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Neuropharmacology of Quinolinic and Kynurenic Acids

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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 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 quinolinic acid was accepted as an intermediate (Gholson et

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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 for several of the kynurenine enzymes.

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 precursor of 5HT.* In retrospect, this was unfortunate because, in peripheral tissues at least, only 1% of dietary tryptophan becomes converted to 5-hydroxytryptophan (Peters, 1991), i.e., >95% is metabolised to kynurenines (Wolf, 1974). It follows that alterations in tryptophan, tryptophan hydroxylase, and 5-hydroxytryptophan levels, which have been interpreted in terms of their effects on 5HT (Price et al., 1990), may have had at least as great an impact, directly or indirectly, on the kynurenine pathway.

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 activity, 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 directly into the brains of rodents (Lapin, 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 excitatory amino acid receptors in neurotransmission, learning and memory, excitotoxicity, and neurodegenerative diseases (Choi, 1988; Stone and Burton, 1988; Collingridge and Lester, 1989), there has been an accompanying expansion of interest in the analysis and understanding of function of the kynurenine pathway from tryptophan in the CNS.

In this review, information now available concerning some aspects of the kynurenines will be summarised and will hopefully serve as a focus for future developments in this area. The emphasis is strongly on the CNS of mammals and excludes the retina, but several published 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 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.

* Abbreviations: 5HT, 5-hydroxytryptamine; CNS, central nervous system; IDO, indoleamine dioxygenase; TDO, tryptophan-2,3-dioxygenase; 3HAO, 3-hydroxyanthranilate oxygenase; QPRT, quinolinate 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-aminocyclopentane-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; PGCL, paragigantocellularis lateralis; NTS, nucleus tractus solitarius; LTP, long-term potentiation; HA966, 1-hydroxy-3-amino-pyrrolidone-2; NADPH, nicotinamide adenine dinucleotide phosphate; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; NBM, nucleus basalis magnocellularis; CPP, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid.

II. Kynurenine Biosynthesis

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 enzyme, which is haem dependent, has a half-life of approximately 2 hours in mammals, its activity being readily 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 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 subsequent 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 induced by glucocorticoids 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 enhancing effect on glucocorticoid induction of this enzyme, whereas insulin prevents induction (Nakamura et al., 1980). Tryptophan dioxygenase is also induced after 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 of L-tryptophan results in the production of L-kynurenine via L-formyl kynurenine (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, 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 IDO is also active in metabolising L- and L-5-hydroxytryptophan, tryptamine, 5HT, and melatonin (Hirata and Hayaishi, 1971). Whereas tryptophan dioxygenase 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 tissues,

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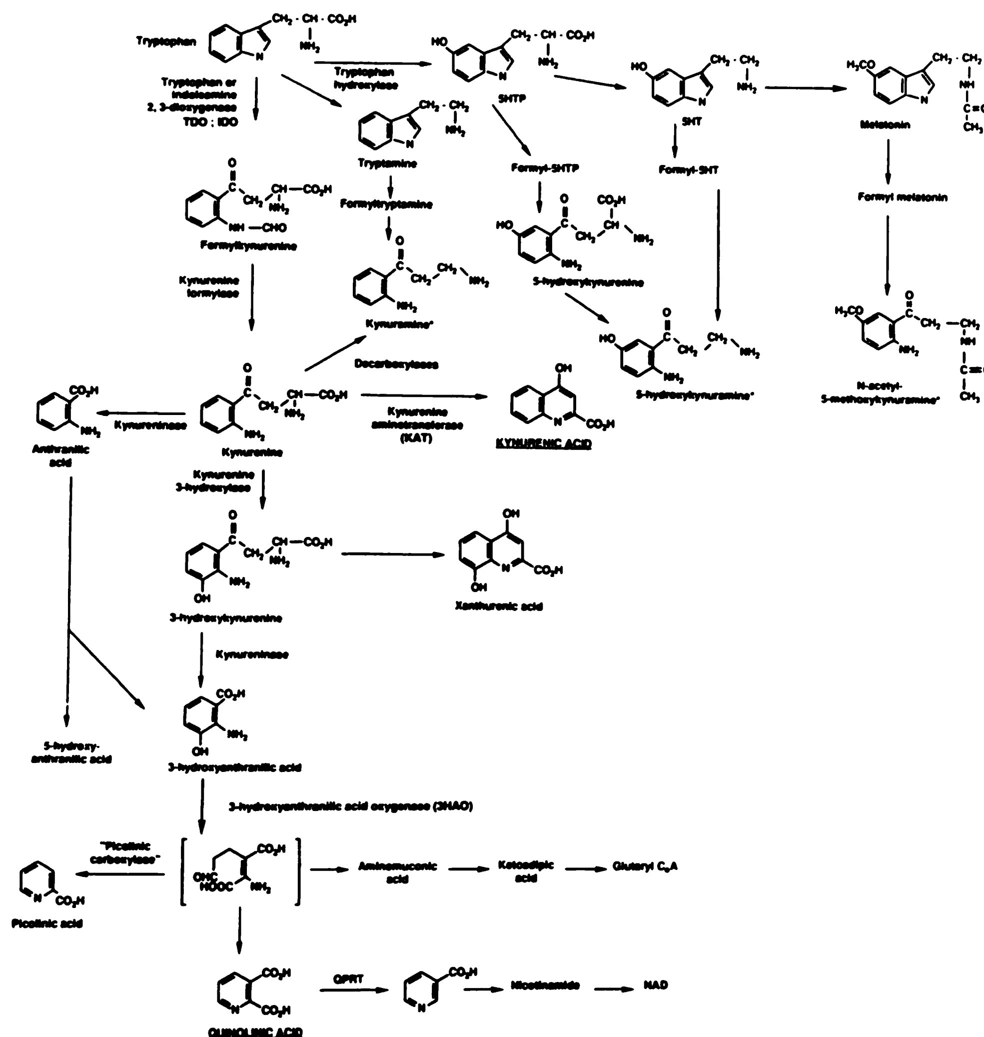

FIG. 1. Kynurenine pathway from tryptophan. The following enzymes are indicated: tryptophan pyrrolase (TDO, EC 1.13.11.11, or indoleamine-2,3-dioxygenase, EC 1.13.11.17); kynurenine formylase, EC 3.5.1.9; kynurenine hydroxylase, EC 1.14.13.9; kynureninase, EC 3.7.1.3; kynurenine aminotransferase, EC 2.6.1.7; 3-hydroxyanthranilic acid oxidase, EC 1.13.11.6; picolinate carboxylase, EC 4.1.1.45. *, kynuramines also known as kynurenamines.

lung, placenta, and brain. In rat brain, the enzyme shows highest activity in the hypothalamus where it has about 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 extensively analysed and discussed by Bender (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 well as peripherally. To this extent, the localisation of enzyme activities within the CNS, as well as the comparability between central enzymes and those occurring peripherally, is of some importance.

A. Kynureninase and Kynurenine Hydroxylase

Although kynureninase is present in large amounts in the liver, kidney and spleen, only small amounts of this 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). In humans the cerebral enzyme is present at a higher relative 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 raises important questions about the ability of brain to metabolise its own kynurenines along the usually described pathway from L-kynurenine to 3-hydroxykynurenine to 3-hydroxyanthranilic acid. However, although it shows greater activity for 3-hydroxykynurenine as substrate, kynureninase is also able to hydrolyse L-kynurenine to anthranilic acid (McDermot et al., 1973; Bender and McCreanor, 1982), which can subsequently undergo hydroxylation to 5- or 3-hydroxyanilic acid via nonspecific microsomal hydroxylating en-

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zymes (Bender, 1989b). This may explain the ability of 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 entry into the kynurenine pathway independently of cerebral tryptophan.

Some oestrogenic compounds are able to inhibit kynureninase 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, potentially modify the cerebral concentrations of L-kynurenine and its metabolites.

1. Inhibition of kynureninase. Several compounds are now known that can inhibit kynureninase. One of these, synthesised by Whitten et al. (1989), is a difluoro-substituted desamino analogue of L-kynurenine; few biological data concerning this compound are presently available.

a. NICOTINYLALANINE. Some success has been achieved in manipulating the kynurenine pathway using an analogue of L-kynurenine: nicotinylalanine. This 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, which is decreased (Moroni et al., 1991a; Connick et al., 1992). This effect is seen especially when nicotinylalanine administration is accompanied by a tryptophan load, when 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 endotoxin (Moroni et al., 1991a). In mice with elevated brain kynurenate levels, nicotinylalanine was able to suppress seizures induced either by pentylenetetrazol or electroshock treatment (Connick et al., 1992). Although the doses required were relatively high, there may be potential therapeutic value in developing other analogues of kynurenines or nicotinylalanine with which to increase brain kynurenate to quinolinate ratios. This may be of special value, for example, in those cases in which a very high concentration of quinolinate is attained, as occurs in some viral infections (see section VI.E.8).

B. L-Kynurenine 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; Noguchi et al., 1975; Harada et al., 1978; Okuno et al., 1991a). One of these enzymes is identical biochemically, physicochemically, and immunologically with an enzyme present in rat brain (Minatogawa et al., 1974; Ishikawa et al., 1991). This led Okuno et al. (1990) to postulate that it might play a central role in the synthesis of cerebral kynurenate. It 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 L-kynurenine was substantially lower when using the latter acid (17 compared with 910 μM).

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 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). 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, 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). 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 that astrocytic cultures or human glioma tissue are able to synthesise kynurenate and quinolinate from L-kynurenine (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 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 emphasised by its remarkable selectivity for substrate. 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 more than 50% with 2 μM L-kynurenine as substrate. 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 kynurenate (as reflected in the release of kynurenate following preincubation with L-kynurenine) (Turski et al., 1989).

There is also a good correlation between the aminotransferase activity and kynurenate release from neurone-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 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 of the rat hippocampus. The highest density of aminotrans-

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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 nonpyramidal in appearance, although immunoreactive 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. Although present predominantly in glial cells, distributed throughout the nucleus and cytoplasm, the enzyme was also found in medium- and large-sized neurones. Here, the enzyme was localised to cytoplasmic organelles, associated with cell membranes. Immunoreactivity was also demonstrated in astrocytic processes making close contact with dendritic synapses. This raises the tantalising possibility that kynurenate is secreted by glial cells 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-α-aminoadipate to inhibit kynurenine aminotransferase activity, it appears that this same enzyme may be responsible in vivo, at least in peripheral tissues, for the transamination of α-aminoadipate to α-ketoadipate. Tobes and Mason (1975) claimed that the two enzymes, formerly believed 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 lysine for aminotransferase activity and could have important implications for conditions in which increased levels of 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 brain has been the potential relevance to an 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 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 properties of both of these proteins, which did not react with antibodies to the rat enzyme, were significantly different from the rodent molecule. Most strikingly, the K_m values for L-kynurenine were 8.3 and 3.3 mM using pyruvate as the amino acceptor, the former showing a pH optimum of 9.6.

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 pathological, levels and conditions. However, no details were provided of the donors, such as their ages, or of important 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 the disappointing human results.

C. 3-Hydroxyanthranilic Acid Oxygenase

The conversion of 3-hydroxyanthranilic acid to quinolinate 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, inappropriately known as picolinic carboxylase, which decarboxylates the unstable intermediate to aminomuconic semialdehyde. The latter can then undergo nonenzymic 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, 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 fraction of rat brain tissue and exhibits a K_m of 3.6 μM 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 moderate 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 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). 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 immunoreactive cells were found in the striatum, neocortex, hippocampus, 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, although, whereas most brain regions exhibited a fairly homogeneous distribution of the enzyme throughout the region, the olfactory bulb demonstrated a high degree of localisation of 3HAO in the internal and external plexiform layers. Immunoreactivity was also relatively intense in thalamic nuclei, especially the ventromedial and dorsomedial portions, with very little 3HAO localised to hypothalamic regions. In the cerebellum, immunoreactivity for 3HAO was localised almost exclusively to the granule cell layer. Despite the primary localisation to glial cells, it was reported that some cells,

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clearly identifiable as neurones, were also stained for 3HAO, especially in the olfactory bulb (Kohler et al., 1988a).

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 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 intracellularly but to yield a 10-fold greater amount than control slices into the medium, with a progressive increase 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 3HAO and is supported by a report that human glioma tissue is also able to synthesise quinolinate from 3-hydroxyanthranilate (Vezzani et al., 1991a). The latter compound is a better precursor compound in this tissue than L-kynurenine or tryptophan. The ability of 3-hydroxyanthranilic acid loading to induce such marked increases of quinolinic acid concentrations would seem to confirm 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 phosphoribosyl-pyrophosphate as well as the decarboxylation of the intermediate conjugate to nicotinic acid mononucleotide. QPRT appears to exist in several isoforms. The enzymes detected in liver, kidney, and brain 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 quinolinate (Kalikin and Calvo, 1988). In the CNS, QPRT was 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 present in the extracellular space and acting at NMDA-sensitive glutamate receptors.

Subsequent work, using immunocytochemical methods and antibodies to liver QPRT, revealed a predominant location in CNS glial cells and some ventricular ependymal cells, with a relatively small portion occurring in neurones. The relevant glial cells were generally small (<10 μm in diameter) and of variable shape, some exhibiting a remarkably close and specific physical relationship with neurones and suggesting a possible oligodendroglial identity (Kohler et al., 1987). Stained neurones were generally 15 to 20 μm in diameter and were located primarily in the thalamus, hypothalamus, and striatum. In both neurones and glia, the enzyme was found in 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 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 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 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 must be catabolised in cells other than those responsible for its production and that, consequently, it must enter the extracellular space in its migration between the two.

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 appearing to include aspiny neurones. It is not clear 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 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 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 established with other neuropharmacological, functional, physiological, or behavioural parameters.

The pharmacology of kynurenine-metabolising enzymes 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 compounds, although emphasis has usually been placed on the peripherally located enzymes. These aspects were reviewed by El-Sewedy (1989).

III. Kynurenines in Brain

Early studies of the biochemistry of kynurenines were concerned primarily with metabolism in peripheral tissues. 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 products of this pathway in the CNS. Joseph et al (1978) and Gal and Sherman (1978) were the first to report the

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identification of L-kynurenine in brain tissue. The latter authors also reported significant concentrations of 3-hydroxykynurenine and kynuramine in brain (Gal and 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 calculation is based on the use of radiolabeled tryptophan 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-Tipping (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-kynurenine concentrations was greater than in control animals. A similar dissociation between plasma and brain L-kynurenine concentrations was also detected after subjecting animals to stress and administering valine, which reduces tryptophan uptake into brain (Kennett and Joseph, 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 concentration throughout the CSF and partly on the fact that the 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 correlation 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 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 nanomolar range (Naito et al., 1987; Joseph, 1989), whereas concentrations at least 1000-fold higher are required to produce a barely detectable reduction of tryptophan uptake into brain.

It should be emphasised that, as anticipated by the discussion of enzyme distributions, there is no relationship between the presence of kynurenines in the brain and the existence of 5HT-releasing neurones. Indeed, reserpine- or toxin-mediated destruction of 5HT neurones results in the elevation of cerebral L-kynurenine concentrations, possibly due to the diversion of tryptophan 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 samples from schizophrenic and normal subjects (Joseph et al., 1979), interpretation is complicated by a 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 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 with 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 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 approximately 2 μM and, although a measurable degree of heterogeneity 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 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 relevant 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 brain at levels remarkably similar to 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 cerebral cortex (with approximately 2 nmol/g wet weight) 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 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 and 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 5-hydroxyindoleacetic acid (all approximately 2-fold changes). However, the basal levels recorded by these workers, approximately 100 fmol/mg tissue, were substantially 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 in the rat striatum using microdialysis (During et

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TABLE 1
*Concentrations of quinolinic acid in brain and blood**

Species/area	Pathology/treatment	Quinolinate content	References
CSF			
Rat	Control	~20 nM	Moroni et al. (1986b); Turski et al. (1989); Heyes and Lackner (1990); Heyes et al. (1990c)
Rat	Control	14 nM	Robinson et al. (1992)
	L-tryptophan, 200 mg/kg	399 nM	Robinson et al. (1992)
Gerbil	Control	38 nM	Saito et al. (1992a)
	4 days postischaemia	223 nM	Saito et al. (1992a)
Monkey	Control	84 nM	Jauch et al. (1993)
Macaque	Control	27 nM	Heyes et al. (1992c)
	Simian immunodeficiency virus positive	~2,800 nM	Heyes et al. (1992c)
Human	Control	21 nM	Martin et al. (1992)
	HIV positive	68 nM	Martin et al. (1992)
	Control	21 nM	Halperin and Heyes (1992)
	CNS *Borrelia* infection	324 nM	Halperin and Heyes (1992)
Brain extracellular fluid (microdialysis)			
Rat: striatum	Basal	5.5 nM	During et al. (1989)
	Tryptophan, 250 mg/kg	1,400 nM	During et al. (1989)
	Basal	~36 nM	Westerberg et al. (1990)
	30 min hypoglycaemia	~79 nM	Westerberg et al. (1990)
	Basal	<20 nM	Speciale et al. (1989a)
Brain tissue			
Rat			
Whole brain		0.35 nmol/g	Moroni et al. (1991a)
Cortex		1.6 nmol/g	Wolfensberger et al. (1983)
Cortex		2.1 nmol/g	Lombardi et al. (1983a)
Striatum		0.6 nmol/g	Moroni et al. (1984a, b; 1986b)
Cortex		1.7 nmol/g	Moroni et al. (1986b)
	Portacaval anastomosis	2.9 nmol/g	Moroni et al. (1986b)
Cortex		0.018 nmol/g	Robinson et al. (1992)
Striatum		0.021 nmol/g	Robinson et al. (1992)
Mouse			
Whole brain		33 nM	Saito et al. (1992b)
Gerbil			
Hippocampus		65 nM	Saito et al. (1992a)
	4 days postischaemia	1,466 nM	Saito et al. (1992a)
Human			
Cortex		0.6 nmol/g	Wolfensberger et al. (1983)
Cortex		0.8 nmol/g	Moroni et al. (1986b)
	Hepatic encephalopathy	2.5 nmol/g	Moroni et al. (1986b)
Blood			
Rat			
Plasma		273 nM	Heyes et al. (1990b)
Plasma		2,600 nM	Robinson et al. (1992)
	Tryptophan, 200 mg/kg	11,500 nM	Robinson et al. (1992)
Mouse plasma		122 nM	Saito et al. (1992b)
Monkey blood		2,715 nM	Jauch et al. (1993)
Human serum		416 nM	Halperin and Heyes (1992)

* This table is not meant to be exhaustive, only to convey an indication of the range of values reported. Approximate values have been given in places according to estimation from figures. Many authors quote values in other brain regions or after treatments not summarized here.

al., 1989). Whereas intravenous infusion of quinolinate 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 approximately 5.5 nM up to 1.4 μM. 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-free 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 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 able to synthesise quinolinic acid from the condensation of aspartic acid and dihydroxyacetate (Bender, 1989b). It has also been emphasised that the disorder of pellagra,

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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 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 oldest group of rats had concentrations of quinolinic acid in the brain approaching 10 μM, levels 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 content of brain samples taken from patients with senile dementia of the Alzheimer type (Moroni et al., 1986a). 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.

In patients dying in a coma resulting from severe liver 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 higher 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 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. Formation and removal of quinolinate. A detailed analysis of the properties of 3HAO and QPRT derived from mammalian forebrain indicates that both have K_m values of approximately 3.5 μM, although values for the maximum reaction velocity were approximately 80-fold 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 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 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 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 is localised primarily in areas of the frontal cortex, striatum, and hippocampus which possess little detectable QPRT. The only brain region that appears to have approximately equal activities of the two enzymes is the olfactory bulb, an area that, interestingly, has a high rate of neuronal turnover. In addition, 3HAO appears to be 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 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 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 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. This raises the interesting possibility that quinolinic acid must exist in the extracellular fluid and, under some circumstances, may accumulate sufficiently to activate or otherwise modify, for example, by potentiation or desensitisation, the NMDA-sensitive population of glutamate 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 kynurenine pathway is that it leads to the formation of nicotinamide and nicotinamide nucleotides (Bender, 1989b), which are essential cofactors in many metabolic processes. Although this does not immediately answer the question as to why 3HAO and QPRT should be located in morphologically 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 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 as 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-hydroxyanthranilic acid into rat brain promotes the formation 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 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-lesioned animals exhibit a substantially higher capacity to produce quinolinate from 3-hydroxyanthranilate than control preparations, a finding consistent with the predominantly glial localisation of 3HAO (Speciale and Schwarcz, 1993).

The magnitude of the stimulation of quinolinate synthesis by 3-hydroxyanthranilate was striking; although some regional variability was observed in different brain regions, elevations of quinolinate concentrations of up

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to 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 contention of Foster et al. (1986) that 3HAO activity may normally be restrained by factors such as product inhibition or the availability of Fe^{2+} ions. It should also be recalled that picolinic acid carboxylase may play a role in diverting some of the aminocarboxymuconic semialdehyde away from quinolinate formation.

These findings raise interest in the report that the 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 agent were normal in brain and CSF (Reynolds et al., 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 μM 3-hydroxyanthranilate perfused through the dialysis probe was sufficient to induce measurable amounts of quinolinate in 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-hydroxyanthranilate 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 μM to yield significantly enhanced flux through the kynurenine pathway.

Although the modulation of quinolinate levels in pathological 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 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 ability of endotoxin to induce IDO (Yoshida and Hayaishi, 1978). Since only the peripheral, not icv, administration of lipopolysaccharides was effective, it is likely that the change of brain concentration was secondary to the 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 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 quinolinic acid within cells. It is known that quinolinic acid is an effective inhibitor of human monoamine oxidase type B (Naoi et al., 1987) and a potent inhibitor of major glycolytic enzymes, such as phosphoenolpyruvate carboxykinase (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 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 that any insult to CNS neurones that results in the damage or lysis of cells containing quinolinic acid could result in a positive feedback in which locally high concentrations of quinolinic acid promote further excitotoxicity.

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 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 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 μM) 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 problem 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 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, 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 its metabolic degradation in the extracellular space by significant amounts of extracellular QPRT or other metabolising enzymes. This conclusion was supported by observations that neither 400-μm 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 quinolinate by either brain or choroid plexus 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 metabolism, it therefore seems unlikely that quinolinic 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, for example, that the usually accepted relationship between neurotransmitter function and the existence of uptake mech-

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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 substances such as quinolinic acid might fulfill a longer term role in the maintenance and regulation of cerebral 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 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 physiologically 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 a concentration of 2 μM, Foster et al. (1984a) calculated that only 0.3% penetrated the blood-brain barrier in a single passage. Although 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 peripheral injections of quinolinate are not prevented by administration of the NMDA antagonist 2AP7 (Czuczwar and Meldrum, 1982), implying that these seizures may not be centrally mediated. On the other hand, unpublished results from Boni et al. (quoted by Heyes and 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 10-fold increase of striatal quinolinate concentration after intravenous quinolinate injection.

Interestingly, quinolinate has recently been shown to increase permeability of the blood-brain barrier. Intracerebroventricular injections of quinolinate or kainate 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

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; 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 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 shown to contain kynurenate at concentrations 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 subjects 70 to 80 years of age. Tests revealed that a postmortem delay of 4 hours caused a 30% increase of kynurenate 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 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 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 tryptophan because no correlation was apparent between neocortical concentrations of this amino acid and kynurenate (Moroni et al., 1988a).

This progressive elevation of brain kynurenate level has been amply corroborated by evidence that kynurenine 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 attributable to an increased astrocytic content of the enzyme rather than to astrocytic proliferation because other markers were unchanged. Correspondingly, kynurenate 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 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 were said to be reached by 7 days postnatally, and the 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 attracted 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 initiation of accelerated plasticity. Alternatively, taken together with the reports of decreased NMDA receptor-associated glycine binding with age, the increase of kynurenate 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 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 micromolar concentrations in brain, values that would certainly be expected to interfere with the glycine site on NMDA

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TABLE 2
*Concentrations of kynurenic acid in brain and blood**

Species	Area/sample	Pathology/treatment	Kynurenate content	References
Rat	CSF	Control	1.13 nM	Heyes and Quearry (1990); Heyes et al. (1990a)
Gerbil	CSF	Control	3.24 nM	Saito et al. (1992a)
		4 days post-ischaemia	3.96 nM	Saito et al. (1992a)
Monkey	CSF	Control	6 nM	Jauch et al. (1993)
		L-kynurenine, 200 mg/kg	300 nM	Jauch et al. (1993)
Macaque	CSF	Control	4.8 nM	Heyes et al. (1992c)
		Simian immunodeficiency virus infected	~68 nM	Heyes et al. (1992c)
Human	CSF	Control	5.1 nM	Swartz et al. (1990b)
		Parkinson's disease	3.63 nM	Vecsei et al. (1992a)
		Alzheimer's disease	3.78 nM	Vecsei et al. (1992a)
		Alzheimer's with probenecid, 50 mg/kg	19 nM	Vecsei et al. (1992a)
		Control	2.6 nM	Halperin and Heyes (1992)
		CNS infection	7.5 nM	Halperin and Heyes (1992)
	Brain extracellular fluid (microdialysis)			
Rat	Striatum	Control	17.1 nM	Swartz et al. (1990a)
		L-kynurenine, 100 mg/kg	~634 nM	Swartz et al. (1990a)
		Control	<275 nM	Speciale et al. (1990)
	Pyriform cortex	Control	Undetected	Wu et al. (1991)
		L-kynurenine, 500 μM	1500 nM	Wu et al. (1991)
	Hippocampus	Control	10.4 nM†	Russi et al. (1992)
		Nicotinylalanine	20 nM†	Russi et al. (1992)
	Brain tissue			
Rat	Brainstem		0.15 pmol/mg protein	Swartz et al. (1990b)
	Thalamus		0.026 pmol/mg protein	Swartz et al. (1990b)
	Striatum		3.5 pmol/mg protein	Vecsei et al. (1992)
		L-kynurenine, 600 mg/kg	~19 pmol/mg protein	Vecsei et al. (1992)
	Whole brain	Control	17.8 pmol/g·tissue	Moroni et al. (1988b)
		Probenecid, 200 mg/kg	72.2 pmol/g·tissue	Moroni et al. (1988b)
		Age 1 week	15 pmol/g·tissue	Moroni et al. (1988a)
		Age 3 months	320 pmol/g·tissue	Moroni et al. (1988a)
		Age 18 months	747 pmol/g·tissue	Moroni et al. (1988a)
		Control	39 pmol/g·tissue	Moroni et al. (1991a)
		Nicotinylalanine + lipopolysaccharide	62 pmol/g·tissue	Moroni et al. (1991a)
		Control	14 pmol/g·tissue	Carla et al. (1988)
Mouse	Whole brain		5.8 pmol/g·tissue	Moroni et al. (1988b)
			34.9 nM	Saito et al. (1992b)
Gerbil	Hippocampus	Control	71.6 nM	Saito et al. (1992a)
		4 days postischaemia	80 nM	Saito et al. (1992a)
Human	Cortex	Control	2.07 pmol/mg protein	Swartz et al. (1990b)
	Putamen	Control	3.38 pmol/mg protein	Swartz et al. (1990b)
	Cortex	Control	150 pmol/g/tissue	Moroni et al. (1988b)
	Cortex area 4	Control	85.2 pmol/g/tissue	Connick et al. (1989)
		Huntington's disease	165 pmol/g/tissue	Connick et al. (1989)
	Blood			
Rat	Plasma		138 nM	Swartz et al. (1990a)
		L-kynurenine, 100/mg/kg	1500 nM	Swartz et al. (1990a)
	Blood	3 months old	28 nM	Moroni et al. (1988a)
		18 months old	65 nM	Moroni et al. (1988a)
Mouse	Plasma		150 nM	Saito et al. (1992b)
Macaque	Serum		1960 nM	Heyes et al. (1992c)
Human	Serum		2 nM	Halperin and Heyes (1992)

* This table is not meant to be exhaustive, only to convey an indication of the range of values reported. Approximate values have been given in places according to estimation from figures. Many authors quote values in other brain regions or after treatments not summarized here.

† These are values uncorrected for recovery; true extracellular levels are likely to be approximately 10 times these values.

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receptors for which the IC_{50} of kynurenate is approximately 15 μM (Birch, et al., 1988a,b; Kessler et al., 1989; 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-hydroxyanthranilate could be detected in this work, although peripherally 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 Schwarcz, 1990), a route somewhat different from that envisaged in classical schemes of kynurenine metabolism. Although probenecid was itself able to produce a significant, although limited, increase of brain kynurenate, the combined administration of this acidic transport blocker with even a low dose (150 mg/kg) of L-kynurenine 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 kynurenine levels and, thus, with liver function and peripheral tryptophan status.

Even greater changes of up to 1300-fold were reported to result from the combined administration of the acidic transport inhibitor probenecid together with L-kynurenine in rats. Striatal kynurenate increased from 1.6 nM to 2.1 μM (Miller et al., 1992). Substantial increases of approximately 50-fold (an increase from 6 to 300 nM) 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 effectively than by slices of several 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. Interestingly, although total L-kynurenine uptake was comparable across several brain regions, there were clear differences in the relative proportions of sodium-dependent and sodium-independent transport; the ratio between these varied >10-fold from 2.3 in striatum to 0.24 in cerebellum. The existence of a significant fraction of sodium-dependent transport may imply that brain uptake is of 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 confirmed by the ability of low-temperature incubation and several metabolic inhibitors, including cyanide, ouabain, and 2,4-dinitrophenol, to suppress the accumulation of L-kynurenine. There was also no apparent binding of L-kynurenine to broken cell preparations to account for its removal for the medium.

The distinction between sodium-dependent and -independent processes probably corresponds to movement 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 independent of sodium (Speciale et al., 1989b). In addition, uptake of L-kynurenine into striatal slices prepared several days 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 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 uptake by about 70% at a concentration of 10 mM. 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 evidence that it can be converted to kynurenic acid in 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 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 (<1% of the L-kynurenine) were released into the extracellular medium with <5% remaining intracellularly. Most kynurenate production was found using slices from hippocampus and pyriform cortex with the least in cerebellar slices. An increased kynurenate efflux from ibotenate-lesioned striatum or quinolinate-lesioned hippocampus (Wu et al., 1992b) supported 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 probably of glial origin. Since release of kynurenate into the extracellular medium persisted in the absence of external 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 microdialysis, was increased from undetectable levels (<250 nM) to >10 μM 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 experimental system and recorded a 37-fold increase after an injection of 100 mg/kg L-kynurenine, to 630 nM. The importance of an aminotransferase enzyme in catalysing the conversion of the L-kynurenine load to kynurenate was emphasised by the decrease of kynurenate production and efflux following administration of aminooxyacetic acid, a com-

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pound that shows inhibitory activity toward several aminotransferases, including kynurenine aminotransferase (K_i approximately 25 μM) (Turski et al., 1989; Swartz et 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 extracellular 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 neuronal activity, the hyperexcitability and behavioural seizures seen after injections of kainate or NMDA agonists could partly result from a decline of extracellular kynurenate levels. However, in experiments in which L-kynurenine 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 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). In contrast, kynurenate levels were elevated 4 weeks after kainate administration, whether measured by in vivo microdialysis or using slices of pyriform cortex or hippocampus. No changes were detected using striatal slices.

These findings are consistent with the relative resistance of striatum to systemic kainate damage as well as with the apparent localisation of kynurenine aminotransferase to astrocytes. When veratridine was applied via the microdialysis probe, a decrease of kynurenate levels was observed in normal, but not excitotoxin-lesioned, 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 neuronal depolarisation and kynurenate release induced by the direct activation of voltage-dependent sodium channels and by the activation of amino acid receptors. This 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 production is obscure, it merits further analysis. Apparently, veratridine does not directly inhibit kynurenine aminotransferase in rat brain (unpublished 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 kynurenate production was observed in excitotoxin-lesioned animals (Wu et al., 1991) in which there is substantial neuronal loss compensated by astrocytic proliferation. Voltage-dependent sodium channels must be required for veratridine to work because the effect is prevented by tetrodotoxin.

It seems possible, therefore, that neuronal depolarisation may result in the release of a factor that suppresses kynurenate synthesis and/or efflux from astroglial cells. In support of this, potassium depolarisation is unable to suppress kynurenate production in the absence of external 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 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 lesioned 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 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 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; Teichberg, 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, Wu et al. (1992b) attempted to investigate the effects of manipulating experimental conditions on the levels of endogenous hippocampal kynurenate. 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 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 implications for understanding the biological role of kynurenate 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 that it can 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 -independent systems were detected, the former 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 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 barrier as a result of transport by the large neutral amino acid carrier. Kynurenic acid, on the other hand, has been

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considered essentially unable to cross the barrier in normal animals. The latter reservation is important because in many of the pathological states in which kynurenines may be implicated (encephalopathies, AIDS-related brain damage, etc.) there is likely to be a significant weakening of the barrier's integrity. The barrier is known to be compromised, for example, in Alzheimer's dementia, 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 nM in rat, 3.6 nM in human) (Heyes and Quearry, 1990; Heyes et al., 1990a; Swartz et al., 1990b). Although systemic administration of L-kynurenine 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 barrier permeability to kynurenate.

The egress of kynurenate from the CNS is probably mediated 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 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 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 evidence of metabolism. The localisation of injected kynurenate 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, which is similar to that drawn from related studies of quinolinic acid, must be questioned in view of the known, albeit 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).

Additional studies in drug-free patients with diagnosed 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 CSF sampled 2 hours after the final dose (Vecsei et al., 1992a). It was noted that such manipulations of endogenous kynurenate might be of therapeutic value in these 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 by Moroni and his group (1991b), involves the oxidative deamination of tryptophan to indolepyruvic acid and the subsequent conversion of the latter 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, 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 produced from 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 et al. (1989) showed that indolepyruvate, injected systemically, can increase cerebral levels of kynurenines, 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 labeled kynurenate rather than tryptophan, indicates strongly that the metabolic flux is from indolepyruvate to kynurenate and not back to tryptophan.

IV. Pharmacology

The pharmacology of kynurenines is intimately associated 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 several subtypes of neuronal receptor (Watkins and 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-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 depolarisation and excitation of neurones; the 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 in many parts of the CNS but also in long-term aspects of neuronal activity. The latter include the phenomenon 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 increase of synaptic efficacy, believed to form the neuronal basis of learning and memory processes.

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 section VII). It is likely that comparable processes are involved in the development, maturation,

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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 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 intracellular calcium to a degree that is believed to activate 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 importance, not only in explaining some cell death occurring with ageing but also the loss of neurones that 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 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, other endogenous excitatory amino acids to an extent that results in activation of NMDA receptors and causes excitotoxicity. These topics will be discussed in detail in 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 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 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 prevented on 16 of 18 cells by the then newly described selective 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 kainate 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 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 and Stone, 1986; Martin and Lodge, 1987; Burton et al., 1987, 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 applied in the vicinity of individual neurones in the CNS (Stone, 1985a), it has the disadvantage 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 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 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-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 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 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 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 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 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 the ejecting characteristics of different iontophoretic electrodes (Stone, 1985a) by using the same electrodes moved between neocortex and spinal cord and, in several animals, back to neocortex.

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 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 glutamate and quinolinate, the latter was a less effective excitant in more posteriorly located regions of the area, the glutamate to quinolinate equieffective current ratios being 0.75 in anterior regions and 0.33 in posterior striatum.

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 agonist at amino acid receptors. It is, therefore, possible that 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, 1983b). Results were obtained, however, that were qualitatively identical with those seen with glutamate. Only five of 23 spinal neurones sensitive to NMDA 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 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 substantial elevations of firing rate were produced in the latter area, 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 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 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 and Stone, 1983a,b).

The difference of neuronal sensitivities was confirmed in a subsequent independent iontophoretic study in anaesthetised rats in which the excitatory activity of NMDA and quinolinate was quantified in relation to the 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 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 (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 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 binding of labeled quinolinic acid itself have been singularly unsuccessful, the compound does displace glutamate from hippocampal membranes with an IC_{50} of 180 μM (French et al., 1984) and can displace the NMDA receptor antagonist 2AP5 with an IC_{50} of 350 μM (Olverman et al., 1984). This should be compared with the inability of quinolinate to produce any detectable displacement of kainic acid at concentrations of 1 mM. The greatest potency of quinolinate was reported in a study of the chloride-/calcium-independent binding 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 μM.

Ffrench-Mullen et al. (1986) performed an iontophoretic 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 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 Magnusson 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 than of quinolinate; the IC_{50} values derived from this work were 2 μM against NMDA, 7 μM against quinolinate, and 20 μM against kainate.

Evidence for some distinction between NMDA and 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 (Stone, 1985b). This work concluded that the ratio 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 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 competitive antagonist 2AP5 and the channel blockers magnesium and ketamine were found to be equally active against both agonists (Martin and Lodge, 1987). This was supported 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 demonstrating the close similarity between the pA_2 values of 2AP5 and kynurenate against NMDA and quinolinate. 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, using 2AP7 in studies of cat caudate nucleus neurones and in isolated 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 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 anomalous results and their elimination was discussed by Burton et al. (1987).

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The restriction of quinolinate's excitatory activity to NMDA receptors was confirmed by Peters and Choi (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, ketamine, or kynurenate, but not glutamate diethylester or glutamylaminomethylsulphonate, provided full blockade. Similarly, Ganong and Cotman (1986) reported that 2AP5 and 2AP7 would antagonise NMDA and quinolinate without affecting kainate or quisqualate in the hippocampus in vitro.

Pharmacological evidence suggests that two molecules of NMDA are needed to activate receptors in the neocortex (Williams et al., 1988), a finding confirmed by later reports of bimolecular kinetics of NMDA in other 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 observation consistent with activation of an identical population of receptors.

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 now lend support to this distinction. When receptors were expressed in *Xenopus* oocytes following the injection of mRNA from guinea pig forebrain or cerebellum, only the former exhibited modulation by 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 sites is also lower in cerebellar tissue (Ebert et al., 1991). Spermidine lacks the ability to enhance dizocilpine binding in cerebellum, whereas this action can be easily demonstrated in hippocampal or neocortical membranes.

Although these and a number of other studies strongly suggest the existence of pharmacologically distinguishable forms of the NMDA receptor in the brain, few workers have tested quinolinate. Monaghan and Beaton (1991) showed that quinolinate is significantly more active in displacing glutamate binding from forebrain than cerebellar preparations. This autoradiographic investigation thus provides independent support for the conclusion 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 (Moriyoshi et al., 1991; Monyer et al., 1992; Meguro et al., 1992; Kutsuwada et al., 1992; Sugihara et al., 1992). The results of the latter group, however, serve to emphasise the caution needed in extrapolating too hastily from molecular biology to pharmacology, because the seven isoforms isolated by this group did not appear 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 relate 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, 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 forebrain 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 electropharmacological, binding, molecular biology, and neurotoxicity 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 sensitivity to quinolinic and kynurenic acids.

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2. Intracellular studies. The effects of quinolinic acid and NMDA were compared using intracellular recording techniques on neurones of the cat caudate nucleus (Herrling 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 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 this type of response in the caudate, L-α-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 in which plateaux were not induced, L-α-aminoadipate showed no antagonism, a finding consistent with the involvement of non-NMDA receptors at some concentrations 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 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 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 hippocampal study, however, entirely supported the view from the caudate experiments that the actions of quinolinic 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. (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 −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 information on single-channel properties. Quinolinate opened channels with a mean conductance of 39 pS in 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 μM magnesium, open time was reduced about 70%. Although the conductances of NMDA- and quinolinate-opened channels were similar, the open time was less for quinolinate than for NMDA. Using patch-clamped hippocampal neurones, Kiskin et al. (1990) examined cross-desensitisation between excitatory amino acids and concluded that quinolinate was a selective agonist at NMDA receptors.

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 (Moroni et al., 1986d). The contractions can be mimicked by NMDA, but not kainate or quisqualate, and 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 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 could also cause contraction of ileal muscle. Of special interest was the observation that kynurenate and 7-chlorokynurenate could antagonise glutamate but that this action appeared to be noncompetitive; this was in marked contrast to the competitive blockade seen with 2AP5. Glycine was able to enhance sensitivity to glutamate. Together, these data indicate the presence not only of functional NMDA receptors but also of the existence of a kynurenate-sensitive, strychnine-resistant, glycine-binding domain (Luzzi et al., 1988; Moroni et al., 1989b; Reggiani et al., 1989).

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 possible that quinolinic acid receptors exist on synaptic terminals and that it is the evoked release of factors from those terminals that contributes to, or is required for, the excitotoxicity. Similar dependence on presynaptic factors has been attributed to the ability of kainic acids to produce neuronal damage in 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 kainic acid and its more potent analogue, dihydrokainate, 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 pharmacological 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 regions of rat brain 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 confirmed effects of kainic acid, neither NMDA nor quinolinic acid had any effect on the basal or potassium-induced release of endogenous glutamate, aspartate, glycine, 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 and specifically, the release of endogenous aspartate and 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 glutamate 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 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 acid action directly on nerve terminals, it was found that kainic acid-induced release in the same in vivo experimental paradigm 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 glutamate and aspartate release, now induced an approximately 60% increase of all of the eight amino acids analysed, including nontransmitter compounds (Connick and Stone, 1988a).

This is the pattern that would be expected for a compound producing nonselective activation and depolarisation of all neurones within the cortex and probably inducing a degree of excitotoxicity. The remarkable selectivity of quinolinic acid in vivo, therefore, remains to be explained, although at the present time the most parsimonious explanation is that the relevant receptors

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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 sites can be demonstrated primarily in the more superficial 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 layers 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 of cell damage and nonspecific membrane permeability 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 quinolinic acid receptors on excitatory amino acid-releasing neurones in parts of the CNS other than the neocortex.

Other attempts to examine the effects of quinolinic 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, 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 rabbit hippocampus, also reported a substantial increase in the efflux of taurine in response to the application of either NMDLA or quinolinic acid. The amounts released were extraordinary: taurine release was increased to 1200% and phosphoethanolamine to 2400% of their resting 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 20–100%" (Lehmann et al., 1985). Quinolinic acid increased extracellular taurine and phosphoethanolamine levels to about 60% of those achieved with NMDLA.

The failure to demonstrate an effect of NMDA or 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 acid at 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, although some of the neurodegenerative properties of quinolinic acid do resemble those of kainic acid rather more than NMDLA, including their dependence on afferent 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. In many in vitro preparations, and conceivably when using microdialysis, glycine may be removed sufficiently 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 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 quinolinate 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 or neurotoxic actions of quinolinate, but structure activity analyses have indicated sufficient comparability between toxicity and spin resonance changes of membrane fluidity 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 these agents are able to produce a release of acetylcholine from striatal slices. Lehmann et al. (1983) detected a release of radiolabeled acetylcholine from rat striatal slices induced by either NMDLA (ED_{50} approximately 70 μM) or quinolinate (ED_{50} about 2 mM); both agents were blocked selectively by 2AP5 or 2AP7. Quinolinate was relatively less effective than NMDLA in the caudal striatum than in rostral slices, a finding that mirrors the electrophysiological 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 directly on cholinergic neurone terminals. Release could have occurred indirectly after the depolarisation of noncholinergic excitatory interneurones.

More recent work, using either tetrodotoxin or synaptosomes, suggests the presence of NMDA receptors on nerve terminals. NMDA under these conditions can evoke a release of noradrenaline (Fink et al., 1990; Pittaluga and Raiteri, 1992), cholecystokinin (Bandopadhyay 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 terminals (Overton and Clark, 1991). Many of these neurones presumably represent sites at which endogenous quinolinate would also act if present in sufficiently high concentrations. The depolarising activity of quinolinate is 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 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 by its action at NMDA receptors. Systemic injections

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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 methysergide, or the 5HT synthesis inhibitor *p*-chlorophenylalanine (Johnson et al., 1985b). Depletion of brain catecholamines, on the other hand, did not affect the luteinising hormone stimulation by quinolinate, and, most intriguing of all, the stimulation by NMDLA was unaffected 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 quinolinate activity on isolated or disrupted cell 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 seem more likely that the action of quinolinate is a local 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 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 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 original experiments, kynurenic acid was equally effective at blocking responses to quinolinic acid, NMDA, and quisqualic 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 acetylcholine. Later analysis of the action of kynurenic acid, as well as 3-hydroxyanthranilic acid, picolinic acid, L-kynurenine, and xanthurenic acid, using isolated hippocampal 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 amino acid sensitivity on some neurones was later confirmed by work in the spinal cord, hippocampus, neocortex, and caudate nucleus (Peet et al., 1986; Herrling, 1985; Curry et al., 1986) in which kynurenic acid was found capable of antagonising responses to quinolinic acid, NMDA, kainic acid, or quisqualate.

1. Selectivity of kynurenate. Evidence has shown a more selective action of kynurenic acid in other parts of the CNS. Kynurenate was, for example, a more consistent antagonist of NMDA and kainate responses compared 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 anaesthetised 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 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 with 100 μM 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 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 slice. Here, kynurenic acid proved able to block completely 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 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 IC_{50} for kynurenate against NMDA or quinolinate was approximately 100 μM, 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 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 potentials (Herrling, 1985). This reflects the depolarisation of ventral horn motor neurones 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 quisqualic 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-response curves to all agonists in the spinal cord were shifted by kynurenate in a parallel fashion, normally 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 microiontophoretically 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 indicated that two other agonists generally believed to be selective for the NMDA population of receptors, ibotenic acid and DL-homocysteic acid, were also more sensitive to kynurenic acid blockade than quisqualic acid. This result is derived from an analysis of the total neuronal population studied, however, and it is important 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 some evidence of a differentiation by kynurenic 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 quinolinate has also been offered in that at 100 μM kynurenate reduced responses to NMDA by 66%, but responses to quinolinate were reduced by only 32% (Ganong et al., 1983).

Kynurenic acid had no direct effect on neuronal membrane properties, including membrane resistance and threshold for action potential initiation or action potential configuration (Ganong et al., 1983; Herrling, 1985; Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewis et al., 1989), even at concentrations severalfold higher 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 receptors, interesting data have also been produced on other amino acid receptors. In many regions of the CNS, responses to kainate and quisqualate are relatively resistant to the 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 peculiar for its exceptionally high density of kainate receptors, many of which are believed to be located on 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 the postsynaptic neurones to locally applied kainate (de Montigny and Tardif, 1981). If the mossy fibre projection is destroyed by lesioning with colchicine, then the sensitivity to kainate declines to a level comparable with that of CA1 neurones. In addition, kynurenate can now block responses to kainate, although actions of quisqualate remain unimpressed (Stone, 1990). These results strongly suggest that kynurenate may be able to distinguish between two subtypes of receptor for kainate, one group located on the postsynaptic CA3 pyramidal cells and sensitive to kynurenate and the second population located on mossy fibre terminals and resistant to kynurenate (Stone, 1990).

Evans et al. (1987) analysed the effect of kynurenate 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. In the same study, kynurenate was a more potent antagonist of kainate (K_d 164 μM) than of quisqualate (K_d 258 μM).

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 finding that may be explicable in terms of an action of both quisqualate and glutamate at metabotropic receptor sites. Although these receptors are primarily 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 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 pharmacology of ACPD was examined by Curry et al. (1987) using intracellular 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 support 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 distinguish pharmacologically between two excitatory subtypes of metabotropic receptor, most probably differentially located 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, including 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 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-glutamylglycine was less effective as an antinociceptive than 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 subpopulation of quisqualate sites able to modulate NMDA sensitivity. Kynurenate would then be regarded as nonselective for any quisqualate receptor subtype. This is an interesting proposal that could be clarified using binding or autoradiographic studies.

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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 because 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 following compilation encompasses a number of studies in which kynurenate helped to yield new insights or ideas.

a. SPINAL CORD. The demonstration that kynurenic acid was an amino acid antagonist led naturally to its testing as a blocker of synaptic transmission. An early such report was of the blockade of monosynaptic and polysynaptic potentials recorded from ventral roots in hemisected spinal cords from neonatal rats (Ganong et al., 1983). Kynurenate (100 μM) was very effective in this preparation and reduced the potentials by 50%.

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 comparison of the ventral root responses to dorsal root stimulation with the dorsal root response to ventral root stimulation in frog spinal cord (Elmslie and Yoshikami, 1985). At 500 μM, 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 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 100 μM, 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 vitro in response to low-intensity stimulation of Ia afferent nerves was unaffected by 2AP5 but blocked by kynurenate. The same concentration of kynurenate blocked sensitivity to glutamate but not carbachol (Jahr and Yoshioka, 1986) and did not modify ventral root-evoked responses in the motor neurones. This confirmed the selectivity of the synaptic blockade to those sites at which glutamate, rather than acetylcholine, 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 kynurenate to the cord and simultaneously stimulating afferent inputs (Walmsley and Nicol, 1991). Intracellular recordings were made of monosynaptic epsps in dorsal spinocerebellar tract neurones evoked by stimulation of hindlimb muscle nerves. The epsps could be totally abolished by kynurenate.

Jahr and Jessell (1985) found that monosynaptic epsps recorded in cultured dorsal horn neurones after the formation of synaptic contacts from dorsal root ganglion cells were sensitive to kynurenate. The excitation of dorsal horn neurones by glutamate, kainate, and quisqualate 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 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 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 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, 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 presumed to involve a mixture of pharmacologically pure synapses.

Kynurenate is also effective in the nonmammalian cord. In isolated CNS preparations of the lamprey, stimulation 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 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 caudate nucleus in response to stimulation of the overlying neocortex (Herrling, 1985). Kynurenate was applied 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 induced action potentials was seen in the cells recorded, and the NMDA-selective antagonist 2AP7 was found to be ineffective in preventing synaptic activation. This strongly supported the view that non-NMDA receptors 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 kynurenate then suppressed these epsps by up to 80%, whereas 2AP7 and nicotinic antagonists had no effect, implicating a kynurenate-sensitive amino acid in neurotransmission within 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-

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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 potentials were reduced by only 48%.

c. HIPPOCAMPUS. Excitation of several of the major afferent pathways into the hippocampal formation produce synaptic potentials that are susceptible to blockade by kynurenate. These pathways include the lateral perforant path to the dentate gyrus, the mossy fibre projection to CA3 pyramidal cells, and the Schaeffer collateral/commissural pathways traveling to the CA1 region (Ganong 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 approximately 500 μM. The blockade of transmission by kynurenate is not accompanied by any changes of membrane properties of CA1 pyramidal neurones; neither membrane 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, the common marmoset (Stone and Perkins, 1984). Across this range, the inhibitory potency of kynurenate is remarkably constant and suggests a comparability of amino acid receptors for neurotransmission across these species.

Robinson et al. (1984) used several different electrode 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 kynurenate with an IC_{50} of 365 μM, whereas the medial and lateral perforant paths to the dentate gyrus granule cells were blocked with IC_{50} values of 280 and 130 μM, respectively, potencies that are significantly different from that demonstrated in the CA1 region. In contrast, 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 comparable to that experienced in the CA1 region.

With recording electrodes nearer to the CA3 pyramidal cell layer, in stratum lucidum, the synaptic potentials were found to be insensitive to kynurenate even at concentrations 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 difference between the report of Robinson et al. (1984) and that of Ganong et al. (1983), who reported that responses in both stratum radiatum and stratum lucidum were sensitive to kynurenate.

Spontaneous miniature epsps recorded in CA3 neurones are sensitive to blockade by kynurenate (Cotman et al., 1986). The mean amplitude of these potentials was 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.

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 because this represents the only realistic opportunity for stimulating selectively the commissural fibre portion of 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 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 latency components of synaptic potentials only under circumstances in which the voltage-dependent 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 of kynurenate needed to block synaptic excitation reduced sensitivity to all the agonists (Perkins and Stone, 1985).

Excitatory synaptic transmission has also been blocked by kynurenate in hippocampal efferent projections to the septum (Stevens and Cotman, 1986).

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 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 cortical 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 primary receiving layers of neocortex (layers IVa,b,c) had their activity substantially depressed by locally applied kynurenate 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 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 geniculocortical pathway to IV and VI results in the activation of excitatory amino acid receptors, the interesting question is raised of the identity of the neurotransmitter(s) to other regions of the neocortex.

Kynurenic acid is also able to block somatosensory

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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 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-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-chlorokynurenate could prevent the potentiation of neurotransmission induced by NMDA.

f. CEREBELLUM. There is general agreement that glutamate 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 blocked Purkinje cell responses to either climbing fibre or parallel 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 parallel fibres to Purkinje 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 blockade 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 responses to kainate and aspartate, leading them to conclude that 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 subpopulations 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. 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 3 mM was used) or CNQX. No NMDA-mediated components were detectable unless high-frequency stimulation 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, aspartate, NMDA, kainate, and quisqualate. Synaptic excitation 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 sensorimotor neocortex could be less clearly categorised. However, the potencies of 2AP5 and *p*-chlorobenzoyl-*cis*-piperazine-2,3-dicarboxylate in blocking synaptic transmission 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 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 movement 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 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 stimulation evoked epsps in supraoptic nucleus neurones that were blocked by kynurenate (250 to 300 μM). 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 of anaesthetised rats, neurones tend to exhibit a pattern of burst firing that seems to be imposed by external synaptic influences. The application of kynurenate 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, kynurenate 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 of its greater access to distal synapses bearing dendrites 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 striatum and mesolimbic regions, respectively, it is probable that amino acid inputs to these cells (probably from prefrontal neocortex) play a critical role in determining major aspects of locomotor and limbic behaviours. Indeed, recent reports that excitatory amino acid antagonists 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 the ventral tegmental neurones in chloral hydrate-anaesthetised rats. 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 antipsychotic properties of the drug. Tung et al. (1991)

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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 releasing neurones to the ventral tegmentum.

k. LOCUS COERULEUS. Local stimulation of the rat locus coeruleus in a slice preparation resulted in depolarising postsynaptic potentials that were depressed by kynurenate (55% reduction at 500 μM). Kynurenate also blocked responses to superfusion with NMDA or quisqualate, 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 in the production of the epsps (Cherubini et al., 1988b). It was emphasised that kynurenate had no effect on neuronal membrane properties at effective antagonistic concentrations. The excitatory projection from ventrolateral medulla to neurones of the locus coeruleus is also blocked by kynurenate (Ennis and Aston-Jones, 1986).

l. RAPHE NUCLEUS. Richter and Behbehani (1991) provided evidence for an amino acid-mediated link between the mesencephalic nucleus cuneiformis and the nucleus raphe magnus in anaesthetised rats. Activation of this projection leads to excitatory responses on a proportion of raphe neurones, which could be blocked by kynurenic acid. The role of this projection as a component of descending nocisponsive control pathways may 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 of excitatory amino acids in the sympathetic effects of stimulating vagal afferent fibres. Injection of 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 stimulation on firing frequency of neurones in the PGCL nucleus. Kynurenate also prevented the excitation of PGCL neurones induced by single-pulse stimulation of the vagus when applied by microiontophoresis, confirming the presence of the necessary amino acid receptors on PGCL cells themselves. Kynurenate prevented excitation of PGCL neurones induced by stimulation of the hypothalamus (Sun and Guyenet, 1986) and thereby blocked activation of sympathetic afferent activity without affecting arterial pressure or baseline firing of the PGCL neurones.

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 sympathetic reflexes were abolished by kynurenate (5 μmol), including the arterial baroreceptor reflex and the vagal depressor and pressor reflexes. Correspondingly, there was an initial increase of firing of cells in the PGCL 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 irregular firing pattern of the cells was changed to a regular 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 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-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 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 both the 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 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 kynurenate would block synaptic responses to stimulation of the solitary tract by recording single-neurone activation in response to electrical stimulation of the pathway. Kynurenate (300 μM) 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 sites involved in baroreflexes. Glutamate was used to activate the NTS and to induce a decrease of blood pressure and heart rate, these being prevented by kynurenate injected into the ventrolateral medullary depressor area. If this region were first blocked by kynurenate, NTS stimulation induced a pressor response that could then be prevented by kynurenate injected into the ventrolateral medullary pressor area.

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 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 were also abolished, but the results of modulating blood pressure, which comprise qualitatively the same cardiovascular effects, were essentially unchanged. The same profile, blockade of the baroreflex responses and sensitivity

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to NMDA and kainate with no effect on glutamate, was seen in the rat preparation (Talman, 1989).

Despite the obvious efficacy of kynurenate in preventing synaptic activation, there is substantial confusion 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 (Guyenet et al., 1987; Blessing, 1989; Le Galloudec et al., 1989; Leone and Gordon, 1989; Talman, 1989; Kubo and Kihara, 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 proposed two explanations. The simplest explanation may be that a transmitter other than glutamate, but sensitive to kynurenate, is involved in transmission. Alternatively, exogenous glutamate may act at receptors that are not sensitive to kynurenate as well as, or instead of, receptors activated by transmitter glutamate. In studies of anaesthetised rats, Pawlowski-Dahm and Gordon (1992) reported that the efficacy of glutamate in producing depressor responses from the NTS was mimicked by the metabotropic receptor agonist ACPD, although neither action was blocked by kynurenate. This observation is consistent with the presence of 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 problem will remain unresolved until the advent of selective antagonists at the metabotropic receptors.

N. AUDITORY AND VESTIBULAR SYSTEMS. Synaptically 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, 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 2AP5 in blocking synaptically evoked responses (Cochran et al., 1984), again supporting the concept that non-NMDA receptors were important in this form of neurotransmission. Similarly, transmission from cochlear nerve afferents to cells in the nucleus magnocellularis of the isolated chick medulla was blocked by kynurenate, whereas selective NMDA blockers were ineffective (Jackson et al., 1985).

Both kynurenate and 2AP5, however, were able to block the transmission at afferent synapses between hair cells and neurones in the frog vestibular apparatus in a study by Annoni et al. (1984). The rather strange observation was reported from this study that the ability of kynurenate to block orthodromic activation appeared to 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 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 kynurenate, 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 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 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 that a full blockade of evoked activity was achieved with approximately 5 μM kynurenate which, taking into account 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 transmitter role for amino acids between sensory receptor 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 physiologically by sound stimulation, drugs being 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 intracellularly from the medial vestibular nucleus in such preparations and noted that kynurenate, but not 2AP5, could 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 pathway of goldfish (Langdon and Freeman, 1987) and in blocking responses to optic nerve stimulation of the suprachiasmatic nucleus (Cahill and Menaker, 1987).

5. Site of action of kynurenic acid. Present evidence strongly suggests that kynurenate is a selective pharmacological agent. The absence of any effect on neuronal membrane properties or action potential initiation produced by intracellularly applied depolarising current pulses clearly indicates the absence of nonspecific actions (Ganong et al., 1983; Ganong and Cotman, 1986; Herrling, 1985; Brady and Swann, 1988; Cherubini et al., 1988a,b; Lewis et al., 1989). Several groups have nonetheless been interested in the possibility that kynurenate may have a component of its action at presynaptic terminals as well as on the postsynaptic amino acid recep-

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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 proposed the possibility of a presynaptic mechanism.

Such a possibility was tested using paired pulse inhibition 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, therefore, no change in the relative magnitude of the paired pulse depression, this observation being entirely 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 by 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 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 kynurenate restricted to postsynaptic and not presynaptic sites.

Despite the preceding work, there remains the possibility of a presynaptic action of kynurenate under some circumstances. Gaiarsa et al. (1990) described the occurrence of giant depolarising postsynapti potentials in neonatal rat CA3 neurones, which appear to involve the activation of NMDA receptors on GABA-releasing terminals, 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 cells themselves, they did enhance the frequency of the depolarising potentials consistent with a facilitatory action at the presynaptic population of NMDA receptors. 7-Chlorokynurenate was shown to reduce the postsynaptic effect of NMDA, this being reversed by glycine or L-serine, but, unfortunately, 7-chlorokynurenate was not examined against the presynaptic NMDA receptor.

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 establish whether there is any correlation between these kynurenate-resistant sites and presynaptically located populations of glycine-modulated NMDA receptors.

There is also an increasing body of evidence consistent 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 (Krebs et al., 1991; Overton and Clark, 1991), and glutamate itself (Connick and Stone, 1988b; Garcia-Munoz et al., 1991). Many of these sites can, in turn, be modulated by 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 membranes, as it appears to be in some cases (Ransom and 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 hippocampus (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 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 agonists and 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 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 for the occupation of a positive allosteric site 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 rat brain mRNA indicate that the presence of glycine is 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 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 antagonist of amino acids in general, the dissociation constant for the strychnine-resistant glycine site being in the range 15 to 35 μM (Watson et al., 1988; Kessler et al., 1989) (fig. 2).

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 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 that it provided a nonsurmountable antagonism of NMDA in the rat hemisected spinal cord. The nonsurmountable 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 apparently competitive antagonist (Birch et al., 1988a,b).

There is some evidence that the glycine site may not be fully saturated under some experimental conditions

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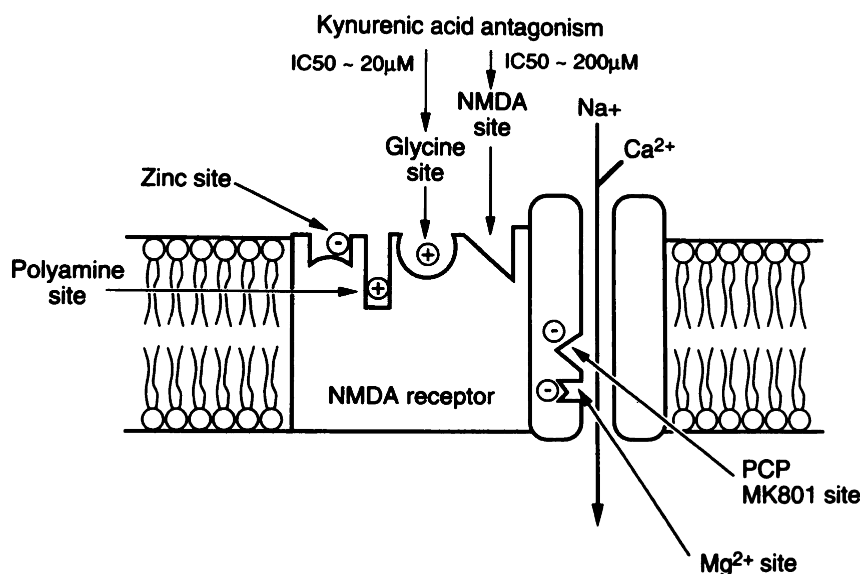

FIG. 2. Schematic representation of the NMDA receptor/channel complex indicating the presence of modulatory binding sites for phencyclidine (PCP) and dizocilpine (MK801), glycine, polyamines, and zinc. Positive (enhancing) or negative (antagonistic) modulation are indicated by plus and minus signs, respectively. Kynurenic acid acts partly as an antagonist at the strychinine-resistant glycine site (IC_{50} approximately 20 μM) and partly as an antagonist at the NMDA-binding site itself.

because glycine or L-serine can potentiate responses mediated 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 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 latency components of these responses or on monosynaptic responses involving non-NMDA receptors. Of some surprise, however, was the finding that the effects of exogenously bath-applied NMDA were not changed by glycine 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 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 NMDA sensitivity, the interaction between kynurenate and the glycine site can be demonstrated 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 reported by Danysz et al. (1989a,b) that kynurenate displacement of glycine binding occurred with an IC_{50} of 43 μM in rat telencephalon, whereas the IC_{50} 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 it displaces 2AP5 binding (Watkins and Olverman, 1988). Glycine was also able to stimulate dizocilpine binding and reversed the inhibitory effect of kynurenate on glutamate binding.

On postsynaptically located receptors at least, kynurenate 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 allosteric modulatory site associated with the receptor (Kemp et al., 1988; Evans et al., 1987; Mayer et al., 1988; Ascher et al., 1988; Henderson et al., 1990; Reynolds et al., 1989).

NMDA responses, studied using the patch-clamp technique in cortical cultures, were antagonised noncompetitively by kynurenate with an IC_{50} of 70 μM, whereas kainate responses were antagonised competitively at higher concentrations (ID_{50} 500 μM). The kynurenate antagonism of NMDA was reversed by glycine (Bertolino 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 examined, glycine at 150 μM 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 noncompetitive with a dose-response Schild slope of 0.6 which increased to 1 in the presence of 100 μM glycine and 1.9 in the presence of 400 μM glycine (Pullan and Cler, 1989). It was concluded that these results are most consistent with a model in which kynurenic acid is acting at two sites, one of which involves a competitive action at the NMDA recognition site and the second at which it interacts with glycine.

In cortical slices, the depolarising effect of NMDA could be reduced by kynurenic acid, but this antagonism

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could be reversed either by glycine added at concentrations ranging from 1 μM to 1 mM 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 responses to quisqualate (Fletcher et al., 1989). The antagonistic actions of kynurenate or its analogues 7-chlorokynurenate or 5,7-dichlorokynurenate are also reversed by glycine or L-serine in other electrophysiological studies, including neocortex and spinal cord (Brugger et al., 1990; Pralong et al., 1992), and 7-chlorokynurenate antagonism 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 by which it antagonises responses mediated through NMDA receptors. This has led to erroneous 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 glycine site unless low concentrations of the antagonist 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 phosphoinositol hydrolysis. In guinea pig brain slices, Kendall 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 inhibitory effect of glutamate against carbachol was not prevented by 7-chlorokynurenate; this may be another 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-resistant fashion (Snell et al., 1987; Reynolds et al., 1987; Kloog et al., 1988). The implication of a close structural relationship between the receptor and channel is supported by the ability of kynurenate to reduce binding of the phencyclidine analogue N-1-(2-thienyl)cyclohexyl)piperidine and of dizocilpine (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 millimolar concentrations can reverse the inhibitory 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 Parkinson's-Alzheimer's motor neurone disease complex of Pacific 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 of β-methylaminoalanine could be demonstrated in intact 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 glycine site compared with the NMDA recognition site. In rat cortex, the IC_{50} against glycine is approximately 0.56 μM, whereas at the recognition site, it is 169 μM (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-chlorokynurenate as a selective antagonist for the glycine site. As for kynurenate itself, the inhibitory effects of 7-chlorokynurenate against dizocilpine binding or as an antagonist of glutamate neurotoxicity in hippocampal cell cultures can be reversed by glycine (Sircar et al., 1989; Shalaby et al., 1989).

Danysz et al. (1989b) and Kloog et al. (1990) explored the differences in mechanism of action between 7-chlorokynurenate 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 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 HA9 do not act in an identical fashion but may possibly work through overlapping sites associated with the glycine receptor.

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; Kleckner and Dingledine, 1989; Benveniste et al., 1990). The dissociation constant for kynurenate itself was approximately 60 times greater, at approximately 15 μM, 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 binding of dizocilpine to the phencyclidine receptor 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 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 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 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 picture of a two-site model for 7-chlorokynurenate by demonstrating that this compound, together with a number of related agents, is able to suppress not only glycine-

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but also magnesium-stimulated binding of N-1-(2-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 could suppress the NMDA receptor-mediated component of synaptic transmission in rat CA1 cells and that this could be reversed by D-serine. In addition, the induction 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 μM) would enhance the transient potentiating effect of a short tetanus in stratum radiatum to the extent that LTP was 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 μM) would facilitate normal unpotentiated orthodromic population 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-reducing agent dithiothreitol. The action 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 both 7-chlorokynurenate and 2AP5 to antagonise the 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, 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 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 ethanol may be partly dependent on local concentrations of glycine at the NMDA receptors. The ability of glycine to potentiate NMDA on acutely isolated pyramidal neurones from rat hippocampus at low micromolar concentrations was also shown by Chizhmakov et al. (1989).

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% (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 of 2AP5 (and related compounds) was reversed by NMDA, affirming the close structural linkage between them. The results emphasise the difficulty of separating actions of kynurenate at the NMDA recognition site from effects at the glycine site.

C. DESENSITISATION. The glycine site, and thus kynurenate, 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 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 μM), 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 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 as the glycine site.

On the other hand, Shirasaki et al. (1990) found that glycine was able to potentiate the inward current responses 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 by 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 between these studies, in particular to examine the effects of blocking the glycine site at concentrations of kynurenate known to be selective, e.g., approximately 20 μM.

A comparison was made of the relationship between the glycine site and the polyamine site of the NMDA receptor. The enhancement of dizocilpine binding induced 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 was 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 the affinity for glycine at its binding site (Sacaan and Johnson, 1989). Because this phenomenon is still apparent even in the presence of 2AP5 and kynurenate, the conclusion was drawn that the polyamine 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 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 kynurenate-insen-

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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-chlorokynurenate or HA966 would displace labeled glycine or D-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 kynurenate-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 indicate that kynurenic acid has a poorer ability to displace kainate binding (IC_{50} 2082 μM) than either glutamate binding at NMDA receptors (IC_{50} 184 μM) or AMPA binding (IC_{50} 101 μM) (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 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 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 kynurenic acid: all were at least 15 times less active (Perkins 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 kynurenate's potency in view of the relative inactivity of 4-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 of kynurenic acid (Curry et al., 1986).

Noting that the pKa of the 4-hydroxy and ring nitrogen 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 pursued more recently by Leeson et al. (1991) who prepared the oxanilide compound 1 (fig. 3) and noted a 10-fold greater potency against NMDA or glycine binding compared with compound 2 (fig. 3). This led to the proposal that the keto group of compound 1 (fig. 3) may 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 functionality by a thiol group yielded compounds with about twice the potency of kynurenate and its halogenated derivatives. Moroni et al. (1991c) tested the 4-thioquinoline-2-carboxylic acid compounds against glycine and

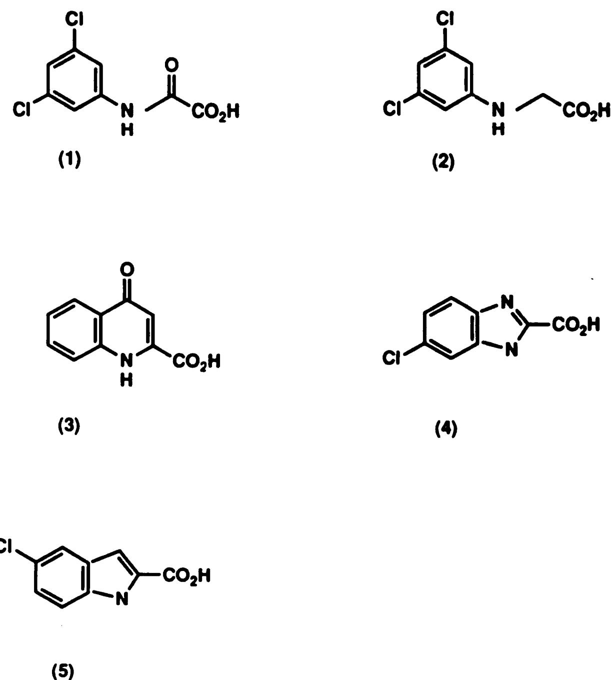

FIG. 3. Structural formulae of kynurenic acid analogues.

(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 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 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 4). This compound 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 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 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 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 affected by steric considerations that dominate any influence of the keto/imino groupings.

The study of simple analogues of kynurenic acid and

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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 reported previously by Birley et al. (1982) and the lack of antagonism shown by xanthurenic acid. The important observation was made, however, that 3-hydroxy-2-quinoxaline carboxylic acid (compound 6, fig. 4) was almost as active as kynurenic acid as an amino acid antagonist, with some preference shown for the NMDA population of receptors. The results were obtained using both the sodium efflux assay in brain slices and protection 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-dinitroquinoxaline-2,3-dione) (compound 7, fig. 4). These substances generated early excitement because of their apparent selectivity for non-NMDA populations of 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 or D-serine (Birch et al., 1988c; Honore et al., 1988).

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 the NMDA receptor complex. An important advance, 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 depolarisations (Kemp et al., 1988; Leeson et al., 1991). The greater selectivity of 7-chlorokynurenate has been critical in determining the role of the strychnine-resistant glycine site in receptor activation.

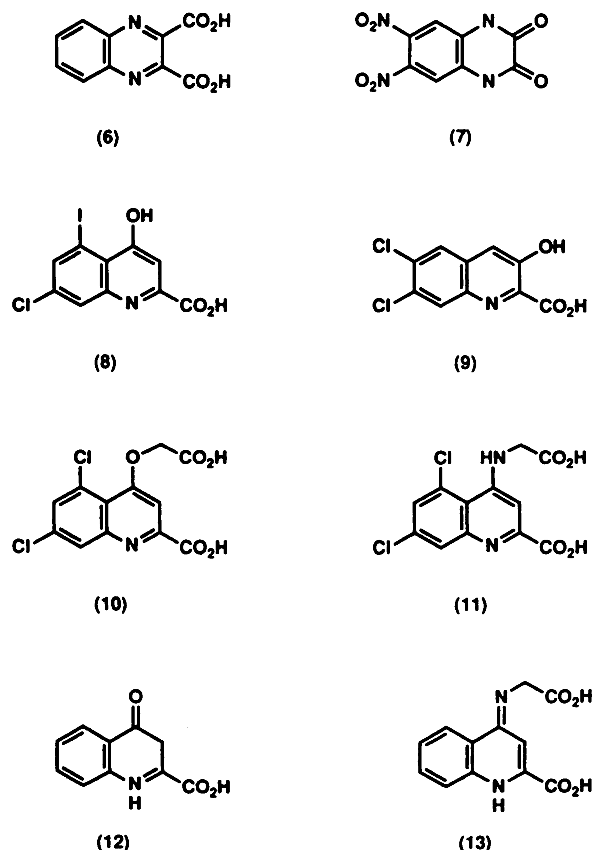

FIG. 4. Structural formulae of kynurenic acid analogues.

Leeson et al. (1991) reported a large number of other 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 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,7-chloro derivative (compound 8, fig. 4) with a K_b of 410 nM against NMDA responses and an IC_{50} of only 32 nM against glycine binding. Against other amino acid-binding sites, this agent had IC_{50} values of >100 μM. For 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 glycine reversible antagonism of NMDA stimulation 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 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 trifluoromethyl groupings at the C6 position resulted in a loss of any selectivity for the NMDA receptor, antagonist potency 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 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 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 the kynurenic acid site, a view that is supported by the report that its antagonistic activity can be prevented by D-serine (Birch et al., 1989). There remain, however, intriguing differences in the activity of 6,7-dichloro-3-hydroxy-2-quinolinecarboxylic acid in different preparations. It appears to distinguish between kainate and quisqualate effects on adult rat brain slices, blocking only the former (Frey et al., 1988), whereas it does not

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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 does not discriminate kainate and quisqualate responses on adult rat neocortex (P. L. Herrling, personal communication). It is likely, therefore, that the lack of quisqualate antagonism is a feature of the sodium efflux assay. There may be other technical or biological considerations to be taken into account, however, because Frey et al. (1988) also reported a parallel displacement of the "agonist" dose-response curves, whereas Birch et al. (1989) observed a nonparallel shift at high concentrations (>30 μM).

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-quinolinecarboxylic 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. 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 authors also noted that 6,7-halogenation increased the potency of quinoxalinediones for the glycine site.

Several studies have now been reported of extending the kynurenate molecule with additional groupings. Harrison 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-dichloroquinoline-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 compound 11, on the other hand, was substantially more potent, having an IC_{50} of 70 nM against 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 potency and selectivity because neither 4-amino nor 4-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 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 tautomer (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 carboxylated ring is fully saturated. The 5,7-dichloro compound is approximately 10-fold less active than the unsaturated 5,7-dichlorokynurenate (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 glycine site. Of several analogues reported, the 4-phenylurea 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 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 (compounds 15 and 16) and has been established also in a 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 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 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 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 μM). The addition of an acetic acid functionality at C3 (compound 19) then further improved affinity at this site (K_i 1.6 μM), a finding that may be taken to compare with the increased 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 pharmacophore, Gray et al. (1991) attempted to reconcile the structural features of compound 19 (fig. 6) with those of

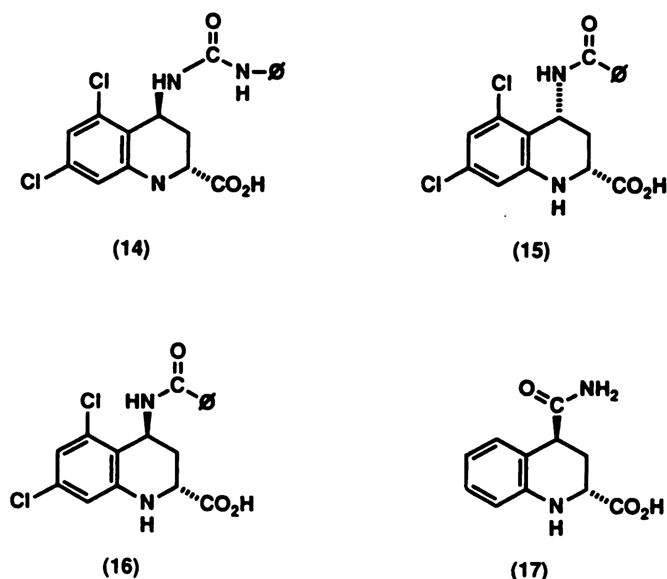

FIG. 5. Structural formulae of kynurenic acid analogues.

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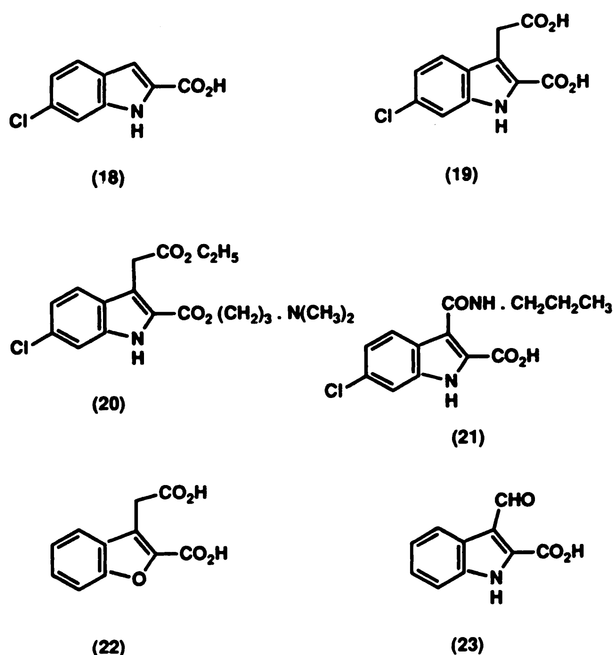

FIG. 6. Structural formulae of kynurenic acid analogues.

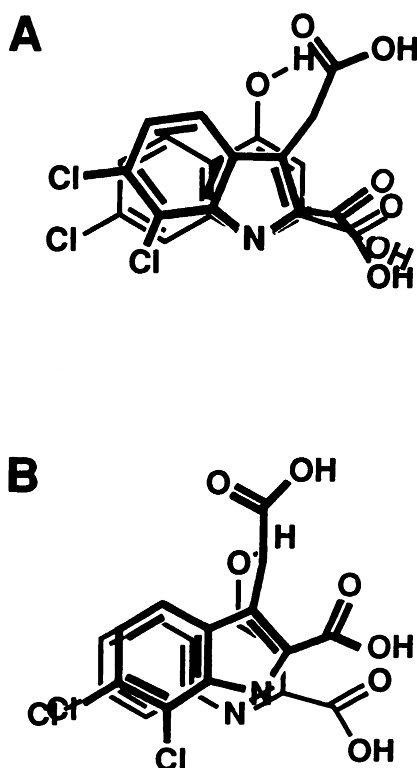

FIG. 7. Superimposed structural formulae of 7-chlorokynurenic acid (thin lines) and 2-(6,7-dichloro-2-carboxyindol-3-yl) acetic acid (thick lines) in two positions (Gray et al., 1991).

7-chlorokynurenate. If the molecules are superimposed such that the ring nitrogen atoms and the carboxyl groups coincide, then the overlay would imply that a chloro substituent at C7 of the indole would enhance activity (fig. 7A). However, this was found not to be the case, the relevant agent having a K_i against glycine binding of >30 μM. The conclusion, therefore, may be 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 substitution in the kynurenate molecule which, as noted earlier, results 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 grouping does not enhance, but rather decreases, glycine 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 indole derivatives was deduced from a series of esterified compounds. Loss of both acidic groupings as in compound 20 (fig. 6) substantially diminished glycine site affinity (K_i > 100 μM). Several 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 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, 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 affinity, whereas an aldehyde or ketone grouping maintained affinity, compound 23 having a K_i of 11 μM. This may imply that a carbonyl grouping is important for receptor binding.

The two approaches of using indole analogues of kynurenic acid and compounds with extended C4 substituents 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 acid is again emphasised by the substantial increase in potency obtained by halogen substitution: the 4,6-dichloro,3-propionic acid analogue, for example, displaces 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 (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 develop an impression of receptor requirement for binding (Salituro et al., 1991). In particular, compound 25 (fig. 8) showed relatively poor affinity for the glycine site (IC_{50} 17 μM), whereas the N-methylated derivative (compound 26) was about 50 times more active (IC_{50} 270 nM). A similar change was seen with the

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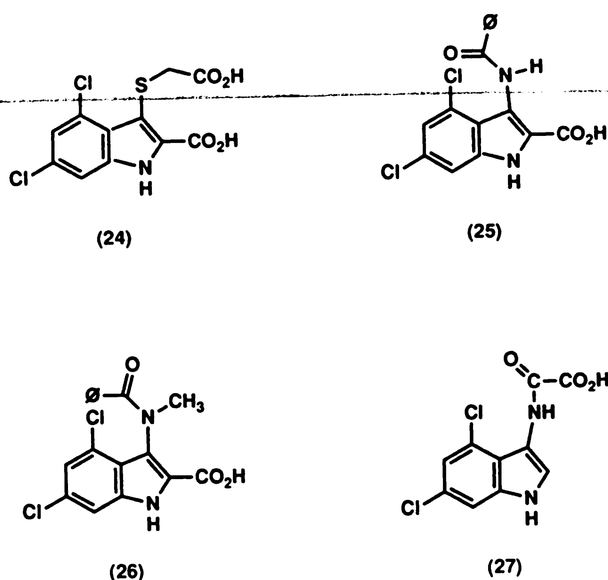

FIG. 8. Structural formulae of kynurenic acid analogues.

7-chloro compounds. Conversely, however, methylation of the nitrogen atom in the oxalic acid analogue (compound 27) led to a compound with 50 times less activity (IC_{50} 170 μM and 9.5 μM, respectively).

To resolve these observations, low-energy conformations 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) preferred the *trans* conformation (as illustrated). Similar preferences were noted for other benzamides, leading to the conclusion that the receptor has a sufficiently sized lipophilic pocket to accommodate the phenyl group, located 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 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 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. Following injection into the cerebral ventricles, both quinolinate and L-kynurenine produced the opposite effects of increasing locomotor activity, with running behaviour 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 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 modified by pretreatment with agents affecting monoamines, including monoamine oxidase inhibitors and reserpine. Nevertheless the kynurenines are able to antagonise some aspects of the 5HT behavioural syndrome 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-kynurenine, respectively (Handley and Miskin, 1977; Gould and Handley, 1978). Several kynurenines are also able to potentiate the effects of agents 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, 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 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 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 of tremor induced by oxotremorine was reduced by 3-hydroxyanthranilic 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 which the activity of 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 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 neurotransmission in the pathway from the subthalamus 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 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 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 lesions, although there is as yet no indication of whether these behaviours, or their sex dependence, are characteristic of quinolinate use or are common to any lesioning procedure.

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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 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 findings imply that kynurenate-derived agents might 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-chlorokynurenate 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 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 collateral/commissural pathway in CA1 and the perforant path/dentate gyrus pathway in hippocampal slices, suggesting that LTP and behavioural learning are closely related. Presumably by preventing neuronal loss, 7-chlorokynurenate reduces the learning deficits seen after cerebral ischaemia (Wood et al., 1993).

D. Sleep

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 180 nmol were able to induce a profound decrease in the 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 quinolinate were examined on the ethanol sensitivity of long-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 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 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 active sleep and to increase the duration of waking behaviour (Loikas and Hilakivi, 1989).

E. Anxiety

Lapin's group noted that L-kynurenine had an anxiogenic action in the mouse social interaction test and in a light/dark box conflict paradigm (Lapin, 1989). Conversely, 7-chlorokynurenate, like other antagonists at the NMDA/glycine site, showed anxiolytic activity in both the elevated plus-maze and separation-induced vocalisation 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 competitive NMDA antagonist 2AP5 and the channel blocker dizocilpine, 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). Interestingly, the glycine site partial agonist 1-aminocyclopropanecarboxylic acid shows both the anxiolytic activity of 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 activity 2 hours later and also had a depressant effect on general 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 passive avoidance paradigm or extinction of an active avoidance response. In humans, Orlikow and Ryzov (1991) induced anxiety by administering caffeine at a dose of 2 g and noted an increase in plasma kynurenate levels at the time of peak anxiety.

F. Nociception and Opioid Interactions

In view of a large amount of evidence that excitatory amino acids may be involved in primary afferent transmission 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 capsaicin solutions. The intravenous administration of dizocilpine failed to affect the capsaicin-induced irritation, whereas intracisternally injected kynurenic acid was able to suppress, and in higher doses to abolish, the eye-wiping behaviour. The data were interpreted to imply an involvement 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 and which can be prevented by amino acid antagonists. Kynurenate is effective in this model, although its use reveals two possible components of NMDA sensitivity that might correlate with the presence of two receptors, as postulated elsewhere (Urca and Raigorodsky, 1988).

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" phenomenon. Using anaesthetised rats, Chapman and Dickenson (1992) showed that 7-chlorokynurenate would prevent wind-up in response to C fibre afferent stimulation. This blockade could be reversed by glycine. Chapman and

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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 synaptic responsiveness with less effect on secondary wind-up. As expected, the combination of low doses of morphine (5 μg) and 7-chlorokynurenate (2.5 μg) administered intrathecally to rats totally abolished the various components of dorsal horn neurone responses to trains 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 as yet impossible to know whether this is able to contribute, directly or indirectly, to heightened NMDA receptor activity via quinolinate or whether it reflects a consequence of abnormal sensory neurone activity. It would seem important to distinguish between these by repeating the work after blocking quinolinate synthesis.

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 directly in the periaqueductal gray matter can be prevented 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 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 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 tolerance to the analgesic effects of the opioid. Neither of the amino acid antagonists had any effect on acutely measured analgesic effects of morphine. Similarly non-sedative doses of kynurenate were able to prevent withdrawal signs seen in morphine-dependent rats treated 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 withdrawal-induced activation of locus coeruleus cells, implying that those aspects of withdrawal prevented by systemic kynurenate (ptosis, writhing, and weight loss) are themselves of peripheral origin.

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 peptide dynorphin (Bakshi and Faden, 1990). The efficacy of 7-chlorokynurenate was interpreted as implicating the NMDA receptor in the dynorphin effects.

G. *Miscellaneous Behaviours*

Even delivered directly icv at subconvulsant doses, L-kynurenine had little effect on learning abilities or overall motor activity. Kynurenate was found to produce only 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 tested (Vecsei and Beal, 1990a,b, 1991). Some of these effects could be prevented by D-serine, implying a role of 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 increase of feeding. The effect was substantial, with a dose of 30 μg inducing a 25-fold increase of food intake within 30 minutes. At the same doses, 7-chlorokynurenate induced no stereotyped activity and no significant changes 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-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 Pinsky, 1989) because it might be expected that this would diminish food intake. This action does reduce the formation of gastric ulcers in stressed animals, a feature that might be a useful secondary action of kynurenate derivatives 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 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, 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 the task. Nevertheless, the results suggested a possible involvement 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 kynurenate (2 to 32 μg) to ovariectomised, oestrogen-primed female rats would induce lordosis. The effect was not secondary to the liberation of steroids because it was not prevented by progesterone antagonists.

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 surrounded the development of work on kynurenines during

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the past 12 years can be attributed to the possibility of relevance to major disorders such as epilepsy, neurodegenerative diseases, and cerebral ischaemia. It is likely, however, that other disease states may be found to depend 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 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. (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 subsequent neurodegeneration, a combination referred to as 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 peroxidation 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 and 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, potassium, and calcium can pass in significant quantities (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 voltage-dependent calcium channels which may admit sufficient calcium to contribute to neuronal damage; the calcium channel blocker nifedipine prevents damage of cultured neurones by quinolinate and other excitotoxins (Weiss et al., 1990).

Based on the assumption that the link between excitation and toxicity is real, the demonstration that quinolinic acid could excite central neurones by activation of the NMDA population of receptors (Stone and Perkins, 1981) led naturally and rapidly to its testing as an excitotoxin. When administered directly into the rat striatum, quinolinate produced "axon-sparing" lesions, with marked swelling of dendrites, vacuolation, and loss of 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 neurotoxicity are the hippocampus and striatum, which are among the areas most clearly sensitive to the excitatory effects of quinolinic acid. Some other regions, including the amygdala, the hypothalamus, substantia 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 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 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 interesting 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. In contrast, NMDA itself appears to differentiate far less between the different neuronal populations of the hippocampus either with respect to excitation or toxicity (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 resembled 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, 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 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 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 of strionigral inhibitory projections (Mazzari et al., 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 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, therefore, not affected by the toxin. Similarly, when injected into the hippocampus, which possesses cholinergic nerve terminals arriving from the septum but few, if any, cholinergic cell bodies, choline acetyltransferase activity is quite unaffected, indicating that quinolinate does not directly inactivate or modify acetyltransferase activity in a manner that would make it invisible to neurochemical probes.

B. Mechanism of Neurotoxicity

In reporting that pyridine-2,6-dicarboxylic acid (dipicolinic acid) was as active as quinolinate in a neurochemical assay of acetylcholine release from the striatum,

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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 and there is evidence from other studies that the excitant activity of dipicolinic acid, measured directly on neuronal 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 possible dissociation of excitation and toxicity for these compounds, therefore, remains an open question, although it should be emphasised that at the low levels of excitation and toxicity involved only a small amount of contamination 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 afferent populations of neurones seem to have no effect on the potency of NMDA as a neurotoxin. Similarly, NMDA 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 produce neurotoxicity only in the presence of afferent fibres to the area of investigation. In the striatum, quinolinic acid is thus ineffective as a neurotoxin before the 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 transection of the perforant path (Keilhoff et al., 1990). Both of these pathways are believed to utilise amino acid 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, in cultures of striatal neurones, quinolinic acid is only able to produce neurotoxic changes in the presence of cocultured explants of cerebral cortex (Whetsell and Schwarcz, 1983, 1989; Galarraga 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 quinolinic acid may promote the release of secondary neurotoxic agents from nerve terminals or the postsynaptic effects of quinolinic acid are dependent on the permissive or enhancing effects of factors released from presynaptic terminals.

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 cerebral cortical surface in vivo (Connick and Stone, 1988b), this has not been demonstrated using microdialysis perfusion 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 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 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 neurotoxic activity of quinolinate, as noted earlier, the details 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 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 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 transcription 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 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 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 hippocampus does not induce the disruption of DNA molecules characteristic of apoptosis ("programmed cell death"), indicating the induction of a different neurodegenerative 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 cellular 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 quinolinate 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 electrophysiologically (Schurr et al., 1991, 1992). The 2,5-, 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 meta- or para-placed carboxyl groups are generally inactive.

Interestingly, a very similar structure-activity profile has been described for the modification of cytoskeletal

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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 resonance of markers attached to the cytoskeletal protein spectrin (Farmer and Butterfield, 1984; Farmer et al., 1984). This protein is almost identical with fodrin and is a major component of the neuronal cytoskeleton in the CNS.

The similarities in the structural requirements for such physicochemical actions and neurotoxicity raises intriguing questions about the mechanisms of toxicity. It is conceivable, for example, that it is an initial disruption of the cytoskeleton that leads to the efflux of amino acids and thus begins the usually accepted cascade of events leading to death. The loss of cytoskeletal rigidity may also contribute to the release of calcium from intracellular pools, further exacerbating the damage.

5. *Lipid peroxidation.* Another interesting discovery was reported by Rios and Santamaria (1991), who examined the formation of thiobarbituric acid derivatives as a measure of lipid peroxidation in rat brain homogenates. Quinolinate, at concentrations of only 20 to 80 μM, increased the amount of lipid peroxidation significantly 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 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-kynurenine actually *decreased* lipid peroxidation compared 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 tetrahydroaminoacridine (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 consistent with the previously demonstrated partial agonist activity of tetrahydroaminoacridine at the phencyclidine site of the NMDA channel and that the phencyclidine location probably represented the main site of action of tetrahydroaminoacridine. However, tetrahydroaminoacridine is an effective inhibitor of cerebral acetylcholinesterase and is now known to block a number of ionic channels, including those for potassium and the nicotinic receptor-associated channels. The mechanism of action 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 phenomena were attributed to the indirect activation of NMDA receptors, partly based on the use of antagonists and partly because of the close similarity between the hippocampal 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 decline of extracellular kynurenate and, thus, less antagonism of NMDA receptor activation. However, aminooxyacetate is a very effective inhibitor of a range of transaminase 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 increased flux along the pathway to quinolinic acid itself. Any of these effects may contribute to the aminooxyacetate neurotoxicity, although it should be emphasised that this compound has a high propensity to cause nonselective 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 channels associated with the NMDA receptor and, thus, reveal an *apparent* NMDA-mediated effect.

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 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; Jhamandas 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 the intracellular accumulation of hydrogen peroxide or free radicals following the iron-catalysed autoxidation of the kynurenine (Eastman 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-hydroxyanthranilic acid, has also been shown to be neurotoxic, and although this is at least 4-fold less active than 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-hydroxykynurenine to L-kynurenine also appears to be elevated in the basal ganglia of patients with Parkinson's disease (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. Thus, competitive NMDA antagonists such as 2AP5 and 2AP7 (Schwarcz et al., 1984a,b; Garthwaite and Garthwaite, 1987), as well as the noncompetitive drugs dizo-

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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 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 selective suppression of NMDA receptor operation. Quinolinate toxicity, at least of GABA and acetylcholine-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 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 cerebral insult, it is not likely that there is any selective activity against quinolinate. Since some protection is seen even in corticostriatal cultures with no apparent requirement for the formation of synaptic connections between the established tissue and the newly added tissue, it is probable that humoral factors such as trophic factors may be involved (Whetsell et al., 1989).

The protective ability of agents such as dizocilpine is not entirely understood because the drug can be administered up to 5 hours after an intrahippocampal injection of quinolinate, whereas quinolinate has entirely disappeared from the injection site by 2 hours (Bakker and 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 release or a developing increase of NMDA receptor sensitivity that reaches a critical threshold for triggering cell damage only some hours later.

In terms of understanding the mechanisms of excitotoxicity and its prevention, it would also be valuable to have a resolution of conflicting results obtained by Engber 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 neurones. Engber and Chase (1988) could not see any protection in vivo against quinolinate injected into the rat striatum by systemically administered dextromethorphan, 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 important distinctions between in vivo and culture techniques, including the uncertainty that must attend the physiological status of cultures. In this particular comparison, however, the amounts of quinolinate administered in vivo were relatively high (150 to 300 nmol), whereas substantial lesions can be produced in adult rat striatum by 24 to 120 nmol (Zhu et al., 1988; Qin et al., 1992; Foster et 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 cortex cultures seem to be relatively insensitive to quinolinate-induced damage (Kim and Choi, 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 unfortunate that there have been relatively few reports of agents that can be applied systemically to provide protection. Most competitive antagonists, including 2AP5 and 2AP7 as well as baclofen, 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) and kynurenic acid (Germano et al., 1987), although a recent 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 μg/kg (MacGregor and Stone, 1992; 1993a,b) but have no effect against intrahippocampal injections of quinolinate 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 quinolinate, an effect that can be mimicked by peripherally administered ganglion-blocking drugs and which may, 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 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 receptors 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 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., 1987). D2 receptor binding is also diminished (Masuo et al., 1990). In the nucleus accumbens, quinolinate injections eliminate D1 receptor binding but not D2 receptors (Filloux et al., 1991).

Interestingly, although dizocilpine given acutely can 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 important, with respect to potential therapies for neurodegen-

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erative disorders, to know whether this reflects up-regulation of NMDA receptors or a component of the post-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 responsible 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 quinolinic acid as an endogenous excitotoxin, therefore, furnished research concerning the aetiology of this hereditary 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 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 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 explanation of Huntington's disease when Beal et al. (1985) 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 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 P which is characteristic of the Huntington's disease striatum, with the preservation of somatostatin and neuropeptide Y concentration. This neurochemical profile reproduces exactly the profile seen in Huntington's disease (Beal et al., 1986).

A more extensive analysis of amino acid concentrations 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 (Davies and Roberts, 1987); the same group later reported 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 latter studies, in turn, received some support from evidence that cholinergic neurones were indeed more resistant to quinolinate than were neuropeptide Y or somatostatin-containing cells (Boegman et al., 1987a; Boegman and Parent, 1988). Interestingly, cells in the neocortex containing these same peptides were resistant to quinolinate, a finding that has been confirmed by Beal et al. (1991b,c). It may be important to emphasise that changes 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).

The original results of Beal et al. (1985) were confirmed more recently in a careful quantitative study of peptide activity in response to selective excitatory amino acid agonists (Beal et al., 1989). Whereas kainate, quisqualate, 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 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 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) and Boegman et al. (1987a) may have been due to their examining the core of their lesions.

Beal et al. (1988b) emphasised that even in Huntington's disease the sparing of some neurones is only relative, and in more severe pathological cases, there is a loss of all neurone types. The neurochemical profile throughout quinolinate lesions is then, perhaps paradoxically, further supportive of a role for a quinolinate-like excitotoxin 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.

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 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 binding, although interesting, remains to be explained, 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 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 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 disease striatum (Ferrante et al., 1984) and that it frequently occurs colocalised with somatostatin or neuropeptide Y (Vincent et al., 1983). Koh et al. (1986) were the first to report that in mouse cortical cultures the

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neurones showing resistance to quinolinate toxicity displayed the presence of NADPH diaphorase. Resistance was also shown to NMDA itself but not to glutamate, 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 immediately raises the question of whether the presence of 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 synthase, a cytosolic calmodulin-dependent enzyme activated by, among other things, an increase of intracellular 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 by 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 nitric oxide, cyclic GMP, and neurotoxicity remains unclear. Similarly, the explanation for the resistance to damage of NADPH diaphorase-positive neurones remains obscure.

It has also been pointed out that, since quinolinate is normally metabolised to nicotinamide adenine dinucleotide, cells bearing the enzyme may have a greater requirement 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. (1985, 1989), because the preservation of NADPH diaphorase cells implies the preservation of a population of somatostatin-/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 be demonstrated in cultures of striatal neurones. Unfortunately, there is still no opportunity for complacency with this picture. Ferriero et al. (1990) stated that, 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 doubts 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 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 of quinolinate, there was a decrease of GABA and substance P levels with sparing of NADPH diaphorase activity and an increase of neuropeptide Y and somatostatin immunoreactivity compared with controls. This 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 significant 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 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) noted that low doses of chronically infused quinolinate (90 nmol/day) depleted striatum of choline acetylase and glutamate decarboxylase without affecting 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 striatum 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 thus uncertainty remains as to whether they may have been sufficient to inflict maximal damage.

The possible role of quinolinate in Huntington's disease 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 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, 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 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 contaminants. Such changes may then yield nonselective cell toxicity that could mask what is currently accepted 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 activity, as 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-sensitive 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 cells showing somatostatin mRNA, a finding that

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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 experiment in which kainate or quinolinate was injected into the hippocampus of freely moving rats and somatostatin was measured. Whereas quinolinate induced a 5-fold increase of extracellular somatostatin concentration, kainate-induced increases were much 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 preprosomatostatin mRNA (Patel et al. 1991) and may thus, 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 expected to stain for somatostatin, whereas kainate did not affect somatostatin-containing cells. This is clearly contrary to the finding reported by Beal's group, unless 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 nmol/day) caused a change of striatal somatostatin concentration, although this was decreased after short-term experiments.

Although the experimental emphasis has been on somatostatin and neuropeptide Y because of the relevance to Huntington's disease, there is little doubt that quinolinate does change the expression of other neuroactive peptides. In the nucleus accumbens, for example, quinolinate produces changes of muscimol, quinuclidinyl benzoate, 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 medial areas. Following quinolinate administration into the rat striatum, levels of neurotensin peptide were increased, 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 neurones.

A similar interpretation may explain the increase of met-enkephalin levels in rat striatum and globus pallidus that were induced by four excitotoxins: kainate, quisqualate, quinolinate, and NMDA (Ruzicka and Jhamandas, 1990). Wherease kainate was the most potent of 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 increase remains obscure because quinolinate halves the activity of pro-enkephalin mRNA and causes no significant alteration in the release of enkephalin immunoreactivity from lesioned striata (Ruzicka et al., 1991).

The argument most frequently raised against an involvement 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 concentrations of 250 to 400 μM quinolinate were needed to induce signs of damage in neocortical cultures, even when exposed 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 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 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 mouse-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 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 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 neuroprotectants 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 desensitising 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 as 92 nM or may reach 3000 nM. Such variation in quinolinate content, if present for extended periods, could well account for the reported differences in neuronal 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 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 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 local concentrations would be several orders of magnitude lower,

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thus supporting 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 quinolinate concentration, however, have not been consistent with the simple concept that increased levels contribute to Huntington's pathology. Neither the urinary excretion of 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 of subjects with Huntington's disease is apparently normal (Schwarcz et al., 1988b), and Reynolds et al. (1988) 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 μM) is about 10 times the 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 lower than, those in control subjects (Heyes et al., 1991a, 1992a). There are, nevertheless, strong suspicions that the kynurenine pathway is hyperactive in Huntington's disease since significant increases in the activity of 3HAO have been demonstrated in postmortem Huntington's brain, the greatest abnormality being in the striatum (Schwarcz et al., 1988a). Although it is probable that this hyperactivity is largely due to the increased glia to neurone ratio in degenerating tissue, it is important not to exclude it as a factor in maintaining or exacerbating 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 et al., 1989a). This indicates that the enzyme is not normally saturated with substrate, and an increased activity of 3HAO per se is not likely to yield increased quinolinate unless accompanied by other metabolic 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 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 found (Connick et al., 1989). The number of samples studied was, however, relatively small (five patients), and in a subsequent analysis of 30 Huntington's brains from patients of comparable age and with similar postmortem delays, Beal et al. (1990) observed a decrease in the formation of kynurenic acid from L-kynurenine in the striatum (putamen) with a significantly lower amount of kynurenate in CSF taken directly from patients with Huntington's disease. The overall concentration of kynurenate 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 formation 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 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 reductions of kynurenate 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 kynurenate levels. Of particular importance in this study, the brains of patients with Parkinson's disease or Alzheimer'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 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 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, in the characteristic neurodegeneration of Huntington's disease. Any relationship between quinolinate and Huntington's disease cannot be a simple one, however, in view of the unchanged quinolinate concentration in postmortem brain, and alternative views of the data must be considered. One possible compromise position may be 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 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 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 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 great 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 (Lekieffre

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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 appears to occur proximal to any change of calcium concentration because kynurenate also prevents the increase of intracellular calcium in response to NMDA receptor stimulation in hippocampal cultures (Oliver et al., 1990).

As predicted, if endogenous amino acids are involved, 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 somewhat controversial, however. Germano et al. (1987) obtained an approximately 40% reduction of infarct size in an adult rat ischaemia model (middle cerebral artery occlusion) when kynurenate was administered intraperitoneally in high doses of 300 mg/kg repeated three times. Similar results were reported by Nozaki and Beal (1992), who measured an approximately 6-fold increase 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, 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 readily 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 effects of kynurenate and other agents. However, Gill and Woodruff (1990) showed that maintenance of core temperature does not diminish the protective effect of kynurenate against cerebral ischaemia in adult rats.

It does remain a strong possibility that the protection provided by kynurenate is indirect and due to induced 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 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 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 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., 1984b; Winn et al., 1991) and, in some cases, kainate (Winn et al., 1991). This phenomenon 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 potentiation seen. It may be necessary to postulate that the block of receptors on inhibitory neurones by kynurenate 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 preventing the neurotoxic effects of the kainate-like toxin, domoic acid, present in a batch of Atlantic mussels (Pinsky et al., 1989). The efficacy of kynurenate was enhanced by the administration of probenecid (Bose et al., 1990).

In addition to being consistent with the histological and neurochemical similarities of quinolinate lesions and 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 suggested that subtypes of NMDA receptor may exist that are differentially sensitive to NMDA, quinolinic 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 kynurenine metabolism should be defective in the first place. Perhaps the most obvious possibility would be a diminished uptake of tryptophan or L-kynurenine into cells of the CNS. The former seems unlikely because the levels of 5-hydroxytryptophan, 5HT, and 5-hydroxyindoleacetic 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 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 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) that Huntington's disease degeneration may stem from a fundamental metabolic defect. This hypothesis is based on reports of reduced glucose metabolism 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-kynurenine away from kynurenate (the concentration of which is decreased), through 3HAO (increased) via quinolinate (decreased) into nicotinamide. This hypothesis accounts for some of the experimental observations made to date, but in view of the relative nonspecificity of kynurenic acid, it is not easy to reconcile with the selec-

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tive striatal neurone loss in Huntington's disease. It carries the added attraction that several metabolic inhibitors are capable of producing neuronal damage which, in some cases, bears marked similarities to quinolinate and human pathological lesions.

E. Seizures

1. Kynurenine concentrations in seizures. Excitatory 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 appropriate handling of genetically mutant animals. It is, therefore, natural to inquire whether there is any change in the levels of quinolinate in epileptic states. Heyes et al. (1990a) found no differences in quinolinate concentrations in epileptic foci compared with nonspiking regions of temporal neocortex removed at the time of surgery from human patients suffering from 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 immediately postictal patients. The decrease in quinolinate is consistent with that found in an investigation by Young et al. (1983) of L-kynurenine levels in the CSF of epileptic patients with or without drug treatment, 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 compared with 9.13 ng/ml, suggesting that the loss of L-kynurenine, and thus possibly of quinolinate, is a disease-related phenomenon not secondary to the effects of antiepileptic 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 al. (1988) claimed a decrease in the activity of the quinolinate-metabolising enzyme 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 nonepileptic subjects (thus eliminating any effect of drug medication). 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 convulse after being tossed into the air, with the parent ddY strain and 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 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 either in levels of 3HAO in the spleen of the various 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 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, it is likely that 3HAO is not normally saturated by its substrates because, as described before, administration 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 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 component of the pathway may also be elevated. The combination of increased 3HAO and its substrate together could certainly lead to elevated quinolinate concentrations, 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 observing correlations between changes of kynurenine metabolism and seizures, several groups have examined the 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 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 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, 1988, 1989a,b; Wu et al., 1987). Paradoxically, the intraperitoneal injection of quinolinate or L-kynurenine 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 kynurenines.

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 et al., 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: L-kynurenine shows an IC_{50} of 36 μM and quinolinate of 31 μM (Zarkovsky, 1986).

Doses as little as 3 nmol quinolinic acid injected di-

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rectly 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 periods of electroencephalographic spiking lasting between 20 and 60 seconds were noted, together with an increasing severity of overt seizure behaviour. Initial wet dog shakes and enhanced locomotor activity were followed 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 pretreatment with the NMDA antagonist, 2AP7, also injected into the hippocampus. This investigation concluded that quinolinic acid is the most potent endogenous convulsant compound to be described. The long latency of the seizures 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 exhausted before a seizure can be initiated. However, the short 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 the hippocampus, possibly the striatum, to induce seizures.

Whatever the mechanisms, quinolinate-induced electrographic seizures can be prevented by a range of anticonvulsant drugs used to treat human grand mal epilepsy, including carbamazepine, phenobarbitone, valproate, diazepam, and, at high dosage, phenytoin (Vezzani et al., 1986); none of these anticonvulsants prevented the neurotoxic effects of quinolinate, indicating an important mechanistic difference between seizures and toxicity. Confirmation of this interesting distinction was achieved 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 calcium, an effect prevented by anticonvulsant drugs. As in the previous study, these same drugs did not 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 injections of nicotine. A number of anticholinergic drugs, including atropine, scopolamine, benactyzine, and chloractyzine, were able to block seizures due to muscarinic or nicotinic agonists without affecting seizures induced by quinolinate or L-kynurenine (Lapin, 1972, 1989).

Catecholamines, including dopamine and noradrenaline injected icv, block L-kynurenine- and quinolinate-induced seizures in mice. Vezzani and Schwarcz (1985) noted a reduction of noradrenaline levels in the hippocampus of rats at the time of seizure and in a later study showed that the destruction of catecholaminergic neurones 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 clonidine enhanced the seizures, suggesting that α_2-adrenoceptors 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). Propranolol and pindolol were also effective in suppressing seizures (Lapin, 1989). Interestingly, 5HTP and 5-methoxytryptamine reduced seizures induced by L-kynurenine but not by quinolinic acid in mice. Conversely, lesions or blockade of 5HT neurones by 5,6-dihydroxytryptamine or metergoline enhanced the convulsant effect of quinolinic 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 required for tremor initiation, although the convulsions were not affected. Because little quinolinate 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., 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 et al., 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 inhibitor of sound-induced seizures in DBA/2 mice than of NMDLA-induced seizures (Chiamulera et al., 1990), the ED_{50} of kynurenate for the former being only 3.8 μg per mouse as against 25 μg 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 selective for the sound-induced seizures in DBA/2 mice, being an effective antagonist at a dose of 10 μg per animal, which had no effect on NMDLA-induced seizures. Coadministration of D-serine at 10 to 100 μg per mouse, i.e., 5 to 50 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.

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 daily periods of electrical stimulation in the amygdala (Croucher and Bradford, 1990). This antiepileptogenic action of 7-chlorokynurenate was prevented if glycine was coadministered simultaneously. The important point was made in this study that the action of 7-chlorokynu-

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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 maximal seizure activity during a period of a further 5 to 6 days at a rate comparable to that in control animals. The point was also made that the treatment with 7-chlorokynurenate had a depressant effect, not only on behavioural 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 production in fully kindled animals, and this effect could be reversed by glycine. The interesting finding was made that, once initiated, the motor and electrical concomitants of the seizure were no different 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 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 the D-serine injected icv at doses of 10 to 200 μg would enhance the ability of NMDLA to induce seizures. The effect was marked, with an approximate 3-fold increase in NMDLA potency that was not shared by L-serine. Evidence that this effect was mediated by the glycine site comes from the fact that D-serine would also prevent the anticonvulsant activity of kynurenic acid but not the competitive NMDA antagonist CPP.

It was noted above that increasing the concentration of endogenous kynurenate by the use of nicotinylalanine also 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 icv injection (Singh et al., 1990). D-Serine also prevented 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 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 fully saturated with ligand, endogenous kynurenate might have important modulatory activity at concentrations attainable in vivo.

b. L-KYNURENINE. Recent work suggests that loading animals with L-kynurenine may delay the onset of pentylenetetrazol- 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 the time of anticonvulsant activity. Similar protection 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 range of acidic compounds whose transport would be affected by probenecid, they must be interpreted with caution.

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 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 kynurenate- and the strychnine-resistant glycine site associated with the NMDA receptor. Certainly, kynurenate or 7-chlorokynurenate are very effective anticonvulsants when administered icv (Chiamulera et al., 1990; Singh et al., 1990).

The antagonism of kynurenine-induced seizures involves some striking species differences. For example, 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, phenytoin, primidone, diazepam, and trimethadione, have some 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, kynurenic 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 benzodiazepine 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 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 convulsant 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 L-kynurenine molecule. When tested on inhibitory responses 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, the isomer active in producing convulsions in rats, could displace GABA binding with an IC_{50} of 10 μM. A quantitative analysis of GABA activity in depressing population spikes in hippocampal slices, however, yielded no functional evidence for antagonism of GABA by L-kyn-

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urenine in concentrations up to 500 μM (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 occurred.

The interesting view has been put forward that one of the major kynurenine metabolites, 3-hydroxykynurenine, might be involved in seizure production. This hypothesis 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 a diet deficient in vitamin B_6 (Guilarte and Wagner, 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 of approximately 200 pmol/g in human brain were reported by Pearson and Reynolds (1991).

The potential relevance of an increased 3-hydroxykynurenine to the occurrence of seizures in neonatal animals was supported by the failure of vitamin B_6-deficient adult rats to display either seizures or elevated 3-hydroxykynurenine. The relationship prompted these authors to examine the effects of 3-hydroxykynurenine on benzodiazepine-binding sites. Although rather high concentrations were needed (approximately 1 mM) to displace flunitrazepam itself, concentrations comparable with those measured in vivo were able to increase significantly the K_d of the GABA stimulation of flunitrazepam binding (Guilarte et al., 1988).

C. VITAMIN B_6 DEFICIENCY. Quite apart from a possible role of kynurenines in idiopathic epilepsy, the relationship 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 Kakshinamurti, 1992), and a partial pyridoxine deficiency can be induced by some common antiepileptic 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, consequently, a lack of the vitamin can result in a dramatic increase of kynurenine excretion (Yeh and Brown, 1977). As an example, Takeuchi and Shibata (1984) recorded a more than 400-fold increase of 3-hydroxykynurenine in vitamin B_6-deficient rats. Indeed, the excretion of excessive amounts of kynurenines following a 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 potential firing usually superimposed on paroxysmal depolarising shifts of membrane potential, has been of interest since the parallel was first drawn between the occurrence of these periodic depolarisations and the interictal electrophysiological activity observed in animal 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 NMDA receptor, because it appears to be the relief of this magnesium blockade that 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 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 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 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 magnesium-free media can be blocked by 2AP5 with an ED_{50} of 66 μM and by kynurenate with an ED_{50} of 110 μM. Bursts also can be induced by GABA antagonists such as picrotoxin, however, and, under these circumstances, the ED_{50} for kynurenate was increased to 132 μM. 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 effect on quisqualate or kainate on CA3 neurones (Stone, 1988). This has raised the possibility that kynurenic 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 CA3 region, probably glutamate or aspartate, has a pharmacological profile on those cells responsible for initiating 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 obtained with exogenously applied selective agonists. Conversely, it may be that there are neurones within the CA3 region involved in initiating bursts that 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 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 quisqualate or kainate responses. It is important to note

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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 no direct effect on postsynaptic cell membrane properties. When examined as inhibitors of epileptiform 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 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 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 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 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 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 group recorded inward currents in CA3 neurones 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 NMDA antagonists, including 2AP5 and CPP, would prevent these periodic inward currents after they were 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 removed for the treatment of intractable epilepsy in children, could be abolished by 2AP5 and kynurenic acid. It would be interesting to determine whether this represents (*a*) a pathological sign related to the establishment of bursts and, thus, epilepsy 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 bicuculline-induced, as opposed to picrotoxin-induced, bursts. It will also be important to repeat this work using a range of kynurenate and 2AP5 concentrations to establish clearer comparability with the animal studies. The administration of daily injections of kynurenate icv (360 nmol) slowed the rate of development of amygdaloid-kindled seizures in mature and immature rats, although no change was noted in either the threshold or duration of afterdischarges (Thompson et al., 1988). Both kynurenate 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-kynurenine, which leads to an increase of brain kynurenate 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 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 ng/g (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, that "... disorders of cerebral metabolism ... in particular indoleamine function are contributing to the development of post-ischaemic brain damage and the complicating oedema."

With the development of specific assays for quinolinate, Heyes and Nowak (1990) reported that quinolinate levels remained normal or possibly were decreased for 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 showing up to 60-fold changes, from approximately 50 up to 3000 fmol/mg. It is intriguing that these latter 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 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). Because these authors further found clear evidence for macrophage infiltration in the damaged areas, it was postulated that these cells were the source of the increased enzyme activity (Heyes et al., 1992b).

Kynurenic acid has proved to be an effective neuroprotective agent against ischaemia-induced damage; a 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 ischaemia when administered by microdialysis locally into the hippocampus (Katayama et al., 1991). This provides 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 pharmacological similarities

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with ischaemia. For example, kynurenic acid was able to 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 the involvement of several types of receptors presumably responding to an enhanced release of glutamate or aspartate.

In related work, Wrathall et al. (1992) induced traumatic spinal injuries in rats and found that neither 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 significant protection up to at least 2 months following injury. The antagonist profile was interpreted to indicate 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, 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 brain and extracellular fluid of animals subjected to hypoglycaemia and reported a 6.5-fold elevation of quinolinate in plasma at the onset of electroencephalographic isoelectricity. Less dramatic changes (2- to 3-fold) were detected in all brain areas examined. Neither 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 extracellular fluid was assessed using microdialysis, the estimated control level of approximately 67 nmol/litre (corrected for recovery) was unaffected by 40 minutes of hypoglycaemia. Coupled with the absence of any extracellular change of quinolinate, it was proposed that some 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 hypoglycaemia. However, these authors were of the opinion that the recorded changes of striatal quinolinate, up to 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 kinetics of quinolinate changes. Although the retarded elevation of quinolinate after ischaemia might be the result of neuronal death and the secondary gliosis, it would seem important to establish the mechanism of the rapid increase of plasma and brain 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 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 (Riederer et al., 1981). Serum L-kynurenine was estimated at 2 μM in control subjects and up to 17.4 μM 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 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 tryptophan 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 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 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 in animals (Rossi-Fanelli et al., 1982). Therefore, this group prepared rats with chronic portacaval anastomoses as a model of hepatic failure and analysed several brain regions for their content of a range of tryptophan 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 concentrations 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 accumulation of central kynurenic acid following peripheral injection 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 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. 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 limitations, the experiment does confirm the ability of liver 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 be of interest to repeat this kind of study but analyse a wider

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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 in control CSF. Consistent with this, analysis of frontal cortex from patients dying after episodes of hepatic encephalopathy showed quinolinate levels of 2.6 nmol/g, or 2.6 μM, more than 3 times those of controls. Two of the patients examined showed cerebral levels of approximately 10 μM quinolinate, concentrations known to be toxic to neurones if maintained (Moroni et al., 1986b). These changes are also consistent with the 7-fold increase of human neocortical 3-hydroxykynurenine 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-injected rat), has not reproduced these findings. No changes of CSF quinolinate concentrations were detected in these models (Robinson 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 years that bacterial endotoxins can promote the synthesis and efflux of kynurenines from peripheral tissues (Rapoport et al., 1970; 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 lipopolysaccharides increased neocortical, but not plasma, quinolinate concentration by 81% (Heyes et al., 1989b). It is not clear whether this change was due to an activation of 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,* injected systemically in rats, were found to elevate whole brain levels of tryptophan and quinolinic and kynurenic acids. Interestingly, the direct administration of lipopolysaccharides 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 increased plasma tryptophan or L-kynurenine resulting from induction of hepatic kynurenine metabolism or that the peripherally administered endotoxin acted to induce the production of a stimulatory factor that secondarily 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 IDO, either peripherally or centrally located, is able to induce kynurenine metabolism in the CNS. This is difficult to understand given that both enzymes elevate 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 endotoxin 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) reported 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 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 diseased monkeys had levels of 643, 1045, and 4148 nmol/litre. These are concentrations comparable with those found to produce neuronal damage after continued exposure (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 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 interferon 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 lipopolysaccharide could be prevented by antibodies to γ-interferon (Saito et al., 1991a, 1992b). In addition, macrophages 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, quinolinate was synthesised from added tryptophan and released 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 experiments was that the quinolinate concentration in the medium could increase to >20 μM after 48 hours. This 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 increases of quinolinate could be at least partly responsible for the seizures, encephalopathy, and 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 an attempt to explain aspects of the so-called AIDS/dementia complex (Navia et al., 1986) that develops in a significant propor-

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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 substantially increased in the CSF of patients infected with HIV; control subjects in these studies had quinolinate concentrations of 21 nmol/litre, whereas infected and demented patients had levels of approximately 1391 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 (simian type-D retrovirus or D/1/California retrovirus) (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 greatest interest, however, was the observation of a correlation 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, also possessed CSF quinolinate levels up to 400-fold greater (>10 μmol/litre) than controls.

A striking correlation was reported between quinolinate concentrations in patients with AIDS and the clinically assessed severity of the AIDS related psychological deficits (Heyes et al., 1991c). Changes in a measure of psychomotor status, reaction times, were also correlated significantly both with absolute quinolinate concentration and with temporal changes in concentration (Martin et al., 1992). Since other psychologically based assessments, such as mood, did not show a comparable correlation, it was noted that reaction times could form the basis of a technique for monitoring the early progress of HIV infection in humans; of more relevance here is the implication that kynurenine metabolism could be related causally to the changes of reaction times.

Concentrations of kynurenate were also increased in viraemic monkeys but to a smaller degree than quinolinate; kynurenate, like quinolinate, was elevated to a far greater extent in the more severely affected animals, but the ratio of quinolinate to kynurenate remained substantially higher, by approximately 5-fold, in the infected 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 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 serum levels in several cases (Heyes et al., 1992c,e). Therefore, it seems extremely likely that the increased kynurenate concentrations were of central origin, either from neurone or glia or from infiltrating macrophages.

The question arises of why the astonishing increases 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 tissue by macrophages and other mononuclear 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 from chick ciliary ganglia or embryonic rat spinal cord, with human cell lines equivalent to mononuclear phagocytes 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 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 the neurotoxicity were heat-stable, protease-resistant molecules of mass <2 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 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. 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 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 conditions, the additional presence of γ-interferon, or a cocktail of this and other infection related cytokines, could stimulate phagocytes to release large quantities of quinolinate.

10. Other neurodegenerative diseases. Olivopontocerebellar 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 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 simplistically, this increased enzyme activity might be expected to diminish local concentrations of quinolinate. However, the authors proposed, instead, that the increased 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 kynurenines in Parkinson's disease. Ogawa et al. (1992) failed to find any significant changes in the concentrations or

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ratios of tryptophan, L-kynurenine, and kynurenic acid, although a higher ratio of 3-hydroxykynurenine to L-kynurenine was observed in three regions of Parkinsonian 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 content of quinolinate. 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 concentration, 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 quinolinate 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 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 "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 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 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).

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 (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 schizophrenic patients appear normal (Schwarcz et al., 1988b).

It has also been proposed that the deficiency of glutaryl-coenzyme A dehydrogenase seen in glutaric aciduria may lead to increased amounts of kynurenines, including quinolinate, in the body. The quinolinate might then contribute to some of the CNS toxicity seen in this hereditary disease (Heyes, 1987).

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 from 3 days to 30 months of age (Moroni et al. 1984b). In several of the animals in the oldest group, the levels of quinolinate 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 quinolinate 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 of clearance. To date, only one study appears to have been performed of quinolinic acid levels in patients with Alzheimer'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 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 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 the reduced sensitivity reflects a down-regulation of 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 stimulation attained in vivo, which may be unchanged or even increased.

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, together with an age-related performance deficit in passive avoidance tests, could be reproduced in young animals (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 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 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 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 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 major source of cholinergic neurones projecting widely to the cerebrum, including the neocortex; a primary

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degeneration of NBM neurones has been proposed as a major factor in Alzheimer's disease.

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 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 periods of at least 3 months (El-Defrawy et al., 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). Quinolinate lesions of the NBM do not cause changes in muscarinic receptors within the cortex, as reflected in binding, autoradiographic, or biochemical studies (Scarth et al., 1989).

In a detailed comparison of several excitotoxins administered into the rat pedunculopontine tegmental nucleus, Rugg et al. (1992) found that low doses of quinolinate produced a substantially greater ratio of damage of the cholinergic neurones compared with general histologically detected cell loss, when compared with 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 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 changes in mean cortical quinolinate concentration in human patients with Alzheimer's disease have been found (Moroni et al., 1986a; Mourdian et al., 1989; Sofic et al., 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

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 normal 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 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 experiments on the development of retinotectal projections under abnormal conditions. The critical period during which changes in eye orientation can lead to synaptic reorganisation in the tectum is extended by treatment with NMDA (Udin and Scherer, 1990); 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 al. (1992), for example, concluded that the activation of NMDA 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 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 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, 1989). The relationship between the neurotoxic and neurotrophic effects of NMDA receptors remains confused because at least one report has claimed that both phenomena can be demonstrated on different populations 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; Cambray-Deakin and Burgoyne, 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 cultures (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 stimulation (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). Nevertheless, quinolinic acid is able to mimic the activity of NMDA in several experimental systems, including the ability to promote the development of cerebellar granule neurones (Balazs et al., 1990; Hunt and Patel, 1990).

VIII. Summary

In a little more than 10 years, the kynurenine metabolites of tryptophan have emerged from their former 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 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 concentrations at the strychnine-resistant glycine modulatory site associated with the NMDA receptor.

It has been argued that these agents cannot be of

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physiological or pathological relevance because their normal extracellular concentrations, in the nanomolar range, are at least 3 orders of magnitude lower than those required to act at NMDA receptors. This is a facile argument, however, that ignores at least two possibilities. One is that both quinolinate and kynurenate may be present in very high concentrations locally at some sites in the brain that cannot be reflected in mean extracellular 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, glial cells that are well recognised as enjoying a close physical and chemical relationship with some neurones in which the intercellular space may be severely restricted may support such a view. Certainly the realisation that NMDA receptors may not be fully saturated functionally with glycine would be consistent with the possibility that even quite low concentrations of kynurenate could maintain a partial antagonism at the glycine receptor.

A second possibility is that there may be a subpopulation of NMDA receptors (or, indeed, for a quite different amino acid) that possesses a glycine modulatory site with a much lower sensitivity to glycine or higher sensitivity to kynurenate, making it more susceptible to fluctuations of endogenous kynurenine levels.

Whatever the specific nature of their physiological roles, the presence of an endogenous selective agonist and antagonist acting at NMDA receptors must continue to present exciting possibilities for understanding the pathological basis of several CNS disorders as well as developing new therapeutic approaches. An imbalance in the production or removal of either of these substances would be expected to have profound implications for brain function, especially if that imbalance were present chronically. These effects would be further compounded if their local concentrations at strategic points in the CNS are far higher than their mean levels in the CSF or microdialysates.

What has emerged relatively recently is the evidence that concentrations of quinolinate can increase to levels that would be unquestionably toxic to central neurones, especially in situations in which there is infection and inflammation. The correlations that have been reported between quinolinate concentrations and various measures of animal or patient status, in such conditions as AIDS or poliovirus infection, are quite startling and argue further for an important role for this agent in pathology.

One of the most tantalising, yet least well-explored possibilities, is for a role of kynurenines in neuronal growth and development. It is now clear that activation of NMDA receptors can influence these aspects not only in cell culture but also in vivo at times when plastic changes of neuronal connectivity are critical, and it becomes important to consider whether a selective NMDA ligand, such as quinolinate, might play a pivotal role in such functions. It may be relevant to recall here that activity along the kynurenine pathway is susceptible to variations in precursor availability (especially tryptophan and L-kynurenine) as well as to cofactors such as iron or pyridoxal phosphate. The concept that some adult or developmental disorders resulting from nutritional deficiency may be linked to changes of kynurenine metabolites should be investigated.

Overall, there seems little doubt that the development of kynurenine pharmacology has prompted much valuable research and new concepts and has introduced several new areas of fruitful discussion, particularly with respect to the neurodegenerative disorders of the CNS. Given the enormous current expenditure of the pharmaceutical industry on research into analogues of quinolinic and kynurenic acids, and other agents capable of modulating kynurenine metabolism, it would be extremely surprising if major new therapies did not arise form this source in the near future.

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