni et al., 1986b). These changes are also consister with the 7-fold increase of human neocortical 3-hydr centrations known to be to
(Moroni et al., 1986b). The
with the 7-fold increase of l
kynurenine in hepatic ence
son and Reynolds (1991).
Unfortunately, recent w Moroni et al., 1986b). These changes are also consistent
th the 7-fold increase of human neccortical 3-hydroxy-
in unrenine in hepatic encephalopathy reported by Pear-
m and Reynolds (1991).
Unfortunately, recent work, usi

with the 7-fold increase of human neocortical 3-hydroxy-
hyperaturenine in hepatic encephalopathy reported by Pear-
son and Reynolds (1991). This important in the hyperammonaernic rat treated with
hepatic damage (the hyper kynurenine in hepatic encephalopathy reported by Pearson and Reynolds (1991).
Unfortunately, recent work, using different models of
hepatic damage (the hyperammonaemic rat treated with
urease, or the ammonium acetate-injec reproduced they incompose finding to the Unfortunately, recent work, using different models
hepatic damage (the hyperammonaemic rat treated w
urease, or the ammonium acetate-injected rat), has inteproduced these findings. hepatic damage (the hyperammonaemic rat treated with urease, or the ammonium acetate-injected rat), has not reproduced these findings. No changes of CSF quinolinate concentrations were detected in these models (Ro-binson e urease, or the ammonium acetate-injected rat), has not reproduced these findings. No changes of CSF quinoli-
nate concentrations were detected in these models (Robinson et al., 1992).
8. Infection. Heyes and his group (199 able and the stimulation of kynurenine metabolism in the bacterial endotoxins, activating IDO in peripheral and the stimulation of kynurenine metabolism in the bacterial endotoxins, activating IDO in peripheral and the sti nate concentrations were detected in these models (Ro-posure (Kim and Choi, 1987; Whetsell and Schwarcz, binson et al., 1992).
 $\frac{1989}{1989}$. Kynurenate was also elevated 4 to 10-fold.

8. Infection. Heyes and his grou

binson et al., 1992).

8. *Infection*. Heyes and his group (1992a) pioneered

and developed the important concept that infection can

lead to the stimulation of kynurenine metabolism in the

CNS. It has been known for many 8. Infection. Heyes and his group (1992a) pioneered and developed the important concept that infection car
lead to the stimulation of kynurenine metabolism in the
CNS. It has been known for many years that bacteria
endotox and developed the important concept that infection can
lead to the stimulation of kynurenine metabolism in the
CNS. It has been known for many years that bacterial
endotoxins can promote the synthesis and efflux of kyn-
ur lead to the stimulation of kynurenine metabolism in the
CNS. It has been known for many years that bacterial
endotoxins can promote the synthesis and efflux of kyn-
urenines from peripheral tissues (Rapoport et al., 1970;
 CNS. It has been known for many years that bacterial cendotoxins can promote the synthesis and efflux of kyn-
urenines from peripheral tissues (Rapoport et al., 1970; p
Rapoport and Beisel, 1971) partly due to the activati endotoxins can promote the synthesis and efflux of kyn-
urenines from peripheral tissues (Rapoport et al., 1970; perl
Rapoport and Beisel, 1971) partly due to the activation fero
of IDO (Takikawa et al., 1986; Yoshida et a urenines from peripheral tissues (Rapoport et al., Rapoport and Beisel, 1971) partly due to the active of IDO (Takikawa et al., 1986; Yoshida et al., 1986) knowledge was extended to the mouse CNS by we which the administra Rapoport and Beisel, 1971) partly due to the activation
of IDO (Takikawa et al., 1986; Yoshida et al., 1986). This
knowledge was extended to the mouse CNS by work in
which the administration of bacterial lipopolysaccha-
ri of IDO (Takikawa et al., 1986; Yoshida et al., 1986). This
knowledge was extended to the mouse CNS by work in
which the administration of bacterial lipopolysaccha-
rides increased neocortical, but not plasma, quinolinate
c knowledge was extended to the mouse CNS by work in of which the administration of bacterial lipopolysaccharides increased neocortical, but not plasma, quinolinate in concentration by 81% (Heyes et al., 1989b). It is no which the administration of bacterial lipopolysaccharides increased neocortical, but not plasma, quinolinate is
concentration by 81% (Heyes et al., 1989b). It is not reflect whether this change was due to an activation of rides increased neocortical, but not plasma, quinol
concentration by 81% (Heyes et al., 1989b). It is
clear whether this change was due to an activatic
cerebral IDO or was secondary to the observed inc
of cortical tryptoph ncentration by 81% (Heyes et al., 1989b). It is not
ear whether this change was due to an activation of
rebral IDO or was secondary to the observed increase
cortical tryptophan (Heyes and Markey, 1988).
Similar results wer

cerebral IDO or was secondary to the observed increase
of cortical tryptophan (Heyes and Markey, 1988).
Similar results were reported by Moroni et al. (1991a)
in which lipopolysaccharides from *Escherichia coli*, in-
jecte cerebral IDO or was secondary to the observed increase not cortical tryptophan (Heyes and Markey, 1988). la Similar results were reported by Moroni et al. (1991a) ol in which lipopolysaccharides from *Escherichia coli*, in of cortical tryptophan (Heyes and Markey, 1988).

Similar results were reported by Moroni et al. (1991a)

in which lipopolysaccharides from *Escherichia coli*, in-

jected systemically in rats, were found to elevate whole
 Similar results were reported by Moroni et al. (1991a)
in which lipopolysaccharides from *Escherichia coli*, in-
jected systemically in rats, were found to elevate whole
brain levels of tryptophan and quinolinic and kynure in which lipopolysaccharides from *Escherichia coli*, in-
jected systemically in rats, were found to elevate whole
hrain levels of tryptophan and quinolinic and kynurenic
acids. Interestingly, the direct administration of jected systemically in rats, were found to elevate whole
brain levels of tryptophan and quinolinic and kynurenic
acids. Interestingly, the direct administration of lipo-
polysaccharides into the cerebral ventricles was una brain levels of tryptophan and quinolinic and kynurenic
acids. Interestingly, the direct administration of lipo-
polysaccharides into the cerebral ventricles was unable
to increase the amounts of these kynurenines in brain acids. Interestingly, the direct administration of lipo-
polysaccharides into the cerebral ventricles was unable
to increase the amounts of these kynurenines in brain,
implying that the increase of both measured compounds
 polysaccharides into the cerebral ventricles was unable
to increase the amounts of these kynurenines in brain,
implying that the increase of both measured compounds
after systemic endotoxin either is derived from the in-
c from increase the amounts of these kynurenines in brain,
implying that the increase of both measured compounds
after systemic endotoxin either is derived from the in-
creased plasma tryptophan or L-kynurenine resulting
fro after systemic endotoxin either is derived from the in-
creased plasma tryptophan or L-kynurenine resulting tial quantities of kynurenine metabolites.
from induction of hepatic kynurenine metabolism or that Whatever the me after systemic endotoxin either is derived from the increased plasma tryptophan or L-kynurenine resulting from induction of hepatic kynurenine metabolism or that the peripherally administered endotoxin acted to induce ithe creased plasma tryptophan
from induction of hepatic kyi
the peripherally administere
the production of a stimula
activated IDO in the CNS.
Since the induction of TD om induction of hepatic kynurenine metabolism or that
e peripherally administered endotoxin acted to induce
e production of a stimulatory factor that secondarily
tivated IDO in the CNS.
Since the induction of TDO by chroni

activated IDO in the CNS.
Since the induction of TDO by chronic administration
of glucocorticoids did not increase cerebral kynurenines
(Connick et al., 1988), it seems that only activation of the production of a stimulatory factor that secondarily pactivated IDO in the CNS. The extinct of TDO by chronic administration of glucocorticoids did not increase cerebral kynurenines L
(Connick et al., 1988), it seems th activated IDO in the CNS. even

Since the induction of TDO by chronic administration

of glucocorticoids did not increase cerebral kynurenines

Leg

(Connick et al., 1988), it seems that only activation of 9.

IDO, either Since the induction of TDO by chronic administration
of glucocorticoids did not increase cerebral kynurenines
(Connick et al., 1988), it seems that only activation of
IDO, either peripherally or centrally located, is able of glucocorticoids did not increase cerebral kynurenines L
(Connick et al., 1988), it seems that only activation of
IDO, either peripherally or centrally located, is able to
pinduce kynurenine metabolism in the CNS. This i

plasma levels of kynurenine. Indeed, if these various FINURENIC ACIDS
plasma levels of kynurenine. Indeed, if these various
findings are considered together, the conclusion seems
inescapable that a peripherally produced agent must be 363

plasma levels of kynurenine. Indeed, if these various

findings are considered together, the conclusion seems

inescapable that a peripherally produced agent must be

responsible for the activation of central IDO afte plasma levels of kynurenine. Indeed, if these various findings are considered together, the conclusion seen inescapable that a peripherally produced agent must lesponsible for the activation of central IDO after endotion a plasma levels of kynurenine. Indeed, if these various findings are considered together, the conclusion seems inescapable that a peripherally produced agent must be responsible for the activation of central IDO after endoto findings are considered together, the conclusion seems
inescapable that a peripherally produced agent must be
responsible for the activation of central IDO after endo-
toxin administration. It is also important to consider inescapable that a peripherally produced agent must be responsible for the activation of central IDO after endotoxin administration. It is also important to consider that other enzymes of the kynurenine pathway may be indu responsible for the activation of central IDO after endo-
toxin administration. It is also important to consider
that other enzymes of the kynurenine pathway may be
induced, directly or indirectly, by endotoxin. In their
s toxin administration. It is also important to consider
that other enzymes of the kynurenine pathway may be
induced, directly or indirectly, by endotoxin. In their
study of epilepsy-prone mice, Nakano et al. (1992) re-
port that other enzymes of the kynurenine pathway may be induced, directly or indirectly, by endotoxin. In their study of epilepsy-prone mice, Nakano et al. (1992) reported that administration of a preparation of bacterial lipo induced, directly or ind
study of epilepsy-prone
ported that administratio
lipopolysaccharides (from
by approximately 50%.
Heyes and Lackner (1 ported that administration of a preparation of bacterial
lipopolysaccharides (from $E.$ coli) elevated 3HAO activity
by approximately 50%.
Heyes and Lackner (1990) demonstrated substantial
increases in CSF quinolinate con

ported that administration of a preparation of bacterial
lipopolysaccharides (from E. coli) elevated 3HAO activity
by approximately 50%.
Heyes and Lackner (1990) demonstrated substantial
increases in CSF quinolinate concen lipopolysaccharides (from *E. coli*) elevated 3HAO activ
by approximately 50%.
Heyes and Lackner (1990) demonstrated substant
increases in CSF quinolinate concentrations in the
moribund rhesus macaque monkeys exhibiting s by approximately 50%.
Heyes and Lackner (1990) demonstrated substantial
increases in CSF quinolinate concentrations in three
moribund rhesus macaque monkeys exhibiting septicae-
mia of unrelated origins. Whereas control an Heyes and Lackner (1990) demonstrated substantial
increases in CSF quinolinate concentrations in three
moribund rhesus macaque monkeys exhibiting septicae-
mia of unrelated origins. Whereas control animals dis-
played CSF increases in CSF quinolinate concentrations in three moribund rhesus macaque monkeys exhibiting septicaemia of unrelated origins. Whereas control animals displayed CSF quinolinate values of 14 to 43 nmol/litre, the disease moribund rhesus macaque monkeys exhibiting septicaemia of unrelated origins. Whereas control animals displayed CSF quinolinate values of 14 to 43 nmol/litre, the diseased monkeys had levels of 643, 1045, and 4148 nmol/litr mia of unrelated origins. Whereas control animals dis-
played CSF quinolinate values of 14 to 43 nmol/litre, the
diseased monkeys had levels of 643, 1045, and 4148 nmol/
litre. These are concentrations comparable with thos played CSF quinolinate values of 14 to 43 nmol/litre, the diseased monkeys had levels of 643, 1045, and 4148 nmol/
litre. These are concentrations comparable with those
found to produce neuronal damage after continued ex-
 diseased monkeys had levels of 643, 1045, and 4148
litre. These are concentrations comparable with
found to produce neuronal damage after continue
posure (Kim and Choi, 1987; Whetsell and Sch
1989). Kynurenate was also ele re. These are concentrations comparable with those und to produce neuronal damage after continued explanation of (Kim and Choi, 1987; Whetsell and Schwarc: 89). Kynurenate was also elevated 4 to 10-fold. It is likely that

and developed the important concept that infection can
lead to the stimulation of kynurenine metabolism in the bacterial endotoxins, activating IDO in peripheral and
CNS. It has been known for many years that bacterial cen found to produce neuronal damage after continued ex-
posure (Kim and Choi, 1987; Whetsell and Schwarcz,
1989). Kynurenate was also elevated 4 to 10-fold.
It is likely that one explanation of this apparent stim-
ulation of posure (Kim and Choi, 1987; Whetsell and Schwarcz, 1989). Kynurenate was also elevated 4 to 10-fold.
It is likely that one explanation of this apparent stimulation of kynurenine metabolism is the presence of bacterial endo 1989). Kynurenate was also elevated 4 to 10-fold.
It is likely that one explanation of this apparent stim
ulation of kynurenine metabolism is the presence of
bacterial endotoxins, activating IDO in peripheral and
central t It is likely that one explanation of this apparent stimulation of kynurenine metabolism is the presence of bacterial endotoxins, activating IDO in peripheral and central tissues, but it is also probable that interferons, p ulation of kynurenine metabolism is the presence obacterial endotoxins, activating IDO in peripheral and central tissues, but it is also probable that interferon produced in response to infection, may contribute to, operha bacterial endotoxins, activating IDO in peripheral and
central tissues, but it is also probable that interferons,
produced in response to infection, may contribute to, or
perhaps potentiate, this action. Several types of i central tissues, but it is also probable that interferons,
produced in response to infection, may contribute to, or
perhaps potentiate, this action. Several types of inter-
feron have been shown to activate IDO (Taylor and produced in response to infection, may contribute to, or
perhaps potentiate, this action. Several types of inter-
feron have been shown to activate IDO (Taylor and Feng,
1991; Saito et al., 1991a,b, 1992b), and the stimul perhaps potentiate, this action. Several types of inter-
feron have been shown to activate IDO (Taylor and Feng,
1991; Saito et al., 1991a,b, 1992b), and the stimulation
of kynurenine metabolism by pokeweed mitogen or li-
 feron have been shown to activate IDO (Taylor and Feng
1991; Saito et al., 1991a, b, 1992b), and the stimulation
of kynurenine metabolism by pokeweed mitogen or li
popolysaccharide could be prevented by antibodies to γ 1991; Saito et al., 1991a,b, 1992b), and the stimulation
of kynurenine metabolism by pokeweed mitogen or li-
popolysaccharide could be prevented by antibodies to γ -
interferon (Saito et al., 1991a, 1992b). In addition, of kynurenine metabolism by pokeweed mitogen or li-
popolysaccharide could be prevented by antibodies to γ -
interferon (Saito et al., 1991a, 1992b). In addition, mac-
rophages appear to convert tryptophan into quinolin popolysaccharide could be prevented by antibodies to interferon (Saito et al., 1991a, 1992b). In addition, marophages appear to convert tryptophan into quinolina (Heyes et al., 1992b). When macrophages isolated from mal h interferon (Saito et al., 1991a, 1992b). In addition, macrophages appear to convert tryptophan into quinolinat (Heyes et al., 1992b). When macrophages isolated from normal humans were cultured and subsequently stimulated rophages appear to convert tryptophan into quinolinate (Heyes et al., 1992b). When macrophages isolated from normal humans were cultured and subsequently stimulated with several concentrations of γ -interferon, quinolin (Heyes et al., 1992b). When macrophages isolated from
normal humans were cultured and subsequently stimu-
lated with several concentrations of γ -interferon, quin-
olinate was synthesised from added tryptophan and re-
l normal humans were cultured and subsequently stimulated with several concentrations of γ -interferon, quinolinate was synthesised from added tryptophan and released into the incubation medium. This is probably attributa 1991a,b). inate was synthesised from added tryptophan and re-
ased into the incubation medium. This is probably
tributable to a stimulation of IDO (Saito et al.,
91a,b).
Perhaps the most dramatic observation in these ex-
riments was

leased into the incubation medium. This is probably
attributable to a stimulation of IDO (Saito et al.,
1991a,b).
Perhaps the most dramatic observation in these ex-
periments was that the quinolinate concentration in the
 attributable to a stimulation of IDO (Saito et al., 1991a,b).

Perhaps the most dramatic observation in these ex-

periments was that the quinolinate concentration in the

medium could increase to >20 μ M after 48 hours 1991a,b).
Perhaps the most dramatic observation in these ex-
periments was that the quinolinate concentration in the
medium could increase to >20 μ M after 48 hours. This
suggests that the infiltration of macrophages Perhaps the most dramatic observation in these
periments was that the quinolinate concentration in
medium could increase to $>20 \mu$ M after 48 hours. T
suggests that the infiltration of macrophages into
traumatized or infe periments was that the quinolinate conce
medium could increase to >20 μ M after
suggests that the infiltration of macror
traumatized or infected brain could cont
tial quantities of kynurenine metabolites
Whatever the suggests that the infiltration of macrophages into the traumatized or infected brain could contribute substantial quantities of kynurenine metabolites.
Whatever the mechanism, it is clearly an important

suggests that the infiltration of macrophages into the traumatized or infected brain could contribute substantial quantities of kynurenine metabolites.
Whatever the mechanism, it is clearly an important idea that such incr traumatized or infected brain could contribute substantial quantities of kynurenine metabolites.
Whatever the mechanism, it is clearly an important
idea that such increases of quinolinate could be at least
partly responsib tial quantities of kynurenine metabolites.
Whatever the mechanism, it is clearly an important
idea that such increases of quinolinate could be at least
partly responsible for the seizures, encephalopathy, and
even neurodeg Whatever the mechanism, it is clearly an important
idea that such increases of quinolinate could be at least
partly responsible for the seizures, encephalopathy, and
even neurodegenerative changes that can result from
chro idea that such increase
partly responsible for
even neurodegenerat
chronic infection in h
Legido et al., 1988).
9. Acquired immun rtly responsible for the seizures, encephalopathy, and
en neurodegenerative changes that can result from
ronic infection in humans (Wood and Anderson, 1988;
gido et al., 1988).
9. Acquired immunodeficiency syndrome. Some o even neurodegenerative changes that can result from
chronic infection in humans (Wood and Anderson, 1988;
Legido et al., 1988).
9. Acquired immunodeficiency syndrome. Some of the
previous considerations have been used in a

chronic infection in humans (Wood and Anderson, 1988;
Legido et al., 1988).
9. Acquired immunodeficiency syndrome. Some of the
previous considerations have been used in an attempt to
explain aspects of the so-called AIDS/d Legido et al., 1988).

9. Acquired immunodeficiency syndrome. Some of the

previous considerations have been used in an attempt to

explain aspects of the so-called AIDS/dementia complex

(Navia et al., 1986) that develops

PHARMACOLOGICAL REVIEWS

STONE
tion of patients infected with the HIV-I, because the of
dementia appears to be accompanied by a substantial be s[.]
dementia appears to be accompanied by a substantial
dementia appears to be accompanied by a substantial
loss of central neurones. Heyes et al. (1989a, 1991b,c) strom

ion of patients infected with the HIV-I, because the

dementia appears to be accompanied by a substantial

loss of central neurones. Heyes et al. (1989a, 1991b,c)

showed that the concentration of quinolinic acid is tion of patients infected with the HIV-I, because the
dementia appears to be accompanied by a substantial
loss of central neurones. Heyes et al. (1989a, 1991b,c)
showed that the concentration of quinolinic acid is sub-
sta tion of patients infected with the HIV-I, because the of dementia appears to be accompanied by a substantial becose of central neurones. Heyes et al. (1989a, 1991b,c) hypothowed that the concentration of quinolinic acid is dementia appears to be accompanied by a substantial loss of central neurones. Heyes et al. (1989a, 1991b,c) showed that the concentration of quinolinic acid is substantially increased in the CSF of patients infected with H loss of central neurones. Heyes et al. (1989a, 1991b,c) hypothometration of quinolinic acid is sub-
stantially increased in the CSF of patients infected with CN
HIV; control subjects in these studies had quinolinate pha
co showed that the concentration of quinolinic acid is sub-
stantially increased in the CSF of patients infected with
HIV; control subjects in these studies had quinolinate
phaconcentrations of 21 nmol/litre, whereas infected HIV; control subjects in these studies had quinolinate phagocytes. Human macrophage cells appear able to concentrations of 21 nmol/litre, whereas infected and convert added tryptophan into quinolinate relatively eas-
deme HIV; control subjects in these studies had quinoncentrations of 21 nmol/litre, whereas infected patients had levels of approximate nmol/litre, with three subjects having levels in e 12,000 nmol/litre (Heyes et al., 1989a,

nmol/litre, with three subjects having levels in excess of 12,000 nmol/litre (Heyes et al., 1989a, 1991b,c).
An increase of quinolinate was also demonstrated in rhesus macque monkeys infected with the AIDS-related virus (nmol/litre, with three subjects having levels in excess (12,000 nmol/litre (Heyes et al., 1989a, 1991b,c).
An increase of quinolinate was also demonstrated in the sus macque monkeys infected with the AIDS-relate
virus (sim 12,000 nmol/litre (Heyes et al., 1989a, 1991b,c).

An increase of quinolinate was also demonstrated in

rhesus macque monkeys infected with the AIDS-related

virus (simian type-D retrovirus or $D/1/California$ retro-

virus) (Hey An increase of quinolinate was also demonstrated in
rhesus macque monkeys infected with the AIDS-related
virus (simian type-D retrovirus or $D/1/California retro-
virus)$ (Heyes et al., 1990a). CSF levels in control animals
were approx rhesus macque monkeys infected with the AIDS-related ovirus (simian type-D retrovirus or $D/1/California$ retro-
virus) (Heyes et al., 1990a). CSF levels in control animals were approximately 27 nM, whereas all infected animals c virus (simian type-D retrovirus or $D/1/California$
virus) (Heyes et al., 1990a). CSF levels in control animals
were approximately 27 nM, whereas all infected animals
showed levels >2 SD from the control mean values. Of
greates virus) (Heyes et al., 1990a). CSF levels in control animative were approximately 27 nM, whereas all infected animation showed levels >2 SD from the control mean values. (greatest interest, however, was the observation of were approximately 27 nM, whereas all infected animals cau showed levels >2 SD from the control mean values. Of HIV greatest interest, however, was the observation of a correlation between quinolinate concentration and showed levels >2 SD from the control mean values. Of greatest interest, however, was the observation of a correlation between quinolinate concentration and symptomatic and pathological signs of CNS involvement. Six monk greatest interest, however, was the observation of a
relation between quinolinate concentration and sy
tomatic and pathological signs of CNS involvement
monkeys that experienced the greatest neurological
turbances, as well relation between quinolinate concentration and symptomatic and pathological signs of CNS involvement. Six monkeys that experienced the greatest neurological disturbances, as well as postmortem signs of neurodegeneration, tomatic and pathological signs of CNS invo
monkeys that experienced the greatest neu
turbances, as well as postmortem signs of
eration, also possessed CSF quinolinate leve
fold greater $(>10 \ \mu mol/litre)$ than controls.
A stri between that experienced the greatest neurological chances, as well as postmortem signs of neurodegention, also possessed CSF quinolinate levels up to 4 dd greater $(>10 \ \mu \text{mol/litre})$ than controls.
A striking correlation wa

turbances, as well as postmortem signs of neurodegeneration, also possessed CSF quinolinate levels up to 400 fold greater $(>10 \mu \text{mol/litre})$ than controls.
A striking correlation was reported between quinolinate concentratio eration, also possessed CSF quinolinate levels up to 400 fold greater $(>10 \mu \text{mol/litre})$ than controls.
A striking correlation was reported between quinolinate concentrations in patients with AIDS and the clinically assessed fold greater $(>10 \mu \text{mol/litre})$ than controls. ti
A striking correlation was reported between quinoli-
nate concentrations in patients with AIDS and the clin-
ically assessed severity of the AIDS related psychological co
def A striking correlation was reported between quinoli-
nate concentrations in patients with AIDS and the clin-
ically assessed severity of the AIDS related psychological
deficits (Heyes et al., 1991c). Changes in a measure o nate concentrations in patients with AIDS and the α ically assessed severity of the AIDS related psycholog
deficits (Heyes et al., 1991c). Changes in a measure psychomotor status, reaction times, were also correl
signi ically assessed severity of the AIDS related psychological conditions deficits (Heyes et al., 1991c). Changes in a measure of concentration of psychomotor status, reaction times, were also correlated the significantly both deficits (Heyes et al., 1991c). Changes in a measure psychomotor status, reaction times, were also correlat significantly both with absolute quinolinate concentration and with temporal changes in concentration (Mart et al. psychomotor status, reaction times, were also correlate significantly both with absolute quinolinate concentration and with temporal changes in concentration (Mart et al., 1992). Since other psychologically based asses men significantly both with absolute quinolinate concentra-
tion and with temporal changes in concentration (Martin
et al., 1992). Since other psychologically based assess-
sen
ments, such as mood, did not show a comparable co tion and with temporal changes in concentration (Martin net al., 1992). Since other psychologically based assess-
ments, such as mood, did not show a comparable corre-
lation, it was noted that reaction times could form th et al., 1992). Since other psychologically based assess-
ments, such as mood, did not show a comparable corre-
lation, it was noted that reaction times could form the
basis of a technique for monitoring the early progress ments, such as mood, did not show a comparable corre-
lation, it was noted that reaction times could form the
basis of a technique for monitoring the early progress of
tell that kynurenine metabolism could be related di
ca lation, it was noted that reaction times co
basis of a technique for monitoring the ear
HIV infection in humans; of more relevan
implication that kynurenine metabolism co
causally to the changes of reaction times.
Concentr asis of a technique for monitoring the early progress of to be IV infection in humans; of more relevance here is the rem
plication that kynurenine metabolism could be related ditionally to the changes of reaction times. Co

HIV infection in humans; of more relevance here is implication that kynurenine metabolism could be related causally to the changes of reaction times.
Concentrations of kynurenate were also increased viraemic monkeys but to implication that kynurenine metabolism could be related d
causally to the changes of reaction times. Concentrations of kynurenate were also increased in c
viraemic monkeys but to a smaller degree than quinoli-
nate; kynure causally to the changes of reaction times.
Concentrations of kynurenate were also increased in
viraemic monkeys but to a smaller degree than quinoli-
nate; kynurenate, like quinolinate, was elevated to a far
greater extent Concentrations of kynurenate were also increased
viraemic monkeys but to a smaller degree than quin
nate; kynurenate, like quinolinate, was elevated to a
greater extent in the more severely affected animals,
the ratio of q viraemic monkeys but to a smaller degree than quinoli-
nate; kynurenate, like quinolinate, was elevated to a far
greater extent in the more severely affected animals, but
the ratio of quinolinate to kynurenate remained sub nate; kynurenate, like quinolinate, was elevated to a far
greater extent in the more severely affected animals, but
the ratio of quinolinate to kynurenate remained substan-
tially higher, by approximately 5-fold, in the in greater extent in the more severely affected animals, but
the ratio of quinolinate to kynurenate remained substan-
tially higher, by approximately 5-fold, in the infected
state. Although the profile of serum content, with the ratio of quinolinate to kynurenate remained substancertially higher, by approximately 5-fold, in the infected solve at the state. Although the profile of serum content, with interessed L-kynurenine but reduced tryptoph tially higher, by approximately 5-fold, in the inferentiate. Although the profile of serum content, with creased L-kynurenine but reduced tryptophan levels, gested that IDO may have been activated in the affereninals [a vi state. Although the profile of serum content, with increased L-kynurenine but reduced tryptophan levels, suggested that IDO may have been activated in the affected animals [a view that has now received direct experimental creased L-kynurenine but reduced tryptophan levels, sug-
gested that IDO may have been activated in the affected is counting an imals [a view that has now received direct experimence or
tal support (Saito et al., 1991a,b; gested that IDO may have been activated in the affected is d
animals [a view that has now received direct experimen-cort
tal support (Saito et al., 1991a,b; Heyes et al., 1992c,e)], simp
such an induction could not account animals [a view that has now received direct experimental support (Saito et al., 1991a,b; Heyes et al., 1992c,e)], sin such an induction could not account for more than a exproportion of the quinolinate and kynurenate lev tal support (Saito et al., 1991a,b; Heyes et al., 1992c,e)], such an induction could not account for more than a proportion of the quinolinate and kynurenate levels in the CSF because these concentrations were higher than such an induction could not account for more than a eproportion of the quinolinate and kynurenate levels in H
the CSF because these concentrations were higher than c
serum levels in several cases (Heyes et al., 1992c,e). d proportion of the quinolinate and kynurenate levels in
the CSF because these concentrations were higher than
serum levels in several cases (Heyes et al., 1992c,e).
Therefore, it seems extremely likely that the increased
ky the CSF because these concentrations were higher the serum levels in several cases (Heyes et al., 1992c Therefore, it seems extremely likely that the increasupplement concentrations were of central origin, either from neur rum levels in several cases (Heyes et al., 1992c,e).
nerefore, it seems extremely likely that the increased
nurenate concentrations were of central origin, either
om neurone or glia or from infiltrating macrophages.
The qu

demented patients had levels of approximately 1391 ily when stimulated with γ -interferon (Heyes et al., nmol/litre, with three subjects having levels in excess of 1992b). The seeding of neuronal cultures, prepared eith NE
of quinolinate occur. This is particularly problematic
because HIV rarely attacks neurones. Although several NE
of quinolinate occur. This is particularly problematic
because HIV rarely attacks neurones. Although several
hypotheses have been proposed (Giulian et al., 1990), WE
of quinolinate occur. This is particularly problematic
because HIV rarely attacks neurones. Although several
hypotheses have been proposed (Giulian et al., 1990),
attention is now focusing on the marked infiltration of of quinolinate occur. This is particularly problematic because HIV rarely attacks neurones. Although several hypotheses have been proposed (Giulian et al., 1990), attention is now focusing on the marked infiltration of CNS of quinolinate occur. This is particularly problematic
because HIV rarely attacks neurones. Although several
hypotheses have been proposed (Giulian et al., 1990),
attention is now focusing on the marked infiltration of
CNS because HIV rarely attacks neurones. Although several
hypotheses have been proposed (Giulian et al., 1990),
attention is now focusing on the marked infiltration of
CNS tissue by macrophages and other mononuclear
phagocytes hypotheses have been proposed (Giulian et al., 1990), attention is now focusing on the marked infiltration of CNS tissue by macrophages and other mononuclear phagocytes. Human macrophage cells appear able to convert added attention is now focusing on the marked infiltration of CNS tissue by macrophages and other mononuclear phagocytes. Human macrophage cells appear able to convert added tryptophan into quinolinate relatively easily when st CNS tissue by macrophages and other mononuclear
phagocytes. Human macrophage cells appear able to
convert added tryptophan into quinolinate relatively eas-
ily when stimulated with γ -interferon (Heyes et al.,
1992b). T phagocytes. Human macrophage cells appear able to convert added tryptophan into quinolinate relatively easily when stimulated with γ -interferon (Heyes et al., 1992b). The seeding of neuronal cultures, prepared either f convert added tryptophan into quinolinate relatively eally when stimulated with γ -interferon (Heyes et a 1992b). The seeding of neuronal cultures, prepared eith from chick ciliary ganglia or embryonic rat spinal cor wi ily when stimulated with γ -interferon (Heyes et al., 1992b). The seeding of neuronal cultures, prepared either from chick ciliary ganglia or embryonic rat spinal cord, with human cell lines equivalent to mononuclear ph 1992b). The seeding of neuronal cultures, prepared either
from chick ciliary ganglia or embryonic rat spinal cord,
with human cell lines equivalent to mononuclear phag-
ocytes and infected with HIV-I resulted in clear sign from chick ciliary ganglia or embryonic rat spinal cord,
with human cell lines equivalent to mononuclear phag-
ocytes and infected with HIV-I resulted in clear signs of
cell damage, including vacuolation and nuclear loss,
 with human cell lines equivalent to mononuclear phag-
ocytes and infected with HIV-I resulted in clear signs of
cell damage, including vacuolation and nuclear loss,
within 10 hours. Seeding with noninfected lymphoid cells
 ocytes and infected with HIV-I resulted in clear signs of
cell damage, including vacuolation and nuclear loss,
within 10 hours. Seeding with noninfected lymphoid cells
caused no such damage. Confirmation was included that
 cell damage, including vacuolation and nuclear loss,
within 10 hours. Seeding with noninfected lymphoid cells
caused no such damage. Confirmation was included that
HIV itself had no effect on neuronal viability; only the
s within 10 hours. Seec
caused no such dama
HIV itself had no ef
secreted products of i
et al., 1990).
Preliminary work used no such damage. Confirmation was included that
IV itself had no effect on neuronal viability; only the
creted products of infected cells were effective (Giulian
al., 1990).
Preliminary work indicated that those compon

HIV itself had no effect on neuronal viability; only the secreted products of infected cells were effective (Giulian et al., 1990).

Preliminary work indicated that those components of cellular exudation responsible for t secreted products of infected cells were effective (Giulian
et al., 1990).
Preliminary work indicated that those components of
cellular exudation responsible for the neurotoxicity were
heat-stable, protease-resistant mole et al., 1990).

Preliminary work indicated that those components of

cellular exudation responsible for the neurotoxicity were

heat-stable, protease-resistant molecules of mass <

kDa. Furthermore, inclusion of kynurenic Preliminary work indicated that those components of
cellular exudation responsible for the neurotoxicity were
heat-stable, protease-resistant molecules of mass <2
kDa. Furthermore, inclusion of kynurenic acid or selec-
tiv cellular exudation responsible for the neurotoxicity were
heat-stable, protease-resistant molecules of mass <2
kDa. Furthermore, inclusion of kynurenic acid or selec-
tive NMDA antagonists, such as 2AP5 and dizocilpine,
pr heat-stable, protease-resistant molecules of mass <2
kDa. Furthermore, inclusion of kynurenic acid or selec-
tive NMDA antagonists, such as 2AP5 and dizocilpine,
prevented the neuronal death, whereas non-NMDA an-
tagonists kDa. Furthermore, inclusion of kynurenic acid or selective NMDA antagonists, such as 2AP5 and dizocilpine, prevented the neuronal death, whereas non-NMDA antagonists, such as CNQX, were ineffective. Neither the concentrat tive NMDA antagonists, such as 2AP5 and dizocilpine,
prevented the neuronal death, whereas non-NMDA an-
tagonists, such as CNQX, were ineffective. Neither the
concentrations of glutamate nor aspartate in the medium
could a prevented the neuronal death, whereas non-NMDA antagonists, such as CNQX, were ineffective. Neither the concentrations of glutamate nor aspartate in the medium could account for the neurotoxicity. Equally, however, the in tagonists, such as CNQX, were ineffective. Neither the concentrations of glutamate nor aspartate in the medium could account for the neurotoxicity. Equally, however, the infected cells yielded $<0.2 \text{ mg/ml}$ (approximately concentrations of glutamate nor aspartate in the medium
could account for the neurotoxicity. Equally, however,
the infected cells yielded ≤ 0.2 mg/ml (approximately 1
mM) quinolinic acid to the culture medium. Althoug could account for the neurotoxicity. Equally, howe
the infected cells yielded $\langle 0.2 \text{ mg/ml}}$ (approximatel
mM) quinolinic acid to the culture medium. Although
neuronal cells studied in this work proved to be v
sensitive t the infected cells yielded ≤ 0.2 mg/ml (approximately 1 mM) quinolinic acid to the culture medium. Although the neuronal cells studied in this work proved to be very sensitive to quinolinate, showing substantial degen mM) quinolinic acid to the culture medium. Although the neuronal cells studied in this work proved to be very sensitive to quinolinate, showing substantial degeneration at 100 nM of added quinolinate, it was concluded that neuronal cells studied in this work proved to be very
sensitive to quinolinate, showing substantial degenera-
tion at 100 nM of added quinolinate, it was concluded
that this agent was secreted in too low a concentration
to sensitive to quinolinate, showing substantial degeneration at 100 nM of added quinolinate, it was concluded that this agent was secreted in too low a concentration to be the sole neurotoxic substance. What importantly rem tion at 100 nM of added quinolinate, it was concluded
that this agent was secreted in too low a concentration
to be the sole neurotoxic substance. What importantly
remains to be examined is whether, under in vivo con-
dit that this agent was secreted in too low a concentration
to be the sole neurotoxic substance. What importantly
remains to be examined is whether, under in vivo con-
ditions, the additional presence of γ -interferon, or a to be the sole neurotoxic substance. What importantly remains to be examined is whether, under in vivo conditions, the additional presence of γ -interferon, or a cocktail of this and other infection related cytokines, c quinolinate. ions, the additional presence of γ -interferon, cktail of this and other infection related cyto uld stimulate phagocytes to release large quantition inclinate.
10. Other neurodegenerative diseases. Olivopont llar atro

cocktail of this and other infection related cytokines,
could stimulate phagocytes to release large quantities of
quinolinate.
 $10.$ Other neurodegenerative diseases. Olivopontocere-
bellar atrophy is a neurodegenerative d could stimulate phagocytes to release large quantities
quinolinate.
10. Other neurodegenerative diseases. Olivopontoce
bellar atrophy is a neurodegenerative disorder usus
classified along with Huntington's disease and Park quinolinate.
10. Other neurodegenerative diseases. Olivopontocen
bellar atrophy is a neurodegenerative disorder usual
classified along with Huntington's disease and Parki
son's disease. Although less is known about this co bellar atrophy is a neurodegenerative disorder usually classified along with Huntington's disease and Parkinson's disease. Although less is known about this condition in terms of excitatory amino acid or kynurenine involve bellar atrophy is a neurodegenerative disorder usually classified along with Huntington's disease and Parkinson's disease. Although less is known about this condition in terms of excitatory amino acid or kynurenine involve classified along with Huntington's disease and Parkinson's disease. Although less is known about this condition in terms of excitatory amino acid or kynurenine involvement, it has been reported that QPRTase activity is dou son's disease. Although less is known about this condition in terms of excitatory amino acid or kynurenine involvement, it has been reported that QPRTase activity is doubled in the cerebellum, but not in the occipital cort tion in terms of excitatory amino acid or kynurenine
involvement, it has been reported that QPRTase activity
is doubled in the cerebellum, but not in the occipital
cortex, of affected patients (Kish et al., 1991). Viewed
s involvement, it has been reported that QPRTase activit
is doubled in the cerebellum, but not in the occipita
cortex, of affected patients (Kish et al., 1991). Viewe
simplistically, this increased enzyme activity might b
ex is doubled in the cerebellum, but not in the occipital cortex, of affected patients (Kish et al., 1991). Viewed simplistically, this increased enzyme activity might be expected to diminish local concentrations of quinolina cortex, of affected patients (Kish et al., 1991). Viewed
simplistically, this increased enzyme activity might be
expected to diminish local concentrations of quinolinate.
However, the authors proposed, instead, that the in simplistically, this increased enzyme activity might be
expected to diminish local concentrations of quinolinate.
However, the authors proposed, instead, that the in-
creased enzyme activity may represent a compensatory
de expected to diminish local concent
However, the authors proposed,
creased enzyme activity may repr
development attempting to prote
from elevated levels of quinolinate
There is little evidence for an inv creased enzyme activity may represent a compensatory
development attempting to protect sensitive neurones
from elevated levels of quinolinate.
There is little evidence for an involvement of kynuren-

creased enzyme activity may represent a compensatory
development attempting to protect sensitive neurones
from elevated levels of quinolinate.
There is little evidence for an involvement of kynuren-
ines in Parkinson's dis development attempting to protect sensitive neurones
from elevated levels of quinolinate.
There is little evidence for an involvement of kynuren-
ines in Parkinson's disease. Ogawa et al. (1992) failed to
find any signific

PHARM
REV

QUINOLINIC AND FRATIOS Of tryptophan, L-kynurenine, and kynurenic acid,
Although a higher ratio of 3-hydroxykynurenine to L-QUINOLINIC AND K

ratios of tryptophan, L-kynurenine, and kynurenic acid,

although a higher ratio of 3-hydroxykynurenine to L-

kynurenine was observed in three regions of Parkinson-QUINOLINIC

ratios of tryptophan, L-kynurenine, and kynurenic

although a higher ratio of 3-hydroxykynurenine t

kynurenine was observed in three regions of Parkin

ian basal ganglia. ratios of tryptopha
although a higher
kynurenine was ol
ian basal ganglia.
Infection with p ition of tryptophan, L-kynurenine, and kynurenic acid,

ithough a higher ratio of 3-hydroxykynurenine to L-

murenine was observed in three regions of Parkinson-

combasal ganglia.

Infection with poliovirus is a well-reco

although a higher ratio of 3-hydroxykynurenine to L-
kynurenine was observed in three regions of Parkinson-
ian basal ganglia.
Infection with poliovirus is a well-recognised cause of
inneuronal death. Following infection o kynurenine was observed in three regions of Parkinson-cul
ian basal ganglia. as:
Infection with poliovirus is a well-recognised cause of
inneuronal death. Following infection of macaques with
the virus, the activity of spi ian basal ganglia.

Infection with poliovirus is a well-recognised cause of

neuronal death. Following infection of macaques with

the virus, the activity of spinal IDO was found to be

elevated at 2 weeks, as was the cont Infection with poliovirus is a well-recognised cause of line
neuronal death. Following infection of macaques with an
the virus, the activity of spinal IDO was found to be can
elevated at 2 weeks, as was the content of quin the virus, the activity of spinal IDO was found to be elevated at 2 weeks, as was the content of quinolinate.
Similar, although less marked changes were noted in the parietal neocortex, which is also attacked by the virus, the virus, the activity of spinal IDO was found to be elevated at 2 weeks, as was the content of quinolinate.
Similar, although less marked changes were noted in the parietal neocortex, which is also attacked by the virus, elevated at 2 weeks, as was the content of quinolina
Similar, although less marked changes were noted in t
parietal neocortex, which is also attacked by the vir
but not in the frontal cortex, which is not suscepti
(Heyes e Similar, although less marked changes were noted in the parietal neocortex, which is also attacked by the virus, but not in the frontal cortex, which is not susceptible (Heyes et al. 1992d). The increase of quinolinate con parietal neocortex, which is also attacked by the virus, performed to the inflamed, which is not susceptible here.
(Heyes et al. 1992d). The increase of quinolinate concentration, which may have been the result of macroph but not in the frontal cortex, which is not susceptible

(Heyes et al. 1992d). The increase of quinolinate concen-

in the quinolinate content of several neocortical samples

tration, which may have been the result of mac tration, which may have been the result of macrophages infiltrating the inflamed, damaged regions of CNS, would
have been sufficient to account for the death of the
affected neurones.
There is also evidence for some involvement of quin-
olinate in the neurological dysfunction

infiltrating the inflamed, damaged regions of CNS, would
have been sufficient to account for the death of the
affected neurones.
There is also evidence for some involvement of quin-
olinate in the neurological dysfunction have been sufficient to account for the death of the 12-1
affected neurones.
There is also evidence for some involvement of quin-
olinate in the neurological dysfunction resulting from keep
infection with *Borrelia burgdor* affected neurones.

There is also evidence for some involvement of quin-

olinate in the neurological dysfunction resulting from

infection with *Borrelia burgdorferi* (Lyme disease). CSF

quinolinate was substantially hig There is also evidence for some involvement of quin-
olinate in the neurological dysfunction resulting from
infection with *Borrelia burgdorferi* (Lyme disease). CSF
quinolinate was substantially higher, by up to about 40
 olinate in the neurological dysfunction resulting from
infection with *Borrelia burgdorferi* (Lyme disease). CSF
quinolinate was substantially higher, by up to about 40
times, in patients with evidence of CNS infection an infection with *Borrelia burgdorferi* (Lyme disease). CSF
quinolinate was substantially higher, by up to about 40
times, in patients with evidence of CNS infection and
inflammation (Halperin and Heyes, 1992). A less marked quinolinate was substantially higher, by up to about 40
times, in patients with evidence of CNS inflammation (Halperin and Heyes, 1992). A less marked
increase of quinolinate was seen in infected patients
without CNS infla times, in patients with evidence of CNS infection and

inflammation (Halperin and Heyes, 1992). A less marked

increase of quinolinate was seen in infected patients

without CNS inflammation, and no changes occurred in

"c inflammation (Halperin and Heyes, 1992). A less marked
increase of quinolinate was seen in infected patients
without CNS inflammation, and no changes occurred in
"control" patients with multiple sclerosis. No evidence
was increase of quinolinate was seen in infected patients in the without CNS inflammation, and no changes occurred in $\frac{N}{2}$ control" patients with multiple sclerosis. No evidence levas obtained in this study for any consi without CNS inflammation, and no changes occurred in

"control" patients with multiple sclerosis. No evidence

was obtained in this study for any consistent parallel

changes in the concentration of several interferons or
 "control" patients with multiple sclerosis. No evidence
was obtained in this study for any consistent parallel
changes in the concentration of several interferons or
tumour necrosis factor in the CSF of patients, such
age was obtained in this study for any consistent paralle changes in the concentration of several interferons of tumour necrosis factor in the CSF of patients, such agents being able to activate extrahepatic IDO (Saito et al., anges in the concentration of several interferons or

mour necrosis factor in the CSF of patients, such

ents being able to activate extrahepatic IDO (Saito et

1991a,b; Yoshida et al., 1986; Bianchi et al., 1988).

11. Mi

tumour necrosis factor in the CSF of patients, such
agents being able to activate extrahepatic IDO (Saito et
al., 1991a,b; Yoshida et al., 1986; Bianchi et al., 1988).
11. Miscellaneous diseases. The existence of a high
se agents being able to activate extrahepatic IDO (Saito et al., 1991a,b; Yoshida et al., 1986; Bianchi et al., 1988).

11. Miscellaneous diseases. The existence of a high above serum level of both L-kynurenine and neopterin al., 1991a,b; Yoshida et al., 1986; Bianchi et al., 1988).

11. Miscellaneous diseases. The existence of a high

serum level of both L-kynurenine and neopterin in pa-

tients with dilated cardiomyopathy was taken as an

in serum level of both L-kynurenine and neopterin in patients with dilated cardiomyopathy was taken as an indication of immune activation as a contributing factor in the pathogenesis of this disorder (Rudzite et al., 1992). I Frame level of both L-kynurenine and neopterin in pa-

ints with dilated cardiomyopathy was taken as an dication of immune activation as a contributing factor

the pathogenesis of this disorder (Rudzite et al., 1992).

In

tients with dilated cardiomyopathy was taken as an indication of immune activation as a contributing factor in the pathogenesis of this disorder (Rudzite et al., 1992). In some cases, an increased level of plasma or urinar indication of immune activation as a contributing factor
in the pathogenesis of this disorder (Rudzite et al., 1992).
In some cases, an increased level of plasma or urinary
manufacture in the psychiatric qui
states such as in the pathogenesis of this disorder (Rudzite et al., 1992).
In some cases, an increased level of plasma or urinary
L-kynurenine has been correlated with other psychiatric
states such as depression (Mangoni, 1974; Hoes and In some cases, an increased level of plasma or urinary
L-kynurenine has been correlated with other psychiatric states such as depression (Mangoni, 1974; Hoes and Sijben, 1981; Lapin and Oxenkrug, 1969), schizophrenia
(Jose L-kynurenine has been correlated with other psychiatristates such as depression (Mangoni, 1974; Hoes and Sijben, 1981; Lapin and Oxenkrug, 1969), schizophrenii (Joseph et al., 1979), or alcohol withdrawal (Friedman e al., states such as depression (Mangoni, 1974; Hoes and
Sijben, 1981; Lapin and Oxenkrug, 1969), schizophrenia
(Joseph et al., 1979), or alcohol withdrawal (Friedman et
al., 1988; Morgan, 1991); however, the significance,
wheth Sijben, 1981; Lapin and Oxenkrug, 1969), schizophren
(Joseph et al., 1979), or alcohol withdrawal (Friedman al., 1988; Morgan, 1991); however, the significance
whether as causative factors or consequences, remain
unknown. (Joseph et al., 1979), or alcohol withdrawal (Friedman et al., 1988; Morgan, 1991); however, the significance, whether as causative factors or consequences, remains unknown. The levels of quinolinate in the CSF of schizoph 1988b). nether as causative factors or consequences, remains

known. The levels of quinolinate in the CSF of schiz-

hrenic patients appear normal (Schwarcz et al.,

88b).

It has also been proposed that the deficiency of glu-

ry

unknown. The levels of quinolinate in the CSF of schippenic patients appear normal (Schwarcz et a 1988b).
1988b).
It has also been proposed that the deficiency of glutaryl-coenzyme A dehydrogenase seen in glutaric acidu-
T ophrenic patients appear normal (Schwarcz et al., 1988b).

It has also been proposed that the deficiency of glu-

taryl-coenzyme A dehydrogenase seen in glutaric acidu-

ria may lead to increased amounts of kynurenines, in 1988b).
It has also been proposed that the deficiency of glu-
taryl-coenzyme A dehydrogenase seen in glutaric acidu-
ria may lead to increased amounts of kynurenines, in-
cluding quinolinate, in the body. The quinolinate m It has also been proposed that the deficiency of glu-
taryl-coenzyme A dehydrogenase seen in glutaric acidu-
ria may lead to increased amounts of kynurenines, in-
cluding quinolinate, in the body. The quinolinate might
the taryl-coenzyme A dehydrogenase s
ria may lead to increased amount
cluding quinolinate, in the body. T
then contribute to some of the CN:
hereditary disease (Heyes, 1987).
12. Ageing. In view of the progre *1* may lead to increased amounts of kynurenines, in-
12. Ageing. In the body. The quinolinate might
the contribute to some of the CNS toxicity seen in this
reditary disease (Heyes, 1987).
12. Ageing. In view of the prog

then contribute to some of the CNS toxicity seen in this hereditary disease (Heyes, 1987).

12. Ageing. In view of the progressive loss of neurone that occurs with normal ageing, it is interesting that the concentrations o hereditary disease (Heyes, 1987). The strategies in the strategies in rate of the progressive loss of neurones neutrations with normal ageing, it is interesting that the 1983 concentrations of quinolinic acid detectable i 12. Ageing. In view of the progressive loss of neurones that occurs with normal ageing, it is interesting that the concentrations of quinolinic acid detectable in the cerebral cortex increase progressively in rats ranging

YNURENIC ACIDS
of the animals in the oldest group, the levels of quino
nate reached 4.5 nmol/g, levels that are toxic to neuro. SNURENIC ACIDS

265

265

265 of the animals in the oldest group, the levels of quinoli-

265 nate reached 4.5 nmol/g, levels that are toxic to neuronal

cultures if maintained for a period of several weeks. It is S65

complement of the animals in the oldest group, the levels of quinoli-

nate reached 4.5 nmol/g, levels that are toxic to neuronal

cultures if maintained for a period of several weeks. It is

as yet not known whether of the animals in the oldest group, the levels of quino
nate reached 4.5 nmol/g, levels that are toxic to neuror
cultures if maintained for a period of several weeks. It
as yet not known whether the 10-fold increase of qui of the animals in the oldest group, the levels of quinoli-
nate reached 4.5 nmol/g, levels that are toxic to neuronal
cultures if maintained for a period of several weeks. It is
as yet not known whether the 10-fold increas nate reached 4.5 nmol/g, levels that are toxic to neuronal
cultures if maintained for a period of several weeks. It is
as yet not known whether the 10-fold increase of quino-
linate concentrations demonstrated with ageing cultures if maintained for a period of several weeks. It is
as yet not known whether the 10-fold increase of quino-
linate concentrations demonstrated with ageing in these
animals is due to an enhanced biosynthesis, a redu as yet not known whether the 10-fold increase of quino-
linate concentrations demonstrated with ageing in these
animals is due to an enhanced biosynthesis, a reduced
catabolism, or restrictions in the extracellular space a linate concentrations demonstrated with ageing in these
animals is due to an enhanced biosynthesis, a reduced
catabolism, or restrictions in the extracellular space and
cerebrovascular system leading to a diminished rate o animals is due to an enhanced biosynthesis, a reduced catabolism, or restrictions in the extracellular space and cerebrovascular system leading to a diminished rate of clearance. To date, only one study appears to have bee catabolism, or restrictions in the extracellular space and
cerebrovascular system leading to a diminished rate of
clearance. To date, only one study appears to have been
performed of quinolinic acid levels in patients with cerebrovascular system leading to a diminished rate of clearance. To date, only one study appears to have been
performed of quinolinic acid levels in patients with Alz-
heimer's disease. In this study, no difference was no clearance. To date, only one stuperformed of quinolinic acid lev
heimer's disease. In this study,
in the quinolinate content of sev
compared with control patients.
Finn et al. (1991) reported the rformed of quinolinic acid levels in patients with Alz-
imer's disease. In this study, no difference was noted
the quinolinate content of several neocortical samples
mpared with control patients.
Finn et al. (1991) reporte

heimer's disease. In this study, no difference was noted
in the quinolinate content of several neocortical samples
compared with control patients.
Finn et al. (1991) reported that the striatum of 4- and
12-month-old rats i in the quinolinate content of several neocortical samples
compared with control patients.
Finn et al. (1991) reported that the striatum of 4- and
12-month-old rats is less sensitive to quinolinate than
the striatum of 1-mo compared with control patients.
Finn et al. (1991) reported that the striatum of 4- and
12-month-old rats is less sensitive to quinolinate than
the striatum of 1-month-old animals, when assessed in
terms of substance P and Finn et al. (1991) reported that the striatum of 4- and 12-month-old rats is less sensitive to quinolinate that the striatum of 1-month-old animals, when assessed if terms of substance P and GABA concentrations. If keep 12-month-old rats is less sensitive to quinolinate than
the striatum of 1-month-old animals, when assessed in
terms of substance P and GABA concentrations. In
keeping with the known pharmacology of quinolinate,
older rats the striatum of 1-month-old animals, when assessed in
terms of substance P and GABA concentrations. In
keeping with the known pharmacology of quinolinate,
older rats were also less sensitive to NMDA. The authors
concluded keeping with the known pharmacology of quinolinate, older rats were also less sensitive to NMDA. The authors concluded that the results excluded quinolinate as a causative factor in age-associated neuronal loss. This inter keeping with the known pharmacology of quinolinate,
older rats were also less sensitive to NMDA. The authors
concluded that the results excluded quinolinate as a
causative factor in age-associated neuronal loss. This
inter older rats were also less sensitive to NMDA. The authors concluded that the results excluded quinolinate as a causative factor in age-associated neuronal loss. This interpretation, however, overlooks the possibility that t concluded that the results excluded quinolinate as a
causative factor in age-associated neuronal loss. This
interpretation, however, overlooks the possibility that
the reduced sensitivity reflects a down-regulation of
NMDA causative factor in age-associated neuronal loss. This
interpretation, however, overlooks the possibility that
the reduced sensitivity reflects a down-regulation of
NMDA receptors in response to chronically elevated
level interpretation, however, overlooks the possibility the reduced sensitivity reflects a down-regulation NMDA receptors in response to chronically elevat levels of quinolinate. It is not possible to predict from the results t NMDA receptors in response to chronically elevated
levels of quinolinate. It is not possible to predict from
the results the overall degree of NMDA receptor stimuincreased. vels of quinolinate. It is not possible to predict from
e results the overall degree of NMDA receptor stimu-
ion attained in vivo, which may be unchanged or even
creased.
In an intriguing study, Aldinio et al. (1985b) rema

the results the overall degree of NMDA receptor stimu-
lation attained in vivo, which may be unchanged or even
increased.
In an intriguing study, Aldinio et al. (1985b) remarked
about the asymptomatic electroencephalograph In an intriguing study, Aldinio et al. (1985b) remarked
about the asymptomatic electroencephalographic spiking
often observed in ageing rats and seen in a majority of
animals older than 15 months of age. This phenemenon. increased.
In an intriguing study, Aldinio et al. (1985b) remarke
about the asymptomatic electroencephalographic spikir
often observed in ageing rats and seen in a majority q
animals older than 15 months of age. This phene In an intriguing study, Aldinio et al. (1985b) remarked
about the asymptomatic electroencephalographic spiking
often observed in ageing rats and seen in a majority of
animals older than 15 months of age. This phenemenon,
t about the asymptomatic electroencephalographic spiking
often observed in ageing rats and seen in a majority of
animals older than 15 months of age. This phenemenon,
together with an age-related performance deficit in pas-
 often observed in ageing rats and seen in a majority of
animals older than 15 months of age. This phenemenon,
together with an age-related performance deficit in pas-
sive avoidance tests, could be reproduced in young ani animals older than 15 months of age. This phenemenon
together with an age-related performance deficit in pas
sive avoidance tests, could be reproduced in young ani-
mals (5 months old) by the daily oral administration of
 together with an age-related performance deficit in passive avoidance tests, could be reproduced in young ani-
mals (5 months old) by the daily oral administration of
quinolinate at doses of approximately 1 g/kg . The elec sive avoidance tests, could be reproduced in young ani-
mals (5 months old) by the daily oral administration of
quinolinate at doses of approximately 1 g/kg. The elec-
troencephalographic changes were not associated with
n mals (5 months old) by the daily oral administration of quinolinate at doses of approximately 1 g/kg . The electroencephalographic changes were not associated with neuronal damage even after 7 weeks of treatment. This stud quinolinate at doses of approximately 1 g/kg. The electroencephalographic changes were not associated with neuronal damage even after 7 weeks of treatment. This study is clearly suggestive, but important questions remain t troencephalographic changes were not associated with
neuronal damage even after 7 weeks of treatment. This
study is clearly suggestive, but important questions re-
main to be answered. In particular, it will be necessary
t neuronal damage even after 7 weeks of treatment. This
study is clearly suggestive, but important questions re-
main to be answered. In particular, it will be necessary
to show that increased amounts of quinolinate or other study is clearly suggestive, but important questions remain to be answered. In particular, it will be necessary
to show that increased amounts of quinolinate or other
kynurenines that are produced in the brain correlate
wi main to be answered. In particular, it will be necessary
to show that increased amounts of quinolinate or other
kynurenines that are produced in the brain correlate
with the changes observed and exclude purely peripheral
e to show that increased amounts of quinolinate or other
kynurenines that are produced in the brain correlate
with the changes observed and exclude purely peripheral
effects. It will also be necessary to repeat the study wit kynurenines that are produced in the brain correlate with the changes observed and exclude purely peripheral effects. It will also be necessary to repeat the study with nonexcitant analogues of quinolinate, such as nicotin with the changes observed and exclude purely peripheral effects. It will also be necessary to repeat the study with nonexcitant analogues of quinolinate, such as nicotinic acid or dipicolinic acid, to ensure that the resul effects. It will also be no
nonexcitant analogues
acid or dipicolinic acid,
merely due to changes
metabolic compensation
13. Alzheimer's disea mexcitant analogues of quinolinate, such as nicotinic
id or dipicolinic acid, to ensure that the results are not
erely due to changes of tissue pH or are secondary
etabolic compensations.
13. Alzheimer's disease. Because t

cluding quinolinate, in the body. The quinolinate might metabolic compensations.
then contribute to some of the CNS toxicity seen in this 13. Alzheimer's disease. Because the statement that
hereditary disease (Heyes, 1987) acid or dipicolinic acid, to ensure that the results are not
merely due to changes of tissue pH or are secondary
metabolic compensations.
13. Alzheimer's disease. Because the statement that
the rat NBM seemed to be particu merely due to changes of tissue pH or are secondary
metabolic compensations.
13. Alzheimer's disease. Because the statement that
the rat NBM seemed to be particularly sensitive to the
neurotoxic effects of quinolinate (Sch metabolic compensations.

13. Alzheimer's disease. Because the statement that

the rat NBM seemed to be particularly sensitive to the

neurotoxic effects of quinolinate (Schwarcz and Kohler,

1983), much attention has been 13. Alzheimer's disease. Because the statement that
the rat NBM seemed to be particularly sensitive to the
neurotoxic effects of quinolinate (Schwarcz and Kohler,
1983), much attention has been focused on the activity
of q the rat NBM seemed to be particularly sensitive to the
neurotoxic effects of quinolinate (Schwarcz and Kohler,
1983), much attention has been focused on the activity
of quinolinate at cholinergic neurones. The NBM is a
maj neurotoxic effects of quinolinate (Schwarcz and Kohler, 1983), much attention has been focused on the activity of quinolinate at cholinergic neurones. The NBM is a major source of cholinergic neurones projecting widely to

366
degeneration of NBM neurones has been proposed as a treat:
major factor in Alzheimer's disease. MMI 366
degeneration of NBM neurones has
major factor in Alzheimer's disease.
The administration of quinolinate

STONE
generation of NBM neurones has been proposed as a treatmer
ajor factor in Alzheimer's disease. NMDA
The administration of quinolinate directly into NBM jections
duces an early increase of choline high-affinity uptake degeneration of NBM neurones has been proposed as a timajor factor in Alzheimer's disease.

The administration of quinolinate directly into NBM joinduces an early increase of choline high-affinity uptake ein the neocortex, major factor in Alzheimer's disease. Note that the administration of quinolinate directly into NBM is
induces an early increase of choline high-affinity uptake et
in the neocortex, presumably as a result of increased
activ The administration of quinolinate directly into NBM
induces an early increase of choline high-affinity uptake
in the neocortex, presumably as a result of increased
activity in the projection neurones, with a decline of
upt induces an early increase of choline high-affinity uptake
in the neocortex, presumably as a result of increased
activity in the projection neurones, with a decline of
uptake over subsequent days as the NBM neurones de-
gen in the neocortex, presumably as a result of increased activity in the projection neurones, with a decline of uptake over subsequent days as the NBM neurones degenerate (Boegman et al., 1987b; Metcalf et al., 1987). The los activity in the projection neurones, with a decline of uptake over subsequent days as the NBM neurones degenerate (Boegman et al., 1987b; Metcalf et al., 1987). The loss of cortical cholinergic afferents is maintained over uptake over subsequent days as the NBM neurones de-
generate (Boegman et al., 1987b; Metcalf et al., 1987). re
The loss of cortical cholinergic afferents is maintained tie
over periods of at least 3 months (El-Defrawy et a generate (Boegman et al., 1987b; Metcalf et al., 1987). rected release of cortical cholinergic afferents is maintained tiouter periods of at least 3 months (El-Defrawy et al., 1986a,b). The loss of choline uptake is reflec The loss of cortical cholinergic afferents is maintained tion
over periods of at least 3 months (El-Defrawy et al., 7
1986a,b). The loss of choline uptake is reflected in a loss NN
of depolarisation-induced release of acet over periods of at least 3 months (El-Defrawy et al., 1986a,b). The loss of choline uptake is reflected in a loss lof depolarisation-induced release of acetylcholine that is not reproduced by injections of excitotoxin dire 1986a,b). The loss of choline uptake is reflected in a loss
of depolarisation-induced release of acetylcholine that is
not reproduced by injections of excitotoxin directly into
the cortex (El-Defrawy et al., 1985). Quinoli of depolarisation-induced release of acetylcholine than
not reproduced by injections of excitotoxin directly if
the cortex (El-Defrawy et al., 1985). Quinolinate lesi
of the NBM do not cause changes in muscarinic recept
wi not reproduced by injections of excitotoxin directly in
the cortex (El-Defrawy et al., 1985). Quinolinate lesion
of the NBM do not cause changes in muscarinic receptor
within the cortex, as reflected in binding, autorad
og e cortex (El-Defrawy et al., 1985). Quinolinate lesions
the NBM do not cause changes in muscarinic receptors
thin the cortex, as reflected in binding, autoradi-
raphic, or biochemical studies (Scarth et al., 1989).
In a de

of the NBM do not cause changes in muscarinic receptors
within the cortex, as reflected in binding, autoradi-
ographic, or biochemical studies (Scarth et al., 1989).
In a detailed comparison of several excitotoxins ad-
min within the cortex, as reflected in binding, autoracographic, or biochemical studies (Scarth et al., 1989).
In a detailed comparison of several excitotoxins a ministered into the rat pedunculopontine tegmental neleus, Rugg ographic, or biochemical studies (Scarth et al., 1989). In a detailed comparison of several excitotoxins ad-
ministered into the rat pedunculopontine tegmental nu-
cleus, Rugg et al. (1992) found that low doses of quino-
l In a detailed comparison of several excitotoxins administered into the rat pedunculopontine tegmental nucleus, Rugg et al. (1992) found that low doses of quino-
linate produced a substantially greater ratio of damage
of th ministered into the rat pedunculopontine tegmental nu-
cleus, Rugg et al. (1992) found that low doses of quino-
inate produced a substantially greater ratio of damage cor
of the cholinergic neurones compared with general h cleus, Rugg et al. (1992) found that low doses of quino-
linate produced a substantially greater ratio of damage
of the cholinergic neurones compared with general his-
tologically detected cell loss, when compared with
NMD linate produced a substantially greater ratio of damage
of the cholinergic neurones compared with general his-
tologically detected cell loss, when compared with
NMDA, kainate, ibotenate, AMPA, or quisqualate. Cell
loss wa of the cholinergic neurones compared with general his-
tologically detected cell loss, when compared with ulations of cerebellar granule cells at the same concen-
NMDA, kainate, ibotenate, AMPA, or quisqualate. Cell tratio NMDA, kainate, ibotenate, AMPA, or quisqualate. Cell loss was associated with intensely staining calcium deposits. This work is of particular interest because it suggests that chronically maintained, low concentrations of quinolinate may be able to produce exactly the same p posits. This worlsuggests that chrownspagests that chrownspages are pairwise the mean of neuron heimer's disease.
Although these. ggests that chronically maintained, low concentrations lever quinolinate may be able to produce exactly the same goy ttern of neurochemical damage reported in Alz-
iner's disease.
Although these results are entirely consis

of quinolinate may be able to produce exactly the same
pattern of neurochemical damage reported in Alzheimer's disease.
Although these results are entirely consistent with a
role for quinolinate in Alzheimer's disease, no heimer's disease.

Although these results are entirely consistent with a

role for quinolinate in Alzheimer's disease, no change

in mean cortical quinolinate concentration in human

patients with Alzheimer's disease have Although these results are entirely consistent with a
role for quinolinate in Alzheimer's disease, no changes
in mean cortical quinolinate concentration in human
patients with Alzheimer's disease have been found (Mo-
roni role for quinolinate in Alzheimer's disease, no changes
in mean cortical quinolinate concentration in human
patients with Alzheimer's disease have been found (Mo-
roni et al., 1986a; Mourdian et al., 1989; Sofic et al.,
19 in mean cortical quinolinate concentration in human
patients with Alzheimer's disease have been found (Mo
roni et al., 1986a; Mourdian et al., 1989; Sofic et al.
1989). This negative result may, of course, conceal sig
nifi patients with Alzheimer's disease have been found (Mo-
roni et al., 1986a; Mourdian et al., 1989; Sofic et al.,
1989). This negative result may, of course, conceal sig-
nificant concentration changes within intracellular c space. 1989). This negative result may, of course, conceal significant concentration changes within intracellular compartments or in localised regions of the extracellular space.
VII. Growth and Development

tors. In the kitten visual cortex, monocular deprivation VII. Growth and Development
In addition to the deleterious consequences, there is a
more positive aspect to the activation of NMDA recep-
tors. In the kitten visual cortex, monocular deprivation
during the critical period VII. Growth and Development
In addition to the deleterious consequences, there is a
more positive aspect to the activation of NMDA recep-
tors. In the kitten visual cortex, monocular deprivation
during the critical period In addition to the deleterious consequences, there is a more positive aspect to the activation of NMDA receptors. In the kitten visual cortex, monocular deprivation during the critical period results in a loss of the norma more positive aspect to the activation of NMDA receptors. In the kitten visual cortex, monocular deprivation during the critical period results in a loss of the normal separation of ocular projections. Neuronal connectivit tors. In the kitten visual cortex, monocular deprivation
during the critical period results in a loss of the normal
separation of ocular projections. Neuronal connectivity
changes, such that all cells now respond to activi during the critical period results in a loss of the normal
separation of ocular projections. Neuronal connectivity
changes, such that all cells now respond to activity
originating in the functioning eye. This loss of binoc separation of ocular projections. Neuronal connectivity
changes, such that all cells now respond to activity
originating in the functioning eye. This loss of binocular
projections can be prevented by the NMDA receptor
anta changes, such that all cells now respond to activity positions originating in the functioning eye. This loss of binocular nen
projections can be prevented by the NMDA receptor severant
agonist 2AP5 (Kleinschmidt et al., 19 originating in the functioning eye. This loss of binocular nen
projections can be prevented by the NMDA receptor seve
antagonist 2AP5 (Kleinschmidt et al., 1987; Rauschecker com
et al., 1990). Similar results were obtained projections can be prevented by the NMDA receptor
antagonist 2AP5 (Kleinschmidt et al., 1987; Rauschecker
et al., 1990). Similar results were obtained from the frog
visual system (Scherer and Udin, 1989) which then led
to antagonist 2AP5 (Kleinschmidt et al., 1987; Rauschecker conditions. The conditions under abnormal conditions. The critical period is determined to experiments on the development of retinotectal projections under abnormal c et al., 1990). Similar results were obtained from the frog are visual system (Scherer and Udin, 1989) which then led one to experiments on the development of retinotectal pro-
to experiments on the development of retinotec visual system (Scherer and Udin, 1989) which then led one
to experiments on the development of retinotectal pro-
where it is extended by the during which changes in eye orientation can lead to site
synaptic reorganisation

STONE
degeneration of NBM neurones has been proposed as a treatment with NMDA (Udin and Scherer, 1990);
major factor in Alzheimer's disease.
The administration of quinolinate directly into NBM jections after implantation o NE
treatment with NMDA (Udin and Scherer, 1990);
NMDA also promotes the plasticity of these same pro-NE
treatment with NMDA (Udin and Scherer, 1990);
NMDA also promotes the plasticity of these same pro-
jections after implantation of a supernumerary eye (Cline WE
treatment with NMDA (Udin and Scherer, 1990);
NMDA also promotes the plasticity of these same pro-
jections after implantation of a supernumerary eye (Cline
et al., 1987). treatment with NM
NMDA also promote
jections after implant
et al., 1987).
More recent work l eatment with NMDA (Udin and Scherer, 1990);
MDA also promotes the plasticity of these same pro-
tions after implantation of a supernumerary eye (Cline
al., 1987).
More recent work has extended these concepts to areas
the C

NMDA also promotes the plasticity of these same projections after implantation of a supernumerary eye (Cline
et al., 1987).
More recent work has extended these concepts to areas
of the CNS unrelated to vision. Rabacchi et jections after implantation of a supernumerary eye (Cline
et al., 1987).
More recent work has extended these concepts to areas
of the CNS unrelated to vision. Rabacchi et al. (1992),
for example, concluded that the activat et al., 1987).

More recent work has extended these concepts to are of the CNS unrelated to vision. Rabacchi et al. (1995)

for example, concluded that the activation of NMI

receptors is important for the plasticity-relat More recent work has extended these concepts to are
of the CNS unrelated to vision. Rabacchi et al. (199
for example, concluded that the activation of NMI
receptors is important for the plasticity-related elimin
tion of sy the CNS unrelated to vision. Rabacchi et al. (1992),
r example, concluded that the activation of NMDA
ceptors is important for the plasticity-related elimina-
on of synapses in the early postnatal rat cerebellum.
These fin

for example, concluded that the activation of NMDA
receptors is important for the plasticity-related elimina-
tion of synapses in the early postnatal rat cerebellum.
These findings implicate an activity-related role of
NMD receptors is important for the plasticity-related elimination of synapses in the early postnatal rat cerebellum.
These findings implicate an activity-related role of NMDA receptors in synaptic plasticity and also may be re tion of synapses in the early postnatal rat cerebellum.
These findings implicate an activity-related role of
NMDA receptors in synaptic plasticity and also may be
related to a role of NMDA receptors in neuronal growth
proc These findings implicate an activity-related role of NMDA receptors in synaptic plasticity and also may be related to a role of NMDA receptors in neuronal growth processes. The activation of NMDA receptors within a limited NMDA receptors in synaptic plasticity and also may be
related to a role of NMDA receptors in neuronal growth
processes. The activation of NMDA receptors within a
limited concentration range of agonist actually promotes
neu related to a role of NMDA receptors in neuronal groprocesses. The activation of NMDA receptors with
limited concentration range of agonist actually prom
neuronal survival and neuritogenesis (Pearce et al., 19
Balazs et al. processes. The activation of NMDA receptors within a
limited concentration range of agonist actually promotes
neuronal survival and neuritogenesis (Pearce et al., 1989;
Balazs et al., 1989; Brenneman et al., 1990; Cambraylimited concentration range of agonist actually promotes
neuronal survival and neuritogenesis (Pearce et al., 1989;
Balazs et al., 1989; Brenneman et al., 1990; Cambray-
Deakin et al., 1990). No comparable stimulation of
g neuronal survival and neuritogenesis (Pearce et al., 1989;
Balazs et al., 1989; Brenneman et al., 1990; Cambray-
Deakin et al., 1990). No comparable stimulation of
growth has been observed for glial cells (Moran and
Patel, Balazs et al., 1989; Brenneman et al., 1990; Cambray-
Deakin et al., 1990). No comparable stimulation of
growth has been observed for glial cells (Moran and
Patel, 1989). The relationship between the neurotoxic
and neurotr Deakin et al., 1990). No comparable stimulation of growth has been observed for glial cells (Moran and Patel, 1989). The relationship between the neurotoxic and neurotrophic effects of NMDA receptors remains confused becau growth has been observed for glial cells (Moran and Patel, 1989). The relationship between the neurotoxic and neurotrophic effects of NMDA receptors remains Patel, 1989). The relationship between the neuroto
and neurotrophic effects of NMDA receptors remai
confused because at least one report has claimed th
both phenomena can be demonstrated on different po
ulations of cerebel and neurotrophic effects of
confused because at least on
both phenomena can be demo
ulations of cerebellar granule
tration (Didier et al., 1990).
The importance of NMDA i

loss was associated with intensely staining calcium de-
posits. This work is of particular interest because it
around their ability to increase intracellular calcium
suggests that chronically maintained, low concentrations Although these results are entirely consistent with a tures (Amano et al., 1992), raising the alternative possi-
role for quinolinate in Alzheimer's disease, no changes bility that this or other growth factors may be produ The importance of NMDA receptors probably revolves both phenomena can be demonstrated on different pop-
ulations of cerebellar granule cells at the same concen-
tration (Didier et al., 1990).
The importance of NMDA receptors probably revolves
around their ability to incre ulations of cerebellar granule cells at the same concentration (Didier et al., 1990).
The importance of NMDA receptors probably revolves
around their ability to increase intracellular calcium
levels (Balazs et al., 1990; C tration (Didier et al., 1990).
The importance of NMDA receptors probably revolves
around their ability to increase intracellular calcium
levels (Balazs et al., 1990; Cambray-Deakin and Bur-
goyne, 1992; Brenneman et al., 1 The importance of NMDA receptors probably revolves
around their ability to increase intracellular calcium
levels (Balazs et al., 1990; Cambray-Deakin and Bur-
goyne, 1992; Brenneman et al., 1990), although NMDA,
alone of t levels (Balazs et al., 1990; Cambray-Deakin and Burgoyne, 1992; Brenneman et al., 1990), although NMDA. goyne, 1992; Brenneman et al., 1990), although NMDA,
alone of the selective amino acid agonists, can increase
the levels of nerve growth factor mRNA in glioma cul-
tures (Amano et al., 1992), raising the alternative possialone of the selective amino acid agonists, can increas
the levels of nerve growth factor mRNA in glioma cul
tures (Amano et al., 1992), raising the alternative possi
bility that this or other growth factors may be produce tures (Amano et al., 1992), raising the alternative possibility that this or other growth factors may be produced
or released under the influence of NMDA receptor stim-
ulation (Rauschecker et al., 1990).
There is a suspic res (Amano et al., 1992), raising the alternative possi-
ity that this or other growth factors may be produced
released under the influence of NMDA receptor stim-
ation (Rauschecker et al., 1990).
There is a suspicion that

partments or in localised regions of the extracellular al., 1990). Nevertheless, quinolinic acid is able to mimic
space.

VII. Growth and Development

In addition to the deleterious consequences, there is a and Patel, 1990 bility that this or other growth factors may be produced
or released under the influence of NMDA receptor stim-
ulation (Rauschecker et al., 1990).
There is a suspicion that the NMDA receptor involved
in the survival of cu or released under the influence of NMDA receptor stim-
ulation (Rauschecker et al., 1990).
There is a suspicion that the NMDA receptor involved
in the survival of cultured neurones may be slightly
different from the normal ulation (Rauschecker et al., 1990).
There is a suspicion that the NMDA receptor involved
in the survival of cultured neurones may be slightly
different from the normal excitatory receptor (Balazs et
al., 1990). Nevertheles There is a suspicion that the NMDA receptor involved
in the survival of cultured neurones may be slightly
different from the normal excitatory receptor (Balazs et
al., 1990). Nevertheless, quinolinic acid is able to mimic
 in the survival of cultured neurones may be slightly
different from the normal excitatory receptor (Balazs et
al., 1990). Nevertheless, quinolinic acid is able to mimic
the activity of NMDA in several experimental systems, different from the normal excitatory receptor (Balazs et al., 1990). Nevertheless, quinolinic acid is able to mimic
the activity of NMDA in several experimental systems,
including the ability to promote the development of
 the activity of NMDA in several experimental systems, **EXECUTE SECONDER**
VIII. Summary
VIII. Summary
han 10 years, the ky

rebellar granule neurones (Balazs et al., 1990; Hu
d Patel, 1990).
VIII. Summary
In a little more than 10 years, the kynurenine meta
tes of tryptophan have emerged from their form and Patel, 1990).

VIII. Summary

In a little more than 10 years, the kynurenine metab-

olites of tryptophan have emerged from their former

position as biochemical curiosities, to occupy a promi-VIII. Summary
In a little more than 10 years, the kynurenine meta
olites of tryptophan have emerged from their form
position as biochemical curiosities, to occupy a pror
nent position in research on the causes and treatmen VIII. SUMMARY
In a little more than 10 years, the kynurenine metab-
olites of tryptophan have emerged from their former
position as biochemical curiosities, to occupy a promi-
nent position in research on the causes and tr In a little more than 10 years, the kynurenine metab-
olites of tryptophan have emerged from their former
position as biochemical curiosities, to occupy a promi-
nent position in research on the causes and treatment of
sev olites of tryptophan have emerged from their former
position as biochemical curiosities, to occupy a promi-
nent position in research on the causes and treatment of
several major CNS disorders. The pathway includes two
com position as biochemical curiosities, to occupy a prominent position in research on the causes and treatment of several major CNS disorders. The pathway includes two compounds, quinolinic acid and kynurenic acid, which are nent position in research on the causes and treatment of several major CNS disorders. The pathway includes two
compounds, quinolinic acid and kynurenic acid, which
are remarkably specific in their pharmacological profiles: several major CNS disorders. The pathway includes tompounds, quinolinic acid and kynurenic acid, where remarkably specific in their pharmacological profil one is a selective agonist at receptors sensitive to NMI whereas th compounds, quinolinic acid and kynurenic acid, which
are remarkably specific in their pharmacological profiles:
one is a selective agonist at receptors sensitive to NMDA,
whereas the other is a selective antagonist at low one is a selective agonist at receptors sensitive to NMDA, whereas the other is a selective antagonist at low concentrations at the strychnine-resistant glycine modulatory site associated with the NMDA receptor.

It has been argued that these agents cannot be of

REVIEW PHARMACOLOGICAL

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QUINOLINIC AND
physiological or pathological relevance because their nor-
mal extracellular concentrations, in the nanomolar QUINOLINIC AND
physiological or pathological relevance because their nor-
mal extracellular concentrations, in the nanomolar
range, are at least 3 orders of magnitude lower than those QUINOLINIC AND KYI
physiological or pathological relevance because their nor-
mal extracellular concentrations, in the nanomolar re
range, are at least 3 orders of magnitude lower than those
required to act at NMDA recepto physiological or pathological relevance because their nor-
mal extracellular concentrations, in the nanomolar ro
range, are at least 3 orders of magnitude lower than those the
required to act at NMDA receptors. This is a f physiological or pathological relevance because their normal extracellular concentrations, in the nanomola range, are at least 3 orders of magnitude lower than thos required to act at NMDA receptors. This is a facil argume mal extracellular concentrations, in the nanomolar rol
range, are at least 3 orders of magnitude lower than those the
required to act at NMDA receptors. This is a facile to
argument, however, that ignores at least two poss range, are at least 3 orders of magnitude lower than those the required to act at NMDA receptors. This is a facile to argument, however, that ignores at least two possibilities. pone is that both quinolinate and kynurenate required to act at NMDA receptors. This is a fa
argument, however, that ignores at least two possibilit
One is that both quinolinate and kynurenate may
present in very high concentrations locally at some s
in the brain tha argument, ho
One is that
present in ve
in the brain
lular levels.
Similar co The is that both quinolinate and kynurenate may be esent in very high concentrations locally at some sites the brain that cannot be reflected in mean extracellar levels.
Similar considerations apply to many neuroactive ent

present in very high concentrations locally at some sites
in the brain that cannot be reflected in mean extracel-
lular levels.
Similar considerations apply to many neuroactive
agents in the CNS. The fact that both compoun in the brain that cannot be reflected in mean extracel-
lular levels.
Similar considerations apply to many neuroactive
agents in the CNS. The fact that both compounds appear
to be synthesised in, and thus emerge from, glia the similar considerations apply to many neuroactive (agents in the CNS. The fact that both compounds appear of it to be synthesised in, and thus emerge from, glial cells ble that are well recognised as enjoying a close ph Similar considerations apply to many neuroactive
agents in the CNS. The fact that both compounds appear of
to be synthesised in, and thus emerge from, glial cells ble
that are well recognised as enjoying a close physical a to be synthesised in, and thus emerge from, glial cells
that are well recognised as enjoying a close physical and
chemical relationship with some neurones in which the
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de and antagonist acting at NMDA receptors must continue
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 would be expected to have profound implications for
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if their local concentrations at strategic points in the CNS are far higher than their mean levels in the CSF or microdialysates.
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especially in situations in which there is infection and

inflammation. The correlations t especially in situations in which there is infection and
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AIDS or poliovirus infection, are quite startling and argue further for an important role for this agent in pathology.
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NMDA ligand, such as quinolinate, might play a pivotal
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deficiency may be linked to changes of kynurenine metabolites should be investigated.

Overall, there seems little doubt that the development

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Overall, there seems little doubt that the development

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