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Excitatory Amino Acid Receptors in the Vertebrate Central Nervous System

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I. Introduction

In the late 1950s Curtis, et al. (175) showed that L-glutamate and a number of other naturally occurring acidic amino acids excited single neurons in the mammalian brain. Since this pioneering discovery, considerable evidence has accumulated that one or more of these amino acids or related analogues may function as excitatory neurotransmitters in the mammalian central nervous system. Indeed, it is now commonly believed that L-glutamate may be the principal mediator of fast excitatory neurotransmission among vertebrate neurons.

The last decade has seen great advances in our understanding of the excitatory amino acid system. This has occurred for several reasons, in particular, the development of selective agonists and antagonists and the introduction of in vitro electrophysiological techniques which permit precise measurements to be made from identified cells. These studies have confirmed the expected and have also revealed some surprises; completely new concepts of neurotransmission have emerged and insights into cognitive function have been achieved. Growing evidence that excitatory amino acid systems are causally related to a number of major pathological states has added great impetus to research in this field.

The purpose of the present review is to document and discuss these recent advances. Earlier literature is considered when necessary for the full appreciation of newer work. A particular emphasis is placed on the types and pharmacology of excitatory amino acid receptors and their roles in neurotransmission in the vertebrate nervous system. The nature of the endogenous ligands, their distribution, synthesis, release, uptake, and metabolism are outside the scope of this review.

Some in-depth reviews of general interest are those by Watkins (735), which is particularly good for historical aspects, Watkins and Evans (739) and McLennan (507), for receptor subtypes, and Mayer and Westbrook (502), which thoroughly covers earlier aspects of the cellular actions of excitatory amino acids. *N*-Methyl-D-aspartate (NMDA) receptors are the subject of a recent book edited by Watkins and Collingridge (736) and have also been reviewed recently by Stone and Burton (685). A consideration of invertebrate systems is beyond the scope of this review but is covered in detail by Nistri and Constanti (565) and Mayer and Westbrook (502). For abbreviations, see table 1.

II. Receptor Subtypes

A. Agonists

The development and use of excitatory amino acid antagonists and studies on structurally related excitatory amino acid analogues have shown that multiple excita-

TABLE 1
Explanation of terms

Abbreviation	Definition
ACh	Acetylcholine
ALS	Amyotrophic lateral sclerosis
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AP4*	2-Amino-4-phosphonobutanoate
AP5	2-Amino-5-phosphonopentanoate
AP7	2-Amino-7-phosphonoheptanoate
APB	2-Amino-4-phosphonobutyrate
APH	2-Amino-7-phosphonoheptanoate
APV	2-Amino-5-phosphonovalerate
ASP-AMP	β-D-Aspartylaminomethylphosphonate
BMAA	β-*N*-Methylamino-L-alanine
CA	Cysteic acid
cGMP	Cyclic guanosine 3′,5′-monophosphate
CGP	DL-(E)-2-Amino-4-methyl-5-phosphono-3-pentenoic acid
CGS	1-(*cis*-2-Carboxypiperidine-4-yl)methyl-1-phosphonate
7-Cl-KYN	7-Chlorokynurenic acid
CNQX	6-Cyano-7-nitroquinoxaline-2,3-dione
CPP	3-((−)-2-Carboxypiperazin-4-yl)propyl-1-phosphonate
CPP-ene	3-((−)-2-Carboxypiperazin-4-yl)propenyl-1-phosphonate
CSA	Cysteine sulfinic acid
DAA	D-α-Aminoadipate
DAP	D-α-Aminopimelate
DAS	D-α-Aminosuberate
DBC	Depolarizing bipolar cell
DLAA	DL-α-Aminoadipate
DGG	γ-D-Glutamylglycine
DNQX	6,7-Dinitroquinoxaline-2,3-dione
DR-DRP	Dorsal root-evoked dorsal root potential
DR-VRP	Dorsal root-evoked ventral root potential
EDRF	Endothelium derived relaxing factor
EPSC	Excitatory postsynaptic current
EPSP	Excitatory postsynaptic potential
GABA	γ-Aminobutyrate
GAMS	γ-D-Glutamylaminomethylsulphonate
GDEE	Glutamate diethyl ester
GLU-AMP	γ-D-Glutamylaminomethylphosphonate
GLU-TAU	γ-D-Glutamyltaurine
HA-966	3-amino-1-hydroxy-2-pyrrolidone
HBC	Hyperpolarizing bipolar cell
HCA	Homocysteic acid
HCSA	Homocysteine sulfinic acid
IP_3	Inositol trisphosphate
JSTX	Joro spider toxin
KYN	Kynurenic acid
LC-VRP	Lateral column-evoked ventral root potential
LGN	Lateral geniculate nucleus
LOT	Lateral olfactory tract
LTD	Long-term depression
LTP	Long-term potentiation
2-MDP	2-Methyl-3,3-diphenyl-3-propanolamine
mRNA	Messenger ribonucleic acid
NAAG	*N*-Acetylaspartylglutamate
NMA	*N*-Methyl-DL-aspartate
NMDA	*N*-Methyl-D-aspartate
NO	Nitric oxide
ODAP	β-*N*-Oxalyl-L-α,β-diaminopropionate
PAG	Periaquaductal grey
PCMP	1-(1-Phenylcyclohexyl)-3-methylpiperidine
PCP	Phencyclidine
PDA	*cis*-2,3-Piperidine dicarboxylate
PI	Phosphatidyl inositides
PKC	Protein kinase C
PSD	Postsynaptic density
SCA	*S*-Sulfocysteine
STIB	Stimulus train-induced bursting
TCP	*N*-(1-Thienyl)-cyclohexyl-3,4-piperidine
TTX	Tetrodotoxin
VRP	Ventral root potential
VR-DRP	Ventral root-evoked dorsal root potential

* Compounds are often referred to as L- or D-stereoisomers where the distinction is important. (D and L is used rather than R and S in keeping with popular usage).

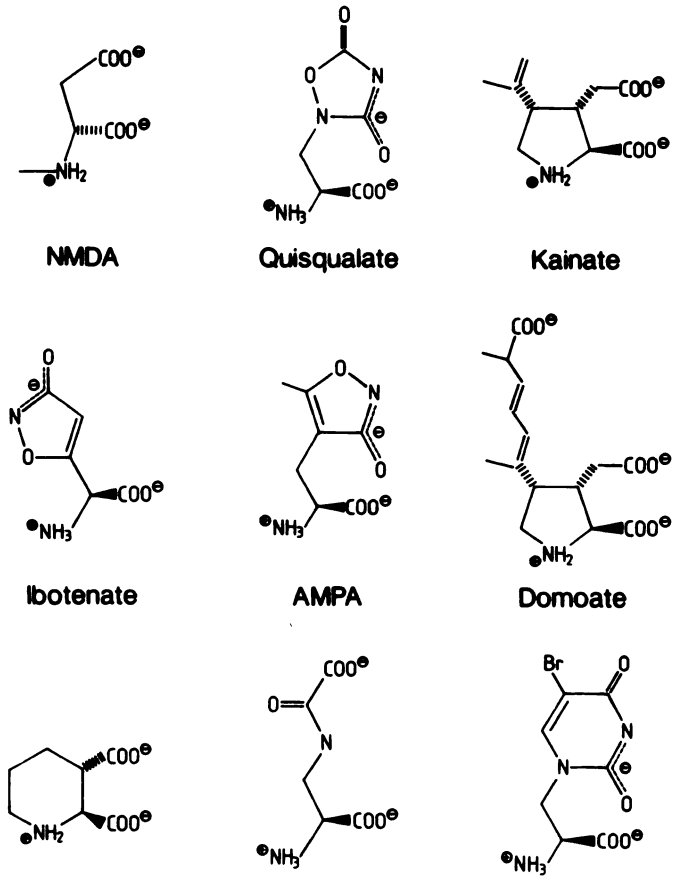

FIG. 1. Exogenous excitatory amino acid agonists. The upper row comprises the prototypic agonists after which the excitatory amino acid receptors are commonly named. Below each of these are other potent agents that have a predominant action on these receptors. Abbreviations: NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; *trans*-2,3 PDA; *trans*-2,3 piperidine dicarboxylate; ODAP, β-*N*-oxalyl-L-α-β-diaminopropionate.

tory amino acid receptors are present in the vertebrate central nervous system (507, 739). These receptors are generally named after the agonists NMDA, kainate and quisqualate, the structures of which are given in fig. 1. When an agonist binds to one of these receptors, it leads to the opening of an ion channel; the properties of the

NMDA receptor-gated ion channel (hereafter referred to simply as the NMDA channel) and the properties of the quisqualate and kainate channels are discussed, together with their macroscopic conductances in section III C. It is emerging, however, that more than just these three types of excitatory amino acid receptors exist. There is, for example, a receptor activated by quisqualate that leads to the production of inositol phospholipids (see section IV) and a receptor that mediates the synaptic depressant actions of L-2-amino-4-phosphonobutyrate (L-APB). The story is further complicated by the likelihood that kainate acts on the classical quisqualate receptor, in addition to its own receptor. The current status of these receptors and a list of some of the more widely used agonists and antagonists are presented in table 2.

1. Prototypic agonists. NMDA. A synthetic analogue of aspartate (734), was first shown to be a potent neuronal excitant in the spinal cord (179). NMLA appears to be a weaker agonist at the same receptor (177) while the racemic mixture (NMA) may be considered equivalent in selectivity to NMDA. NMLA occurs naturally in *Halopytis incurvus* (646).

Kainate. The antihelminthic L-α-kainic acid was shown to be a powerful excitant of rat cortical neurons (654).

Quisqualate. This was first described as a potent excitant at the crayfish neuromuscular junction (655) and in frog and rat spinal cord (69). It also stimulates phosphoinositide (PI) turnover (see section IV).

The identification of NMDA, kainate, and quisqualate receptors arose from two lines of evidence: differential sensitivity analysis (i.e, differences in the rank order potency of agonists between neuronal types) and studies of pharmacological antagonism. NMDA and kainate were found to have different relative potencies on two types of spinal neurons (505). In addition, a series of organic competitive antagonists (e.g., D-α-aminoadipate (DAA) (68, 196), and certain divalent cations (e.g., Mg^{2+}) (39, 234), blocked responses to NMDA but not to quisqualate or kainate. Subsequently, compounds were developed (e.g., γ-D-glutamylaminomethyl sulfonate and γ-D-glutamyltaurine) that depressed responses to quisqualate and kainate to a somewhat greater extent than responses to NMDA (389). More recently, compounds have been made (e.g., 6-cyano-7-nitroquinoxaline-2,3-dione) (CNQX) (355) that can block responses to kainate and quisqualate without affecting responses to NMDA.

The distinction between kainate and quisqualate receptors is less clear but is based on similar lines of evidence. For example, dorsal root C-fibres of immature rats were 30 times more sensitive to kainate than to quisqualate, whereas motorneurons had a similar sensitivity to both agonists (7). Certain antagonists (e.g., γ-D-glutamylglycine) (DGG) (197) and kynurenic acid (KYN) (281) may block responses to kainate to a greater extent than responses to quisqualate, while other antagonists (e.g., glutamate diethylester) (GDEE) may show the opposite selectivity (196, 348, 509).

Intracellular and single channel measurements (see section III) and binding studies (see section II C) have lent support to this receptor classification.

2. Other exogenous agonists. A large number of synthetic and naturally occurring substances have actions at one or more of the above mentioned receptors. These include domoate and bromowillardine (kainate agonists), α-amino-3-hydroxy-5-methyl-5-isoxazolepropionate (AMPA) and β-*N*-oxalyl-L-α,β-diaminopropionate (β-L-ODAP) (quisqualate agonists) and ibotenate and *trans* 2,3 piperidine dicarboxylate (*trans* PDA) (NMDA agonists) (fig. 1). Recently, acromelic acid has been reported to be an even more potent excitatory amino acid than any of the above (372).

AMPA. This compound is one of a series of synthetic isoxazole amino acids that were reported to be potent excitants of spinal neurons and to act at GDEE-sensitive sites (433). It is used to label quisqualate receptors.

TABLE 2

Excitatory amino acid receptor subtypes and some commonly used agonists and antagonists

Prototypic agonist	NMDA	Quisqualate	Quisqualate	Kainate	L-APB
Selective agonists	NMDA	AMPA			
Other agonists	Quinolinate Ibotenate	Kainate	Ibotenate		
Allosteric potentiators	Glycine D-serine				
Selective antagonists	APV, APH, CPP	CNQX			
Divalent ion antagonists	Mg^{2+}, Zn^{2+}				
Allosteric antagonists	HA-966, 7-Cl-KYN				
Other antagonists	Ketamine, MK-801, PCP, tricyclics	Barbiturates JSTX			
Mechanism	Opens ion channel to $Na^+/K^+/Ca^{2+}$	Opens ion channel to Na^+/K^+	Produces IP_3		
Function	Slow EPSPs Synaptic plasticity	Fast EPSPs	Mobilizes Ca^{2+}	Presynaptic?	Presynaptic?

Note the imbalance in the number of compounds for each receptor. At one extreme is NMDA (for which many more compounds are described in the text.

Where direct comparisons have been made AMPA is more potent than quisqualate (73, 363). There is evidence to suggest that quisqualate may be a partial agonist and AMPA a full agonist at the same quisqualate receptor (363).

β-L-ODAP. This is a component of an extract from *Lathyrus sativus*, a plant indigenous to India, and is believed to be responsible for the neurodegenerative disease lathyrism. It is a potent neuronal excitant (737) acting preferentially on receptors of the non-NMDA type (105, 506). It appears, on the basis of binding studies, to act to a greater extent on quisqualate than kainate receptors (89).

Ibotenate. Ibotenic acid, and the potent $GABA_A$ agonist muscimol, are isoxazoles from mushrooms of the genus *Amanita*. Ibotenate was shown to be a potent excitant in cat spinal cord (388), with a prominent action on NMDA receptors (174). Ibotenate-induced excitation is often followed by depression (479). It has been suggested that the inhibition is not due to activation of GABA or glycine receptors (479). Conversely, it has been proposed that ibotenate is converted in vivo to muscimol or to a related depressant that acts at $GABA_A$ receptors (174). Ibotenate is also a potent agonist for the stimulation of phosphatidyl inositide (PI) turnover (see section IV).

3. Endogenous agonists. In the early 1950s, Hayashi found that L-glutamate and L-aspartate produced convulsions when injected intracerebrally (329, 330). When applied by microiontophoresis (176) or perfusion (177) of the spinal cord, both amino acids proved to be potent neuronal excitants. Since then a large number of compounds that occur naturally in the brain have been shown to excite neurons through interactions at excitatory amino acid receptors (735). It is still not known which of these substances function as neurotransmitters. Some of the more widely studied compounds are described below and their structures are shown in fig. 2.

L-Glutamate. L-Glutamate is considered by many to be the most likely candidate as the principal neurotransmitter acting at excitatory amino acid receptors. In numerous pharmacological studies in vivo and in brain slices, L-glutamate activity is blocked by broad spectrum antagonists but is relatively insensitive to selective NMDA antagonists (e.g., refs. 140, 190). These observations have led many workers to suggest that L-glutamate acts preferentially at quisqualate or kainate receptors. However, in cultured cell preparations (in the presence of glycine) L-glutamate often behaves like an NMDA agonist (386). A reasonable explanation for this disparity may involve variations in cellular uptake processes for L-glutamate (289). Thus, in more intact preparations (e.g., tissue slices and in vivo) neuronal and glial glutamate uptake mechanisms may be localised such that they are more efficient in the vicinity of NMDA receptors than certain other types of excitatory amino acid receptors. This would cause exogenously administered L-glutamate to act predominantly on certain types of non-NMDA receptors. In addition, in vivo Mg^{2+} is probably affording a sizeable block of NMDA receptor gated ion channels (see section 11 B3). In contrast, in many in vitro studies Mg^{2+} concentrations are artificially low, thereby potentiating actions mediated via NMDA receptors. L-Glutamate should therefore be considered as a mixed agonist.

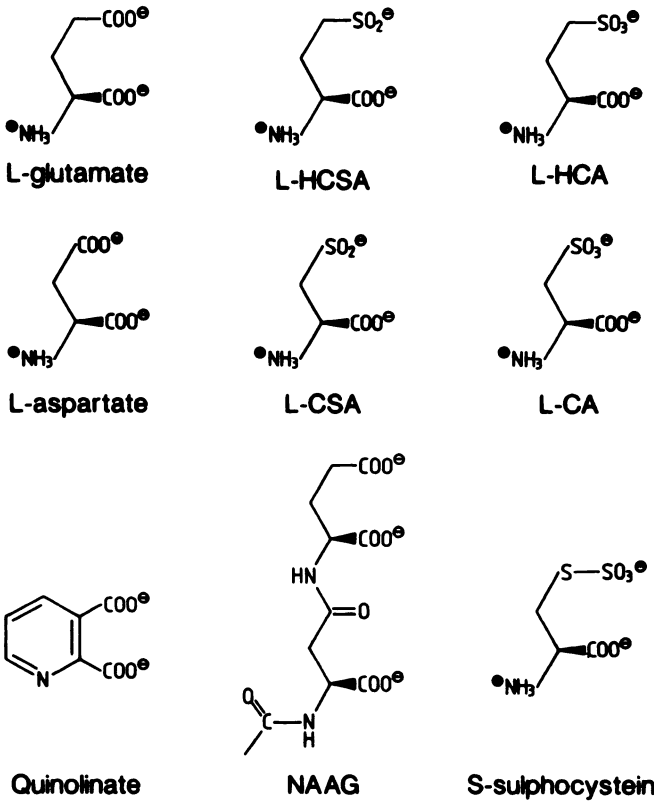

FIG. 2. Endogenous excitatory amino acid agonists. Abbreviations: L-HCSA, L-homocysteine sulphinic acid; L-HCA, L-homocysteic acid; L-CSA, L-cysteine sulphinic acid; L-CA, L-cysteic acid; NAAG, *N*-acetylaspartylglutamate.

L-Aspartate. L-aspartate, along with L-glutamate, is often considered as a major transmitter candidate (739). Compared to L-glutamate a greater proportion of the effects of L-aspartate are mediated through NMDA receptors.

Sulfur-containing amino acids. The sulfur-containing amino acid analogues of L-glutamate, cysteic acid (CA) (176), homocysteic acid (HCA), cysteine sulfinic acid (CSA), homocysteine sulfinic acid (HCSA) (177, 179), and *S*-sulfocysteine (SCA) (fig. 2) (517) are neuronal excitants. Their approximate relative potency on immature spinal motorneurons in the hemisected cord is D-HCSA > NMDA > D-HCA > L-HCA = *S*-(L)-CA > *S*-(D)-CA = L-HCSA > L-CA = D-CA = L-CSA = D-CSA = L-glutamate (517). The effects of D-HCSA are highly susceptible to antagonism by 2-amino-5-phosphonovalerate (APV) indicating that D-HCSA might be a selective NMDA agonist. The other sulfur-containing amino acids

appeared to be mixed agonists with a large proportion of the effects of L-HCA, L-HSCA, *S*-(L)-CA, and D-CA being mediated through NMDA receptors (517).

On the basis of the nature of the agonist response and/or sensitivity to NMDA antagonists, mixed agonist responses of sulfur-containing amino acids have also been reported in other preparations (213, 499, 509, 705, 717), and are in general agreement with the above categorisation. An anomaly is the report that L-HCA is non-NMDA-like and D-HCA is NMDA-like on the basis of their effects on cat motorneurons in situ (440).

NAAG. N-Acetylaspartylglutamate (NAAG) (fig. 2) excites neurons including cortical neurons (40), pyramidal neurons of the piriform cortex (255), cultured chick cerebellar Purkinje cells (538), neurons in the hippocampal formation (761) including hippocampal CA1 pyramidal cells (56), septal neurons (385), and cultured embryonic mouse spinal cord neurons (745). NAAG seems to be a weak agonist; for example, it requires concentrations above 300 μM to excite cultured mouse spinal cord neurons (745). There is some disagreement as to whether the actions of NAAG are mediated primarily via NMDA receptors or at the so-called "L-APB receptor" (see table 2) (255, 745).

Quinolinate. The tryptophan metabolite quinolinic acid (fig. 2) is a convulsant following its intracerebroventricular injection in mice (444, 445). Other compounds with a succinic acid moiety also induce clonic seizures; these include succinic, phthalic, citric and laevulinic acids, and l-kynurenine sulfate. These findings prompted an investigation of the electrophysiological effects of quinolinate on central neurons. Quinolinate (687), as well as the structurally related compounds homoquinolinate and phthalate (684) were found to excite central neurones. Related substances that appeared inactive as excitants include kynurenine, kynurenic acid, nicotinic acid, and nicotinamide (587). It was suggested that the convulsant activity of these kynurenines might be due to their metabolism to quinolinate (587).

Quinolinate appears to act as an agonist at NMDA receptors, since quinolinate-induced excitations are blocked by selective NMDA antagonists (340, 508, 687) and quinolinate elicits NMDA-like burst firing (340, 583). Quinolinate is, however, a fairly weak NMDA agonist (492, 590). It has been suggested that quinolinate may interact with a subtype of NMDA receptor (686) since there are reports of regional differences in the relative potency of quinolinate and NMDA as neuronal excitants (508, 586, 686). In particular quinolinate is less potent in spinal cord compared to neocortex. However, in cord, but not cortex, quinolinate may hyperpolarize cells by a mechanism not involving NMDA receptors (492), and this additional action could complicate regional comparisons of its excitatory potency. In one study, APV differentially antagonised responses to NMDA and quinolinate (254), whereas in another report antagonism of these excitants by APV, ketamine and Mg^{2+} was similar (492). Overall, the extent to which quinolinate and NMDA interact with the same receptors is uncertain.

B. Antagonists

To a large extent our current knowledge of the physiological and pathological roles of excitatory amino receptors has resulted from the development of useful antagonists. These antagonists can generally be divided into two categories: (*a*) The *broad spectrum antagonists* are compounds that block responses to acidic amino acids, but not other neuronal excitants (e.g., acetylcholine (Ach)), and which show little or no selectivity towards the various excitatory amino acid receptor subtypes; and (*b*) *selective antagonists* which spare one or more of the acidic amino acid receptor subtypes.

1. Broad spectrum antagonists. DGG. The first really useful antagonist of excitatory amino acid receptors of the non-NMDA type was DGG. This dipeptide (fig. 3) depressed amino acid-induced responses in the frog (276) and cat (197) spinal cord and in the CA1 (140) and dentate regions (160, 161) of the rat hippocampal formation. Its order of potency against the prototypic agonists was NMDA > kainate > quisqualate. Importantly, synaptic antagonism was not associated with any change in the passive membrane properties of the cell; the antagonism appeared to be postsynaptic in origin (160, 161). DGG has been widely used with selective NMDA antagonists, to determine the physiological role of acidic amino acid receptor subtypes (section V).

PDA. cis-2,3-Piperidine dicarboxylic acid (PDA) (fig. 3) is reported to be an antagonist of all three receptor subtypes (140, 160, 161, 186), and has been widely used in synaptic investigations. PDA, however, possesses a direct excitatory action (140, 160, 161) which may seriously complicate interpretation of its effects.

KYN. Kynurenic acid is a tryptophan metabolite (fig. 3) found in the brain. It was first described as an antagonist of responses to NMDA, quinolinate, and quisqualate in rat cortical neurons in vivo (587). In hippocampus it depressed responses (order of potency NMDA > kainate > quisqualate) without affecting passive membrane properties (281). Its selectivity, therefore, resembles that of DGG. Since high concentrations (~1 mM) of these broad spectrum antagonists are required and KYN is readily available, it has superseded DGG as the broad spectrum antagonist of choice and has been widely used in synaptic studies (section V). Occasionally, however, KYN can produce weak excitatory effects (203). Since it is an effective antagonist of the endogenous convulsant quinolinate, there has been speculation as to a possible role of KYN as an endogenous anticonvulsant (685). More recently KYN was shown to block responses to NMDA via the NMDA receptor-associated glycine site (see section II B 5); this has led to further speculation about a possible physiological role for KYN.

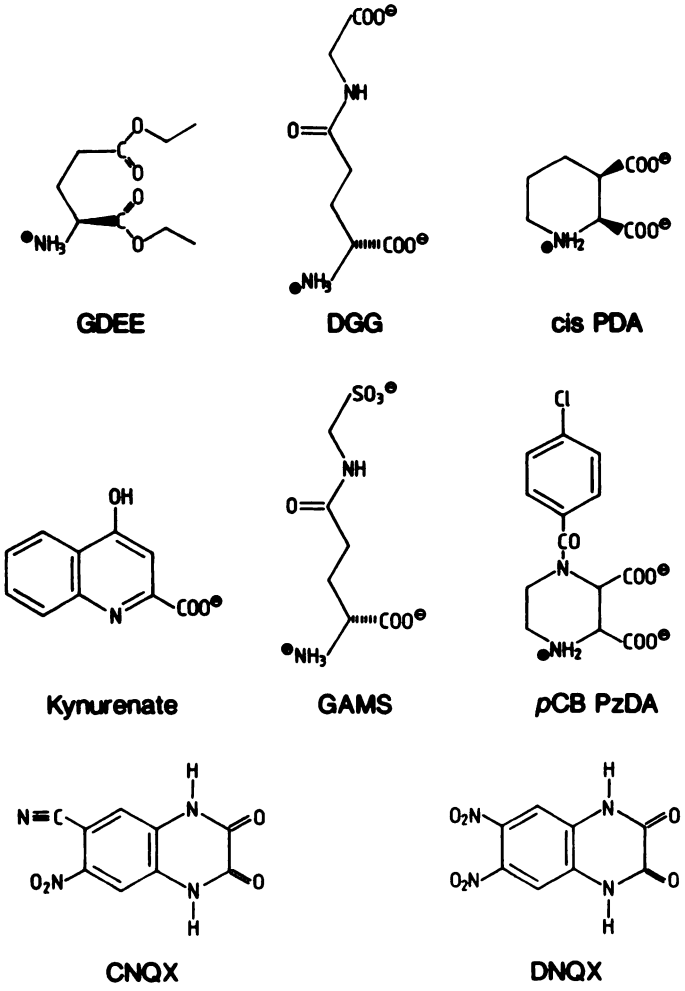

FIG. 3. Antagonists with actions at non-NMDA type excitatory amino acid receptors. Abbreviations: GDEE, glutamate diethylester; DGG, γ-D-glutamylglycine; *cis* PDA, *cis*-2,3-piperidine dicarboxylate; GAMS, γ-D-glutamyl-aminomethyl sulphonate; pCB PzDA, 1-(p-chlorobenzoyl)-piperazine-2,3-dicarboxylate; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; DNQX, 6,7-dinitroquinoxaline-2,3-dione.

pCB PzDA. 1-*p*-Chlorobenzoyl-piperazine dicarboxylic acid (fig. 3) and its brominated equivalent are antagonists with a KYN-like spectrum of activity (191).

2. Competitive NMDA antagonists. There is a plethora of substances that block responses to NMDA, but not quisqualate or kainate. Some of these compounds are also ineffective against all other neuronal excitants tested (e.g., Ach) The structures of some of the most widely used NMDA antagonists are shown in fig. 4.

Early antagonists that were selective for, but not particularly potent at, NMDA receptors included 3-amino-1-hydroxy-2-pyrrolidone (HA-966) (172, 193, 236) (±)-α,ε-diaminopimelic acid (DAP) (236), DL-α-aminoadipate (DLAA) (319), DAA (67, 68, 232, 236), and DL- and D-α-aminosuberate (DAS) (129). These agents were useful in demonstrating the existence of multiple types of excitatory amino acid receptors and were used to show that these receptors play a role in the mediation of synaptic excitation in the central nervous system. They were soon superseded by more potent, highly selective, NMDA antagonists.

APV. The replacement of the ω-carboxyl terminal of DLAA with a phosphono group led to the highly selective and potent NMDA antagonist called either DL-2-amino-5-phosphonovalerate (APV) or DL-2-amino-5-phosphonopentanoate (AP5) (190, 233). The corresponding modification of DLAS led to DL-2-amino-7-phosphonoheptanote (APH or AP7) which has a potency and selectivity similar to APV (233, 588). Other members of the series, AP4, AP6 and AP8, are considerably less potent as NMDA antagonists (233).

The active form of these antagonists is the D (−) enantiomer (140, 141, 198, 233, 585, 688). The weak activity of the "L-isomer" (140, 198) may be accounted for by contamination by the D-isomer. In comparative studies, DLAA and DL-APV but not DAA and D-APV were found to depress synaptic responses in the hippocampus (137, 138, 141). Since the D-isomers possess the NMDA antagonist properties, the effects of the racemic mixtures were attributed to effects mediated at sites (e.g., the L-APB receptor, see section VB) distinct from NMDA receptors. Therefore, the effects of racemic mixtures of these agents on synaptic responses should be interpreted with caution.

Construction of a Gaddum-Schild plot for the antagonism of NMDA-induced depolarizations in frog spinal cord by DL-APV over a wide concentration range (1–1000 μM) yielded a slope of unity and an apparent K_D of approximately 2 μM (190, 233). When examined against synaptic responses, the threshold effective concentration is <1 μM and maximum effects are produced around 50 μM in both spinal cord (190) and hippocampus (119).

In addition to having no effect on kainate- or quisqualate-induced responses, DL-APV also has no effect on responses to ACh (140, 190, 198), carbachol, 5-hydroxytryptamine, noradrenaline, or substance P (108).

Two peptides with similar profiles to APV have been described. These are β-D-aspartylaminomethylphosphonic acid (ASP-AMP) and γ-D-glutamylaminomethylphosphonic acid (GLU-AMP) (191, 389).

Although these antagonists, in particular D-APV, are perfectly adequate for use as pharmacological tools in vitro, the need for more lipophilic agents for potential therapeutic substances has led to the development of more potent NMDA antagonists.

CPP. 3-((±)-2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid is a structurally more rigid analogue of APH (fig. 4) and is approximately 3 times more potent than DL-APV as an NMDA antagonist (189). At a concentration of 50 μM it yielded a dose-ratio of approximately 100 for antagonism of the NMDA-induced depolarization of immature rat spinal cord preparations, and was without effect on responses to carbachol, 5-hydroxytryptamine, noradrenaline, or substance P (108). At 10 μM it failed to interact with a large number of binding sites

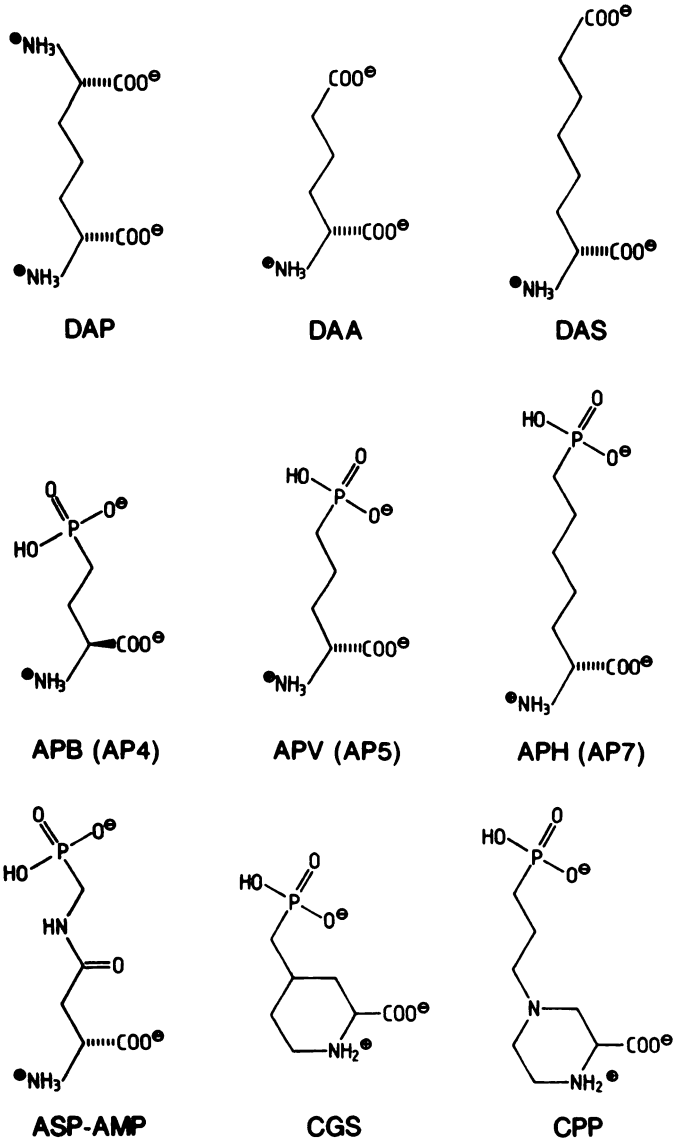

FIG. 4. Competitive NMDA antagonists. Abbreviations: DAP, α-ε-diaminopimelate; DAA, D-α-aminoadipate; DAS, D-α-aminosuberate; APB, L-2-amino-4-phosphonobutyrate; APV, D-2-amino-5-phosphonovalerate; APH, D-2-amino-7-phosphonoheptanoate; ASP-AMP, β-D-aspartylaminomethylphosphonate; CGS, 1-(cis-2-carboxypiperidine-4-yl)methyl-1-phosphonate; CPP, 3-((−)-2-carboxypiperazin-4-yl)propyl-1-phosphonate.

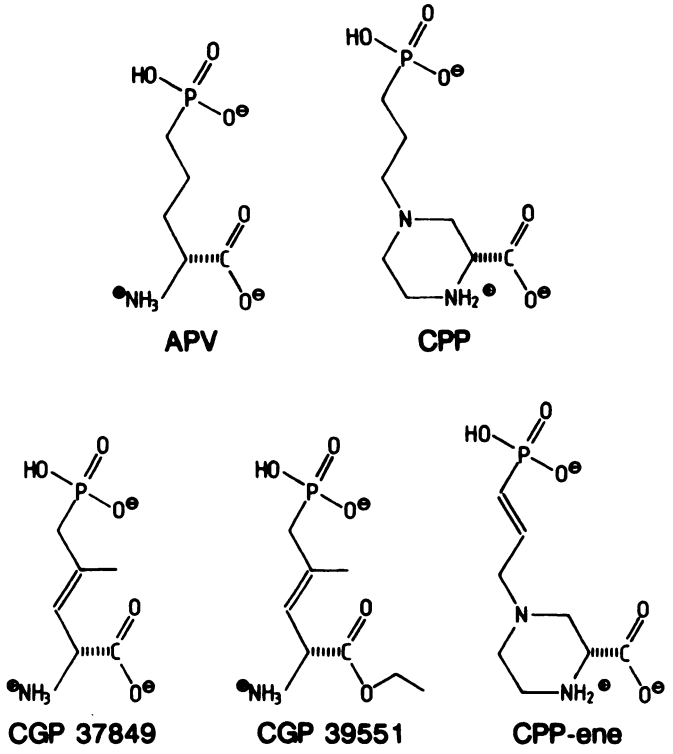

FIG. 5. Some new orally active NMDA antagonists based on the structures of APV and CPP. (For full chemical names see text).

thought to represent neurotransmitter receptors for various monoamines, opioids, and adenosine (450). It is the D- form of CPP that possesses the NMDA antagonist properties (339).

CGS. 1-(*cis*-2-Carboxypiperidine-4-yl)methyl-1-phosphonic acid (CGS 19755) is the CPP equivalent of APV (fig. 4). Neurochemical evidence indicates that it acts competitively and is effective following systemic administration (448, 449).

CGP. DL-(E)-2-Amino-4-methyl-5-phosphono-3-pentenoic acid; 4-methyl-APPA (CGP 37849) (fig. 5) is a potent orally active, selective, competitive NMDA antagonist (249). Both CGP 37489 and its carboxyethylester, CGP 39551, are potent anticonvulsants following oral administration (639).

CPP-ene. 3-(2-Carboxypiperazin-4-yl)-propenyl-1-phosphonate is the unsaturated derivative of CPP (fig. 5) and is also a potent, orally active NMDA antagonist and anticonvulsant (6, 339).

3. Divalent cations. A major breakthrough in excitatory amino acid research, albeit not widely appreciated at the time, was the finding by Evans and Watkins and their colleagues that in spinal cord low concentrations of Mg^{2+} (threshold ~10 μM; IC_{50} ~200 μM) blocked depolarizations induced by NMDA, but not kainate or quisqualate (39, 187, 234). Since micromolar concentrations of Mg^{2+} did not block ganglionic transmission and since Ca^{2+} (in higher doses) mimicked, rather than competed with, Mg^{2+}, it was reasoned that effects were postsynaptic and not due to a depression of transmitter release. The much greater potency of Mg^{2+} compared to Ca^{2+} on depressing NMDA-induced responses argues against a major effect on the transmembrane electrical field. Pharmacological experiments indicated the Mg^{2+} acted at a site different from that of the organic (competitive) antagonists; it was suggested that Mg^{2+} might be acting at the level of the ion channel.

Although Mg^{2+} was selective against NMDA compared to non-NMDA type excitatory amino acids, responses to ACh, substance P, and noradrenaline were also depressed by Mg^{2+} (39, 195). Other divalent cations, Ni^{2+}, Co^{2+}, and Mn^{2+} were found to duplicate this effect, with a rank order of potency $Ni^{2+} > Co^{2+} > Mg^{2+} > Mn^{2+} > Ca^{2+}$ (39). More recent studies have extended the list of ions that block NMDA responses to include Zn^{2+} (and the

other Group 11B metals, Cd^{2+} and Hg^{2+}) (591, 744). The mechanism of blockade of NMDA responses by divalent cations is considered in section III B 1.

4. "Non-competitive" NMDA antagonists. A large number of substances, with diverse chemical structures (see figs. 6 and 7), share the ability to block responses to NMDA but not kainate or quisqualate. They often have effects on other transmitter systems or ion channels and are, therefore, only selective in terms of their effects on excitatory amino acids. These substances produce their blockade by a mechanism distinct from the competitive NMDA antagonists; they will be considered together as "non-competitive" NMDA antagonists. Their precise modes of action are not known, but recent biophysical studies on the actions of certain of these drugs are discussed in section III B 2.

Early studies showed that the antipsychotic agent chlorpromazine (50 to 100 μM), the anxiolytics diazepam (500 μM) and chlordiazepoxide (1 mM), and the tricyclic antidepressant amitryptyline (100 μM) blocked the depolarization of frog motorneurons produced by NMDA (and/or L-HCA), but had little or no effect on depolarizations caused by kainate and quisqualate (235). To what extent other members of these classes of drugs affect

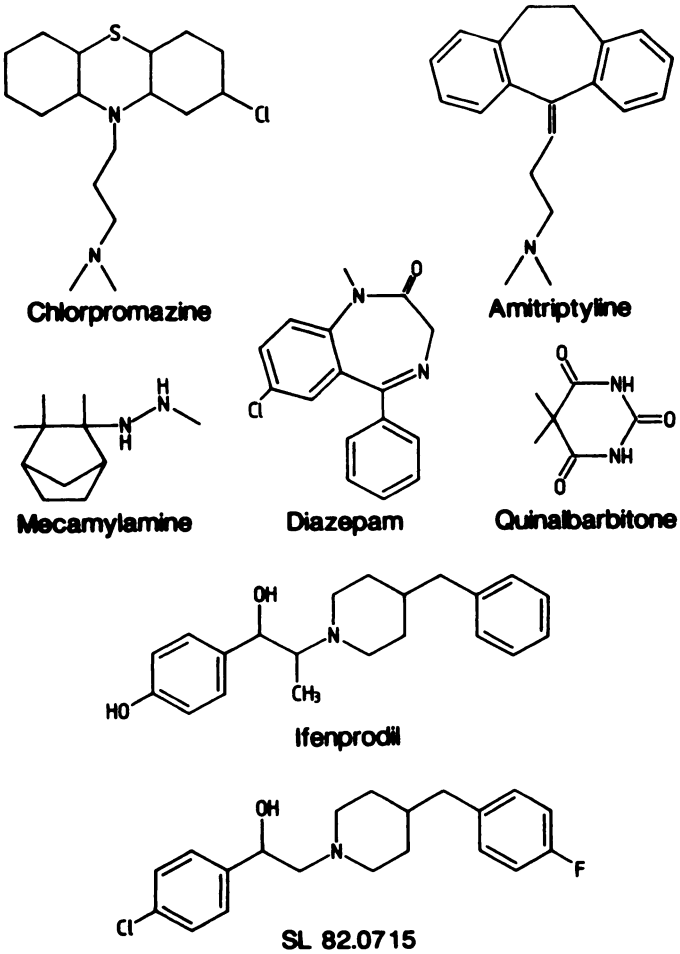

FIG. 6. Some excitatory amino acid antagonists that are better known for certain of their other properties.

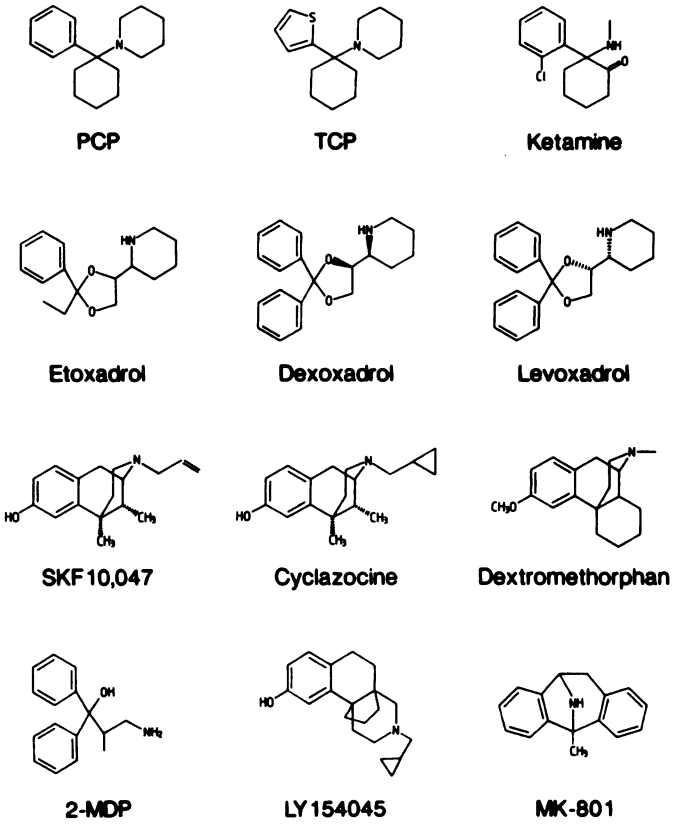

FIG. 7. NMDA antagonists that act via the PCP receptor (i.e., probably blockers of the NMDA receptor-operated ion channel). Abbreviations: PCP, phencyclidine; TCP, *N*-[1-thienyl]-cyclohexyl-3,4-piperidine; SKF 10,047, *N*-allylnormetazocine; 2-MDP, 2-methyl-3,3-diphenyl-3-propanolamine; MK-801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate.

responses to NMDA and whether such effects contribute to their therapeutic actions has not been fully explored.

a. PCP AND RELATED DRUGS. More recently, a large number of drugs known as, or related to, the dissociative anaesthetics have been shown to be selective NMDA antagonists when tested against the excitation of neurons (usually in the spinal cord) in vivo, using iontophoretic or intravenous administration of drugs, or in vitro. These include the following compounds; some of the structures are given in fig. 7:

i. Arylcyclohexylamines. Early studies had shown that ketamine (661) and phencyclidine (*N*-(1-phenylcyclohexyl)piperidine; PCP) (170) depressed responses to excitant amino acids, such as L-glutamate. Recognition by Lodge and his colleagues that these substances were in fact selective NMDA antagonists has generated considerable interest. This property has been demonstrated for ketamine (pA_2 5.2 to 5.6), PCP (pA_2 5.6 to 5.9), tiletamine, and *N*-[1-thienyl]-cyclohexyl-3,4-piperidine (TCP) (pA_2 6.1) (20, 457, 460). As far as could be determined within the limitations of the iontophoretic techniques; (+) ketamine was approximately three times as potent as (−) ketamine in this regard (458). Similarly, two PCP analogues displayed some stereoselectivity; the *cis* isomer of *N*-(1-phenyl-4-methylcyclohexyl)piperidine

was more potent than the *trans* enantiomer, and the (+) isomer of 1-(1-phenylcyclohexyl)-3-methylpiperidine (PCMP) pA_2 5.9 to 6.0) was more potent than the (−) form (pA_2 4.3 to 4.7) (59, 460).

ii. σ-"Opioid" benzomorphans. (e.g., cyclazocine and SKF 10,047 (*N*-allylnormetazocine)). The (+) isomer of SKF 10,047 (pA_2 5.1–5.6) was somewhat more potent than the (−) one (pA_2 4.5–4.9), whereas the (−) isomer of cyclazocine (5.5–6.0) was marginally more potent than the (+) form (5.3–5.6) (60, 460, 461). The κ-opiate ethylketocyclazocine did not block responses to NMDA (60).

iii. Dioxolanes. (etoxadrol, also a dissociative anaesthetic and dexoxadrol ((+)dioxadrol). Of interest, levoxadrol ((−)dioxadrol) had little effect (58), thus dioxadrol shows marked stereoselectivity.

iv. Benz(f)isoquinoline. LY154045. Of interest is that whereas this compound is bridged, the unbridged, but otherwise similar, LY154005 is not an NMDA antagonist (61).

v. Morphinan derivatives. dextorphan, dextromethorphan and levorphanol (112).

vi. 2-Methyl-3,3-diphenyl-3-propanolamine (2-MDP). the (−) isomer was approximately three times as potent as the (+) form (70).

vii. Dibenzocycloheptenimine. MK-801 ((+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate; dizocilpine) (757). The realisation of the NMDA antagonist properties of this agent, originally developed as an anticonvulsant (115), generated a lot of interest because of its potency (threshold ~75 nM) and because it possesses some remarkable neuroprotective properties.

To varying extents these non-competitive NMDA antagonists have been examined for their ability to interfere with other neuronal processes. Some of the more pertinent findings are outlined below:

K^+ channels. The ability of PCP to block a variety of K^+ channels is well documented (e.g., refs. 8, 257). These effects usually require higher doses of PCP. In comparative studies in rat locus coeruleus slices the IC_{50}'s for PCP were 0.4 μM for NMDA-induced depolarizations, ~4 μM for σ-opioid receptor gated K^+-dependent hyperpolarizations, and >30 μM for K^+ channels involved in spike repolarization (439). Only effects on NMDA-induced depolarizations were blocked by PCMP in a stereoselective manner.

ACh. Ketamine (20) and PCP (170) blocked the excitation of central neurons induced by ACh. Ketamine appears to be less potent and less stereospecific in its ability to block ACh compared to NMDA, but detailed quantitative comparisons are lacking.

GABA. In doses (200 to 500 μM) higher than those needed to block responses to NMDA, ketamine has been reported to potentiate the actions of GABA in lamprey spinal neurons (169) and GABA-mediated synaptic inhibition in guinea pig olfactory cortex (643) and rat hippocampus (279). Conversely, PCP has been shown to depress GABA-mediated synaptic inhibition in the hippocampus (83).

Monoamines. There is a wealth of information that suggests that PCP potentiates the actions of noradrenaline, dopamine, and 5-hydroxytryptamine, largely by preventing their re-uptake (see ref. 387). MK-801 has central sympathomimetic properties and has been shown to potentiate noradrenaline and 5-hydroxytryptamine induced-depolarizations of rat spinal neurons in parallel with the depression of NMDA-induced depolarizations (108).

Opioids. SKF 10,047 is the archetypal agonist for what was termed the σ-"opiate" receptor (494). Both the racemic form of this compound and of cyclazocine possess μ-antagonist and κ-agonist activities. The σ-actions of SKF 10,047 are resistant to the actions of narcotic antagonists (721) and therefore the term "opiate" should not be used. This site is now referred to as the σ-site (604, 675). Potent displacers of binding to the σ-site include certain dopamine receptor ligands such as haloperidol.

Sigma (σ) site. Most of the compounds described in this section appear, on the basis of binding studies, to interact to varying degrees with the σ-site. It is clear, however, that this site is distinct from that associated with the antagonism of NMDA and thus, interactions at the σ-site can be considered as non-specific effects. The site that is specifically associated with the NMDA receptor is now termed the PCP-site (604).

Actions at the σ-site and the PCP-site can be distinguished in several ways. The order of potency at the PCP site is MK-801 > PCP > SKF 10,047 > haloperidol whereas at the σ-site the order is reversed. At the PCP site, but not the σ-site, dioxadrol shows marked stereoselectivity with dexoxadrol > levoxadrol. Conversely, at the σ-site, but not the PCP site, SKF 10,047 displays marked stereoselectivity with (+) SKF 10,047 being the most potent.

On the basis of these criteria, when these drugs have been found to interfere with physiological responses it seems that the PCP-, but not the σ-site, is involved. This applies, for example, to synaptic transmission in the hippocampus (118) and the spinal cord (581).

b. MECHANISM OF DRUG ACTION AT THE PCP SITE. Quantitative pharmacological studies have indicated that ketamine blocks NMDA-induced depolarizations of rat cortex (328) and frog spinal cord (491) in a manner which is not competitive. The effect of a combination of ketamine and APV was greater than the addition of their effects alone, suggesting that ketamine acts at a site distinct from that used by the competitive organic antagonists. Although the combined effects of ketamine and Mg^{2+} also were much greater than additive, similar conclusions about the relationship between these sites

cannot be drawn since neither agent acts in competitive manner.

In cultured spinal neurons of the mouse, in the presence of tetrodotoxin (TTX), ketamine and PCP blocked responses to NMDA-type ligands in a highly voltage- and use-dependent manner (354, 478). These results were interpreted as an open channel block at a binding site that senses approximately 55% of the transmembrane field. A voltage-dependency in the blocking action of ketamine on NMDA receptor-mediated synaptic transmission also has been noted (201).

Consistent with an open channel blocking action of this class of drug, MK-801 was found to display marked use-dependence in its ability to block NMDA-induced depolarizations of rat cerebral cortical tissue (409). In contrast PCP, cyclazocine and ketamine showed little use-dependency under similar conditions (206). The extent of the use-dependence with this preparation, however, appears to be temperature-dependent. Thus, MK-801 was less use-dependent at 33°C compared to 23°C and PCP which displayed little use-dependence at 23°C was more use-dependent at 13°C. None of these drugs caused use-dependent block in rat spinal cord in vivo, although use-dependent recovery from blockade by MK-801 was detected (206). Changing the temperature can affect the rate of action of MK-801 in the absence of any applied agonist (459). It was suggested, therefore, that at body temperature the NMDA channel can adopt configurations that allow MK-801 access to its binding site in the absence of excitatory amino acids.

In cultured neocortical neurons, MK-801 blocked NMDA-induced currents in a highly use-dependent manner (368). Although onset rates were similar at negative and positive membrane potentials, recovery from blockade was highly voltage-dependent, being much faster at positive potentials. High concentrations of Mg^{2+} at negative potentials totally suppressed responses to NMDA and prevented MK-801 from working (368). These data provide compelling evidence that MK-801 needs to enter an open channel in order to produce a block.

c. OTHER "NONCOMPETITIVE" NMDA ANTAGONISTS. *Mecamylamine.* The nicotinic antagonist mecamylamine (10 to 100 μM) (fig. 6), but not hexamethonium, was shown to block responses to NMDA but not quisqualate, kainate or AMPA in rat hippocampal slices (71). In horizontal cells dissociated from catfish retina mecamylamine acted in a manner that was not competitive. Furthermore, mecamylamine, and another nicotinic channel blocker pempidine, blocked NMDA-induced currents in a voltage-dependent manner, indicating that these agents act at the level of the NMDA receptor gated ion channel (570). Neurochemical studies suggest an action at the PCP site (394, 573).

Ifenprodil. The anti-ischemic agent ifenprodil and its derivative SL 82.0715 ((+)-α-(4-chloro-phenyl)-4-[4-fluorophenyl)methyl]-1-piperidineethanol) (fig. 6) were shown to be NMDA antagonists with a potency intermediate between CPP and MK-801 in a variety of experimental models (102). Although non-competitive in nature, these agents do not appear to act at the PCP site.

Polymyxin B. The anti-biotic and protein kinase C (PKC) inhibitor polymyxin B selectively blocks, in a non-competitive manner, responses to NMDA in olfactory cortex (149).

In summary, a large number of compounds (many of which contain a secondary or tertiary amine group) are able to block responses to NMDA. These substances often have many other properties and should, therefore, be used with caution as experimental tools to identify NMDA receptor function. Perhaps the most fascinating aspect of these drugs is the clues they may provide about the role of NMDA receptors in higher mental function and pathological states (see sections VI through VIII).

5. Glycine antagonists. The discovery by Johnson and Ascher (386) that glycine potentiates responses to NMDA provided a new dimension in the search for drugs acting through this receptor system. Since in their studies glycine was effective in outside-out patches, it is likely that glycine acts directly on the NMDA receptor-channel complex. The first compound, suggested on the basis of binding studies (413), to antagonise the actions of glycine at this site was KYN (32, 65, 263). In this regard, KYN is more potent than it is as a non-NMDA antagonist. Other antagonists which act at the glycine site include HA-966 (215, 262, 410), the quinoxalinediones, CNQX and DNQX (64), and 7-chlorokynurenate (215, 410). The structures of some glycine antagonists are presented in fig. 8 and their mechanism of action is considered in section III B 3.

6. Non-NMDA antagonists. GDEE. The first compound to show selective antagonism between classes of excitatory amino acids was GDEE (fig. 3). This agent

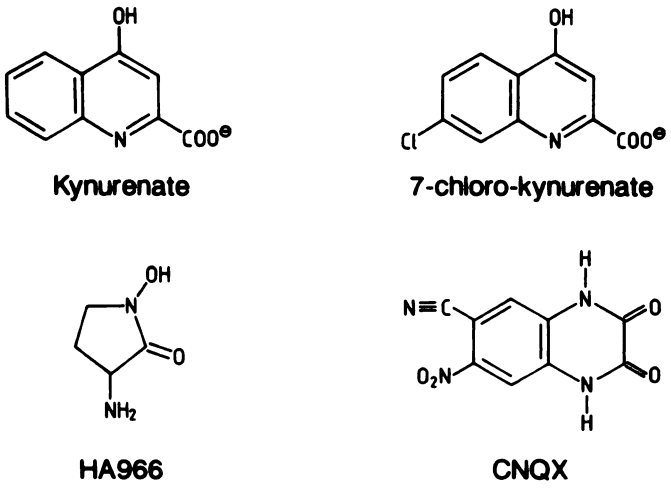

FIG. 8. Glycine antagonists. Some of the first compounds shown to block responses to NMDA, at least in part, via an action at the allosteric glycine site. Abbreviations: HA-966, 3-amino-1-hydroxy-2-pyrrolidone; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione.

was reported to block responses to L-glutamate to a greater extent than responses to DL-HCA (318). Subsequent studies have suggested that GDEE is an antagonist at quisqualate, but not NMDA or kainate, receptors (196, 509). In numerous other studies, however, the efficiency and selectivity of GDEE has been questioned (e.g., ref. 140). It is at best of marginal usefulness in synaptic studies and should be used with the utmost caution.

GAMS. γ-D-glutamyl-aminomethyl sulfonate (GAMS) (fig. 3) and the homologue γ-D-glutamyltaurine (GLUTAU) are broad spectrum antagonists that may be somewhat less active at NMDA receptors than at quisqualate or kainate receptors (389). Their usefulness is limited since they are fairly weak non-NMDA type antagonists. They enjoyed transient use as non-NMDA-preferring antagonists in synaptic and behavioural studies.

CNQX. A major breakthrough in the excitatory amino acid field was the development by Honoré and colleagues (355) of certain quinoxalinediones (fig. 3) which depress responses to quisqualate and kainate to a considerably greater extent than responses to NMDA. In their binding studies, which used rat cortical membranes, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and the slightly less potent 6,7-dinitroquinoxaline-2,3-dione (DNQX) displaced AMPA binding at submicromolar concentrations (IC_{50} for CNQX; 0.3 μM); they were 5 times less effective at displacing kainate (1.5 μM) and weak or ineffective against a variety of other neurotransmitter ligands, including the competitive NMDA antagonist CPP (25 μM). They also displayed potent antagonism in functional neurochemical assays; CNQX and DNQX competitively antagonised quisqualate-, kainate-, and to a lesser extent NMDA-induced [^{3}H]GABA release from cultured mouse cortical neurons (respective pA_2 values 6.0, 5.7, and 5.3) and ^{22}Na efflux from striatal slices (218).

In electrophysiological experiments, CNQX and DNQX have been found to antagonize responses to quisqualate and kainate to a greater extent than responses to NMDA (18, 72, 133, 265, 355, 651), except in one study (555) where NMDA was depressed more than kainate (but not more than quisqualate). It has been suggested that these antagonists may block NMDA-induced responses through an action at the glycine site (64); consequently their ability to depress responses to NMDA will depend on the existing glycine concentration.

The ability of these quinoxalinediones to distinguish between responses induced by quisqualate and kainate is less clear; they have been reported to depress responses to quisqualate greater than (555), less than (18), or similar to (355, 651) responses to kainate. Where antagonism has been expressed more quantitatively, in terms of dose ratios and pA_2 values rather than percent depressions, these antagonists distinguish poorly, if at all, between responses induced by kainate, quisqualate, and AMPA, but invariably depress responses to NMDA far less (72, 133, 265). It has been suggested that the lack of selectivity seen in these electrophysiological studies is because in these preparations both kainate and AMPA act to a large extent on the same receptors. Overall, it seems that (with appropriate doses) quinoxalinediones can be used to distinguish between NMDA and non-NMDA receptor mediated responses. They may also be able to help determine the functional correlate of the kainate site (since responses to kainate at this site should be less sensitive to CNQX than actions of kainate on the quisqualate receptor). It seems probable, however, that in many situations these compounds will not distinguish kainate- and quisqualate-induced responses, possibly since these two agonists can act at the same (i.e., quisqualate) receptor.

diCl⁻HQC. 6,7-Dichloro-3-hydroxy-2-quinoxalinecarboxylic acid has been shown to depress responses to NMDA and kainate to a greater extent than AMPA (277). Thus, in a Na^+ efflux assay it yielded pA_2 values for NMDA and kainate of 5.6 and 5.4, and in binding assays it displaced kainate and AMPA with respective Ki values of 5.4 and 4.2. (A pA_2 value of 5.8 was obtained for antagonism of NMDA in electrophysiological experiments using frog spinal cords.) Whether the differential antagonism of AMPA and kainate will be reflected in electrophysiological and other functional assays has yet to be determined.

Toxins. A number of spider toxins are excitatory amino acid antagonists. Joro spider toxin (JSTX), an extract from the glands of *Nephila clavata*, blocks excitatory postsynaptic potentials (EPSPs) and responses to glutamate and in a number of preparations, including a crustacean neuromuscular junction (1), the giant synapse of the squid (403), and hippocampal pyramidal neurons (626, 627). In isolated hippocampal pyramidal neurons, prepared using an enzyme treatment which removed their ability to respond to NMDA, JSTX is a very potent blocker of responses to both kainate and quisqualate (and L-glutamate) (10).

Toxins from the spiders *Argigope trifasciata* and *Araneus diadematus* (*gemma*) are also blockers of glutamate receptor operated channels at the locust neuromuscular junction (719). In cultured chick spinal cord neurons, however, the venom from Araneus was found to act as an agonist at excitatory amino acid receptors (728). Conversely, in rat cortical neuronal cultures, argiopine (3–30 μM) selectively blocked responses to NMDA in a voltage- and use-dependent manner (411). In contrast, the structurally similar philanthotoxin-435 from the Digger wasp preferentially blocked responses to quisqualate (392).

Barbiturates. Barbiturates depress responses to various excitatory amino acids in a number of systems. At concentrations of 20 μM or higher, pentobarbitone depressed responses to glutamate in crayfish muscle (43) and responses to both glutamate and aspartate in frog

motorneurons (561). Barbiturates are not selective in this regard but act at many sites, including nicotinic and adenosine A1 receptors. The best studied action of the barbiturates is their ability to potentiate inhibition through an action at $GABA_A$ sites. Although this effect can contribute to the depression of excitatory amino acid-induced responses, it is not the principal mechanisms of antagonism; thus excitatory amino acid antagonism is seen after doses of barbiturates that do not depress cells directly and antagonism is preserved in the presence of the GABA antagonist picrotoxin (45, 562).

The majority of evidence suggests that barbiturates depress responses to quisqualate and kainate to a greater degree than responses to NMDA (145, 362, 519, 637, 701). It appears that barbiturates exhibit a degree of voltage-dependency in their antagonism (519); they may, therefore, be acting at the level of the ion channel. The ability of a range of barbiturates to block responses to quisqualate and to potentiate responses to GABA do not directly correlate. For example, relative to (+) pentobarbitone, both phenobarbitone and (+)quinalbarbitone are more potent as quisqualate antagonists (658).

7. Summary. In summary, a large number of compounds have been found to possess activity as excitatory amino acid antagonists. This is particularly the case for NMDA antagonists; new compounds with activity at this receptor system are being made at such a rate that it is practically impossible to keep pace while writing this review. Thus new NMDA antagonists have no doubt been omitted.

The role of NMDA receptors in brain function has been elucidated primarily on the basis of the use of APV. This compound has been extensively evaluated and displays a remarkable degree of specificity. As such (in its resolved form), it is the NMDA antagonist of choice, unless penetration into the brain is required. In that case certain newer NMDA antagonists are preferable. Drugs such as the dissociative anaesethetics are not as selective as NMDA antagonists and should be used with great caution as experimental tools for this purpose. They are, however, very interesting compounds and NMDA antagonism probably accounts for many of their important pharmacological properties.

Only recently have potent and selective non-NMDA antagonists been developed. CNQX seems to be a very useful non-NMDA antagonist, providing that glycine levels are high enough to saturate its allosteric site on the NMDA receptor channel complex. The role of non-NMDA and NMDA receptors in the synaptic function is the subject of section V.

C. Excitatory Amino Acid Binding Sites

Several pharmacologically and anatomically distinct binding sites for acidic amino acids have been demonstrated in mammalian brain membrane preparations (268). Over the last few years the relationship between the radiolabelled binding sites and the physiological receptors has become clearer. It is this aspect of the binding studies that this section focuses on.

1. Glutamate: the effect of ions on binding. ^{3}H-L-glutamate has been a popular agent used in binding studies (268). However, there has been confusion concerning the functional significance of the sites labelled by this ligand. The wide variety of tissue preparations and assay conditions employed appear to have been the main cause of debate. The ionic composition of the incubation medium/assay buffer has profound effects on the sites labelled by ^{3}H-L-glutamate (see., e.g., refs. 268, 534). In the presence of normal extracellular concentrations of Na^+ (i.e., 150 mM), the majority of binding is to high-affinity Na^+-dependent glutamate uptake sites (49, 725).

Binding studies evaluating ligand/receptor interactions have, in general, used Na^+-free buffers. Under these conditions, ^{3}H-L-glutamate binding is markedly enhanced in the presence of Cl^-/Ca^{2+} (515). Cl^- was shown to be the factor required, and Ca^{2+}, which alone had no effect, produced a further enhancement of the Cl^--stimulated binding (243, 515, 48). The pharmacological characteristics of the Cl^-/Ca^{2+}-dependent site were different from the Cl^-/Ca^{2+}-independent ^{3}H-L-glutamate site. Although L-glutamate itself had similar potencies at both sites (244). L-APB was found to be a potent and selective inhibitor of Cl^-/Ca^{2+}-sensitive ^{3}H-L-glutamate binding, and it was suggested that this site may represent the physiological L-APB receptor (243, 244). In addition, both quisqualate and ibotenate were reported to be potent inhibitors of Cl^-/Ca^{2+}-dependent ^{3}H-L-glutamate binding (742). The absence of this site in postsynaptic density preparations (PSDs) would suggest, however, a possible non-synaptic (247) or presynaptic function (268). Since L-APB is believed to act presynaptically in some regions of the central nervous system (see section V), this might not seem unreasonable. Upon detailed examination, however, ligands which inhibited the Cl^-/Ca^{2+}-dependent L-APB-sensitive ^{3}H-L-glutamate or ^{3}H-APB binding were generally weak or inactive as either agonists or antagonists at the L-APB receptor, defined electrophysiologically (i.e., depression of the lateral perforant path-evoked field potentials). This suggests that the APB binding site and the "physiological receptor" are not equivalent (88, 246, 619).

There now seems to be general agreement that the majority of ^{3}H-APB or APB-sensitive ^{3}H-L-glutamate sites labelled in the presence of Cl^- represent a Cl^--dependent sequestration of glutamate into resealed membrane vesicles. Such a suggestion is supported by the findings that binding at the APB site is decreased by increasing the osmolarity, which causes breakdown of vesicles (88, 414) or lowering the temperature, which is known to reduce membrane transport (594). Additionally, the ionic specificity of binding can be correlated with an anion transport system (594, 246), and compounds that block Cl^- transport inhibited the Cl^--stim-

ulated ^{3}H-L-glutamate binding (607). Freeze-thaw procedures were already known to prevent Cl^- from stimulating ^{3}H-L-glutamate binding (248). However, Cl^--stimulated ^{3}H-glutamate binding sites that were insensitive to APB but displaced specifically by quisqualate have been detected autoradiographically in frozen sections of rat brain (305, 530). These sites have been suggested to represent Cl^--stimulated ^{3}H-glutamate binding to high affinity quisqualate receptors (103). The exact nature of the Cl^-/APB-dependent sites remains unclear, although their presence on astrocytes has been equated with a high affinity uptake system (90).

In the absence of Cl^-, APB, although not with high affinity, can displace ^{3}H-L-glutamate binding (268). As yet the biochemical binding site representing the L-APB synaptic receptor remains to be detected (88), a problem which may be related to the apparently sparse and specific effects of L-APB in the CNS. In the absence of Na^+, Cl^- and Ca^{2+}, it has been suggested that the majority of sites labelled by ^{3}H-L-glutamate correspond to the three main types of excitatory amino acid receptors, NMDA, quisqualate, and kainate (530, 595). The interaction of ligands at these sites will be considered in the following sections.

2. NMDA "receptors". The NMDA site is the most clearly defined in excitatory amino acid radioligand assays (154, 155). Since the demonstration that a subpopulation of Cl^-/Ca^{2+}-independent ^{3}H-L-glutamate binding to synaptic membranes was sensitive to compounds acting at NMDA receptors (244), a variety of membrane preparations and ligands have been used to further characterize this site.

The selective NMDA antagonist APV (as ^{3}H-D-APV) has been used to label the NMDA site (270, 535, 575). Although the pharmacology (see below) of this site correlates well with that of the NMDA receptor, the rapid dissociation rate and a high degree of non-specific binding have limited the use of ^{3}H-D-APV as a marker for the NMDA receptor (270, 575, 576, 740). The more potent competitive NMDA antagonists, ^{3}H-CPP and ^{3}H-CGS, have now superseded ^{3}H-APV as the preferred radioligand (545, 546, 576).

Of the agonists, ^{3}H-NMDA exhibited low affinity and low specific binding and has not been employed routinely as a ligand (see 270). As discussed above, L-glutamate interacts at several receptor sites and therefore may, initially, appear not to be a useful specific ligand. Recent observations suggest, however, that this may not be the case. Olverman et al. (575) originally demonstrated that, of the compounds tested, L-glutamate showed the highest affinity for the ^{3}H-APV binding site. In the study by Foster and Fagg (270) several radioligands, including ^{3}H-NMDA, ^{3}H-APV, and ^{3}H-L-aspartate, were compared to ^{3}H-L-glutamate, and although the pharmacology of the sites labelled by each of these compounds resembled the NMDA receptor, ^{3}H-L-glutamate showed the highest degree of specific binding and affinity and remained the ligand of choice.

However, in assays employing ^{3}H-L-glutamate non-NMDA sites also will be labelled (see, e.g., 270), although binding to the NMDA site can be enhanced under appropriate conditions. Thus, in postsynaptic density preparations a large proportion (around 90%) of ^{3}H-L-glutamate binding can be displaced by NMDA ligands (240, 247, 270). This is also the case for binding to enriched synaptic plasma membrane (SPMs) fractions, suggesting that NMDA receptors are preferentially located in synaptic structures (528, 536).

The pharmacology of the NMDA binding site, as defined by several NMDA receptor radioligands, corresponds well to that of the physiological NMDA receptor. For example, the series of phosphono-antagonists show the same inhibition profile at this site (240, 270, 528, 536, 575) as compared to NMDA receptor-induced depolarizations in spinal cord (233), with APV possessing a similar affinity in both types of assay. The stereoselectivity of the site is also conserved, D-APV being a more potent inhibitor than L-APV (240, 528, 536, 575). Of the agonists, L- and D-aspartate, NMDA, and ibotenate were found to be good inhibitors, as expected, whereas ligands for the two other major classes of excitatory amino acid receptors, AMPA and kainate were poor inhibitors (240, 247, 270, 528, 536, 546, 575). In these studies quisqualate showed micromolar affinity for the NMDA site, although it was 100-fold less potent than at the proposed high affinity quisqualate site (see 270, 528, and below).

Based on structure-activity relationships, a model has been proposed for the NMDA recognition site consisting of 4 points (see 240, 740). Two of these points are common to the 1-carboxyl and the α-amino group of both competitive agonists and antagonists. Two further points accomodate the ω-amino group, one for the shorter chain D and L-forms of agonists (e.g., L-glutamate, NMDA), and a separate point for the longer chain antagonists favouring the D-conformation (e.g., D-APV).

In addition to direct interactions at the NMDA ligand binding site, the NMDA receptor-system is subject to several kinds of allosteric control. The psychotomimetic class of compounds, comprising the sigma "opioids" and dissociative anaesthetics (e.g., PCP), are known to be potent "non-competitive" NMDA receptor antagonists (see section II B 4). Two membrane binding sites have been demonstrated for these compounds. One of these, the "PCP" site, can be labelled by ^{3}H-TCP, a PCP analogue (724), and more specifically by ^{3}H-MK-801 (758), and has properties consistent with an interaction with the NMDA receptor-system (see 408). Thus, the potencies of PCP/sigma-opioids as NMDA antagonists and as inhibitors of either ^{3}H-TCP or ^{3}H-MK-801 binding are highly correlated (239, 467, 758).

This class of compounds does not displace ^{3}H-D-APV or ^{3}H-CPP binding (546, 740) or affect NMDA-sensitive

^{3}H-L-glutamate binding (239, 528, 536), suggesting a site of action distinct from the NMDA ligand receptor site. However, an interaction is suggested by the findings that the binding affinities of both ^{3}H-MK-801 (273, 757) and ^{3}H-TCP (239, 466, 467) were enhanced by NMDA ligands. Indeed, the binding of these compounds was markedly affected by the levels of endogenous NMDA ligands, such as L-glutamate, in the preparation. Washing the membranes produced a parallel reduction in binding of ^{3}H-TCP (466) and/or ^{3}H-MK-801 (273) and the levels of endogenous L-glutamate; restoration of binding could be achieved by the subsequent addition of glutamate (273). Further support for a specific interaction between NMDA receptors and the "PCP" site is derived from the results that the NMDA receptor antagonists, APV and CPP, decrease ^{3}H-TCP binding (383, 467). The agonist-dependency reported in these binding studies supports the suggestion that these ligands bind to the active or open state of the NMDA associated channel and are, therefore, dependent on the presence of an NMDA agonist.

Some divalent cations (e.g., Mg^{2+}) produce a voltage-dependent block of the NMDA receptor-operated channel (see section III B 1). In physiological concentrations these ions cause only a small inhibition of NMDA ligand binding (536), suggesting that their NMDA antagonism occurs at a site distinct from the NMDA recognition site. However, Mg^{2+} ions were found to decrease the affinity of ^{3}H-MK-801 binding in a dose-dependent manner (615, 616, 758) and attenuated glutamate-stimulated ^{3}H-TCP binding (466, 467), as would be expected if both MK-801/TCP and Mg^{2+} were competing for sites located inside the open channel (see 269, 758). A more complex interaction between these compounds is suggested by the observations that in extensively washed membranes, where endogenous ligand concentrations are decreased, cations such as Mg^{2+}, alone, produced an enhancement of ^{3}H-MK-801 binding (467, 758) and that Mg^{2+} at low concentrations ($< 30\ \mu M$) increased the ability of glutamate to stimulate ^{3}H-MK-801 binding (467). Zn^{2+}, which modulates the NMDA receptor-system in a different manner to Mg^{2+} (591, 744), produced only an inhibition of ^{3}H-MK-801 binding (758).

Glycine, which enhances NMDA receptor-induced current (386), potentiates both ligand binding at the NMDA site (413, 556; although see 240) and NMDA-dependent ^{3}H-TCP (82, 674) or ^{3}H-MK-801 (616) binding in a strychnine-insensitive manner. Glycine. however, failed to increase ^{3}H-TCP binding in the presence of APV, suggesting that glutamate is required for this action of glycine (55). The interaction between NMDA ligands and glycine were reported to be reciprocal, thus glutamate could enhance ^{3}H-glycine binding (413, 556). The enhancement of binding could be inhibited by a variety of competitive NMDA antagonists (82, 413). Interestingly, Kessler et al. (415) demonstrated that the broad spectrum antagonist, KYN, was a potent (Ki = 15 μM) inhibitor at the glycine binding site. The actions of glutamate and glycine on the binding of channel blockers, such as ^{3}H-MK-801, have been suggested to be due to an increase in the rates of association and dissociation of ^{3}H-MK-801 from its site, presumably reflecting an increased access to the channel (422, 614).

Monaghan and Cotman (528) have shown that NMDA displacable ^{3}H-L-glutamate binding is reduced by guanine nucleotides (e.g., GTP), suggesting the possible involvement of a G-protein link in NMDA receptor-mediated events.

3. Quisqualate "receptors". Binding sites for quisqualate have also been described (268). However, the use of quisqualate itself in the binding studies has lead to questions concerning the selectivity of this compound for the quisqualate receptor.

In binding studies employing ^{3}H-L-glutamate, quisqualate showed a biphasic displacement, even in the absence of Cl^-/Ca^{2+} (304) or in postsynaptic density preparations (247, 270), procedures that eliminate labelling of the APB/Cl^--sensitive-^{3}H-glutamate site. The lower affinity site has been attributed to displacement at the NMDA-sensitive ^{3}H-glutamate site, and the higher affinity site was suggested to represent the quisqualate receptor (247, 270, 271, 304, 534, 536). As this site is present in the postsynaptic density preparations it appears that, similar to NMDA sites, quisqualate sites are localized synaptically (247). There is evidence that displacement of binding from the "low-affinity" site may be due to contamination of quisqualate samples by glutamate and aspartate (104, 575).

AMPA, however, is perhaps a more selective ligand for the quisqualate receptor subtype (358, 433). Following extensive washing and freeze-thawing procedures, ^{3}H-AMPA was reported to bind with high affinity to a single site in rat brain membranes (358). However, Murphy et al. (547) report that both high and low affinity sites persist even following freeze-thaw procedures (see below). The potencies of other ligands as inhibitors of this binding led to the suggestion that this site represented the quisqualate receptor; thus, AMPA, quisqualate, and glutamate are potent inhibitors, whereas kainate (see below) showed moderate inhibition, and NMDA ligands (e.g., APV and APH) were described as inactive (358, 533, 547, 574, 605). Furthermore, this order of potency is similar to the AMPA-sensitive ^{3}H-glutamate binding (530), suggesting that glutamate can be used to label the quisqualate/AMPA site (see 533). The greater selectivity of AMPA over quisqualate is further suggested by the findings that both ^{3}H-AMPA binding and AMPA-sensitive ^{3}H-glutamate binding (533, 605) are little affected by Cl^-/Ca^{2+} (although see 574) or L-APB, and that AMPA, unlike quisqualate, does not displace binding at the ^{3}H-kainate site (358, 547).

Several procedures have been shown to affect ^{3}H-

AMPA binding. The affinity of ^{3}H-AMPA for its binding site is stimulated by chaotropic ions (e.g., SCN^-) and by high energy radiation (359, 547). It was suggested that radiation acts to remove/uncouple a high molecular weight subunit which down regulates binding at the AMPA site, although this would appear to be independent from the SCN^- effect (359). Honoré and Drejer (356) have suggested that the ^{3}H-AMPA site can exist in two interconvertible forms, and that the effect of SCN^- is to promote formation of the state for which ^{3}H-AMPA has a higher affinity.

4. Kainate "receptors". ^{3}H-Kainate has been reported to bind to two populations of sites, with high and low (both nanomolar) affinities (see 268). Both of these sites are present in synaptic membrane fractions and have a similar pharmacological profile (268, 272, 659). L-Glutamate, kainate, and domoic acid, and quisqualate are potent inhibitors of ^{3}H-kainic acid binding (464, 671).

A subpopulation of ^{3}H-L-glutamate binding sites, apparent in autoradiographical studies (see below), is sensitive to kainate receptor ligands (304, 530, 534). Monaghan et al. (534) suggested this site to be equivalent to the high affinity ^{3}H-kainate site, since L-glutamate displaces binding at both of these sites with high affinity, whereas it is 10-fold weaker at the low affinity ^{3}H-kainate site.

A distinction between the two ^{3}H-kainate sites was found in their sensitivity to Ca^{2+}. Binding at the high affinity site was markedly reduced in the presence of this ion (534), as was binding at the kainate-sensitive ^{3}H-L-glutamate site (304, 357, 530). The functional significance of this effect is at present unclear (531).

The observed overlap in the pharmacology of kainate and quisqualate binding sites has been compared to that observed in functional studies, although it was argued that kainate and AMPA could distinguish between the two sites (534). Greenamyre et al. (304) presented a model in which kainate binds to a subpopulation of high-affinity quisqualate-sensitive ^{3}H-L-glutamate sites. Irradiation inactivation of ^{3}H-kainate binding, in the presence of Ca^{2+}, produced a pattern similar to that observed with ^{3}H-AMPA, and it was suggested that the low affinity ^{3}H-kainate binding site was equivilant to the "high-affinity" quisqualate site (359).

5. Autoradiography. Over the last few years, autoradiographical techniques have provided further evidence for the existence of multiple excitatory amino acids binding sites/receptors and information on their distribution in brain (see 155). Sites with the appropriate pharmacology for the three major receptor subtypes have been demonstrated in autoradiographs utilizing the radioligands described in the above sections. The specific ligands ^{3}H-APV (535) or ^{3}H-CPP (382, 576), ^{3}H-AMPA (533, 605) and ^{3}H-kainate (527, 531, 718) label NMDA, quisqualate, and kainate receptor sites, respectively. The distributions of sites obtained with these compounds follow closely the binding patterns obtained with the NMDA, kainate, AMPA (or quisqualate) displacable portions of ^{3}H-L-glutamate-labelled sites under appropriate ionic conditions, i.e., Na^+, Ca^{2+}, and Cl^- free (304, 530, 534). Sites defined in the presence of Cl^- have also been studied in autoradiographs (e.g., 103, 305, 530).

NMDA, kainate, and quisqualate/AMPA binding sites all show distinct anatomical distributions in brain. Generally, the highest levels of binding for all sites are found within telencephalic structures, with lower levels observed in the midbrain and brainstem. Interestingly, of all brain areas the hippocampus shows the highest densities of binding for each site, although there exists clear differences in localizations of specific sites to particular hippocampal subfields (304, 530). NMDA sites are highest in stratum radiatum/oriens of CA1, and also the inner molecular layers of the dentate gyrus (304, 488, 529, 530), which may explain the large APV-sensitive long-term potentiation (LTP) observed in these regions (see section VI A 1 d). High densities of NMDA receptors in areas such as CA1 (or Sommer's section) may explain their high susceptibility to neurotoxic damage (529) (see section VIII B). A selective loss of hippocampal NMDA binding sites has also been implied in Alzheimer's disease (487). Geddes et al. (297) suggest, however, that a decrease in binding sites is observed only in cases where major cell loss is seen, although neurofibrillary tangles and plaques have been correlated with the distribution of NMDA sites.

AMPA/quisqualate sites are also high within these regions, although a higher level of binding is observed in stratum pyrimadale (533); this co-localization may parallel the role of the two receptor types in fast "quisqualate" and slow "NMDA" synaptic transmission, such as that found in the Schaffer collateral-commissural pathway. A subsynaptic co-localization of NMDA and quisqualate receptors is further supported by the finding that ^{3}H-L-glutamate binding in PSDs can be divided into two populations consisting of NMDA and quisqualate-sensitive sites (247). Kainate binding sites in the hippocampus are primarily confined to the termination zone of the dentate granule cell-mossy fibres in stratum lucidum of area CA3 (272, 304, 527, 534, 718), a region low in NMDA/AMPA sites. This may explain the high sensitivity of the hippocampal CA3 subfield to kainic acid. The ^{3}H-kainic acid binding sites have been suggested to be in part localised presynaptically on the mossy fibre terminals (609; although see 241).

In other brain regions, Cotman et al. (155) have proposed a general rule of AMPA/NMDA co-binding and a more distinct and separate distribution for high-affinity kainate sites. However, exceptions exist; for example, in cerebellum kainate/NMDA sites are preferentially labelled in the granule layer, whereas AMPA sites are found in the molecular layer (see also 304). With respect to overall functioning, the localization of NMDA recep-

tors alongside quisqualate receptors may provide a guide to modifiable/plastic central nervous system regions, since the joint roles of these two receptors in LTP is well established (see section VI A 1). NMDA receptors, however, are not observed at all glutaminergic pathway terminals and may tend to be associated with cortical/sensory areas as opposed to ventrally located motor systems.

Further evidence that allosteric modulators exert their effects through the NMDA receptor-system has been forthcoming from autoradiographic studies which have demonstrated that both ^{3}H-TCP (382, 488), ^{3}H-MK-801 (84), and ^{3}H-glycine (91) show very similar binding patterns to the NMDA ligand site. As discussed by Cotman and colleagues (155), the distributions of ^{3}H-TCP and NMDA-sensitive ^{3}H-L-glutamate sites are not quite identical. For example, in the cerebellar granule cell layer ^{3}H-TCP binding is relatively low and appears to be kinetically distinct (724). This observation has been confirmed by Maragos et al. (488) who, in addition, suggest that NMDA ligand sites are 5-fold more numerous than the binding sites labelled by ^{3}H-TCP. Recently, subtypes of NMDA ligand binding sites have been implied from autoradiographical studies which show a slightly different distribution of ^{3}H-CPP compared to NMDA-sensitive ^{3}H-glutamate sites (154, 155, 576). Monaghan et al. (532) have reported that NMDA-sensitive ^{3}H-glutamate binding is more readily displaced by antagonists than agonists in thalamus and cerebral cortex, whereas the relationship is reversed in striatum and cerebellum; and that glycine is a more potent stimulator of binding in thalamus and cerebral cortex than in cerebellum and striatum.

6. Summary. At present the sites described in binding studies do not completely conform to the excitatory amino acid receptors as defined functionally. For the NMDA receptor, there is a good correspondence between the biochemical and neuropharmacological studies. Recent evidence points to the possible existence of NMDA receptor subtypes. Some debate exists over the binding sites representing the quisqualate and kainate receptors. A high-affinity quisqualate site labelled specifically by AMPA probably represents the quisqualate receptor. However, the functional receptor corresponding to the high-affinity kainate binding site is less clear. Sites representing the L-APB and the metabotropic receptors have yet to be resolved.

III. CONDUCTANCE MECHANISMS

A. Early Studies

Since Watkins and colleagues (176, 179) demonstrated that excitatory amino acids excited neurons by membrane depolarization, the nature of the underlying conductance mechanisms have been extensively investigated. During the 1960s and 1970s, several groups confirmed that L-glutamate depolarized neurons and found this to be associated with either no change or an increase in conductance (432, 490). The lack of change in conductance was attributed to an action of L-glutamate on dendrites too remote to be detected by the intrasomatic electrode.

That the actions of acidic amino acids may be more complex than originally thought was shown by Engberg et al. (226), who investigated these compounds in considerable detail for their effects on cat motorneurons in vivo. They found that depolarizations induced by DL-HCA were associated with an *increase* in the size of electrotonic responses to constant current pulses and attributed this action to a decrease in potassium conductance (gK^+). L-Glutamate, on the other hand, induced either no changes, small decreases, or small increases in membrane conductance (gM), the latter effect being attributed to a consequence of low affinity L-glutamate uptake. After further investigation and correction for membrane rectification, they classified agonists in three groups (440): (*a*) L-aspartate, L-glutamate, L-HCA, quisqualate (increase in gM, fast on/off); (*b*) NMDA, ibotenate, D-HCA (decrease in gM, slow on/off); and (*c*) kainate (increase in gM, very slow on/off). Although some of the interpretations from these studies are now believed to be incorrect, this work was important in that it provided the first clear evidence that the action of excitatory amino acids may involve more than one conductance mechanism.

At about the same time, MacDonald and his colleagues, using cultured spinal neurons, reached a similar conclusion. They found that L-glutamate and L-aspartate, as well as NMDA and DL-HCA (but not kainate), could apparently decrease gM (482). DL-HCA and NMDLA were also found to have similar effects in hippocampal slices (315). MacDonald's group, however, then went on to show that the "decreases in gM" were dependent on membrane potential (483). This suggested that the conductance mechanism was voltage-dependent and, therefore, could not be properly analysed using current-clamp techniques. Using voltage-clamp techniques they demonstrated, for the first time, that L-aspartate induces a region of negative slope conductance in the I-V relationship (481). They suggested that the "increases in resistance" produced by L-aspartate and other analogues, such as NMDA, are only apparent and may result from activation of a TTX-resistant voltage-dependent sodium conductance (gNa^+). Quisqualate was found to activate a voltage-insensitive conductance (480). These studies showed, therefore, that the receptors, defined pharmacologically, could be equated with conductance mechanisms with differing voltage-dependencies: NMDA with a voltage-dependent conductance and quisqualate and kainate with, to first approximation, voltage-insensitive conductance(s). The variable actions of L-glutamate might be the result of differing degrees of L-glutamate action on NMDA versus non-NMDA receptors. Subse-

quent studies by Mayer and Westbrook (499), also using cultured spinal neurons, presented clear evidence that this is the case. On the basis of voltage-sensitivity agonists can be ranked: NMDA >= L-aspartate > L-HCA > L-glutamate >= D-HCA ≫ quisqualate = kainate.

Similar voltage-dependent actions of NMDA were observed in voltage-clamp studies of neocortical neurons (260, 261), where activation of a TTX-resistant gNa^+ was also suggested, and in current-clamp investigations of hippocampal neurons (211), where rapid activation of a voltage-sensitive calcium conductance (gCa^{2+}) was favoured. The explanation for the voltage-dependence was provided by Philippe Ascher and his colleagues (567) who showed that Mg^{2+} blocked whole-cell responses to NMDA receptor ligands in a highly voltage-dependent manner.

At the same time these authors (567) provided the first description of channels activated by excitatory amino acids in the central nervous system. They showed that NMDA receptor ligands gate a channel of ~50 pS which is blocked by Mg^{2+} in a highly voltage-dependent manner. In contrast, non-NMDA receptor ligands, such as kainate and quisqualate, activate smaller conductance channels that are not blocked by Mg^{2+} (36). These results are consistent with the concept that the different "selective" agonists, as characterised pharmacologically, gate distinct types of ion channels. On the basis of other data (167, 380), it has been suggested that there is only one excitatory amino acid channel and that the "selective agonists" predominantly activate different conductance states of this channel. Current evidence, however, favours discrete channels as described originally by Ascher's group. In particular, organotypic slice cultures of cerebellar Purkinje cells, in contrast to hippocampal pyramidal cells, neither responded to NMDA nor gave 50 pS openings in response to quisqualate (455). The following description, therefore, will consider the properties of the NMDA conductance and kainate/quisqualate conductances in turn.

B. NMDA conductance. Under physiological conditions responses to NMDA receptor ligands reverse at potentials close to 0 mV (162, 480, 499). When direct comparisons have been made responses to NMDA and non-NMDA receptor ligands usually reverse at the same potential (480, 499), although in hippocampal granule cells the NMDA reversal was reported to be significantly more depolarized (162). NMDA responses are often studied using whole-cell patch clamp techniques. In this regard, it is worth noting that the inclusion of high-energy phosphates minimizes run-down of these currents (525). In addition, NMDA responses are sensitive to enzyme treatment, of the sort that is often used to acutely isolate cells (9).

The NMDA receptor-channel complex has several unique properties that have important implications with respect to the role of this receptor in physiological and pathological processes. Fluctuation analysis has been employed by a number of groups in the study of the elementary properties of excitatory amino acid receptor-gated conductances. This approach has yielded some useful data (see 502 for review). However, the estimates from fluctuation analysis do not agree with the direct measurements obtained using single channel recording. One problem with fluctuation analysis is the space clamp limitations imposed by the dendritic location of most excitatory amino acid receptors. This review will concentrate on the elementary properties as determined by the pioneering single channel patch clamp studies in the field.

NMDA predominantly activates channels with a unitary conductance of approximately 50 pS (at room temperature, Q_{10} 1.6 (31)). Lower conductance states (~10, 15, 20, 30, 35, and 40 pS) are also seen, but, in total, account for far fewer openings (31, 165, 167, 380). Transitions between most of these states have been seen. Since the frequency of transitions was much higher than that expected on the basis of the superimposition of openings of independent channels, it was concluded that transitions represent complex gating of a single macromolecular complex (167, 380).

The 50 pS channel has been reasonably well characterized. Its conductance is fairly linear (over the range −80 to +60 mV); the channel is roughly equi-permeable to Na^+, K^+, and Cs^+, but is blocked by choline in a voltage-dependent manner (31). Of great interest are the discoveries that the channel is blocked by Mg^{2+} (and certain other divalent cations) in a highly voltage-dependent manner (567), is permeable to Ca^{2+} (36), and its probability of opening is greatly affected by low concentrations of glycine (386). These observations mean that any detailed kinetic measurements will need to take account of these parameters.

In nominally Mg^{2+}-free medium (and unknown glycine concentration) the channel exhibits complex kinetics. The mean open time histogram can be described by two exponentials of 1 to 3 and 10 to 15 ms (31, 364, 380); a single-exponential fit to the data yields values (5 to 6 ms) equivalent to that derived from noise analysis in the same cells (31). Openings occur in bursts (31, 364), which in turn can occur in clusters, lasting for several hundreds of milliseconds (364, 380). Neither mean channel open time nor mean burst duration are appreciably affected by membrane potential (31). Open time decreases with increasing temperature with a Q_{10} of approximately 2 (31).

Some channel openings are interrupted by brief (<1 ms) and intermediate (1 to 5 ms) closures. Since the number and duration of these gaps appear to be independent of membrane potential, they are not due to blockade of the channel by either residual Mg^{2+} ions present in the nominally "Mg^{2+}-free" medium or to other

charged molecules (31, 364). Their significance is currently unknown.

1. Blockade by Mg^{2+} and other divalent cations. The highly voltage dependent nature of the conductance induced by NMDA is now known to be caused by the presence of Mg^{2+} in the extracellular fluid, as first reported by Ascher and his colleagues (567). Thus, the channel molecule itself does not exhibit significant voltage-gated behaviour, but it is blocked by Mg^{2+} in a highly voltage-dependent manner. The block is maximal at negative membrane potentials and decreases with depolarization. This effect can account for the region of negative slope conductance and apparent increase in membrane resistance (164, 500). The blockade occurs rapidly and exhibits uncompetitive kinetics, reminiscent of channel block. Ni^{2+} has similar voltage-dependent effects, whereas Cd^{2+}, at doses that block voltage-gated Ca^{2+} channels, has little effect (500). The blockade of NMDA responses by Zn^{2+} appears to be at a different site, since the antagonism does not display voltage-dependence between −60 and +40 mV (503).

The mechanism of the Mg^{2+} block is best described using single channel recording (31, 567). Mg^{2+} characteristically blocks the NMDA channel recorded at negative, but not positive, membrane potentials. Thus, channel openings are interrupted by flickerings such that currents appear as bursts of brief openings separated by brief closures. The mean brief open time is dependent on $[Mg^{2+}]$, decreasing as the ion concentration is raised, whereas mean brief closed (i.e., blocked) time is independent of $[Mg^{2+}]$. The burst duration shows no change or decreases with increasing $[Mg^{2+}]$, rather than increasing as would be expected for a simple open-channel block (551). This may be accounted for by either entry into a slower, long-lasting blocked state or the channel closing while in the blocked state (i.e., trapping of Mg^{2+}).

With membrane depolarization, open time increases and closed time decreases. The voltage-dependence of the blocking rate constant (e-fold increase for 17 mV hyperpolarization) is ~3 times greater than that of the unblocking rate constant (e-fold for 47 mV). The asymmetrical rates may be explained by Mg^{2+} both permeating and blocking the channel. If the usual assumptions of a Boltzman distribution are made then the binding site for Mg^{2+} has to be placed very close to the cytoplasmic side of the channel. However, NMDA channels are blocked by intracellular Mg^{2+}, with an inverse voltage-dependence to that seen with extracellular Mg^{2+} (33). Analysis of this block places the binding site for Mg^{2+} in the middle of the channel. These findings are incompatible with a single site block. A more likely explanation, compatible with the extremely high voltage-dependence of the blocking rate, is that Mg^{2+} interacts with other ions in the channel. The equilibrium dissociation constant (K_D) for the binding of Mg^{2+} to the channel is ~70 μM at −60 mV and ~9 mM at 0 mV.

In agreement with measurements of macroscopic currents or field depolarizations (39, 500), Co^{2+} and Mn^{2+} have similar effects being more and less potent than Mg^{2+}, respectively, whereas Cd^{2+} caused no flickering of the channels. There is a close correlation between the ease that ions lose their water of hydration (210) and their ability to permeate NMDA channels. Ions that give up their water slowly (e.g., Ni^{2+}, Co^{2+}, Mg^{2+}) are considered blockers, whereas those that dehydrate more quickly (e.g., Ca^{2+}, Ba^{2+}, Cd^{2+}, Sr^{2+}) are considered to be permeant. It has been reasoned (35, 119) that if dehydration is the rate-limiting step for permeation then this property can explain the ability of ions to "block" or "permeate" the channel, i.e., all these ions may enter the cell but at vastly different rates. Since Mg^{2+} would reside in the channel for a relatively long period it would block the passage of other ions. Although Ca^{2+} would enter much more quickly than Mg^{2+}, it would be considerably slower than Na^{+}. Thus, increasing $[Ca^{2+}]_o$ would increase Ca^{2+} entry, but decrease total channel conductance.

2. Organic channel blockers. The use- and voltage-dependence of the actions of PCP (354) MK-801 (368), ketamine (354, 478, 503), and tricyclic antidepressants (e.g., desipramine) (648) suggest that these compounds may block open NMDA channels. This idea is supported by single-channel studies; PCP (62); MK-801 (368), and desipramine (648) reduce channel opening frequency and mean open time with no effect on single-channel conductance. The dose-dependent decrease in mean open time can be explained by channel openings being terminated to a significant degree by drug block. This would mean that the block of open-channels occurs rapidly over a few ms. To explain the slow development of block of macroscopic current, it then becomes necessary to place a very low probability on NMDA channel opening (368). This finding may have important implications for the functioning of NMDA channels.

3. The Glycine site. As first shown by Johnson and Ascher (386), a remarkable property of the response to NMDA is that it is greatly potentiated by low concentrations of glycine. The presence of an endogenous potentiating substance was first suspected since (*a*) responses to NMDA decreased when a fast perfusion method of application was used, and (*b*) patches placed near to cells were more effectively activated by slow perfusion of NMDA than patches placed far from the same cells. Together these observations suggested that cells were releasing a substance that can augment responses to NMDA and which can be washed away with fast perfusion. Johnson and Ascher went on to show that glycine potentiated whole cell responses to NMDA (and L-glutamine and L-aspartate), but not kainate or quisqualate, in cultured central neurons.

The effect of glycine was detectable at 10 nM and was near saturation at 1 μM. It was insensitive to antagonism by strychnine, thus demonstrating that the effect did not

involve the receptors that mediate the inhibitory neurotransmitter action of glycine. Glycine was fully effective in outside-out patches, indicating that second messengers were not required for the potentiation. In this recording, configuration the predominant change was a pronounced increase in the frequency of channel opening; glycine did not affect single channel conductance and only slightly prolonged mean open-time. Alanine and serine also caused a small augmentation of the response to NMDA. Glycine was found to be present in sufficient concentrations to account for the potentiation produced by the release of conditioning substances from the cultured cells.

Johnson and Ascher initially thought glycine may be an allosteric modulator of the NMDA receptor-channel complex, acting in a manner analogous to the benzodiazepines at the $GABA_A$, receptor-channel complex. Ascher's group found that low concentrations of kynurenic acid, which displaces glycine from strychinine-insensitive binding sites (413), blocks responses to NMDA in the absence (as far as could be achieved) of glycine, in a manner that was not competitive (32). They suggested that kynurenate may be acting directly to reduce the frequency of channel opening at the glycine site and is thus equivalent to an inverse agonist at the benzodiazepine-$GABA_A$ receptor complex. At higher doses, kynurenate appeared to block responses to NMDA by an additional action, which may involve competition with NMDA for its recognition sites (503).

A different role for glycine was proposed by Kleckner and Dingledine (419) who worked with *Xenopus* oocytes in which NMDA receptors had been expressed following injection of rat brain messenger RNA (mRNA). According to extrapolations from their dose-response relationships, glycine is an absolute requirement for NMDA to generate a response. Thus, the effect of kynurenate would be explained by blockade of residual amounts of glycine present in nominally glycine-free medium. In their scheme, glycine must occupy one site and NMDA another for the channel to open. They suggest that glycine could be termed a co-agonist. A more recent analysis of the kinetics of the glycine effect and its blockade by antagonists lends support to this idea. Using "concentration jump" experiments Ascher and Johnson (33) have found that the time-constant of onset of the effect depends on the glycine concentration whereas the time-constant of the decay, when glycine is removed, is independent of the starting glycine concentration. The K_D determined from this kinetic data (110 nM) is in agreement with measurements made at equilibrium. The time constant of decay was of the order of 1 s. A similar time-constant was obtained for the block by a high concentration of KYN, 7-ClKYN or HA-966 of the effect produced by a low glycine concentration. The simplest explanation for this finding is that the antagonist can only block when glycine unbinds.

It has been suggested that a major part of the action of glycine is to speed up the rate of recovery from desensitization of NMDA-induced currents. Using cultured mouse hippocampal neurons, Mayer and colleagues (498) found that responses to NMDA and L-glutamate desensitized relatively slowly, with a time-constant of ~250 ms (in the presence of 0.2 mM Ca^{2+} to reduce Ca^{2+}-dependent inactivation of the response (496, 500)). Desensitization was depressed by glycine, in a dose-dependent manner (K_D 185 nM), and also by D-serine and D-alanine. Glycine had little effect on the rate of onset of desensitization but dramatically speeded up the rate of recovery from this state. As a consequence, at equilibrium less channels may be in a desensitized state as the glycine concentration is raised. This finding could therefore account, at least in part, for the marked potentiation of NMDA responses by glycine. It is consistent with the increase in frequency of channel opening seen in detached patches (386) (assuming that the time spent in the desensitized state is long relative to the normal gating behaviour of NMDA channels). Ascher and Johnson (33), however, have obtained conflicting results. On the basis of either whole cell records from small cells or single channel data from outside-out patches, glycine did not affect the rate of desensitization of responses to NMDA (33). The reason for this discrepancy with the study of Mayer et al. (498) is not known.

The physiological significance of the glycine potentiation is unclear. In neuronal cultures, glycine potentiates synaptic transmission (267). In more physiological preparations, however, it is likely that the site is normally fully occupied since the effects of glycine are near maximal at 1 μM and extracellular glycine levels are likely to be well above this level (253, 662). In support of this, in brain slices and in vivo, glycine or D-serine do not potentiate responses to NMDA, unless a glycine antagonist is first used to depress the response to NMDA (64, 264, 407, 741) (but see 630, 708). Also favouring the "normally saturated" hypothesis, glycine produces little or no potentiation of whole-cell responses to NMDA in hippocampal neurones in organotypic slices, although the potentiation of NMDA-induced channel activity can be readily seen in isolated patches removed from the slice environment (455).

4. Ca^{2+} permeability. A third important feature of the NMDA conductance is the significant Ca^{2+} contribution, first suggested by measurements with ion selective electrodes.

a. Ca^{2+} ION MEASUREMENTS. There is a considerable body of information on the possible Ca^{2+} permeability of excitatory amino acid-gated channels. Thus, in frog spinal cord Bührle and Sonnhof showed, using ion sensitive electrodes, that L-glutamate elevated motorneuronal $[Ca^{2+}]_i$ and concomittantly reduced $[Ca^{2+}]_o$ (99). The Ca^{2+} changes did not correlate with changes in membrane potential, suggesting that L-glutamate-gated

channels were directly permeable to Ca^{2+}. Although these experiments shed no light on the receptor type involved, similar studies by Padjen and Smith (579) indicated that NMA caused the greatest Ca^{2+} influx into spinal neurons.

Heinemann, Pumain, and their colleagues have similarly used ion-sensitive electrodes to measure excitatory amino acid induced changes in $[Ca^{2+}]_o$ in hippocampal (489, 762) and neocortical tissue (335, 601). It was suggested that the major source of Ca^{2+} entry was post-, rather than pre-, synaptic and that Ca^{2+} may enter through both chemically and voltage-gated channels (334). In cerebral cortex, NMDA induced far greater changes in Ca^{2+} than did either kainate or quisqualate (602), and it was reasoned that practically all the NMDA-induced fall in $[Ca^{2+}]_o$ was due to entry into neurons through NMDA-gated channels. It was estimated that Ca^{2+} contributed 5 to 10% of the total NMDA-gated current.

Direct evidence that NMDA can cause Ca^{2+} entry via receptor-coupled ion channels was provided by experiments that combined the use of whole-cell patch clamp techniques and the Ca^{2+} indicator Arsenazo III in cultured spinal cord neurons (477, 496). In these experiments NMDA was shown to elevate intracellular free Ca^{2+} in voltage-clamped cells. This effect involved the NMDA receptor since glutamate, but not kainate or quisqualate, produced Ca^{2+} transients of a comparable magnitude, and the effects of L-glutamate and NMDA were blocked by Mg^{2+} in a voltage-dependent manner. Since Ca^{2+} entry through voltage-gated channels would be greatly reduced or eliminated (depending on the effectiveness of the clamp of fine dendritic processes), a direct entry through NMDA channels was indicated. Furthermore, the Ca^{2+} signal was not seen when the neuron was depolarized to a level where NMDA induced an outward current (i.e., such that the net outward movement of monovalent ions would greatly hinder the inward flux of Ca^{2+}). This argued against a receptor-coupled change in $[Ca^{2+}]_i$ independent of permeation via the NMDA channel. Unfortunately, due to difficulties with the calibration of Arsenazo III the changes in Ca^{2+} could not be expressed in absolute terms.

With the introduction of the fluorescent indicator FURA-2 (309), NMDA-induced changes in Ca^{2+} have been measured quantitatively, albeit not yet under voltage-clamp conditions. In cultured hippocampal neurons, Kudo and Ogura (437) reported that L-glutamate elevated Ca^{2+} in a dose-dependent manner from a resting level of around 30 nM up to 500 nM (with 100 μM L-glutamate). The effect of L-glutamate was dependent on the presence of extracellular Ca^{2+}, was depressed by Mg^{2+}, but was unaffected by addition of either nitrendipine or replacement of Na^+ with tetramethylammonium. It was, therefore, argued that Ca^{2+} was entering through receptor operated channels. Essentially identical results were obtained in studies on cultured striatal neurons (549). L-Glutamate and NMDA have also been shown to elevate Ca^{2+} from a mean basal level of around 85 nM in acutely isolated CA1 hippocampal neurons (150).

b. REVERSAL POTENTIAL MEASUREMENTS. From reversal potential measurements, using whole-cell recording, it was estimated that Ca^{2+} has approximately a 10-fold greater permeability than Na^+. It was calculated that with physiological solutions at −60 mV, Ca^{2+} would carry ~10% of the total inward current (501).

Using outside-out patches it has been shown that the 50 pS NMDA channel is permeable to Ca^{2+} (35, 36, 380). Seemingly, at least some of the lower conductance channels are also permeable to Ca^{2+} (380). If the $[Ca^{2+}]_o$ is raised three effects are seen: (*a*) there is a decrease in inward current conductance, suggesting that gCa^{2+} is less than gNa^+; (*b*) there is a positive shift in the reversal potential, which could be interpreted as a greater permeability of Ca^{2+} than Na^+; and (*c*) a parallel shift to the right in the outward I-V relationship. This shift has been attributed to the presence of a −ve surface potential which is altered as the Ca^{2+} concentration is changed. Such a surface potential would tend to concentrate Ca^{2+} ions at the surface of the channel and thereby increase the relative concentration of Ca^{2+} over that on Na^+ ions. Without knowing the value of the surface potential the permeability ratio of Ca^{2+} to Na^{2+} cannot be calculated. The disparity between the conductance measurements (*a*) and the permeability estimate (*b*) could be explained if ions first need to bind before they can permeate and if Ca^{2+} binds more tightly (35). Thus, although Ca^{2+} certainly permeates NMDA channels, it probably carries considerably less current than does Na^+. This Ca^{2+} current, however, is likely to play an important role in physiology (see section VI) and pathological (see section VIII) processes.

C. Kainate and quisqualate conductances. Using conventional microelectrode recording techniques and physiological extracellular solutions, responses to kainate and quisqualate were found to reverse at ~0 mV (162, 480, 499) suggesting a mixed ionic mechanism, similar to that occurring in the end-plate nicotinic channel.

More detailed information about ionic selectivity can be obtained using whole cell recording with patch electrodes since this enables the intracellular ion concentrations to be controlled more precisely. Under these conditions kainate and quisqualate channels are both roughly equipermeant to Na^+ and Cs^+ (34, 727). Neither channel appears to have an appreciable permeability to Ca^{2+} (501). It is believed, therefore, that kainate and quisqualate channels are relatively non-selective between Na^+ and K^+ (and Cs^+). It is of interest to note that kainate produces greater outward rectification than does quisqualate (34).

Kainate and quisqualate have complex interactions, which may be explained by both agents acting through the same receptor-channel complex. In a variety of prep-

arations, quisqualate depresses currents induced by kainate (371, 418, 497, 569, 589, 726). The nature of the response of these two ligands is very different. Quisqualate (and L-glutamate) produce rapidly fading responses whereas kainate induces a sustained response (371, 418, 589, 714). One possibility, therefore, is that quisqualate and kainate activate the same receptor, but with quisqualate the response rapidly desensitizes. The quisqualate-induced block of the kainate response could then be explained by cross-desensitization. Alternatively quisqualate may simply compete with kainate for, while being less efficacious at, the receptor. Other evidence indicates independent actions of kainate and quisqualate (589).

The desensitization of responses to quisqualate, L-glutamate, and AMPA, but not the desensitization of responses to NMDA, is reduced by the lectin concanavalin A (497). In contrast to its action on L-glutamate-induced responses of invertebrate muscle preparations (495), concanavalin A does not completely prevent the desensitization of quisqualate-induced responses.

1. Quisqualate channels. Quisqualate predominately activates channels of a relatively low conductance (<20 pS) (34, 36, 165, 167, 380). Ascher and Nowak (34) observed mainly channels of 8 pS. Channels of a similar conductance have also been observed in cerebellar (165, 167) and hippocampal (380) neurons. Quisqualate is able to activate large (40 to 50 pS) channels also, but the occurrence of these channels is highly variable between patches. The openings tend to be brief (~2 ms) and may be due to actions of quisqualate (or L-glutamate, which may be a contaminant of the quisqualate sample) on NMDA receptor-channels (34). Another quisqualate channel described by Ascher and Nowak (34) has fast kinetics and an intermediate conductance (15 to 30 pS).

More recently, Tang et al. (699) described a high conductance (35 pS) rapidly inactivating (3 to 8 ms) channel in hippocampal neurones. This channel, which may be the same as the intermediate conductance channel described above, has several properties which suggest that it may generate fast quisqualate receptor-mediated excitatory postsynaptic currents (EPSCs): it reverses near 0 mV and shows little voltage-dependence; it inactivates with a time-constant of ~3 ms and recovers quickly (<100 ms) from this desensitized state; and it is blocked by KYN but not by APV. It was only observed in a minority of patches, but when present the patch contained a large number of these channels. This would be suitable for the production of large focal currents of the type that would underlie EPSCs. This high conductance channel was activated by quisqualate in a dose-dependent manner (1 to 300 μM) and was also activated by L-glutamate, but not by kainate or NMDA. In these experiments quisqualate (50 nM to 1 μM) also activated the low (8 pS) channel. An interesting possibility, if this channel is the one that underlies quisqualate receptor mediate EPSPs, is that the time-course of these EPSPs could be determined by desensitization (699). Modification of this desensitization would be a possible means of altering the efficiency of synaptic transmission.

2. Kainate channels. Kainate primarily activates low conductance channels (34, 36, 165, 167, 380). The predominant channel encountered by Asher and Nowak (34), determined by applying fluctuation analysis to outside-out patches, showed marked outward rectification and had a conductance of ~4 pS and life-times of approximately 0.5 and 3 ms. However, the appropriate channel could not be seen directly. Under optimal conditions a very brief channel of intermediate size (~20 pS) could be recorded as could an increase in baseline noise, presumably generated by a very low conductance channel. The "4 pS channel" might, therefore, represent the weighted sum of these two channels.

Similar findings were obtained from cerebellar cells where kainate was seen to open 8 and 15 pS channels, while noise analysis (from whole-cell experiments) suggested a channel conductance of ~3 pS. It was suggested that a very low conductance channel (140 fS), determined by fluctuation analysis of L-glutamate responses in these cells (166), might account for the low conductance kainate channel (165).

Kainate, to a small extent, also activates a high conductance channel(s) of 30 to 50 pS (165, 167, 380); however, this might be a "nonspecific" action at the NMDA channel.

D. Summary. Clearly, it is not possible to relate channels to receptors on a one-to-one basis. With available data it is not even possible to state categorically how many distinct excitatory amino acid channels there are. One interpretation is that there is a large conductance channel, which predominantly adopts a 50 pS conductance, but can exist in lower conductance states (e.g., 30 and 40 pS). This channel is primarily activated by NMDA, but can be opened by quisqualate and, to a lesser extent, by kainate. "Non-specific" effects such as these are not surprising since a pure selective agonist is unlikely to exist. This channel is therefore the NMDA channel. The ~8 and ~15 to 20 pS channels activated to varying degrees by quisqualate and kainate probably constitute a second channel class and may correspond to two separate entities or subconductance states of the same channel. Finally, there probably is a very low conductance state channel (~0.1 pS) that is activated by kainate.

As might be expected, L-glutamate and L-aspartate activate most of these channels/conductance states (34, 167, 168, 380, 567). Consequently, the actions of these "mixed agonists" may be more difficult to interpret. Furthermore, the extent that mixed agonists open NMDA versus non-NMDA type channels will depend on a number of factors, including the concentration of glycine (386).

IV. Second Messenger Systems

Traditionally, excitatory amino acids have been viewed as influencing neuronal excitation through the gating of receptor-operated ion channels. There is, however, a growing body of literature on the influence of excitatory amino acids on second messenger systems. In this respect, it is important to separate direct alterations in the levels of second messengers from secondary changes arising from receptor activation or the consequential depolarization. For example, the large increase in cGMP in cerebellum induced by glutamate or NMDA appears to occur as a consequence of the Ca^{2+}-dependent release of endothelium-derived relaxing factor (EDRF or NO) (293, 294). The present section considers only those systems where changes are a primary consequence of excitatory amino acid receptor activation. In this context, the ability of excitatory amino acids to elevate cytosolic calcium via permeation through the NMDA channel is discussed in section III B 4.

There is strong evidence that a glutamate receptor is coupled to the enzyme phospholipase C, which catalyses the hydrolysis of PIs to two classes of second messengers, inositol 1,4,5-triphosphate (IP_3), which mediates the release of Ca^{2+} from intracellular stores, and diacylglycerol, which activates PKC (57, 564).

Excitatory amino acids, in particular quisqualic acid, were first found to increase the production of IP_3 in cultured striatal neurons (663) and in rat hippocampal slices (558). This effect has since been seen in other preparations (e.g., cultures of cerebellar granule cells (560) and slices of neocortex (301). Evidence that this effect was directly linked to the activation of an excitatory amino acid receptor and not due to a secondary action such as membrane depolarization and Ca^{2+}-influx was provided by Sugiyama and colleagues (692). In voltage-clamped *Xenopus* oocytes injected with rat brain messenger RNA, quisqualate and glutamate induced an oscillatory Ca^{2+}-dependent Cl^- current, which was mimicked and occluded by the IP_3-stimulated release of intracellular Ca^{2+}, and blocked by the intracellular injection of EGTA. Incubation of oocytes with pertussis toxin inhibited the response to glutamate and quisqualate suggesting that the receptor coupling to the effector system was via a GTP-binding protein. The Ca^{2+}-dependent Cl^- channel activated by glutamate in mRNA-injected oocytes is native to the oocytes and therefore may not represent the conductance mechanism activated in central neurones (577). Using fura-2 measurements of intracellular Ca^{2+} in single hippocampal neurons, Murphy and Miller (548) showed that quisqualate and glutamate can elevate intracellular Ca^{2+} in a manner that is not dependent on the presence of extracellular Ca^{2+}. It seems probable that the IP_3 mobilizing receptor is responsible for this effect.

Although quisqualate is a potent agonist at this receptor, the overall pharmacology does not resemble that of the quisqualate receptor-gated ionophore, and therefore appears to be a new type of glutamate receptor, sometimes referred to as the metabotropic receptor (692). The most striking differences with the classical quisqualate receptor are: (*a*) AMPA is extremely weak or inactive at stimulating PI hydrolysis (580, 641) and does not mobilize intracellular Ca^{2+} (548); and (*b*) the antagonists, JSTX, GAMS, GDEE, and CNQX do not block these responses to quisqualate (548, 558, 580, 692). Neither NMDA nor kainate mobilize intracellular Ca^{2+} and are either inactive (558) or weak stimulators of PI turnover (608, 663). (This latter effect might be an indirect consequence of receptor-gated Ca^{2+} entry.) NAAG and quinolinate are also inactive (558), whereas CA, CSA, HCA, and L-aspartate may display some activity (558, 663). Ibotenate, however, is a powerful stimulator of PI turnover and works through an NMDA receptor-independent mechanism (558, 641). DL-APB depresses the stimulation of PI turnover induced by ibotenate (IC_{50} ~200 μM), quisqualate, L-glutamate, and L-aspartate in the hippocampus (558), but not in the cortex (301) or in mRNA-injected oocytes (692). This activity of APB in the hippocampus resides with the L-isomer and is associated with weak stimulation of basal activity, suggesting that it may be a partial agonist (641). The reason for the regional differences in susceptibility to antagonism to APB is not known. Phorbol 12,13-dibutyrate blocks both quisqualate- and ibotenate-stimulated PI hydrolysis in hippocampal slices, presumably by activation of PKC which then uncouples the receptor from phospholipase C (642).

The metabotropic glutamate receptor has been implicated in a number of physiological and pathological roles, including synaptic plasticity (see section VI) and neurodegeneration (see section VIII).

In addition to stimulating PI hydrolysis, excitatory amino acids can also depress PI turnover that has been elevated by high K^+ in the medium or by certain neurotransmitters (e.g., carbachol, histamine, 5-hydroxytryptamine) (47, 557). There seems to be some specificity in this effect since noradrenaline-stimulated PI hydrolysis is relatively resistant (47, 301, 566). The inhibitory effect is seen with kainate, NMDA, and, to a lesser extent, quisqualate. It does not depend on extracellular Ca^{2+} but is blocked in Na^+-free medium. These data indicate that the inhibitory effects on PI turnover may be due to a build-up of intracellular Na^+, resulting from strong excitatory stimulation rather than a direct consequence of the activation of a specific type of receptor (47, 301, 566).

V. Neurotransmission

Over the last few years, evidence has accumulated indicating that acidic amino acids function as excitatory neurotransmitters in many pathways in the vertebrate central nervous system. It seems likely that these simple amino acids are responsible for practically all fast excitatory neurotransmission in the brain. For this reason it

is not intended to present a complete description of all the pathways where acidic amino acids have been implicated as neurotransmitters. Instead, particular attention has been devoted to those regions (e.g., spinal cord and hippocampus) which have been most fully studied and from which some general principles may be drawn. Some other pathways are discussed in less detail. For the remaining excitatory pathways (that have not yet been studied pharmacologically or that have been omitted from this review) it is safest to assume, in the absence of any strong evidence to the contrary, that an acidic amino acid is the most likely neurotransmitter candidate and that similar receptor-operated mechanisms occur.

On the basis of the pharmacological, binding, and electrophysiological studies discussed above, it is clear that several types of excitatory amino acid receptors exist. However, the exact number of receptors/ion channels has yet to be finalized. In general, all of the above studies distinguish NMDA receptors from the rest. There is also a receptor which seems to recognize quisqualate, kainate, and AMPA and is commonly referred to as either the quisqualate receptor, the quisqualate/kainate receptor, or the non-NMDA (excitatory amino acid) receptor. Since antagonists are available for these two types of receptor, considerably more is known about their roles in synaptic mechanisms; these two receptors, therefore, are considered in most detail in the following section.

In addition, there are at least the following excitatory amino acid receptors/sites: the kainate receptor proper, the L-APB "receptor," and a metabotropic quisqualate receptor (table 2). The possible functions of these receptors will be discussed where appropriate.

A. Spinal Cord

1. Effects of NMDA antagonists. An early suggestion of a likely role of excitatory amino acid receptors in synaptic transmission was the finding by Evans et al. that addition of 0.5 to 1.0 mM Mg^{2+} to a nominally Mg^{2+}-free perfusate markedly depressed the dorsal root-evoked ventral root potential (DR-VRP) in frog spinal cord, as well as responses to NMDA (234). It was argued that, since the [Mg^{2+}] added was quite low and increasing the [Ca^{2+}] did not fully reverse the synaptic depression, the effect was due in part to blockade of Mg^{2+}-sensitive (i.e., NMDA) receptors. Since Mg^{2+} also depresses responses to non-amino acid excitants, albeit to a lesser degree than responses to NMDA (39, 195), this observation alone does not offer conclusive evidence for a transmitter role for NMDA receptors. However, a similar pattern of amino acid and synaptic antagonism, often with little or no change in responses to non-amino acid excitants, was soon observed with a variety of organic NMDA antagonists (DAP, HA-966 and, in particular, DAA) (66, 236, 237). As more potent and selective NMDA antagonists (e.g., DAS, APV) have appeared, this finding has been repeatedly substantiated (190, 232).

Organic antagonists were also found to depress certain dorsal root-evoked synaptic excitations of spinal interneurons in vivo. Most notably, DAA and DAS depressed dorsal root-evoked excitations of Renshaw cells without affecting the ventral root-evoked cholinergic innervation of these neurons (67, 68, 196, 462). Thus, a selective synaptic excitation involving NMDA receptors had, for the first time, been reported.

In in vitro experiments, when the synaptic responses (recorded in Mg^{2+}-free solutions) were investigated more closely, it became apparent that NMDA antagonists depressed the latter part of the response and often left the early part unaffected (578, 738). Padjen and Smith (578) showed, using sucrose-gap recording in frog spinal cord, that DL-AA depressed the late part of the DR-VRP, DR-DRP, and LC-VRP (evoked by stimulation of lateral columns). They also showed that this antagonist depressed the late component of the EPSP which had been recorded intracellularly from motorneurons in response to DR and LC stimulation. This effect was interpreted as being due to blockade of NMDA receptors in polysynaptic pathways. In contrast, the early component of the DR-VRP, LC-VRP and DR-DRP were relatively or completely unaffected. The entire VR-DRP was also unaffected (but see 353). Since the VR-DRP is considered to be mediated by cholinergic and neutral amino acids, this observation was interpreted as representing a selective synaptic antagonism. A similar selective depression of the late component of the DR-VRP and DR-DRP, with no effect on the VR-DRP, was also achieved using 250 μM Mg^{2+} or Co^{2+} (673).

2. Effects of non-NMDA antagonists. Antagonists that are active at non-NMDA type excitatory amino acid receptors, such as PDA and DGG, can depress the early (NMDA antagonist-resistant) component of the DR-VRP, recorded in Mg^{2+}-free medium (733, 738). These compounds are also effective synaptic antagonists of certain pathways that are resistant to NMDA antagonists in vivo. Thus, PDA, and to a lesser extent DGG, depressed the short latency, presumed monosynaptic, response of spinal interneurons to stimulation of low threshold afferents in amounts that also depress responses to kainate and quisqualate (199). In the same study, the longer latency (presumed polysynaptic) burst of spikes was blocked by APV. These findings were supported as new NMDA and non-NMDA antagonists were tested on these responses (191, 200, 225, 259, 281, 456).

Evidence obtained using paired intracellular recording in lamprey spinal cord is consistent with this idea (92). Thus, PDA or kynurenate, but not APV, depressed the monosynaptic EPSP in giant interneurons in response to intracellular stimulation of dorsal cells; the latter cells are equivalent to dorsal root ganglion cells that relay mechanosensory information in higher vertebrates. A small component resistant to these antagonists was con-

sidered to be electrical in nature. APV depressed some longer latency EPSPs that were considered to be polysynaptic in nature.

These studies all suggest that kainate and/or quisqualate receptors mediate monosynaptic responses and NMDA receptors mediate polysynaptic responses in the spinal cord in response to stimulation of afferent nerves. However, not all studies concur with this view. Curtis and his colleagues (584), while confirming that selective NMDA antagonists, such as APV, can block polysynaptic excitations, found no effect of the non-NMDA antagonists, DGG and PDA, on monosynaptic responses of spinal interneurons of the cat in vivo. Nistri and his colleagues (25, 152), working on frog spinal cord (bathed in Mg^{2+}-free medium), reported that the NMDA antagonists DAA and D-APV preferentially blocked the monosynaptic, rather than the polysynaptic, EPSP recorded in motorneurons in response to stimulation of lumbar dorsal roots.

3. Dual-component EPSPs. A major advance in the understanding of the role of excitatory amino acid receptors in synaptic transmission came from the work of Dale and Roberts (183). Working with *Xenopus* embryos (in Mg^{2+}-free perfusate), these authors showed that unitary EPSPs evoked in motorneurons by focal stimulation of longitudinal axons or intracellular stimulation of an interneuron could be classified into one of three categories depending on their shape: (*a*) a fast EPSP (rise time 3 ms, half-width 9 ms) which was seen in isolation very rarely; (*b*) a slow EPSP (mean rise time 22 ms, half-width 72 ms) which occurred in isolation quite frequently; and (*c*) a mixed EPSP which was the algebraic sum of one or more fast and slow EPSPs. Both the fast and slow EPSPs had similar latencies and were considered monosynaptic. Pharmacological experiments with PDA and APV indicated that the fast EPSP is mediated by kainate or quisqualate receptors and that the slow EPSP is mediated by NMDA receptors. Interestingly, for a given synaptic pair of neurons, either component could fail thereby leaving a pure fast EPSP or a pure slow EPSP in isolation. The authors interpreted their work as evidence for a dual-component excitatory synapse whereby transmitter released from one neuron is able to activate both NMDA and non-NMDA receptors on another neuron. Furthermore, it was suggested that NMDA and non-NMDA receptors may be separately distributed at different synaptic contacts between cells. Essentially identical physiological and pharmacological results were obtained by Dale and Grillner using the lamprey (181). The synapse between reticulospinal neurons and motorneurons in the lamprey also appears to be similar, except for an additional electrical component (98). This concept has now been adopted for excitatory amino acid synapses at many sites in the central nervous system.

The observation that NMDA receptors can mediate a short-latency, long duration (~200 ms) monosynaptic response in motorneurons has immediate implications for the earlier interpretation that NMDA receptors mediate polysynaptic responses in the cord. In the earlier experiments part, or in some cases all, of the NMDA receptor-mediated component could have been monosynaptic in nature.

4. Mg^{2+} concentration. There is another important factor that needs to be considered when evaluating the role played by NMDA receptors in spinal transmission. All the early in vitro experiments, such as those described above, were performed using Mg^{2+}-free perfusates. Since Mg^{2+} was known to be an NMDA antagonist and since the in vitro experiments appeared to correlate with parallel studies in vivo, it was believed that the Mg^{2+} levels that exist in close proximity to NMDA receptor-utilizing synapses, must be in the low micromolar range (733). The observation that only low iontophoretic currents, applied to Mg^{2+}-containing barrels, are needed to depress responses to NMDA in vivo was offered as support of this idea. It should be noted, however, that the barrels contained 200 mM $MgCl_2$ (195).

Elsewhere in the brain, studies have usually been performed using perfusates that contain at least 1 mM Mg^{2+}. In the hippocampus, if the perfusate was changed to one containing no added Mg^{2+} then the EPSP (341) and corresponding extracellular field (119) were markedly enhanced, especially in duration. The responses are remarkably similar in profile and pharmacology to the "monosynaptic-polysynaptic" reflexes and spontaneous discharges recorded in the spinal cord. Of possible relevance is the finding that at high stimulus strengths the early component (equatable with the "monosynaptic component") is unaffected or enhanced by NMDA antagonists while at low intensities the early component is reduced. Assuming that the pharmacology of the monosynaptic component in the spinal cord is similar, this could explain the discrepancy between the work of Evans and colleagues (e.g., 233) who used supramaximal volleys and Nistri and co-workers (152) who used weak volleys. The underlying synaptic event in the hippocampus was shown to be a dual-component EPSP (134) with marked similarity to that described by Dale and Roberts in the spinal cord (183). Unquestionably, the response recorded in the hippocampus in Mg^{2+}-free perfusate is non-physiological and represents an extreme epileptiform state (see section V B 4 a). Therefore, it seems most likely that spinal cords in Mg^{2+}-free medium are in a highly non-physiological (epileptiform) state (see also 181). Recent studies, described below, have begun to investigate spinal transmission in vitro with Mg^{2+} present in the perfusate.

5. In vitro studies in Mg^{2+}-containing medium. Jahr and Yoshioka (381) reported that the early component (presumed monosynaptic 1A EPSP) recorded in newborn rat motorneurons in response to stimulation of dorsal

roots was depressed by KYN, PDA, and DGG, but not APV. Later components of the EPSP (presumed polysynaptic) that were present in 1.15 mM Mg^{2+}, but blocked by higher divalent cation concentrations, were suppressed by APV. KYN appeared to be acting through a postsynaptic mechanism which apparently was specific for amino acid-mediated synaptic excitation since it did not affect recurrent IPSPs that were blocked by nicotinic or glycine antagonists.

Evans and colleagues have noted, in both immature (230) and mature (465) preparations of rat spinal cords bathed in 1 mM Mg^{2+}, that APV can depress a small slow synaptic component. This effect may be equated with the "polysynaptic components" described by Jahr and Yoshioka (381) and a greatly reduced version of the "polysynaptic response" observed in Mg^{2+}-free perfusates (233). Of particular interest is the additional finding in the immature preparation (230) that NMDA receptors may mediate a DR-VRP with a time to peak of 6 s and a duration of 20 s.

6. Studies on defined sensory input. In the dorsal horn, Davies and Dray (185) reported that DAA depressed the response of neurons to non-noxious, but not to noxious, mechanical stimulation, suggesting a role of NMDA receptors in the mediation of non-noxious inputs. However in a more recent study, Headley and colleagues (331), using ketamine in doses selective for NMDA antagonism, found no antagonism of responses of dorsal horn neurons to either noxious or non-noxious inputs. They found, however, that PDA somewhat depressed these responses. These data indicate a possible involvement of non-NMDA receptors in the mediation of certain sensory afferent information, while the role of NMDA receptors is contentious.

In the dorsal horn, NMDA receptors have clearly been shown to be involved in the phenomenon of "wind-up" (516). This term refers to the progressive increase in the response of certain (class 2) neurons to successive electrical stimuli applied to the receptive field at rates above 0.3 Hz and at intensities sufficient to recruit C-fibres. Wind-up is reduced by ketamine, applied iontophoretically or intravenously in doses selective for NMDA antagonism (205), or by topical application of APV to the spinal cord (209).

A role for both NMDA and non-NMDA receptors has been implicated in synaptic transmission between unmyelinated cutaneous afferent neurons (Rohon-Beard cells) and dorsolateral interneurons in *Xenopus* embryos (657). In these studies, an early component of the EPSP was depressed by KYN and a late component by APV or Mg^{2+}, in a manner reminiscent of that found in *Xenopus* (183) or lamprey (181) motorneurons. Interestingly, Rohon-Beard cells are a type of mechanosensory afferent that responds to transient indentation of the skin. These cells stain positively for substance P-like immunoreactivity and therefore bear some similarity to certain mammalian C fibres. This observation raises the possibility that C fibres, in general, may utilize excitatory amino acids as the mediators of conventional synaptic responses. Certain neurochemical evidence lends credence to this idea (759).

In the ventral horn, Headley and colleagues (331) found that systemic ketamine consistently reduced nociceptive and, to a lesser degree, non-nociceptive responses of motorneurons. The response of some ventral horn interneurons to noxious stimuli was also depressed. These authors concluded that NMDA receptors play a role in the mediation of nociceptive and non-nociceptive sensory inputs into the ventral, but not dorsal spinal cord. However, the location of the synapses could not be determined.

NMDA receptors have also been implicated in the tonic drive of γ-motorneurons, since this activity was depressed by APH (597) or CPP (598).

7. Primary afferent depolarization. It is well documented that excitatory amino acids both depolarize and increase the excitability of the central terminals of primary afferent fibres (44, 173, 178, 738). Outside of the spinal cord primary afferents and dorsal root ganglia are insensitive to excitatory amino acids (207, 563). Kainate, quisqualate, and NMDA can induce DRPs (228), indicating an involvement of various receptors subtypes in these responses. It is likely that these effects are generated largely indirectly and not through actions on excitatory amino acids receptors on primary afferent terminals. Excitatory amino acids elevate $[K^+]_o$ in the spinal cord (99, 436, 676, 729). In this respect, their order of potency, in Mg^{2+}-free medium, is quisqualate > kainate > NMDA > L-glutamine > L-aspartate (184). A similar rank order is seen for the generation of VRPs, an indication of the potency of these amino acids as excitants in the cord (184).

An association between the levels of K^+ and primary afferent depolarization is suggested by the work of Evans (229) who showed that the depolarization of dorsal roots by excitants correlated in time with elevations in extracellular K^+. Furthermore, prolonged applications of kainate, that irreversibly impaired motorneuronal function, did not irreversibly affect dorsal root activity. This was taken as evidence that these fibres did not possess excitatory amino acid receptors. It was suggested that excitatory amino acids may depolarize neurons within the spinal cord and that the resultant release of K^+ then depolarizes primary afferents. A similar conclusion was reached on the basis of studies in the cat spinal cord in vivo (171).

An alternative hypothesis, developed to explain the greater effect of glutamate on afferents that made monosynaptic rather than polysynaptic connections with motorneurons is that depolarization of afferents is mediated through motorneurons to which they are electrotonically coupled (650). This observation, however, may just re-

flect the location of particular classes of afferents in relation to K^+ sources within the cord (171, 184).

The elevation of K^+ in the spinal cord in response to repetitive stimulation of afferents has been investigated extensively (see 184 for references). The role of excitatory amino acid receptors in the mediation of this event has been examined in the frog spinal cord preparation by Davidoff and his colleagues (184). In response to a 25 Hz stimulation of the sciatic nerve, approximately 15% and 30% of the K^+ elevation was considered to originate from the stimulated afferents in Mg^{2+}-free and 1 mM Mg^{2+}-containing medium, respectively. In Mg^{2+}-free solution, KYN depressed the K^+-elevation by 85%, an amount corresponding to the entire postsynaptic component. D-APV (10 μM) was also effective, albeit less so. These data indicate a potential role of both non-NMDA and NMDA receptors in the mediation of K^+-elevations. In the presence of 1 mM Mg^{2+}, APV had, as would be expected, a much smaller effect. It is noteworthy, however, that it did have some effect (see fig. 2 in ref. 184) since high frequency stimulation of afferents was employed (see section V B 3). Of interest, also, was the finding that physalaemin, eledoisin, and substance P all induced VRPs and increases in K^+ and that these effects were reduced by APV and practically abolished by KYN.

The above findings strongly suggest that excitatory amino acid receptors are involved in the mediation of most, if not all, stimulus-induced K^+-elevations, other than that originating from the afferent fibres themselves.

8. Presynaptic receptors. a. KAINATE RECEPTORS ON C-FIBRES. Evans and colleagues (7, 188) have presented clear evidence that certain primary afferents possess kainate receptors. They showed that isolated dorsal roots of both immature and mature rats are depolarized by kainate. Domoate and bromowillardiine are also very potent, whereas quisqualate, AMPA, ODAP, and willardiine are only weakly active and NMDA is inactive. This preparation, therefore, provides a useful means of distinguishing between kainate and quisqualate receptors (kainate is 30 times more potent than quisqualate). Of the endogenous excitant amino acids, L-glutamate is potent, L-HCA is very weakly active, and L-aspartate, D-aspartate, D-glutamate, and D-HCA are all inactive. The response to L-glutamate fades rapidly and, during a prolonged exposure to L-glutamate, responses to kainate (but not GABA) are greatly depressed. In contrast, responses to kainate neither fade nor depress responses to L-glutamate more than would be expected on the basis of its depolarizing action.

Kainate-induced responses are depressed by kynurenate (231). It is of interest that kynurenate is a more potent antagonist of kainate-induced depolarizations of fibres K_D 70 μM) than of motorneurons (K_D 164 μM) since this indicates the possibility of differences in the kainate "receptor" at the two locations.

Kainate selectively blocks the C-fibre volley whereas GABA and capsaicin, which are other presynaptically-acting agents, are far less selective in their actions (7). It seems, therefore, that kainate receptors are present only on C-fibres. Kynurenate blocks the kainate-induced depression of C-fibre volleys without directly affecting the volleys. It has been suggested that kainate receptors on C-fibres may be acted upon physiologically by L-glutamate released from primary afferents and that C-fibre kainate receptors may provide a useful target site for the development of new analgesic drugs.

b. L-APB RECEPTOR. As occurs in other regions of the CNS (144, 360, 426), L-APB is a synaptic depressant in the spinal cord. Since it does not depress responses to either excitatory amino acids, ACh or substance P (590) and since L-APB pathways are sensitive to antagonism by broad spectrum antagonists, such as DGG and PDA, it has been proposed that L-APB blocks synaptic transmission in excitatory amino acid receptor utilising-pathways by a presynaptic mechanism (233, 590). Not all presumed excitatory amino acid pathways, however, appear equally susceptible to the actions of L-APB. Thus, although L-APB depressed both presumed mono- and polysynaptic responses of cat spinal neurons in vivo (590), it preferentially blocked the monosynaptic component of the DR-VRP in vitro (233). This effect was stereoselective and dose-dependent over the range 5 to 250 μM; at higher concentrations L-APB was itself excitatory in an APV-sensitive manner. It is presumably therefore also a weak NMDA agonist.

9. Autonomic nervous system. There has been little investigation into the role of excitatory amino acid receptors in the autonomic nervous system. However, Mo and Dun (522) have studied EPSPs evoked in sympathetic preganglionic neurons by stimulation of dorsal rootlets in neonatal rat thoracolumbar spinal cord slices. Interestingly, the EPSP generated appears to be mediated entirely by NMDA receptors, since it was reported to be abolished by D-APV or ketamine, in 1.3 mM Mg^{2+}-containing or Mg^{2+}-free medium.

10. Fictive locomotion. There have been a number of studies concerning the role of excitatory amino acids in motor behaviour in lower vertebrates in view of their simpler spinal cords. L-Glutamate, D-glutamate, and HCA were found to elicit rhythmic activity in ventral roots which alternated from side to side (125, 599). Since this activity would lead to swimming in intact preparations, it has been termed "fictive locomotion."

Grillner and Wallén and their colleagues (307) showed that activation of NMDA receptors elicits fictive locomotion in the lamprey, in either 1.8 mM Mg^{2+}-containing or Mg^{2+}-free medium. Further studies by Grillner and co-workers on lampreys (96) and by Dale and Roberts using *Xenopus* embryos (182) demonstrated that activation of kainate, but not quisqualate, receptors also could elicit fictive locomotor activity. In lamprey, kainate could support a faster burst frequency range (0.5 to 8 Hz) than

NMDA (0.05 to 4 Hz). With NMDA, the lower burst rates were more regular and stable in the presence of Mg^{2+} (95). A subsequent study in the lamprey found that AMPA has similar effects to kainate and that both effects are antagonised to the same extent by quinoxalinediones (Alford and Grillner, personal communication). It is likely, therefore, that the receptor involved in this type of fictive locomotion is of the quisqualate type (see section II B 6).

A role for excitatory amino acid receptors in swimming comes from studies employing receptor antagonists. In the *Xenopus* embryo (182), PDA and DGG blocked the excitation of motorneurons and the associated ventral root output associated with swimming; APV was also effective but to a lesser degree. Together with the finding that kainate, but not quisqualate, induced fictive locomotion, these data support a role for NMDA and kainate receptors in the motor pattern generation involved in swimming. Similar findings and conclusions were also reported in the lamprey where fictive locomotion was initiated by sensory stimulation to the tailfin (94) or by localised application of NMDA to other regions of the spinal cord (180). Further evidence for a role of excitatory amino acids in locomotion was the finding that the putative amino acid uptake inhibitors, dihydrokainate and p-chloromercuriphenylsulfonate, facilitated the ability of L-glutamate and L-aspartate to elicit fictive locomotion and that dihydrokainate prolonged fictive locomotion induced by sensory stimulation of the tailfin (93).

Grillner and associates have studied the role of NMDA receptors in the generation of locomotor activity in considerable detail. They found that NMDA induced membrane potential oscillations of 10 to 25 mV, and that these oscillations were phase-linked with the locomotor rhythm. In some cells the oscillations were preserved after addition of TTX, indicating that they were intrinsic to the neuron under investigation (656). The frequency and timing of the oscillations were affected by alterations in membrane potential in a manner that suggested that they may be influenced by synaptic inputs (730). Indeed, synaptic modulation of appropriate voltage-dependent conductances has been demonstrated (11).

Other studies showed that the oscillations were dependent on the presence of Mg^{2+} (308, 731). The depolarizing phase appeared to be carried by Na^+, since neurons remained at a hyperpolarized state if Tris was substituted for Na^+. The hyperpolarizing phase seemed to involve a $gK^+(Ca^{2+})$, since cells remained in the depolarized state in Ca^{2+}-free medium and when Ca^{2+} was replaced with Ba^{2+} (which substitutes for Ca^{2+} but blocks certain K^+ conductances).

It was suggested that Na^+ entering via NMDA channels depolarizes the neuron and that the depolarization accelerates as the Mg^{2+}-block is lifted; Ca^{2+} also enters through these channels and activates repolarizing K^+ fluxes. The resulting hyperpolarization will, by increasing the Mg^{2+}-block, reduce inward current and accelerate the hyperpolarizing phase. The consequential reduction in Ca^{2+} influx will in turn reduce gK^+ (Ca^{2+}), and the cell will again start to depolarize. Under voltage-clamp conditions, oscillatory responses are abolished, and the expected region of negative-slope conductance in the I-V relationship is observed, confirming that the oscillations are due to voltage-dependent conductances (537). The oscillatory behaviour observed in the presence of NMDA can therefore be explained on the basis of known properties of NMDA channels and other voltage-dependent conductances found in neurons. It should be added that voltage-gated Ca^{2+} channels could also contribute to the potential changes.

11. Studies in cultured neurons. Jahr and Jessel (379) studied the pharmacology of synapses that form in culture between dorsal root ganglia and dorsal horn neurons of the rat, in the presence of 3 mM Mg^{2+}. Electrical stimulation of DRG explants evoked a presumed monosynaptic EPSP that was depressed by KYN and, to a lesser extent, by PDA and DGG. APV had only a small effect when applied, as the racemate, at 1 mM. These data imply that the primary afferent transmitter acts on kainate/quisqualate receptors. Similarly, Nelson et al. (552) reported that presumed monosynaptic EPSPs made between pairs of cultured mouse spinal neurons were depressed by PDA. APV had very little effect in either 5 mM Mg^{2+} or Mg^{2+}-free medium and the peak of the EPSC was linearly related to the membrane potential. These authors concluded that NMDA receptors did not contribute to the synaptic response but suggested that NMDA receptors may be extrasynaptic in origin and "booster" other inputs.

In contrast, O'Brien and Fischbach (568) detected an APV sensitive, voltage-dependent component in spontaneous EPSCs recorded, in the presence of 0.8 mM Mg^{2+}, in cultured chick motorneurons. They favoured a dual-component nature of the synapse. In a reappraisal, Forsythe and Westbrook (266) were also able to detect both APV-sensitive and APV-resistant components in EPSPs in cultured spinal neuronal pairs, recorded in Mg^{2+}-free perfusates in the presence of a $GABA_A$ antagonist. The APV-sensitive component had a short latency, but slow rise and decay times, similar to that recorded in *Xenopus* and lamprey spinal cords (183). The component was voltage-dependent in the presence of Mg^{2+} and its reversal potential depended on $[Ca^{2+}]_o$, further indicative of the involvement of NMDA receptors.

B. Hippocampus

There is compelling evidence suggesting that L-glutamate, L-aspartate, or related amino acids are neurotransmitters in the major excitatory pathways in the hippocampus. For example, in the Schaffer collateral-commissural pathway, the reversal potentials for the EPSP and L-glutamate-induced responses in CA1 pyramidal cells are both around 0 mV. This is consistent with glutamate

being the transmitter in this pathway (316). A similar finding has been reported in granule cells for the medial perforant path EPSP (162). In this study, L-glutamate, quisqualate and kainate had reversal potentials similar to the EPSP, whereas NMDA had a slightly more positive reversal potential. The strongest evidence, however, for a role of excitatory amino acids in synaptic transmission comes from neuropharmacological studies.

1. Neuropharmacological investigations. Early studies using first generation excitatory amino acid antagonists, such as GDEE and APB, supported neurochemical and anatomical work which indicated that excitatory amino acids may be neurotransmitters in the hippocampus (222, 349, 647, 746). The selectivity of these antagonists, however, is not in itself sufficient to conclude that acidic amino acids are involved and provides no useful information concerning the role of receptor subtypes. As a direct consequence of the development of more selective antagonists, in particular DGG and APV and then CNQX, the last few years have seen dramatic increases in the understanding of the role of specific receptor subtypes, in particular the NMDA receptor, in hippocampal neurotransmission. This topic can now be discussed in depth.

The involvement of NMDA receptors in synaptic transmission is highly dependent upon the experimental conditions used. Important factors include: (*a*) the extracellular Mg^{2+} concentration; (*b*) the membrane potential; (*c*) the state of synaptic inhibition; and (*d*) the frequency of activation of the excitatory pathway. For the purposes of simplifying the following sections, recordings obtained in vitro in the presence of Mg^{2+} (typically 1 to 4 mM) and in the absence of any convulsant drug will be termed "normal" (except for those intracellular recordings where the membrane potential had been greatly perturbed or clamped). Unless stated to the contrary, experiments have been performed in hippocampal slices, usually obtained from adult rats or guinea pigs. Low frequency stimulation applies to rates of below 1 Hz; typically hippocampal pathways are stimulated at intervals of between 10 s and 30 s (i.e. at 0.1 to 0.033 Hz).

2. Low frequency transmission under 'normal' conditions. The selective NMDA antagonist APV has essentially no effect on EPSPs, recorded either intracellularly or extracellularly (i.e., field EPSPs), evoked by stimulation of any hippocampal pathway so far investigated; these pathways include the Schaffer collateral-commissural input to CA1 (137, 427), medial (160, 161) and lateral (141) perforant path inputs to dentate gyrus, perforant path input to CA3 (138), commissural input to CA3 (138), and mossy fibre input to CA3 (138, 760). Other selective NMDA antagonists, such as APH and DAA, were similarly without effect on these pathways (137). However, in high concentrations DL-APV or DL-AA can depress transmission in these pathways (137, 138, 250, 316). This presumably reflects a non-specific effect of these drugs since equivalent concentrations of the D-isomers (i.e., the enantiomers which are NMDA antagonists) have no effect (137, 138).

In agreement with studies using hippocampal slices, APV also has little or no effect on perforant path-induced responses in the dentate gyrus of anaesthetized rats (227, 539) or on synaptic responses recorded using dissociated embryonic hippocampal cells maintained in culture (623).

In contrast to the lack of effects of APV, broad spectrum excitatory amino acid antagonists, such as DGG and KYN, depress EPSPs evoked by stimulation of most of the hippocampal pathway so far investigated, including the Schaffer collateral-commissural input to CA1 (137, 281, 618), medial (160, 161, 281, 322, 618) and lateral (141, 281, 321, 618) perforant path inputs to dentate gyrus, and commissural inputs to CA3 (281, 618). Monosynaptic EPSPs recorded in cultures of dissociated hippocampal neurons also are depressed by broad spectrum antagonists (623). However, the situation with the mossy fibre input to the CA3 region of hippocampal slices is controversial. While most studies report that this pathway is sensitive to broad spectrum antagonists (153, 281, 636), Robinson et al. (618) present evidence that KYN does not antagonise the mossy-fibre-evoked response, and they argue that findings to the contrary may be explained by the inadvertent activation of other (KYN-sensitive) pathways. It is notable, however, that spontaneous miniature EPSPs recorded in CA3 pyramidal neurons are depressed in size by KYN (153), since this antagonism is likely to be postsynaptic and it is believed that the spontaneous release of transmitter comes from mossy-fibres.

Generally, none of the synaptic antagonists appear to produce appreciable effects on presynaptic fibre volleys (137, 160). Intracellular studies indicate that synaptic antagonism is not accompanied by changes in passive membrane properties or excitability (160, 161, 281; but see 203). A quantal analysis, performed on the effects of DGG (160, 161) and kynurenate (97) in the medial perforant path, suggests that the synaptic antagonism is postsynaptic in nature; but such data need to be interpreted with caution since multiple fibres are stimulated, the anatomical correlate of the "quantal event" is uncertain, and the "quantal size" is small compare to the background noise. A postsynaptic locus of action of kynurenate is also indicated from studies of paired-pulse plasticity in the lateral (321) and medial (322) perforant pathways. In area CA3, kynurenate and pBB-PzDA depressed the amplitude of spontaneous miniature EPSPs suggesting that these antagonists were acting by a postsynaptic mechanism (153).

Synaptic antagonism approximately parallels the antagonism of kainate and quisqualate receptors, a finding consistent with one of these receptors mediating the EPSP (137, 160, 281). Antagonists, however, do not

distinguish sufficiently between responses to quisqualate and kainate to permit any firm conclusions as to which, if either, receptor mediates the EPSP. Since these antagonists are selective for the excitatory amino acids, as compared to all other neurotransmitter agents tested, the EPSPs in these hippocampal pathways are commonly referred to as being mediated by acidic amino acid receptors of the non-NMDA type. On the basis, however, of pharmacological (see below and section II B 6) and autoradiographical (see section II C 5) studies, the receptor that mediates the EPSP is probably of the quisqualate type.

The concept that non-NMDA receptors, but not NMDA receptors, predominantly or exclusively mediate EPSPs during low frequency transmission under "normal conditions" was re-inforced with the development of selective non-NMDA antagonists, the quinoxalinediones. Thus, CNQX and DNQX powerfully antagonise excitatory synaptic responses in CA1 evoked by stimulation of the Schaffer collateral-commissural pathway in vitro (19, 72, 128, 202, 265, 555) and in vivo (336), without affecting passive membrane properties (19, 128, 555). The quinoxalinediones also antagonise EPSPs in area CA3 evoked by activation of mossy fibres (555) and EPSPs in the denate gyrus elicited by stimulation of the perforant path (441). Most pertinent is the finding that CNQX, in doses that depress responses to kainate and quisqualate (and AMPA) but not NMDA, can totally abolish the EPSP evoked by low intensity stimulation of the Schaffer collateral-commissural pathway (72, 128, 202). This further emphasises that NMDA receptors need not be involved in the mediation of the EPSP. Just as with broad spectrum antagonists, however, CNQX fails to distinguish adequately (if at all) in the hippocampus between the excitations induced by quisqualate and kainate (74).

CNQX suppresses IPSPs that are evoked polysynaptically in the area CA1 (19, 128, 202). This suggests that non-NMDA receptors mediate the excitation of inhibitory (GABAergic) interneurons in this region of the brain. However, if a stimulating electrode is placed close to the recording site the EPSP can be selectively blocked by CNQX (128). The conserved biphasic, γ-aminobutyric-acid-(GABA)-mediated IPSP is presumably the result of direct activation of inhibitory interneurons and hence constitutes a monosynaptic response (128).

3. High frequency transmission under 'normal' conditions. The first indication of a synaptic role of NMDA receptors in the hippocampus was the finding that APV blocked the induction of LTP in the CA1 region (see section VI A 1 d). Since LTP is characteristically induced by high frequency stimulation, it could be inferred that NMDA receptors participate somehow in high frequency transmission. Recently, an APV-sensitive component of the "normal" synaptic response recorded intracellularly in CA1 neurons (135, 342), or its extracellular correlate (365), has been recorded during high frequency transmission in the Schaffer collateral-commissural pathway. The characteristics of this synaptic response are described in section VI A 1 e in relationship to the induction properties of LTP.

The extent of which NMDA receptors are involved in frequency-dependent transmission in other regions of the hippocampus and elsewhere in the brain is not known. It may be inferred, however, from the activation characteristics of the NMDA receptor system that frequency-dependent NMDA receptor-mediated transmission may be of widespread importance.

High frequency stimulation can, under certain circumstances, lead to the generation of sustained epileptiform or otherwise transformed activity that is mediated, in part, by activation of NMDA receptors (17, 523, 664). The role of NMDA receptors in the induction and maintenance of this plastic change is considered with respect to kindling in section VI A 2.

In vivo, hippocampal pyramidal cells may fire spontaneously with high frequency bursts of action potentials, known as complex spikes. It has been found that urethane-anesthetized rats intraventricular injection of DL-APV reduces the number of spikes per burst (3).

4. NMDA receptor mediated responses during low frequency transmission. In addition to participating in synaptic transmission during high frequency transmission under "normal" conditions, NMDA receptors have been found to contribute during low frequency transmission following a variety of experimental manipulations. These are documented below:

a. THE LOW MG^{2+} MODEL. *Area CA1.* Prior to 1984 all experiments with hippocampal slices had been performed with Mg^{2+} in the bathing medium (typically at a concentration of 1 to 4 mM) to mimic the extracellular enviroment. Since Mg^{2+} is a potent NMDA antagonist (39, 234), Coan and Collingridge examined the effects of a perfusate which was nominally Mg^{2+}-free (i.e., no added Mg^{2+}; Mg^{2+} concentration $< 10\ \mu M$) on a synaptic transmission in the Schaffer collateral-commissural pathway at both room (116) and elevated (117) temperatures. This treatment had striking effects: following the introduction of a Mg^{2+}-free medium, the primary population spike increased many fold in amplitude, an effect insensitive to APV. With continued perfusion of Mg^{2+}-free medium (and hence a further lowering $[Mg^{2+}]o$) secondary population spikes appeared, an effect which was completely and reversibly blocked by APV. Corresponding changes were observed in the field EPSP (117) and the intracellular correlate comprised an EPSP greatly increased in duration such that it could elicit several action potentials (341). There also was an appearance of spontaneous population discharges which were reduced or eliminated by APV or removal of the CA3 region of the slice (119, 341, 524). This spontaneous and evoked activity recorded in Mg^{2+}-free medium can be described as epileptiform or

interictal-like in nature. Ictal-like bursts, which can have durations of seconds and associated afterdischarges, are usually not observed, but have been recorded (390). An effect which has been observed in Mg^{2+}-free medium is the sudden episodic loss of synaptic activity and a corresponding massive depolarization of neurons (119, 524). This effect, which may be sensitive to APV (524), has been equated with spreading depression.

The sensitivity of the epileptiform activity to APV suggests an involvement of NMDA receptors. This is supported by the observations (119) and (*a*) APV is effective in a dose-dependent and stereo-selective manner over the range (1 to 50 μM) where it effectively and selectively blocks responses to NMDA (233); (*b*) Mg^{2+} is effective over the concentration range (10 to 100 μM) where it blocks responses to NMDA (39); and (*c*) Ca^{2+} mimicks, rather than blocks, the effects of Mg^{2+} over the concentration range (1 to 3 mM) where it depresses responses induced by NMDA (39). In addition, there is a positive correlation between the ability of a diverse series of non-competitive NMDA antagonists to block both this synaptic component (118, 123, 256, 429) and responses to NMDA (460). Lowering $[Mg^{2+}]_o$ undoubtedly has other actions on neurotransmission; it would be expected to enhance transmitter release (398) and decrease membrane stabilization and hence lower firing threshold by affecting the surface charge screening (351). Such effects probably account for such APV-resistant effects, as the increase in the size of the primary population spike, in low Mg^{2+}-containing medium (117, 320).

Following the re-introduction of Mg^{2+}-containing medium, the secondary and spontaneous population spikes are abolished and the primary population spike is reduced in amplitude. However, several groups have reported that the primary population spike remains larger than it was prior to perfusion with Mg^{2+}-free medium (41, 117, 323, 553). This point is discussed further in section VI A 4 in relationship to LTP.

The epileptiform discharge recorded in Mg^{2+}-free medium resembles that seen in Mg^{2+}-containing medium to which a convulsant drug, such as a GABA antagonist, has been added. However, it is probably not due to a loss of inhibition, since recurrent GABAergic IPSPs are not depressed and indeed may actually be enhanced in Mg^{2+}-free medium (134, 698). It would seem more likely that in Mg^{2+}-free medium the primary effects are a potentiation of the non-NMDA receptor component and an unblocking of an NMDA receptor component of the EPSP such that it overwhelms the IPSP (which is still present).

If the stimulus intensity is reduced or the cell is clamped, to prevent action potential firing, then the nature of the NMDA and non-NMDA receptor-mediated components in Mg^{2+}-free medium can be compared. It has been shown (134) that both components have similar thresholds and latencies to onset, indicating that they both are monosynaptic in origin. However, the NMDA receptor-mediated component has a much slower time course; its time to peak is approximately 20 to 30 ms and it lasts for approximately 100 to 200 ms (considerably longer than the membrane time-constant of the cell).

Area CA3. The observation by Herron et al. (341) that spontaneous population discharges occurred in area CA1 in Mg^{2+}-free medium suggested, by analogy to other convulsant models, that NMDA receptors were contributing to spontaneous epileptiform events in the CA3 region. This was confirmed by the finding that the spontaneous population bursting in CA1 is eliminated by removal of the CA3 region from the slice and is depressed by APV (119, 524). Also, during the course of the experiments reported in (341), spontaneous epileptiform discharges, sensitive to APV, were recorded directly in CA3 (Herron et al., unpublished).

More recently, the nature of the epileptogenesis, recorded in the CA3 region of the slice bathed in Mg^{2+}-free medium, has been reported (16, 524, 552, 640). Most notably, in addition to spontaneous and evoked interictal-like activity, epileptiform bursts lasting for up to tens of seconds were observed and have been termed ictal-like (or ictaform) in nature (16). Sequences or spontaneous ictaform events last for many minutes in Mg^{2+}-free medium and for many hours following the addition of the $GABA_B$ antagonist phaclofen to the Mg^{2+}-free medium (696). Interestingly, in contrast to interictal-like activity, ictal-like bursts recorded in the CA1 region precede those in the CA3 region by up to 10 ms (391). The epileptogenesis recorded in area CA3 in Mg^{2+}-free medium is reduced, but is commonly not abolished, by APV (16, 524, 554, 640, 755).

The above data have two important implications. First, NMDA receptors can contribute to epileptogenesis in the CA3 region. Second, other factors such as the increased transmitter release and reduced membrane charge screening that occur in Mg^{2+}-free medium may be sufficient, at least in some cases, to generate spontaneous epileptiform events.

Dentate gyrus. In Mg^{2+}-free medium, stimulation of the perforant path, or just its medial component, elicits APV-sensitive interictal-like epileptiform activity in the dentate gyrus (122, 513). However, stimulation of the lateral perforant path has been reported to evoke only a small APV-sensitive component (122) or to have no effect unless the hippocampus has been kindled (523, 526). Brief exposure to Mg^{2+}-free medium has also been reported to lead to a potentiation of synaptic transmission in the perforant path, as assessed following re-introduction of Mg^{2+}-containing medium (513). This aspect is discussed further in section VI A 4. Spontaneous population discharges are not observed in dentate (122, 524), unless the entorhinal cortex is included in the slice preparation (732).

b. DEPOLARIZED CELLS. The ability of Mg^{2+} to block responses to NMDA is voltage-dependent, decreasing as

cells are depolarized (500, 567). As might be expected, an NMDA receptor-mediated component of the response to stimulation of the Schaffer collateral-commissural pathway can be recorded in a CA1 neuron that is depolarized strongly by current injection (134). This component has a slow time-course, similar to that recorded at resting membrane potentials in the absence of Mg^{2+} (124).

c. THE CONVULSANT DRUG MODEL. Many investigators interested in the mechanisms that underlie epilepsy have recorded from hippocampal slices in the presence of Mg^{2+} and a convulsant drug, such as penicillin (644). In area CA1, studies have shown that APV and other NMDA antagonists depress a part of the epileptiform burst elicited by stimulation of the Schaffer collateral-commissural pathway in the presence of convulsant agents, such as bicuculline (212, 344), picrotoxin (212), pentylenetetrazol (344, 697), kainic acid (344), folic acid (344), and normorphine (697). The size of the APV-sensitive component increases with membrane depolarization as expected for a NMDA receptor-mediated response in the presence of Mg^{2+} (212). The susceptibility of the discharge to NMDA antagonists appears to depend on the nature of the convulsant used; epileptiform activity induced by kainate and pentylenetetrazol is fairly sensitive, whereas that induced by bicuculline, picrotoxin, and folic acid is only slightly sensitive. In no case is the epileptiform activity as sensitive as that recorded in Mg^{2+}-free medium (119). These differences may relate to the mechanisms by which the drugs produce convulsant activity.

The involvement of NMDA receptors in convulsant-induced activity may be explained on the basis of the voltage-dependent block of NMDA channels by Mg^{2+} (35, 567). It has been hypothesized that drugs that block $GABA_A$ responses, and consequently the early phase of the IPSP, prolong the non-NMDA receptor-mediated EPSP sufficiently to reduce the Mg^{2+}-block of NMDA channels, and thereby allow NMDA receptors to contribute to the EPSP (212, 344). Such a mechanism can explain why only the latter part of the epileptiform burst is sensitive to NMDA antagonists; the early part is due to the enhanced non-NMDA receptor-mediated component. Alternative or additional mechanisms are required to account for the actions of those convulsants, such as kainic acid, that are more sensitive to the effects of APV. Kainate may work in part by directly depolarizing cells and consequently removing the voltage-dependent Mg^{2+} block of NMDA channels (567).

In the CA3 region of picrotoxin-treated guinea pig hippocampal slices, DGG reduced the duration of spontaneous and evoked bursts, and substantially suppressed afterdischarges (518). DL-APV and GDEE were also effective. With the high concentration of antagonists used, the role of the specific receptor subtypes could not be deduced. Nevertheless, these studies provided evidence for excitatory amino acid-utilizing synaptic mechanisms in epileptiform events. More recent studies have shown that convulsant-induced activity in the CA3 region of the hippocampus is sensitive to the actions of APV applied in selective concentrations. Wilson and his associates (17) investigated the effects of NMDA in the CA3 region; at a concentration of 10 μM it induced evoked and spontaneous bursting behaviour. As would be expected, prior application of APV prevented these effects. However, if APV was added after NMDA-induced bursts had been generated it blocked the spontaneous bursting but only reduced the size of the evoked bursts. Therefore, in this model, APV was described as a very effective anti-epileptogenic agent, (because it blocked the induction of bursting activity) but only a weak anticonvulsant (since it was not very effective once the activity had been established).

Ben-Ari and colleagues (52, 107, 554) have confirmed the ability of APV to prevent NMDA-induced epileptogenesis. However, if they used kainate or mast cell degranulating peptide as convulsant agents (or gave the slices transient anoxia) they found that APV, added prior to the treatment, did not prevent the induction of this activity. When added after the convulsive activity had been induced, APV reduced the duration of spontaneous and evoked bursts, but did not reduce, and sometimes increased, the frequency of spontaneous bursts. This increase in frequency may, however, be a consequence of the decreased burst duration and the consequential reduction in after-hyperpolarizations.

Brady and Swann (87) have found that the addition of GABA antagonists to hippocampal slices obtained from immature rats leads to prolonged synchronized afterdischarges in the CA3 region that last for several seconds. They presented evidence that NMDA receptors were important in the generation of these afterdischarges. Ketamine (100 to 250 μM) reduced the initial paroxysmal depolarizing shift and blocked the afterdischarges. DL-APH also completely blocked afterdischarges if applied in very high concentrations (5 mM); only partial reductions were seen with 1 mM APH. The necessity of high doses of APH was explained on the basis of the release of large amounts of transmitter during seizures, overcoming the competitive block.

d. HIGH K^+-INDUCED EPILEPTOGENESIS. Raising $[K^+]_o$ in the perfusate from a physiological level of around 3 mM to, for example, 7 mM induces interictal bursting in the CA3 region. APV is unable to prevent the development of these interictal bursts but can reduce their duration (554). NMDA receptors are, therefore, not necessary for, but can contribute to, interictal burst generation in high K^+ models of epilepsy. In elevated K^+ (8.5 mM), provided that slices are maintained close to 37°C, full-blown seizures are sometimes seen in the CA1 region; APV reduces the frequency of occurrence and duration of these events (712).

e. COMBINATIONS OF TREATMENTS. To demonstrate

an NMDA receptor component of synaptic transmission it is only necessary to use one of the following treatments: delivery of high frequency trains, depolarization of the cell, removal of Mg^{2+}, or depression of synaptic inhibition. However, to describe the nature of the NMDA receptor-mediated synaptic component a combination of these treatments has been used. For example, Wigstrom and Gustafsson have described an APV-sensitive response after blockade of synaptic inhibition that was elicited either by high-frequency stimulation (749, 752) or by single volleys in depolarize cells (752), or in the absence of Mg^{2+} (751). This response had the same slow characteristics as that described with single treatments (see also ref. 58).

Reversal potentials have been determined after blockade of IPSPs that would otherwise dominate the synaptic response at depolarized potentials. In the presence of 2 mM Ca^{2+} (and 1 mM Mg^{2+}) both NMDA and non-NMDA receptor-mediated synaptic currents, evoked by stimulation of the Schaffer collateral-commissural pathway, reverse at around −5 mV (134). Similar reversal potentials, of around 0 mV, were also found for NMDA and non-NMDA receptor components of synaptic responses recorded from cultured embryonic hippocampal cells, in the presence of 1 mM Ca^{2+} (and no added Mg^{2+}) (266). Increasing the Ca^{2+} concentration to 20 mM shifted the reversal potential of the NMDA receptor component, but not the non-NMDA receptor component, to about +10 mV. This observation is consistent with a significant Ca^{2+} permeability of NMDA channels.

f. SYNAPTIC TRANSMISSION AFTER BLOCKADE OF NON-NMDA RECEPTORS. With the advent of antagonists such as CNQX that block responses to agonists acting at non-NMDA receptors while not affecting responses to NMDA, it has become possible to study the NMDA receptor component of synaptic transmission in isolation. This has been achieved for the Schaffer collateral-commissural pathway. Thus, Blake et al. (72) showed that the addition of CNQX to Mg^{2+}-free medium can block the non-NMDA receptor component to leave a pure APV-sensitive response. Interestingly, CNQX can also reveal an EPSP with properties characteristic of an NMDA receptor-mediated response in the presence of Mg^{2+} (19, 128); thus this CNQX-resistant EPSP is blocked by APV, displays an anomalous voltage-dependence, and is potentiated greatly if Mg^{2+} is then omitted from the medium. Under these conditions, the intensity required to evoke (in CNQX) an NMDA receptor-mediated EPSP is higher than that needed to evoke an EPSP prior to addition of CNQX. However, intensities that evoke an NMDA receptor-mediated EPSP (in CNQX) do not evoke an NMDA receptor component to the EPSP prior to the addition of CNQX. Thus the NMDA receptor-mediated EPSP appears as a consequence of the actions of CNQX. This may be the result of CNQX depressing polysynaptic IPSPs in area CA1 because, under conditions of reduced synaptic inhibition, NMDA receptors contribute to the otherwise "normal" low frequency response (212, 344) (see section V B 4 c).

With increasing stimulus strengths the NMDA receptor EPSP becomes limited by a biphasic GABAergic IPSP (128, 202). Since the excitatory drive of inhibitory interneurons can no longer be mediated by non-NMDA receptors (due to the presence of CNQX), and since these IPSPs are depressed by APV in parallel with the CNQX-resistant EPSP, it would appear that NMDA receptors are, under these conditions, mediating the excitation of inhibitory interneurons. At stimulus strengths too low to evoke, these IPSPs or following blockade of the GABAergic IPSP, the time-course of the NMDA receptor-mediated EPSP can be measured directly. It has a short latency, similar to that of the CNQX-sensitive component, a slow rise to peak (approximately 20 ms), and a long duration (approximately 100 to 200 ms). It is thus very similar to the NMDA receptor component as determined previously by subtraction procedures (i.e., responses recorded in the presence of APV subtracted from controls).

5. The L-APB "receptor(s)." L-APB (L-AP4) depresses, in a stereo-selective manner, synaptic transmission in certain hippocampal pathways. The lateral perforant path is especially sensitive (apparent K_D for antagonism by L-APB is 2.5 μM) (242, 426). The medial perforant path seems to have two components: one moderately sensitive to L-APB (K_D of perhaps 45 μM) and one essentially insensitive to L-APB (426). The mossy-fibre projection in guinea pigs (153, 443, 760), but not in rats (443), is also sensitive to this phosphonate (but see ref. 618), while transmission in the Schaffer collateral-commissural pathway is relatively insensitive to the effects of L-APB (137, 426). L-serine-*O*-phosphate (L-SOP) has a similar, but weaker stereo-selective effect on transmission in the lateral perforant path (242, 428) and mossy fibre pathway (153). L-APV also seems to have a weak but stereo-selective depressant action on transmission in the lateral perforant path (141). The pharmacological profile of this receptor site does not match that of the Cl^- dependent L-APB binding site (88, 245).

A number of studies suggest that the effect of L-APB is mediated presynaptically: (*a*) In the CA1 region of the hippocampus (140), as in the spinal cord (198), L-APB does not depress, but rather tends to increase, excitations induced by NMDA, kainate, quisqualate, L-glutamate, and L-aspartate, and also weakly excites cells. Also, L-glutamate- and quisqualate-induced focal potentials in the termination region of the lateral perforant path are little affected by L-APB (280); (*b*) antagonism of lateral perforant path evoked responses is associated with a reduction in the extent of paired-pulse depression (321); (*c*) there is a decrease in the size of the presynaptic fibre volley (141); and (*d*) synaptic blockade of mossy fibre evoked responses occurs without any depression in the

amplitude of spontaneous miniature EPSPs (153). L-APB also has no effect on the frequency of these miniature EPSPs, suggesting that it acts by a mechanism that interferes with evoked, but not spontaneous, neurotransmitter release.

An unusual observation has been made by Robinson et al. (620) who observed that if slices were exposed briefly to quisqualate (for 4 min at 16 μM, a dose that depressed the synaptic potential by 50%) then responses evoked by stimulation of the Schaffer collateral-commissural pathway (or medial perforant path) were potently depressed by L-APB. Thus, after a "priming" dose of quisqualate, L-APB had an IC_{50} for depression of 54 μM compared to 1800 μM normally; L-APB was effective within 4 min and remained so for at least 90 min after the priming dose. On the basis of extracellular (620) and intracellular studies (326), it was suggested that a primed depression involved a depolarizing effect. Neither AMPA nor NMDA was able to sensitize the slice to the actions of L-APB. Of other phosphonates, D-APB and AP6, and to a lesser extent L-APV and D-APV also could be primed into action, whereas APH and CPP could not. CPP was unable to prevent the priming effect of L-APB.

This pharmacological profile of priming (326, 620) correlates closely with that of the Cl^--dependent L-APB binding site that is believed to be associated with an uptake process (see section II C 1). It was therefore suggested that uptake was involved in the priming effect of quisqualate (326). Quisqualate excites cells through the receptor that is also sensitive to AMPA but, unlike AMPA, is then taken up at the APB-sensitive site. Agents that can act at this site, such as L-APB, then cause release of quisqualate (by heteroexchange) such that is can again depolarize the cells. In support of this idea, quisqualate-primed L-APB-induced depolarizations in cerebral cortex are depressed by CNQX, as are responses to quisqualate (651).

C. Neocortex

There is considerable evidence demonstrating that excitatory amino acid receptors mediate synaptic transmission at many synapses throughout the neocortex. There appear to be similarities to, and comparisons are often drawn to, transmission in the hippocampus. However, due to the more complex anatomy of neocortical structures, compared with the hippocampus, it generally has been more difficult to determine with certainty the identity of the neuronal projections under investigation and to perform as detailed investigations. In the following section, a brief description of roles of excitatory amino acid receptors in neuronal transmission is described for some neocortical regions.

1. Olfactory cortex. The olfactory cortex slice is a relatively well-defined neocortical preparation. Collins and colleagues (144), in particular, have exploited this preparation, applying quantitative pharmacology, nerve-evoked release, and synaptic physiology to the study of excitatory amino acid function. Hori et al. (361) showed that GDEE and NMDA antagonists such as DLAA did not affect the synaptic potential evoked in the prepyriform cortex by stimulation of the lateral olfactory tract (LOT). Collins (144) found that PDA, but not DGG or APV, depressed the initial synaptic response (the N wave) recorded as a surface potential in response to LOT stimulation. It was suggested that quisqualate receptors mediate synaptic excitation at the LOT superficial pyramidal cell synapse. Subsequent studies have found this potential to be sensitive to other broad spectrum antagonists, such as kynurenate and pCB-PzDA (332) and by DNQX (148).

In the studies of Collins (144) PDA, but not low doses of APV or DGG, also depressed the late N wave and its equivalent in the presence of picrotoxin (N'a' wave, a potential believed to represent a presynaptic inhibitory action of GABA on LOT terminals). Thus the PDA-sensitive component is presumed to correlate with an action at the LOT-GABAergic interneuron synapse. In contrast, still later components of the field potential (the I wave, recorded in normal perfusate, and the N'b'- and P-waves, recorded in picrotoxin-containing perfusate) were markedly depressed, but not abolished, by APV, with IC_{50} values of between 5 and 32 μM. DLAA, DGG, and PDA had similar effects in higher concentrations that related to their potency as NMDA antagonists. Thus, a role for NMDA receptors in synaptic transmission in olfactory cortex was clearly established. The synaptic origin of these APV-sensitive late waves is not known for certain; the following synapses were suggested: GABA-ergic inhibitory interneuron-pyramidal cells (I), superficial pyramidal cell-deep pyramidal cell (N'b'), and pyramidal cell-polymorph inhibitory interneuron (P). However, in view of the role of NMDA receptors in slow monosynaptic responses in other brain regions, such as spinal cord (183) and hippocampus (134), it is possible that these late APV-sensitive waves are, in part, monosynaptic (i.e., LOT-pyramidal cell synapse) in origin.

The LOT-superficial pyramidal cell synapse is fairly sensitive to the depressant effects of L-APB (144, 332, 360, 361). As found in other regions of the brain, L-APB is more potent than D-APB and does not affect the postsynaptic actions of excitatory amino acids on olfactory cortical cells (147, 332, 361, 693). A presynaptic action is also indicated by the observations that L-APB potentiates paired-pulse facilitation and reduces the K^+-evoked release of L-glutamate and L-aspartate (but not GABA) from olfactory cortex slices (21). Thus, these data suggest that L-APB receptors are located on LOT terminals. Other neurochemical evidence indicates that NMDA and kainate, but not quisqualate, receptors also may be located presynaptically within the olfactory cortex (146). From the studies of Hearn et al. (332) it seems that only one component of the LOT-prepyriform cortex synapse is sensitive to L-APB (332).

2. Cingulate, medial frontal, motor and sensorimotor cortex. Stone (683) presented evidence for a role of excitatory amino acid receptors in synaptic responses in the cortex elicited by stimulation of the cortical surface or pyramidal tracts. Iontophoretically applied DLAA, when applied in concentrations sufficient to depress responses to L-glutamate (but not ACh), reduced short latency evoked spikes in urethane anaesthetised rats. These studies, although important in focusing attention on excitatory amino acid receptors in cortical transmission, provided little information on the subtypes of receptors involved.

Using coronal slices, which contain several cortical areas, Thomson and colleagues investigated the pharmacology of EPSPs evoked in pyramidal cells, particularly in layers II and III, by stimulation of the underlying white matter. Within the complex potential comprising both EPSPs and IPSPs was a component with characteristics of an NMDA receptor-mediated event, i.e., it increased in size with membrane depolarization or by exchange to a Mg^{2+}-free perfusate and was blocked by APV, ketamine or cyclazocine (704, 707, 710). The component of the EPSP resistant to NMDA antagonists was assumed, but not shown, to be mediated by non-NMDA receptors. It was claimed that in many cells the NMDA receptor-mediated EPSP was the lowest threshold component and thus could be studied in isolation. In Mg^{2+}-free, but not Mg^{2+}-containing, perfusate, the NMDA receptor-mediated EPSP potentiated following repetitive stimulation at 0.5 to 2 Hz, and the potentiation could last several minutes after the last stimulus. It was suggested that the NMDA receptor-associated EPSP was mediated polysynaptically rather than directly by the cortical afferents activated by stimulation of the white matter. The NMDA receptor-mediated synapse was postulated to exist between intracortical interneurons and pyramidal cells. Thus, the NMDA receptor-mediated EPSP often had a long latency to onset (7 to 20 ms compared with 2 to 7 ms for non-NMDA receptor-mediated EPSPs in the same tissue) and, under certain circumstances, spontaneous NMDA receptor-mediated EPSPs could be recorded. In keeping with this suggestion, an APV-sensitive "unitary" potential has been recorded in layer III cells, using spike-triggered averaging (the presynaptic cell being a glutamate-driven cell in the III/IV border) (706). Whether this EPSP also had a non-NMDA receptor component was not determined.

Sutor and Hablitz (694) have studied the response of layer II/III cells of rat frontal cortex following stimulation in layer IV. The lowest threshold response was a short latency EPSP which had a similar voltage-dependence to that of the NMDA-receptor mediated EPSPs described by Thomson (710). However, this EPSP was insensitive to APV; it was suggested that the "anomalous" voltage-dependence is due to non-linear membrane properties of the neurons studied. With higher stimulus intensities, long latency (10 to 40 ms) EPSPs were also seen. These were blocked by APV, but they had a conventional voltage-dependence (i.e., decreasing with depolarization). It was suggested, therefore, that this EPSP is mediated polysynaptically and that NMDA receptors are involved in its generation by contributing to synaptic transmission between neurones presynaptic to the recorded cell.

In layer V cells of sensorimotor cortex, an EPSP with both NMDA and non-NMDA receptor-mediated components was evoked by stimulation of subcortical white matter (22). Thus, in slices perfused with medium containing Mg^{2+} and bicuculline a late component of the EPSP was blocked by APV and APV-resistant component was depressed by kynurenate.

In the studies of Thomson and co-workers (704, 707, 710), slices displayed spontaneous interictal-like epileptiform discharges in Mg^{2+}-free medium; these effects were blocked by NMDA antagonists. In contrast, when epileptiform activity of a similar appearance was generated by the addition of GABA antagonists (to Mg^{2+}-containing medium) NMDA antagonists were only weakly effective or, more commonly, completely ineffective (709). However, in studies by Aram and Lodge (23, 24) ictal-like epileptiform activity induced in slices of cingulate cortex by a variety of treatments was highly sensitive to NMDA antagonists. Thus, APV and ketamine reduced the frequency of spontaneous bursts and the number of after-potentials per burst in slices perfused with Mg^{2+}-free medium or with standard medium containing either a GABA antagonist (picrotoxin or bicuculline), a K^+ channel blocker (4-aminopyridine or tetraethylammonium), or elevated bicarbonate (pH > 7.7).

Addae and Stone (4, 5) have investigated the role of NMDA receptors in the mediation of synaptic responses in the somatosensory cortex of anaethetised rats elicited by electrical stimulation of either the thalamus or the contralateral forepaw. Topical application of APV had little or no effect on these evoked potentials. However, repetitive stimulation of the thalamus at 10 Hz elicited a potential which progressively grew in amplitude with the first few stimuli; APV or APH slowed the development and accelerated the decline of this augmentation. Thus, NMDA receptors seem to be involved in frequency-dependent transmission in thalamo-cortical pathways.

3. Visual cortex. Hicks and colleagues (345–347) have investigated the role of excitatory amino acids in transmission in the suprasylvian visual (Clare-Bishop) area of the anaesthetised cat. DLAA, applied iontophoretically, depressed single cell evoked activity elicited by stimulation of the contralateral homotropic lateral suprasylvian area or the ipsilateral 17/18 border region. However, DLAA had little or no effect on the excitation of these cells by stimulation of the ipsilateral lateral geniculate nucleus or pulvinar nucleus complex. In con-

trast, atropine had the opposite effects on these various synaptic inputs. When cells were activated by a light stimulus, the synaptic response was reduced by both atropine and DLAA (or APV) in an additive manner. Thus, both an excitatory amino acid, possibly acting in part through NMDA receptors, and ACh are implicated in the cortical processing of visual information.

Tsumoto and colleagues (716) found that iontophoretically administered kynurenate, PDA, or DGG depressed light-evoked responses in the visual cortex of anaesthetised cats. Simple cells were more susceptible than were either complex or special complex cells; cells in layers IVab, IVc and the upper part of layer VI were more sensitive than those in other layers. APV was relatively less effective in the adult cat (317, 715). Other studies showed that responses of visual cortical cells to electrical stimulation of the lateral geniculate nucleus or optic chiasm also were greatly depressed by kynurenate and, to a lesser extent, by APV (317). Thus, it was suggested that excitatory amino acid receptors of the non-NMDA type were the principal mediators of transmission in geniculo-cortical synapses. Of particular interest, however, was the finding that APV was much more effective at antagonising visual responses of cortical neurons during the critical period of young kittens. Thus, it was suggested that NMDA receptors play a greater role in synaptic processing during the time of major developmental plasticity in the primary visual cortex (see section VI B 2).

The role of NMDA receptors in synaptic transmission has been further explored by Artola and Singer (29), who obtained intracellular recordings in response to stimulation of the underlying white matter in rat visual cortex slices. On the basis of the sensitivity to APV and anomalous voltage-dependence (in the presence of Mg^{2+}), they demonstrated that NMDA receptors mediate only a very small component of the EPSP in most (so called "regular spiking") cells. However, in cells that normally displayed bursting activity or in regular spiking cells that had been "transformed" into bursting cells by addition of bicuculline, they observed large NMDA receptor-mediated components of the burst discharge.

4. Entorhinal cortex. Synaptic responses have been evoked in cells in layers IV/V of entorhinal cortex by stimulation of the subiculum in combined slices of hippocampus and cortex (393). The lowest threshold response, recorded in the presence of 2 mM Mg^{2+}, is a slow EPSP that shows some anomalous voltage-dependence and which can be blocked totally by APV. It would, therefore, appear to be a pure NMDA receptor-mediated event. In the absence of Mg^{2+} this EPSP is enhanced and marked epileptiform activity develops (732).

D. Limbic System

The hippocampus and neocortical regions that form part of the limbic system have been described in preceding sections.

1. Septum. There is a projection to the lateral septum from the hippocampus. It was reported that this pathway was depressed by iontophoretically applied GDEE, but not APV, suggesting that the synaptic receptor may be the quisqualate type (384). It was subsequently found that kynurenate and pBB-PzDA, but not D-APV or L-APB, depressed the EPSP recorded intracellularly from lateral septal neurons in slices (680). Since the potencies of the effective antagonists were similar to those for antagonism of responses to kainate in hippocampal cells, it was suggested that kainate receptors may mediate transmission at this synapse. In general (except for the positive finding with GDEE), the pharmacology of this projection seems to be the same as that found in the Schaffer collateral-commissural pathway, which is perhaps not surprising since both pathways originate from the same CA3 neurons.

2. Hypothalamus. Neurons of the suprachiasmatic nucleus of the hypothalamus receive a direct projection from the retina. Stimulation of the optic nerve within hypothalamic slices elicits a field potential that can be depressed by high concentrations of GDEE, DLAA, and APB (652), as well as by kynurenic acid (100), but not by cholinergic antagonists (100, 652). These data indicate a role for excitatory amino acid receptors in the mediation of synaptic transmission in the retino-hypothalamic pathway.

E. Cerebellum

There is evidence that excitatory amino acid receptors mediate synaptic transmission in certain well-defined pathways which project to or within the cerebellum.

1. Parallel fibres. The parallel fibres provide a major excitatory input from granule cells onto Purkinje cells. In early studies, Stone (682) observed that iontophoretically administered DLAA could depress, if applied together with GABA, the monosynaptic spike elicited in Purkinje cells by stimulation of parallel fibres in the anaesthetised rat. On its own, DLAA was ineffective. It was argued that diffusion barriers or distance of the iontophoretic barrel from the synapses prevented blockade when DL-AA was used alone and that an excitatory amino acid receptor mediated synaptic transmission in this pathway.

Subsequent studies from several groups have implicated non-NMDA receptors as mediators of transmission at this synapse: (*a*) in decerebrate rabbits it was shown that iontophoretically administered DGG or kynurenate, but not APV, depressed synaptic transmission in this pathway (395, 396). Of the agonists tested, quisqualate was depressed in parallel with the synaptic response, suggesting that quisqualate rather than kainate receptors were involved; (*b*) in grease-gap recordings from rat cerebellar slices DGG, but not APV, depressed the parallel fibre-evoked responses (290); (*c*) the monosynaptic EPSC evoked in rat Purkinje cells by stimulation of single granule cells, grown in dissociated cell culture, was

depressed by kynurenate, but not APV, and was not potentiated in Mg^{2+}-free medium (352).

2. Climbing fibres. The climbing fibre pathway originates in the inferior olive and terminates on the dendrites of Purkinje cells. Using guinea-pig cerebellar slices, Kumura et al. (417) found that this pathway was highly sensitive to iontophoretically administered APV (and to a slightly lesser extent DGG), while GDEE had little effect. Unusually, NMA itself was not an excitant, but depressed the synaptic response. Since these antagonists depressed L-asparate-, but not L-glutamate-, induced excitations in parallel with the synaptic response, the receptor was deemed to be of an aspartate-preferring type.

3. Mossy fibres. Mossy fibres provide an excitatory projection onto granule cells. Using grease-gap methods applied to adult rat cerebellar slices, Garthwaite (290, 292) has shown that DGG, KYN, and CNQX, but not APV, depressed mossy-fibre-evoked responses, implicating a role of non-NMDA type excitatory amino acid receptors in this pathway. An APV-sensitive component, however, was observed if either a Mg^{2+}-free perfusate was used or high frequency stimulation (i.e., 100 Hz) was employed. In immature slices (obtained from 14-day-old rats), a sizeable APV-sensitive component was observed in the presence of 1.2 mM Mg^{2+}.

F. Thalamus

1. Ventral basal nucleus. Evidence for a role of excitatory amino acid receptors in the thalamus was initially based on the observation that iontophoretically administered GDEE and DL-α-methylglutamate blocked the excitation of cells in the ventrobasal nucleus of the thalamus, in response to electrical stimulation of hind limb nerves (318). In more recent extracellular studies in the rat in vivo, the excitation of neurons in this nucleus by single shock electrical stimulation in the vicinity of vibrissa was blocked by iontophoretically-administered KYN, but not D-APV (628, 629). Interestingly, in the same experiments the excitation of these neurons by high frequency electrical stimulation (20 Hz) and the physiological excitation of vibrissa follicle afferents using an air jet was antagonized by D-APV. The response to an air jet was also reduced by ketamine and MK-801 in doses selective for NMDA receptor (633). NMDA receptors also appear to be involved in the response of these thalamic neurons to noxious stimulation (224).

Using a different approach an involvement of non-NMDA receptors in the ventrobasal nucleus of the thalamus has been supported. The potential recorded from the somatosensory cortex of the rat, in response to single shock electrical stimulation of the contralateral forelimb, was depressed by the microinjection of pCB-PzDA but not APH into the thalamus (421). Thus, a role of non-NMDA receptors in low frequency transmission and NMDA receptors in high frequency transmission is indicated in this nucleus. In this respect, synaptic transmission in the ventrobasal nucleus of the thalamus resembles the situation in the hippocampus (section V B).

2. Lateral geniculate nucleus. Kemp and Sillito (412) found that the NMDA antagonists DAA and HA-966 (but not GDEE or DAP) depressed visually-evoked responses of X and Y cells in the dorsal lateral geniculate nucleus (LGN) of the anaesthetised cat. Responses to NMDA ligands, but not ACh, were also depressed, and the cholinergic antagonists atropine and dihydro-β-erythroidine were without effect on the synaptic response. This study, therefore, provided strong evidence, contrary to an earlier report (700), that excitatory amino acid receptors are involved in the mediation of synaptic transmission from the optic nerve to the LGN.

The implication that NMDA receptors may be involved at this synapse was not supported in a subsequent study by Crunelli et al. (163). Working with slices of rat LGN, these authors found that the EPSP was depressed by DGG, but not by APV, even in the absence of Mg^{2+} in the perfusate. Their data implicated a role of non-NMDA receptors in the mediation of the optic nerve EPSP. A species difference was offered as an explanation for the difference. An alternative explanation could be that NMDA receptors contribute to the natural response since this comprises high frequency trains, conditions ideal for activating synaptic NMDA receptors (342, 628).

G. Striatum and Mesencephalic Nuclei

1. Striatum. The striatum receives a major projection from the cerebral cortex, a pathway for which there is considerable neurochemical evidence that the neurotransmitter might be an acidic amino acid.

It was reported that DAA depressed cortically evoked responses recorded extracellularly in rat striatum (683). However, synaptic responses, recorded intracellularly in cat caudate in vivo in response to low frequency stimulation of precruciate cortex, were not depressed by DAA in doses greater than those needed to completely block depolarizations induced by NMA (340). This and the observation that synaptic stimulation, at rates of 0.5 or 50 Hz, did not induce NMA-like burst firing (termed "plateau potentials") led the authors to conclude that NMDA receptors did not mediate the cortico-striatal EPSP and that the depressions reported by Stone may have been the result of non-specific effects.

A subsequent study reported that broad-spectrum, but not selective, NMDA antagonists depressed the cortically evoked EPSP, indicating that receptors of the kainate- or quisqualate-, but not of the NMDA-, type, mediate this synaptic response (337).

Several studies have examined synaptic responses recorded in striatal slices evoked by local stimulation within the slice. In coronal slices, a component of a field potential, termed N2, has been reported to be sensitive to cholinergic nicotinic antagonists (521). However, a similar potential recorded in parasagittal slices was blocked by DGG and PDA, but not APV, indicating a

role for acidic amino acid receptors of the non-NMDA type (151). Intracellular recording has identified an EPSP that under "normal conditions" was blocked by KYN but not APH. An APH-sensitive component was detected, however, in cells depolarized above −50 mV or in Mg^{2+}-free medium (106). Thus, intrastriatal EPSPs have been recorded that are reminiscent of those in the hippocampus (section V B). It is quite possible, in view of the size of the cortical projection, that these EPSPs result from stimulation of cortico-striatal fibres within the slice.

2. Substantia nigra. Stimulation within the striatum evokes periods of excitation, as well as GABA-mediated inhibition, in the substantia nigra (130). This excitation, recorded extracellularly from single nigral neurons of the rat in response to 1 to 2 Hz striatal stimulation, was insensitive to DAA or DAS, applied in doses that abolished responses to L-aspartate (129). This indicates that NMDA receptors are not involved in the mediation of the synaptic response recorded in this manner. Whether broad spectrum antagonists suppress the response and whether NMDA antagonists would be effective under different conditions, such as during high frequency stimulation, is not known. It is also not clear whether the fibres stimulated originated within or passed through (e.g., cortico-nigral fibres) the striatum.

3. Red nucleus. Davies and colleagues (192) have investigated the effects of iontophoretically administered excitatory amino acid antagonists on synaptic responses evoked in neurons in the magnocellular red nucleus of the anaesthetised cat. Monosynaptic responses evoked by stimulation of the contralateral interpositus nucleus were depressed by a range of broad spectrum antagonists but not by APV, indicating a role of non-NMDA receptors in this pathway. By contrast, mono- and polysynaptic responses evoked in these cells by stimulation of the ipsilateral sensorimotor cortex were depressed by either APV or broad spectrum antagonists. Since the latter compounds were more effective, despite being weaker NMDA antagonists, it was considered that non-NMDA receptors as well as NMDA receptors were involved in these synaptic projections.

4. Subthalamus. Single-shock stimulation of the cortex elicits a burst of action potentials in neurons located in the subthalamic nucleus of anaesthetised rats. It has been reported (625) that this synaptic response, but not that evoked by stimulation of the pedunculopontine nucleus, was antagonised by GDEE. More convincing evidence for a role of excitatory amino acid receptors was the additional finding that PDA and kynurenate, but not NMDA or other neurotransmitter antagonists, were also effective against this synaptic response, indicating that receptors of a non-NMDA type mediate synaptic transmission in the corticosubthalamic projection.

5. Periaqueductal grey. The ventromedial nucleus of the hypothalamus provides a large input into the periaquaductal grey (PAG). In anaesthetised rats, iontophoretically administered APV depressed the firing of some PAG neurons evoked by single shock stimulation of the ventromedial nucleus, indicating a role of NMDA receptors in this pathway. With other cells APV was not particularly effective, whereas kynurenate did depress the synaptic response, suggesting a role also for non-NMDA receptors in this pathway (753).

H. Brainstem

1. Cuneate nucleus. The cuneate nucleus was one of the first regions where the possibility was explored that excitatory amino acid receptors may be involved in synaptic transmission. Davies and Watkins (194) found, in anaesthetised cats, that iontophoretically applied HA-966 depressed the excitation of cuneate neurons induced by stimulation of various nerves or hair, or pressue or joint receptors. Stone (681) observed, in anaesthetised rats, that HA-966 reduced cortically evoked monosynaptic responses in these cells.

2. Trigeminal nucleus. In the caudal trigeminal nucleus (a brainstem nucleus receiving facial afferents and which is analogous to the dorsal horn of the spinal cord), Hill and Salt (350, 631) found no effect of DAA on responses to either noxious or non-noxious inputs. In contrast, PDA and DGG depressed responses to non-noxious sensory stimulation (350, 631) and to noxious mechanical-, but not to noxious heat-, evoked responses (632).

3. Vestibular Nucleus. Labyrinthine afferents project into the brain via the VIII cranial nerve and synapse with neurons within the vestibular nucleus. These second-order vestibular neurons also receive a smaller projection from the contralateral vestibular neurons. Initial studies suggested that both NMDA and non-NMDA receptors could mediate the VIII nerve-evoked response (e.g., refs. 378, 493, 571). More recently, using intracellular recordings in Mg^{2+}-free medium, Cochran et al. (124) found that in the frog the early component of the ipsilateral EPSP is blocked by non-NMDA antagonists such as DGG and KYN, but not by selective NMDA antagonists such as APV. However, later components of the ipsilateral (presumed polysynaptic) EPSP and a large proportion of the contralateral EPSP were substantially reduced by APV. In the presence of 1 mM Mg^{2+}, Knopfel (423) found that the ipsilateral EPSP was essentially unaffected by APV, whereas the contralateral EPSP was partially depressed. Of interest, the ipsilateral EPSP has a fast rise-time and (in Mg^{2+}-containing medium) is short-lasting, while the contralateral EPSP has a slow rise and is long-lasting. Thus, the fast ipsilateral EPSP appears to use principally non-NMDA receptors (but NMDA receptors can contribute in Mg^{2+}-free medium), whereas the slow contralateral EPSP is mediated by both non-NMDA and NMDA receptors.

4. Nucleus tractus solitarii. Several groups have presented evidence, based on the micro-injection of antagonists, that excitatory amino acid receptors in the nu-

cleus tractus solitarii (NTS) and regions in the ventrolateral medulla may be involved in cardiovascular regulation. For example, injections of kynurenate (312) or APV (434, 435) into these regions suppressed baroreflexes and the consequent bradycardia and hypotension.

I. Retina

There exists evidence that the transfer of sensory information through the retinal network is mediated in part via excitatory amino acid transmitters (see ref. 520). The best characterized and perhaps the most interesting aspect of synaptic pharmacology in this area is the unconventional excitatory transmission found between photoreceptors and depolarizing (ON) bipolar cells (DBCs) in the outer plexiform layer. Light-induced hyperpolarization of photoreceptors induces a depolarization in DBCs, a response which can be blocked by APB (653, 665). Light responses in other classes of retinal neurons are insensitive to APB, and thus it appears that this action is highly specific to DBCs (665). Experiments performed in the presence of Co^{2+}, to eliminate synaptic transmission, demonstrated a direct APB-induced hyperpolarization of DBCs, accompanied by an increase in input resistance, suggesting channel closing (653, 665). These studies are readily understood if APB is acting to mimic the rod transmitter, presumably L-glutamate, which is continuously released in the dark and maintains the DBCs in a hyperpolarized state; in the light, transmitter release is shut down and the DBCs depolarize (see ref. 520). However, in the presence of APB the synaptic receptors are saturated and the light-induced depolarization can no longer occur (665). Overall, these data provide evidence for a postsynaptic location of APB receptors in mediating a hyperpolarizing action of L-glutamate. Pharmacological studies indicate that the APB receptor in the retina is similar to that described elsewhere in the CNS where a presynaptic function of APB receptors has been implied (321). For example, the depression of both lateral perforant path and DBC responses by APB is mimicked by L-serine-*O*-phosphate and 1,3,amino-dicarboxylcyclopentane and is stereoselective for the L-conformation of APB (158, 242, 426, 670).

An additional hyperpolarizing action of L-glutamate in DBCs has also been proposed, although in this case the hyperpolarization is achieved through channel opening (430). Recently, Nawy and Copenhagen (550) demonstrated that L-glutamate caused a hyperpolarization in DBCs with no change in cell input resistance. In the presence of concentrations of APB sufficient to block glutamate actions at the APB-channel closing receptor, glutamate was observed to hyperpolarize the membrane and decrease the input resistance of the neuron, suggesting a dual action of glutamate in operating both the APB-sensitive and insensitive conductance mechanisms (550). The pharmacological nature of the receptor mediating the latter response is as yet unknown.

Two other populations of second-order neurons, the hyperpolarizing (OFF) bipolar cells (HBCs) and horizontal cells, also receive input from photoreceptors. Here, both the transmitter and L-glutamate cause a depolarization and, since these neurons are excited by kainic acid (666) and their light responses are blocked by the antagonists PDA and DGG (223, 668), a transmitter role for glutamate acting through kainate-like receptors is suggested. However, the selective action of D-serine-*O*-phosphate in blocking the light response in horizontal, but not HBCs, suggests that differences in the pharmacology of these receptors exist (669). Interestingly, bipolar and horizontal cells are not excited by NMDA (666). Indeed NMDA has been reported to act as a weak synaptic antagonist (26, 80).

In the inner plexiform layer, transmission would appear to be in keeping with excitatory amino acid synapses throughout of the rest of the CNS. For example, the ganglion cells, which receive input from bipolar cells, respond conventionally to kainate, quisqualate, and NMDA (79, 472, 666). Furthermore, as the broad spectrum acidic amino acid antagonist PDA blocked light responses in ganglion cells (667) and since APV reduced sustained but not transient responses (472), both non-NMDA and NMDA receptors are implicated in mediating the actions of L-glutamate at these synapses.

J. Summary

In general, there are marked similarities in the pharmacology of synaptic transmission among those excitatory pathways in the brain that have been subjected to intensive investigation. It seems that under normal conditions EPSPs that have been evoked by low stimulus frequencies are mediated largely, or exclusively, by receptors of a non-NMDA type. However, NMDA receptors may contribute to the synaptic response under conditions that favour removal of the voltage-dependent Mg^{2+}-block of NMDA receptor-gated ion channels. This may be achieved experimentally, for example, by removing Mg^{2+} or by blocking synaptic inhibition.

Physiologically, NMDA receptor activation will occur more prominently during high frequency transmission, a situation when synaptic inhibition often fatigues. It will also occur in regions of the brain where synaptic inhibition does not efficiently curtail the non-NMDA receptor-mediated EPSPs. The synaptic activation of NMDA receptors may, but does not necessarily, lead to synaptic enhancement. The physiological roles of the kainate receptor, the L-APB receptor, and the metabotropic quisqualate receptor have not yet been determined.

In summary, it can be stated with confidence that both NMDA and non-NMDA (i.e., kainate/quisqualate) receptors have well-defined roles in synaptic transmission in the central nervous system.

VI. Synaptic Plasticity

Excitatory amino acid-utilizing pathways can display pronounced synaptic plasticity. This property is particularly evident in the hippocampus of adult animals and is probably an important feature of excitatory amino acid systems, at various stages of development, throughout the central nervous system. To reflect the widespread interest and rapid progress made recently in this field, the involvement of excitatory amino acid receptors in synaptic plasticity in the hippocampus is considered in depth. Excitatory amino acid receptors and plasticity in other regions of the brain is then discussed more briefly.

A. Hippocampus

1. Long term potentiation in the hippocampus. a. BASIC FEATURES OF LTP. The observation that brief high frequency trains of stimuli, delivered to certain pathways, can induce a sustained enhancement of synaptic responses is commonly referred to as long-term potentiation (LTP). The first detailed studies of LTP were made by Bliss and Lømo (77) and Bliss and Gardner-Medwin (76) in the medial perforant path in vivo and were based on the original observations reported by Lømo in 1966 (463).

In the anaesthetised rabbit, Bliss and Lømo found that repetitive stimulation at 10 to 20 Hz for 10 to 15 sec, or at 100 Hz for 3 to 4 sec, could induce a potentiation which could last for up to 10 h. LTP increased with repetition of the trains and eventually saturated. In chronically implanted animals LTP could be shown to last for several days to weeks (76, 217). Thus, LTP was distinguished from other types of post-tetanic potentiation which have shorter lifetimes on the order of seconds/minutes (511). LTP has been demonstrated subsequently in all the major excitatory pathways within the hippocampal formation, e.c., including the Schaffer collateral-commissural pathway and mossy fibre projection (12, 645).

The alterations in synaptic potentials that constitute LTP, measured extracellularly, are an increase in the amplitude and slope of the field EPSP and an increase in the amplitude and a decrease in the latency of the population spike (13, 77). LTP consists of two distinct components which can occur independently of one another. These are: (*a*) an increase in the amplitude or slope of the field EPSP to a given afferent volley (termed synaptic potentiation); and (*b*) an increase in the population spike amplitude for a given sized field EPSP (termed E-S potentiation). Synaptic potentiation is taken to reflect an increase in the efficacy of synaptic transmission while E-S potentiation is believed to reflect an increase in the excitability of postsynaptic neurons. With intracellular recordings, synaptic potentiation is seen as an increase in the EPSP and E-S potentiation as a lower threshold for the EPSP to elicit an action potential.

Following the induction of LTP, there do not appear to be any changes in the presynaptic fibre volley or the gross passive properties of neurons (14, 15, 221). Synaptic inhibition is either unaffected or enhanced, possibly as a result of increased excitatory drive (306, 313, 314). Thus, LTP appears to be confined to excitatory synapses.

b. SPECIFICITY, CO-OPERATIVITY, AND ASSOCIATIVITY. An important property of LTP is its specificity to the tetanized pathway (14, 15, 221, 474, 512). Other inputs to the neurons are often depressed (2, 14, 77, 221, 474). This heterosynaptic depression occurs independently of LTP and also may occur in the tetanized pathway (i.e., homosynaptic depression) and thereby influence the extent and time-course of LTP.

The observation that high frequency trains of low intensity were ineffective at inducing LTP, whereas similar trains at higher stimulus strengths produce LTP, suggested that there was a threshold for the induction of LTP. Above this threshold, the degree of LTP increased as a function of stimulus strength suggesting that a "co-operative" interaction between afferent fibres was necessary for the induction of LTP (76, 447, 645). The finding that the co-operative interaction occurred heterosynaptically gave LTP an "associative" nature (46, 447, 452, 512, 748).

The long, although not indefinite, time-course of LTP (76), its activation by brief (physiological" periods of high frequency stimulation (216), and the properties of specificity, co-operativity, and associativity have led many authors to suggest that the LTP model may involve mechanisms of the sort that underlie higher forms of learning and memory in the vertebrate brain (e.g., 78, 702).

c. THE INDUCTION OF LTP. The pathways which display LTP in the hippocampus seem to use excitatory amino acids as neurotransmitters. Under "normal" conditions the EPSP evoked by low frequency stimulation is depressed by broad spectrum and non-NMDA receptor specific excitatory amino acid antagonists, but not by selective NMDA antagonists, suggesting that the receptor that mediates "normal" low frequency transmission at these synapses is of the non-NMDA, possibly kainate or quisqualate, type (see section V B 2). The findings that in area CA1 the broad spectrum antagonists APB (222) and DGG (137) depress transmission and prevent the induction of LTP suggests that the activation of excitatory amino acid receptors is a prerequisite for the induction of LTP. In the dentate gyrus it was reported that DGG did not prevent the induction of LTP, but masked its appearance by depressing transmission (214). This would be consistent with a presynaptic locus of induction, but has not been supported by more recent studies (227).

d. NMDA RECEPTORS AND THE INDUCTION OF LTP. The role of NMDA receptors in the induction of LTP in a number of hippocampal pathways is firmly established.

Thus, APV has been shown to selectively and reversibly prevent the induction of LTP in the Schaffer collateral-commissural pathway (126, 137, 138, 208, 325, 402, 485, 613, 749, 752), medial perforant path input to dentate gyrus (227, 446, 539), and associational/commissural input to CA3 (324, 402). An early claim that the LTP-preventing effect of APV was unrelated to amino acid antagonism (635) has not been substantiated. Indeed, the ability of APV and a series of its homologous to prevent LTP (325) correlates closely with their potency as NMDA antagonists (233). Furthermore, certain arylcyclohexalyamines, dioxolanes, benzomorphan opioids and dibenzocycloheptenеimines block both the induction of LTP (123, 689–691) and the Mg^{2+}-sensitive synaptic events (118, 123) in area CA1 in doses at which they "non-competitively" block responses to NMDA (439, 460); lowering the Mg^{2+} concentration facilitates the induction of LTP (365). Finally, NMDA application alone can induce LTP-like effects in an APV-sensitive manner (131, 137, 399, 401).

It should be stressed that NMDA receptor activation is required only for the induction of LTP, not for its maintenance. Thus, potentiated responses, like control responses, are not affected by NMDA antagonists (137, 227) unless the potentiation is excessive (i.e., in classical kindling and kindling-like phenomena (17, 523, 592, 664)). Furthermore, both potentiated and control responses are depressed in parallel by CNQX, suggesting that a similar non-NMDA (presumably quisqualate) type receptor type mediates both events (204).

NMDA receptors do not mediate all forms of LTP in the hippocampus. While APV prevents LTP of the associational/commissural input to CA3 neurons, it has no effect on LTP of the mossy fibre input (324, 402). These findings are consistent with the receptor distribution within the hippocampus as identified by autoradiography; the mossy fibres innervate a region dense in kainate, but sparse in NMDA, receptors while the commissural fibres (and other pathways where LTP is blocked by APV) innervate regions rich in NMDA receptors (see section II C 5). It is possible that kainate receptors are somehow involved in the induction of LTP in the mossy fibre pathway.

e. THE MECHANISM OF INDUCTION OF APV-SENSITIVE LTP. Over the last few years a theory, which now receives general acceptance, has developed concerning the mechanism of induction of LTP in area CA1. It was originally suggested that NMDA receptors may be activated specifically during high frequency stimulation and that activation of these receptors may lead to postsynaptic calcium entry sufficient to induce LTP (137). With the finding that Mg^{2+} prevents synaptic activation during low frequency stimulation, a critical role for Mg^{2+} in the induction of LTP was assumed (116, 117). Based on the finding that Mg^{2+} blocks NMDA channels in a highly voltage-dependent manner (35, 567), it was hypothesized that tetanic stimulation provides sufficient depolarization to alleviate temporarily the Mg^{2+} block of NMDA channels (126, 341, 750). It appears that a single volley does not activate the NMDA receptor system because of concurrently activated IPSPs which rapidly hyperpolarize the membrane into the region of maximal Mg^{2+} block (134, 212, 344). This scheme is outlined in fig. 9. Thus, a single transmitter substance, such as L-glutamate, has the potential of activating the non-NMDA receptor system in isolation or together with the NMDA receptor system depending on the state of depolarization of the postsynaptic neuron. This voltage-sensing agonist-dependent mechanism can explain the properties of specificity (the requirement for an NMDA receptor ligand) and co-operativity and associativity (the requirement for sufficient membrane depolarization, provided homo- or hetero-synaptically, to reduce the Mg^{2+} block of NMDA channels). The requirement for both pre- and post-synaptic activity has been likened to the original hypothesis by Hebb (333) that for synaptic strengthening to take place presynaptic activity needs to occur simultaneously with spiking in the postsynaptic cell. Thus, although the postsynaptic requirement is for sufficient depolarization to relieve the Mg^{2+} block not for the generation of action potentials, the NMDA receptor can be said to endow a hebbian-like property upon synapses.

If high frequency stimulation is required solely for the purpose of depolarizing the cell, it follows that single shock stimulation should induce LTP in cells depolarized sufficiently out of the region of Mg^{2+} block by experimental manipulation. This conjunction experiment has been performed successfully (311, 406, 447, 634) and has been shown to be APV-sensitive (311, 447).

The NMDA receptor component can be observed during high frequency stimulation (342, 749) and displays the properties consistent with a role in the initiation of LTP (135). Thus, this receptor component is apparent at frequencies of above approximately 5 Hz and its participation increases with increasing stimulation frequency in a manner similar to LTP (221). The amplitude of the NMDA receptor component can be blocked by hyperpolarization and will increase with a depolarization of the postsynaptic membrane from rest. This observation is consistent with the behaviour of NMDA channels in the presence of Mg^{2+} (35, 567) and the finding that the induction of LTP in a cell is facilitated by depolarization and blocked by sufficient hyperpolarization of the membrane (406, 486).

A number of events which occur during high frequency stimulation may be responsible for the depolarization that is required for activation of the NMDA receptor system. These include: (*a*) non-NMDA receptor-mediated EPSPs will depolarize the membrane and, at sufficient frequencies, summate; (*b*) there will be an increase in extracellular K^+ which will further depolarize cells; (*c*) GABA-mediated IPSPs, which normally pres-

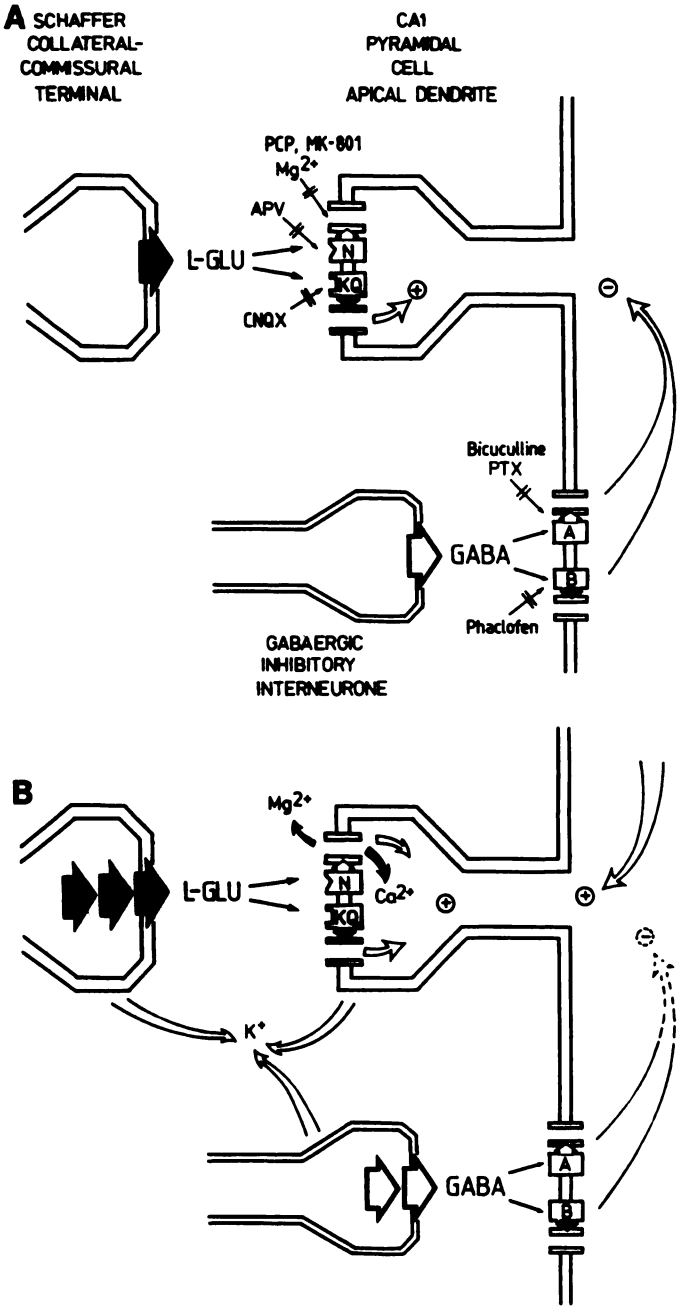

FIG. 9. Scheme for the induction of LTP in the Schaffer collateral-commissural pathway. (*a*) Synaptic events during low frequency transmission and the sites of action of some drugs. Note that GABA systems provide powerful synaptic inhibition; when activated they hyperpolarize cells into the region where NMDA receptor-gated ion channels are subjected to substantial blockade by Mg^{2+} (present in the synaptic cleft). (*b*) During high frequency transmission, synaptic inhibition fatigues and extracellular K^+ elevates. Under these conditions cells stay depolarized for longer, the Mg^{2+} block of NMDA channels is reduced and NMDA receptors mediate a slow EPSP. Ca^{2+} enters the cell via the NMDA channels where it may activate local processes that sustain the enhanced response.

ent a powerful opposition to neuronal depolarization, will fatigue (504); and (*d*) the NMDA receptor-mediated component will itself summate. It is interesting to note that the threshold frequencies for summation of the NMDA receptor mediated EPSP and the induction of LTP are similar (~5 Hz).

One possible scenario for the induction of LTP is as follows. With the first shock in a train there is little activation of the NMDA receptor system since the cell membrane is for the most part maintained at a hyperpolarized level by $GABA_A$ and $GABA_B$-receptor mediated IPSPs. It is important to note at this juncture that, at the stimulus intensities used to induce LTP, an NMDA receptor-mediated EPSP rises slowly (time to peak, ~20 ms) and that the IPSP is rapidly activated (134); consequently NMDA receptors contribute very little to the first EPSP. It does, however, retain the capacity to contribute to the response for a period of time (up to ~200 ms) following the stimulus that corresponds to the normal duration of an NMDA receptor-mediated EPSP (134) (i.e., NMDA receptors are activated but the associated channels are blocked). This is indicated by the finding that depolarizing steps given within this time after single volleys can generate LTP (311). With successive volleys, the IPSPs fatigue (possibly due to feedback inhibition of GABA on $GABA_B$ receptors (327)), and the chloride equilibrium potential may shift in a depolarizing direction. Thus, the cell remains at a level where synaptic volleys can activate the NMDA receptor system. At frequencies of 5 Hz or more, depending on the stimulus intensity used, the NMDA receptor components will, due to their duration, summate, and this summation will increase non-linearly with depolarization due to the nature of the Mg^{2+} block. When NMDA receptor activation reaches a certain point, LTP will begin to be induced. The other factors (summation of non-NMDA receptor-mediated EPSPs and elevation of extracellular K^+) should facilitate, but may not be essential for, the induction of LTP.

If the only requirements for the induction of LTP are the availability of an NMDA receptor ligand and sufficient depolarization to relieve the Mg^{2+}-block of NMDA channels, then it should be possible to induce LTP in a number of ways. For example, pairing any input that can provide sufficient depolarization with an input that releases an NMDA receptor ligand should be sufficient. This depolarizing input could use ACh or a monoamine as the neurotransmitter. Indeed, it is conceivable that the primary function of the non-amino acid pathways is to set the tone upon which excitatory amino acid pathways operate.

f. THE MECHANISMS OF MAINTENANCE OF LTP. As discussed in the preceding section, the mechanism of induction of the type of LTP that involves NMDA receptors is fairly well understood. Considerably less is known about the mechanisms that maintain the synapse in a potentiated state and how NMDA receptor activation evokes these processes. Clues to some of the elements involved have been provided by studies using excitatory amino acids and their antagonists. These as-

pects will be considered in this section. For a detailed review on all aspects of LTP see (78).

There is considerable controversy as to the locus of change responsible for the maintenance of LTP. On the one hand, it is proposed that LTP is maintained by presynaptic mechanisms; evidence in favour of this is particularly strong for the perforant pathway-dentate gyrus synapse. Bliss and colleagues have shown that LTP is associated with an increase in the release of L-glutamate (75) and that this change is prevented by treatments that block the induction of LTP, such as the addition of APV (227). The strongest evidence that LTP is maintained by postsynaptic mechanisms comes from electrophysiological studies of the Schaffer collateral-commissural pathway in hippocampal slices. Experiments were performed under conditions where both quisqualate and NMDA receptors contribute to the EPSP (e.g., low Mg^{2+} (543) or depolarized cell (400)). It was found that conditions that induce LTP produced a selective or greater potentiation of the quisqualate receptor component. It was argued that had LTP been due to an increase in neurotransmitter release then both quisqualate and NMDA receptor components should be potentiated in parallel. It was suggested, therefore, that LTP is due to a selective postsynaptic modification involving quisqualate receptors. In support of this, it was shown that a pure NMDA receptor-mediated EPSP, recorded after blockade of the quisqualate receptor component with CNQX, did not potentiate following tetanic stimulation. This was attributed to the failure of an NMDA receptor EPSP to support LTP rather than the need for quisqualate receptors to induce LTP since LTP of the quisqualate receptor component, induced by the tetanus in CNQX, was seen after washout of CNQX (400, 542). In a separate study, however, tetanic stimulation was found to induce a short-lived (15 to 20 min) potentiation of the NMDA receptor mediated EPSP, recorded in the presence of CNQX (132).

Other direct evidence for a postsynaptic locus of change in the Schaffer collateral-commissural pathway is derived from iontophoretic experiments (204). It was found that LTP is associated with an increase in the sensitivity of CA1 neurones to quisqualate and AMPA. This change, like the induction of LTP, was prevented if APV was present during the tetanus. Unlike LTP, however, this change developed slowly, reaching a maximum after ~1 h. It was suggested, therefore, that LTP may be maintained initially by presynaptic and at later stages by postsynaptic mechanisms.

Another major issue is how NMDA receptor activation could lead to these changes in synaptic efficiency. There are strong theoretical arguments that the initial intracellular messenger is Ca^{2+} entering the postsynaptic cell through NMDA channels. Evidence supporting this includes the following. The induction of LTP can be blocked by the injection of Ca^{2+} chelators into the postsynaptic cell and elevating Ca^{2+} in a cell can induce an LTP-like effect (475, 484); the NMDA channel is permeable to Ca^{2+} (see section III B 4); blocking the synaptic activation of NMDA receptors (and hence preventing Ca^{2+}-influx through these channels) prevents the induction of LTP (see section V1 A 1 d), while promoting Ca^{2+} entry through voltage-gated channels, by depolarizing a cell, does not induce LTP (406). These experiments specifically implicate Ca^{2+} flux through NMDA channels and provide an explanation for the synapse specificity of LTP. It is argued that the elevated Ca^{2+} is restricted to those dendritic spines where synaptically released glutamate has activated the NMDA receptor system. The magnitude, time-course and spatial distribution of the NMDA receptor gated Ca^{2+}-flux during the induction of LTP has not been measured. It is likely, however, that the Ca^{2+} elevation is transient and that this initiates a sequence of biochemical processes that ultimately produce the persisting changes.

There is considerable evidence that protein phosphorylation may be involved in LTP (see ref. 78). In particular, it has been shown that the phosphorylation of protein F1 (also known as GAP43, B-50, pp46) correlates with the induction of LTP in the dentate gyrus, and that this phosphorylation is prevented if the induction of LTP is blocked by APV (454). Protein F1 is a substrate for PKC; however, the evidence that PKC is involved in LTP is controversial. Although phorbol esters, that activate PKC directly, can potentiate synaptic transmission this effect does not persist upon washout of the phorbol ester, and it does not occlude tetanus-induced LTP (and vice versa) (544). Tetanic stimulation in the presence of any one of a number of inhibitors of PKC (i.e., polymyxin B, mellatin H-7, sphingosine) leads to a short-lasting form of LTP only (471, 485, 611). It has been suggested, therefore, that activation of PKC is required for the later phases of LTP. Unfortunately, these PKC inhibitors are not highly selective agents. For example, polymyxin B is an NMDA antagonist (see section II B 4 c) and H-7 interferes with GABA-mediated synaptic inhibition (544). K-252-b is a potent PKC inhibitor, competing with ATP for the catalytic site (K_i = 20 nM). It has somewhat weaker effects on cAMP- and cGMP-dependent protein kinases (397). This agent, in concentrations appropriate for blocking PKC (e.g., 50 nM), prevents the induction of both the late phase of LTP (610) and the delayed increase in sensitivity of CA1 neurones to AMPA (143). This suggests that PKC may be involved in the slowly developing post-synaptic phase of LTP. However, since the potency of K-252-b against all kinases, in particular Ca^{2+}/calmodulin-dependent protein kinase II, is not known the precise identity of this K-252-b-sensitive kinase cannot be unequivocably defined. At the present time, therefore, all that can be concluded is that a protein kinase is likely to be involved in the slowly developing postsynaptic component of LTP.

One scenario is that Ca^{2+} entering via NMDA channels activates a Ca^{2+}-sensitive kinase (or kinases) in, or close to, a dendritic spine and this somehow results in an increase in local quisqualate receptor function. Since protein F1 is believed to be located presynaptically it is unlikely to be the substrate for this kinase. One possibility is that it is the quisqualate receptor per se that is phosphorylated and that this phosphorylation affects its conductance properties (e.g., decreased desensitization).

Several other intracellular processes have both been suggested to function in LTP and to be influenced by excitatory amino acids. Lynch and Baudry (473) proposed that Ca^{2+} activates a protease known as calpain and that this degrades a spectrin-like protein called fodrin. Since this protein is a major dendritic cytoskeletal protein, it was suggested that its proteolysis results in a structural change in the membrane of the postsynaptic spine that allows previously occluded glutamate receptors to contribute to the synaptic response. In terms of the specific receptor subtypes, the Ca^{2+} needed to activate calpain may enter via NMDA channels, since NMDA has been shown to cause proteolysis of spectrin in hippocampal slices (649). The newly exposed glutamate receptors would presumably be of the quisqualate receptor type.

It has been suggested that arachidonic acid metabolites (754) and EDRF (293) may be involved in LTP. Since these agents can freely diffuse across membrane, it has been proposed that they may act as intercellular messengers where they could, for example, communicate to the presynaptic terminal that the NMDA receptor system on the postsynaptic spine had been activated. In this context, NMDA receptor stimulation causes the release of EDRF from cerebellar neurones (293) and activation of the arachidonic acid cascade system in striatal neurones (220). A delayed release of proteins has also been detected following the induction of LTP. This release is dependent on NMDA receptor activation since it is blocked by APV (251).

There is some controversy as to whether NMDA receptor activation alone is sufficient to induce non-decremental LTP (131, 399, 703) (and see section VI A 3). One possibility is that during tetanic stimulation another receptor is activated. It has been suggested that this might be the metabotropic glutamate receptor, since APB, which may be an antagonist of this receptor (see section IV), prevents the development of the late phase of LTP (612). Activation of this receptor leads to stimulation of phospholipase C and hence the production of diacylglycerol and IP_3. In this context, DAG will activate PKC and this might explain the phosphorylation of protein F1. Furthermore, increased levels of IP_3 have been implicated in LTP (476). The finding that pretreatment with pertussis toxin, which blocks the metabotropic receptor, does not prevent the induction of LTP in the Schaffer collateral-commissural pathway is not inconsistent with this notion, since only the early phase of LTP was studied (373). Of interest was the observation that pertussis toxin treatment blocked the induction of LTP in the mossy fibre pathway, since this suggests that the metabotropic receptor may play an important role in this form of LTP (373). Several other observations have implicated a role for the metabotropic receptor in synaptic plasticity in the hippocampus. The activity of this system declines with age, indicating a possible role in developmental plasticity (557), whereas its activity is enhanced by spatial learning (559) and by kindling (370).

2. Kindling and kindling-like phenomena in hippocampus. A major advance in the study of epilepsy was the discovery by Goddard (300) that if periods of high frequency stimulation of certain brain regions were repeated at daily intervals then animals developed seizures. The stimulus intensity required does not initially need to induce changes in either behaviour or in the electroencephalogram. With successive kindling periods focal seizures appear which are detected as afterdischarges in the EEG; these then lengthen and spread and behavioral seizures develop. The culmination of the effect and attainment of the kindled state is the appearance of widespread clonic motor seizures which may last for the lifetime of the animal. Kindling may also be induced by focal injections of convulsive agents. A number of brain structures, particularly those of the limbic system, can be kindled. Most progress in the understanding of the mechanisms that underlie kindling have been made using the hippocampus.

The electrical stimulation that is required to produce kindling is similar to that which is employed acutely to elicit LTP; early stages of the kindling process involves LTP-like potentiation (695). This has led to the hypothesis that kindling is an excessive state of LTP. Based on the identification of the pivitol role of NMDA receptors in the induction of LTP (137) as well as the contribution of NMDA receptors to various models of epileptogenesis in situ (159) and in vitro (117, 212, 344) (and see section V B), attention has now focused on possible involvements of NMDA receptors in kindling.

The first evidence for an involvement of NMDA receptors in the induction of kindling comes from studies with hippocampal slices which use kindling-like stimuli to generate epileptiform activity. Wilson and colleagues (678) observed that high frequency trains delivered in stratum radiatum (typically 60 Hz for 2 s at 2 to 3 times maximum intensity for an orthodromic response) induced epileptiform activity in CA3. This activity was characterised by afterdischarges and spontaneous and evoked interictal-like bursts that persisted for several hours after the last stimulus train; this phenomenon is referred to as stimulus train-induced bursting (STIB). At about this same time Slater et al. (664) reported a similar phenomenon in the CA1 region. They applied five trains at 10 s intervals to stratum radiatum (each

train comprised 50 Hz, 2 s at maximum intensity for an orthodromic response) and observed progressively increasing LTP. After several of these episodes (each delivered at 30 min intervals), spontaneous and evoked interictal-like activity developed.

Slater and colleagues went on to show that if APV was applied throughout the tetanic trains, it completely prevented the development of epileptogenesis. However, if it was added after the epileptogenesis had been established it depressed, but did not abolish, the epileptiform events. Wilson's group (17) also found that APV prevented the induction of STIB in the CA3 region, but if added after the induction of STIB it reduced, but could not abolish, the epileptogenesis. They concluded that APV was strongly anti-epileptogenic but only weakly anticonvulsant.

The above in vitro models may be thought of as techniques giving data that are intermediate between LTP and classical kindling. Demonstrating that NMDA receptors are involved in the generation of classical kindling is more difficult due to the time-course of development. However, early studies had found that the dissociative anaesthetics ketamine and PCP were effective at preventing or prolonging the development of amygdaloid-kindled seizures, but were only weakly active at suppressing established seizures (85, 86, 101). At that time it was not known that PCP and ketamine were NMDA antagonists. After this realisation, essentially identical results were obtained with the more potent noncompetitive NMDA antagonist MK-801 (510). Additionally, dextromethorphan, which is a fairly weak NMDA antagonist (460), was found to prevent the development of full amygdala kindling and to reduce the seizure intensity of fully kindled animals (252). Furthermore, intrahippocampal infusion of APH has been found to slow the development of hippocampal kindled seizures (723). APH was also effective in depressing convulsions and the duration of afterdischarges in fully, but not partially, kindled animals.

In most of the above studies, NMDA antagonists displayed some ability at suppressing seizures if given after the seizures had been induced. These findings support the work of Bradford and colleagues who had found that both APV and APH reduced the duration of afterdischarges following amygdaloid-kindling (592), although these antagonists were not very effective on hippocampal seizures when injected into the lateral ventricle (593). Mody and Heinemann found that in slices prepared from rats that had received kindling of the amygdala or hippocampal commissures, NMDA receptors contributed to EPSPs in the perforant pathway under conditions where they did not in control animals (523, 526). Thus, unlike the situation in LTP, NMDA receptors contribute towards the enhanced synaptic activity following kindling. These receptors do not seem to account for the entire plastic change; presumably potentiation of non-NMDA receptor-mediated components are also involved.

3. Agonist-induced plasticity. Another strategy in the investigation of the receptor types required for the induction of LTP has been to examine the ability of amino acids applied alone, or in conjunction with single volleys, to induce LTP. Similar approaches have also been applied to the study of the generation of epileptiform activity. These experiments are discussed below with respect to the agonists used.

a. KAINIC ACID. Perhaps surprisingly, the first successful attempt to elicit an agonist-induced lasting potentiation of synaptic transmission used kainic acid. When applied briefly (e.g., 10 to 30 s) by iontophoresis into the cell body region, kainate was able to potentiate the size of the population spike evoked by low frequency stimulation of the Schaffer collateral-commissural pathway for fairly long periods (e.g., 45 min) (142). The ability of slices to be potentiated by kainate correlated with the ability of the slices to display LTP, suggesting that the two forms of potentiation may have common mechanisms.

The effect of iontophoretic application could be mimicked by brief perfusion with kainate (e.g., 10 μM for 1 min) and similar potentiation was also seen in the medial or lateral perforant paths and, with lower doses, in the mossy fibre pathway (136). Similar potentiating effects were observed following high concentrations (e.g., 1 mM) of folic acid, but not with quisqualate, NMDA, ibotentate, L-glutamate, or L-aspartate. These latter substances produced transient potentiations that were followed by long-lasting depressions of the evoked responses. Potentiation, however, has been reported in response to perfusion of quisqualate followed by NMDA, while K^+ was elevated (377).

Although kainate mimicked the effects of high frequency stimulation on the population spike, its effects on the EPSP, measured extracellularly in the dendritic region (136), were not the same; kainate produced a long-lasting depression in the size of the EPSP. The simultaneous potentiation of the population spike and depression of the field EPSP could be explained by a prolonged depolarization of the cells. However, potentiation, observed as an increased probability of an EPSP generating an action potential, was not associated with any change in passive membrane properties, as recorded intracellularly (139). Thus the mechanism of the kainate potentiation and its relationship to LTP remain obscure.

With higher doses or more prolonged exposure to low doses (e.g., 1 μM applied continuously in area CA1) kainate readily induces evoked and spontaneous interictal like activity, which may outlast considerably the period of application (53, 136, 142, 405, 468, 617, 743). The mechanisms responsible for this transformation are unclear, but may involve several factors including depolarization (617), a depression of GABA-mediated inhi-

bition (404, 405, 672) by presynaptic (258) and postsynaptic mechanisms (54), and a blockade of certain K^+ conductances (298). As in other models of epilepsy, NMDA receptors may contribute to the epileptiform activity generated. The duration of the interictal-like bursts elicited by stimulation of the Schaffer collateral-commissural pathway, in the presence of kainate, is quite sensitive to APV (343). In area CA3, the duration of spontaneous and evoked bursts is shortened by APV but their frequency is not reduced (554). It is interesting, however, that APV prevents transient applications of kainate (and elevated K^+) from inducing long-term synaptically evoked epileptiform discharges in the CA3 region (53). This finding implies that NMDA receptors are important for the induction, but only contribute partly to the maintenance, of kainate-induced epiletogenesis, a situation resembling kindling induced by electrical stimulation.

Another form of kainate-induced epileptogenesis also involves NMDA receptors. Intracerebroventricular injections of kainate produce a specific loss of CA3 cells ipsilateral to the lesion. Stimulation of the commissural afferents then elicits interictal-like bursts in the ipsilateral CA1 region (442). APV substantially reduces, but does not abolish, the duration of these epileptiform discharges, recorded extra- (37) or intracellularly (38). It is possible that the epileptogenesis in CA1 is caused by kainate-induced spontaneous discharges in CA3 (occurring during and for sometime after the injections of kainate) "kindling" the CA1 region. In this respect it would be interesting to know whether the changes in CA1 can be prevented by NMDA antagonists applied during this critical period.

b. NMDA. Although it is established that NMDA receptor activation is required for the induction of LTP in many pathways, it is not known whether activation of this receptor alone is sufficient to induce LTP. That this might be the case, however, was indicated by the observation that NMDA applied iontophoretically to the dendrites of CA1 neurons was able, after causing a transient depression, to potentiate the field EPSP evoked by stimulation of the Schaffer collateral-commissural pathway (137). The potentiation, like the initial depression of the field EPSP (and fibre volley), was completely prevented by APV (137). Kainate, quisqualate, L-glutamate, and L-aspartate applied similarly were not able to elicit potentiations of the field EPSP (137). A similar selective effect of NMDA was also noted in studies on the medial perforant path (141). In studies in both regions, a few low frequency shocks were applied during the application of NMDA to monitor its ability to reach the synaptic site. However, low frequency shocks do not seem to be necessary for the potentiation to occur. Using intracellular recording, the effects of NMDA can be monitored without the need for synaptic stimulation until after the acute effects of NMDA have subsided; under these conditions potentiation of the EPSP by NMDA can be demonstrated (401) (and our unpublished observations).

The time-course of potentiation induced by iontophoretically applied NMDA is shorter than that of tetanus-induced potentiation in the same slices (399). This led to the suggestion that NMDA receptor activation alone may be sufficient for only the early phase of LTP (399), and that other factors, in addition to NMDA receptor activation (446, 613), are required for non-decremental LTP. An alternative explanation is that with iontophoresis it is difficult to achieve the appropriate amount of NMDA receptor activation for non-decremental LTP. That this could be the case is indicated by the early observation that iontophoretic application of NMDA to the cell body region or perfusion of the whole slice with 100 μM NMDA leads to lasting depression, not potentiation, of the synaptic response (136). Indeed, some more recent studies have reported fairly long-lasting potentiation of synaptic transmission in the Schaffer collateral-commissural pathway following perfusion of hippocampal slices with NMDA. In one study perfusion of 1 μM quisqualate, followed by 1 μM NMDA, in the presence of 15 mM K^+, was reported to potentiate synaptic transmission for at least 25 min (377). In another study that used a complex protocol of drug administration (which involved lowering Mg^{2+}, elevating glycine and Ca^{2+}, and applying spermine) brief perfusion of 2.5 mM NMDA was able to potentiate synaptic transmission for at least 80 min (703). In a third study potentiation lasting at least 3 h was obtained by simply applying 50 μM NMDA for 1 to 2 min to hippocampal slices maintained under standard conditions (131). In these latter experiments, the CA3 region of the slice had been removed to prevent indirect effects from this area. These findings do not necessarily mean that NMDA receptor activation alone is sufficient to induce LTP since NMDA could, for example, release other substances from within area CA1 which then act on different receptors. This question is once again an open issue.

In the CA3 region, Wilson and his associates (17) found that NMDA could induce evoked and spontaneous bursting activity that persisted for hours after washout of NMDA. The induction of this bursting could be prevented by APV. However, if APV was added only after persistent bursting had been elicited by NMDA, then it was only weakly effective at depressing the duration of the activity. This pattern of sensitivity to APV is reminiscent of kindling. Although this study demonstrates that NMDA is able to elicit long term alterations in synaptic efficiency in the CA3 region of the slice, it does not determine whether it is the NMDA per se or the resultant bursting activity that causes the plastic change.

c. L-GLUTAMATE. As mentioned above, L-glutamate, applied by iontophoresis to the dendritic region in conjunction with low frequency stimulation, fails to produce a lasting potentiation of the field EPSP in the Schaffer

collateral-commissural pathway (137, 399) or in the EPSP recorded intracellularly (369). Similarly, when applied to the somatic region or to the whole slice in conjunction with low frequency stimulation, it fails to produce lasting potentiation of the population spike in this pathway (136, 142). However, when applied briefly to the dendrites and paired with single shocks in the Schaffer collateral-commissural pathway, L-glutamate has been reported to increase, for at least 30 min, the probability of an EPSP firing an action potential, an effect that might relate to E-S potentiation (369). In general, however, L-glutamate is not very good at eliciting LTP-like phenomena, although it can activate both NMDA and non-NMDA receptors. The probable explanation is that uptake protects NMDA receptors from exogenously applied L-glutamate, such that it acts predominently on non-NMDA type receptors; this is indicated by the relative insensitivity of L-glutamate to NMDA antagonists in slices and in vivo.

A quite different form of synaptic transformation has been described by Krishtal and colleagues in the Schaffer collateral-commissural pathway of rat hippocampal slices (431). They found that with prolonged perfusion of L-glutamate (0.25 to 1.5 mM) the following sequence of events occurs: the synaptic response is depressed; it then recovers (in the continued presence of L-glutamate) to a state that is now sensitive to blockade by APV and ketamine; in the presence of an NMDA antagonist (and L-glutamate) it then recovers again, but this time to a state resistant to all antagonists, including DGG (which normally blocks synaptic transmission in this pathway). All states are able to support LTP. In the presence of L-aspartate (1 mM) there also was recovery from blocked transmission, but this time straight to the state insensitive to all antagonists. No recovery from blocked transmission was seen with either perfusion of NMDA or kainate. It was suggested that these transitions may represent different functional states of synaptic transmission in the Schaffer collateral-commissural pathway. This is an intriguing possibility, but as yet physical changes in the slice cannot be ruled out. For example, excessive uptake of L-glutamate and L-aspartate may, by causing glial swelling, impose diffusion barriers in the slice which can alter the effectiveness of antagonists.

4. Mg^{2+}-free solutions and synaptic plasticity. Interest has focused on Mg^{2+} ions and their regulation of synaptic plasticity in view of this ions ability to block the NMDA receptor system (39) in a voltage-dependent manner (567). LTP is classically produced by high frequency stimulation in the presence of Mg^{2+}. Under these conditions the NMDA receptor system is activated since the depolarization associated with high frequency stimulation temporarily alleviates the Mg^{2+} block of NMDA channels (126). At other times (i.e., during single shock stimulation) Mg^{2+} sufficiently blocks NMDA channels to prevent significant activation of this system. However, if Mg^{2+} is omitted from the perfusate, single shock stimulation is able to activate the NMDA receptor system (117). Therefore, it has been reasoned that if high frequency stimulation is required only to overcome the Mg^{2+} block, and not for some other purpose such as to release an additional factor necessary for LTP, then it should be possible to elicit LTP in a Mg^{2+}-free medium using single shock stimulation.

In the first experiments to address this issue, Coan and Collingridge (117) noted that transient removal of Mg^{2+} during stimulation of the Schaffer collateral-commissural pathway at 0.1 Hz led to potentiation of the synaptic response in a proportion of slices, as assessed after re-addition of Mg^{2+}. This potentiation was not seen if the Mg^{2+}-free perfusate contains APV (41, 323). Saturation of LTP by repeated periods of high frequency stimulation prevented Mg^{2+}-free induced potentiation and vice versa, suggesting that both processes involved similar mechanisms (323). However, Mg^{2+}-free potentiation was not seen if the CA3 region was surgically removed, suggesting that potentiation by this method requires the propagation of spontaneous synchronised epileptiform events from this region (323, 553). It has been argued, therefore, that removal of Mg^{2+} does not directly result in LTP, but that the resultant synchronised discharge in area CA3 is able to lead to potentiation. On the other hand, in the dentate gyrus of standard hippocampal slices, a region where synchronised spontaneous discharges do not develop in Mg^{2+}-free medium, potentiation of the perforant path was achieved by brief perfusion with Mg^{2+}-free medium (513). This potentiation required low frequency stimulation and was prevented by APV, data which strongly suggest that low frequency stimulation is a sufficient condition to elicit LTP (when the necessity of overcoming the Mg^{2+} block of NMDA channels is by-passed).

If high frequency trains are delivered in Mg^{2+}-free medium, it might be expected that LTP, at least as great as that produced in Mg^{2+}-containing medium, should be produced. Surprisingly, it is actually more difficult to induce LTP of the Schaffer collateral-commissural pathway in Mg^{2+}-free medium (120). The reason for this does not appear to be that high frequency stimulation cannot elicit LTP in Mg^{2+}-free medium, but rather that the prior low frequency activation of the NMDA receptor system somehows "turns off" the LTP activation mechanism. Evidence supporting this conclusion includes the following observation. If APV is added in a concentration (e.g., 20 μM) that is sufficient to prevent activation of the NMDA receptor system during low frequency stimulation, but is insufficient to block its activation during high frequency stimulation, then LTP is readily elicited. If, however, APV is used at a dose (e.g., 200 μM) that blocks activation of the NMDA receptor system during high frequency transmission as well, then LTP is not elicited (121).

These results have several implications for the generation of LTP. First, extracellular Mg^{2+} is not required. Second, low frequency activation of the NMDA receptor system can, by some unknown mechanism, switch off the induction process. This effect is reversible, since upon re-addition of Mg^{2+} LTP can be easily elicited. It is conceivable that to generate LTP some intracellular event requires appropriate amounts of NMDA receptor activation within a certain time window. If the activation conditions are inappropriate, this process acutely down-regulates.

B. Neocortex

1. Adult neocortex. In view of the major role of the neocortex in processes of learning and memory, there has been considerable interest in the phenomenon of LTP in various neocortical preparations. The role of NMDA receptors in neocortical LTP was first demonstrated by Artola and Singer (29), who obtained intracellular recordings from layer III and IV cells, in response to stimulation of the underlying white matter, in slices of rat visual cortex. High frequency stimulation (20 to 50 Hz) delivered to the white matter induced a form of LTP in the small percentage of cells that responded to synaptic stimulation with a burst discharge. In contrast, LTP could not be induced in regular spiking cells. However, if synaptic inhibition was depressed by a $GABA_A$ antagonist, regular spiking cells were transformed into bursting cells and LTP could be readily induced. This was seen as an increase in size of the burst discharge and of the underlying EPSP and was prevented if the tetanus was given in the presence of APV. These data indicate that visual cortical cells can support a form of NMDA receptor-mediated LTP similar to that seen in the hippocampus. The major difference, however, is the necessity in the visual cortex to depress GABA-mediated synaptic inhibition (and hence LTP is manifested as an increase in epileptogenesis). One possible explanation for the lack of LTP under normal conditions is that there are insufficient NMDA receptors in visual cortex slices of adult rats. An involvement of NMDA receptors in LTP has also been demonstrated for layer V and VI cells in rat neocortex (63) and local circuit neurones in layer II/III of rat frontal cortex (694).

2. Developing neocortex. Evidence that NMDA receptors, and the plasticity in which they are involved, are more prevalent in the neocortex and various stages of development derives from several lines of investigation. Tsumoto and colleagues (715) found that APV was much more effective at antagonising visual responses of cortical neurons during the critical period of young kittens. It was suggested that NMDA receptors play a greater role in synaptic processing during the time of major developmental plasticity in the primary visual cortex. In other studies they found that LTP could be readily induced in visual cortex slices of young rats (21 to 40 days old), and that the induction of this LTP was blocked by APV (416).

A well studied form of synaptic plasticity is the activity-dependent modifications of neural connections in the developing visual system. Hubel and Wiesel (366, 367) showed that the connections between visual thalamic afferents (i.e., from the LGN) and neurons in the primary visual cortex (also known as striate cortex or area 17) are very malleable during early postnatal development. One way of studying this developmental plasticity is by using monocular deprivation, whereby one eye is deprived of visual experience for about 1 wk during the "critical" period of development (which lasts in the cat from about 3 wk to 3 mo of age). Upon subsequent testing, most neurons in striate cortex respond to visual stimuli presented to the eye that had always been open, and few neurons respond to visual stimuli presented to the previously deprived eye. An ocular dominance shift had occurred during the period of monocular deprivation. A considerable amount of work has gone into understanding the mechanisms that underlie this form of plasticity (see ref. 30). It shares many features in common with LTP in the hippocampus, in particular a hebbian-like nature, and this suggested a possible role for NMDA receptors in its generation. Direct evidence supporting such a conclusion was presented by Singer and colleagues (420) who found that an intracortical infusion of DL-APV, but not L-APV, rendered the striate cortex of the kitten resistant to the effects of monocular deprivation.

The effects of APV were not specific for preventing the ocular dominance shift. APV also caused a reduction in light-evoked synaptic responses, an effect that should not have been surprising in view of the well established role of NMDA receptors in synaptic transmission (see section V). APV also disrupted orientation selectivity, an effect usually seen with binocular deprivation. Surprisingly, orientation selectivity was also disrupted if APV was administered after it had been established, indicating that NMDA receptors are required for the maintenance as well as the acquisition of this form of plasticity. In complementary studies, Rauschecker and Hahn (606) found that ocular dominance shifts could be prevented if kittens were briefly anaesthetised with ketamine-xylazine after each period of monocular deprivation. Thus, the anaesthetic was disrupting a "consolidation" period that occurred immediately following the conditioning. Since xylazine alone was not effective, it was suggested that the disruption of consolidation was due to an action of ketamine, possibly on the NMDA receptor system. Considered together, these results strongly implicate a role for NMDA receptors in plasticity, as well as in neurotransmission, in the visual cortex, particularly during development.

NMDA receptors are, therefore, believed to function as an associative device to increase synaptic strength in

the visual cortex. It is proposed that geniculate afferent connections are consolidated if these afferents are active when their target cell is depolarized (51). A separate mechanism is required, however, to weaken the synaptic strength and eventually eliminate afferents that are active out of phase with their target cell. Bear and colleagues (219) have suggested that the metabotropic glutamate receptor may subserve this function. This receptor could be activated by the afferent cell and would not depend upon the state of membrane depolarization of postsynaptic cell. Interestingly, in synaptoneurosomes of rat neocortex the activity of this receptor, to stimulate the accumulation of inositol phosphate, is absent at birth, peaks after 1 wk and declines to adult levels by 5 wk. This time-course parallels the activity-dependent elimination of exuberant connections in visual cortex.

C. Optic Tectum

A form of developmental plasticity in the visual system that is believed to use similar mechanisms as the formation of ocular dominance columns in visual cortex is the formation of eye-specific stripes of retinal projections to the optic tectum. In surgically produced three-eyed tadpoles, there is eye-specific segregation of the terminals of the retinal ganglion cells from the two retinas that innervate the same tectal lobe. APV was found to specifically desegregate the afferent terminals whereas NMDA caused sharper segregation (114). These findings were interpreted as NMDA receptor activation favouring synapse stabilization of coactive visual afferents.

D. Cerebellum

1. Quisqualate receptors. Transmission in the parallel-fibre-Purkinje cell synapse can be depressed for long periods by conjoint activation of this and the climbing fibre pathways. This form of plasticity is called long-term depression (LTD) and is believed to underlie learning in the cerebellum (374). LTD is associated with a reduction in the sensitivity of Purkinje cells to iontophoretically administered L-glutamate (375). Kano and Kato (395) have shown iontophoretic application of quisqualate (or L-glutamate), but not kainate or L-aspartate, can be substituted for stimulation of the parallel-fibres. Thus, conjunction of quisqualate with climbing fibre stimulation leads to a depression of the parallel fibre-evoked response which reaches a maximum within 20 min and lasts for at least 50 min. The authors proposed that quisqualate receptors are involved in both synaptic transmission and plasticity in the parallel fibre pathway.

2. NMDA receptors. It is of interest that in the adult rodent cerebellar cortex NMDA is not a potent excitant of Purkinje and granule cells (156, 295, 417, 603). Often the application of NMDA inhibits activity in Purkinje cells, but this is indirect due to a preferential excitation of neighbouring inhibitory interneurons (156, 395, 603). However, NMDA-induced excitations of Purkinje neurons can be observed (156), particularly in the presence of picrotoxin, which blocks GABA-mediated inhibition (603). These data suggest that NMDA receptors are present on adult Purkinje cells but in relatively low numbers. In contrast, in the immature cerebellum NMDA is a potent excitant of Purkinje and granule cells (157, 295). Sensitivity to NMDA is high in 5 to 8 day old rats (157, 288) and declines especially between days 14 to 21, at which time it reaches adult levels (288). Comparable changes in the sensitivity of these cells to kainate and quisqualate during development are not seen (288).

The transient expression of high levels of NMDA receptors at a time critical in the development of the cerebellum, and the known role of NMDA receptors in synaptic plasticity in other brain regions (127), indicate a role for NMDA receptors in developmental plasticity in the cerebellum. In this regard, it is particularly interesting that activation of NMDA receptors can stimulate neurite outgrowth from (582) and prevent excessive cell loss of (42) granule cells. Thus, in a study by Pearce et al. (582), neurite outgrowth was inhibited by enzymatic removal of glutamate from, or by the addition of kynurenate or APV to, the culture medium. In the work of Balazs et al. (42) NMDA supplementation of the culture medium prevented the extensive granule cell loss that normally occurs. These two independent studies suggest that NMDA receptors can exert trophic influences upon developing granule cells.

E. Summary

It is well established that the NMDA receptor, in addition to being involved in synaptic transmission, has a fundamental role in synaptic plasticity in the vertebrate nervous system. This was first found to be the case for LTP in the hippocampus, where it was shown that the NMDA receptor confers hebbian-like and associative properties upon a synapse. A similar type of LTP involving NMDA receptors has been demonstrated in neocortex and is likely to be a fairly widespread phenomenon throughout the brain. A similar sort of hebbian-like mechanism involving NMDA receptors seems to be important in types of developmental plasticity, such as the ocular dominance shift that can be experimentally induced in the visual system.

Several mechanisms, spanning different time-periods, probably account for the persisting alterations in synaptic strength that underlies NMDA receptor-induced plastic change. There may be an increase in neurotransmitter release and a specific change in quisqualate receptor function. Ultimately, however, the change is likely to be anatomical involving the consolidation of the synapse at the expense of others. There is also evidence that NMDA receptor function itself is increased in, for example, the kindling model of epilepsy. It is not known, however, if there is a primary change or a consequence of, for example, depressed synaptic inhibition and/or potentiated quisqualate receptor mediated synaptic excitation.

The role of other excitatory amino acid receptor subtypes in plasticity is more speculative. The metabotropic receptor has been implicated in plasticity in both hippocampus and neocortex. The kainate receptor could be involved in LTP in the mossy fibre pathway. Until the development of selective antagonists for these receptors, their roles in synaptic plasticity will probably remain a matter of speculation.

VII. Behaviour

Since excitatory amino acid receptors mediate most fast and some slow forms of excitatory synaptic transmission, as well as important forms of plasticity in the vertebrate central nervous system, it is likely that they will play a role in all forms of behaviour. With the development of selective antagonists that can readily penetrate into the central nervous system, more precise information on the roles of the excitatory amino acid receptor subtypes is likely soon to emerge. For this reason gross behaviours are not discussed at length in this review. However, the neural basis of certain behaviours are described in relationship to synaptic transmission in various brain regions (e.g., fictive locomotion as a model for understanding motor pattern generation is discussed in section V A 10). For some work on the behavioural effects of competitive NMDA antagonists and the similarities to the effects of (and cross-discrimination with) PCP-like compounds see refs. (275, 424, 425, 713). For studies concerning the roles of excitatory amino acid receptors in sleep see refs. (27, 28, 274).

The development of selective NMDA antagonists has led to important new insights into cognitive processes, in particular about the mechanisms of learning and memory. This section will briefly focus on this area from a behavioural stance. For a more detailed account see ref. (540). The theoretical basis for these experiments (i.e., the involvement of NMDA receptors in hippocampal LTP) is described in section VI A 1.

Morris and colleagues (539) showed that intraventricular infusion of APV can impair a spatial learning task while at the same time leaving a visual discrimination task unaffected. Similar positive and negative impairments were obtained with local injections into hippocampal and cortical areas, respectively (540, 541). The effect of APV is not specific to spatial learning since it also impairs a hippocampal non-spatial operant task, known as DRL schedules (711). Thus, APV impairs some but not all forms of learning. The doses of APV that impair spatial learning are similar to those that prevent the induction of LTP, consistent with a cause and effect relationship (540). Interestingly, doses of APV that impair the learning of new spatial information do not affect information retrieval (540). In a different type of behavioural experiment, Laroche and colleagues (446) used LTP of the perforant path as a Pavlovian conditioning stimulus for footshock suppression of a food-motivated lever pressing task. Chronic infusion of APV blocked both the induction of LTP and the associative learning.

These data argue strongly, if not yet conclusively, that NMDA receptors through an LTP-like mechanism are involved in certain forms of learning in the brain.

VIII. Neuropathology

A major impetus in excitatory amino acid receptor research has been the implication of these receptors in neuropathological conditions, and hence the potential for new therapeutic approaches. The most compelling evidence comes from studies with selective antagonists, and as such most of our present knowledge concerns the role of the NMDA receptor in pathological states. In this section, an attempt is made to explain the role of excitatory amino acid receptors in pathology on the basis of the knowledge of the synaptic function of these receptors (see sections V and VI). Other, including more clinical, aspects of the role of excitatory amino acid receptors in disease states are discussed in refs. (338, 376, 514).

A. Epilepsy

The first compelling evidence that excitatory amino acid antagonists may be of therapeutic value was the finding that competitive NMDA antagonists, in particular APH, are anticonvulsant in a variety of experimental models of epilepsy (159). There is, however, a large variability in the susceptibility of various models of epilepsy to the action of NMDA antagonists. This variability may reflect the extent that NMDA receptors contribute to synaptic mechanisms in the particular region of the brain involved in generating the seizure. It is noteworthy that sensory-induced seizures in genetically prone mice and baboons are particularly sensitive to the effects of NMDA antagonists, since NMDA receptors seem to play a major role in the mediation of sensory information (see section V). In certain other models, for example, some chemically induced seizures NMDA antagonists are only weakly, if at all, anticonvulsant. In these models, NMDA receptors may contribute to, but are not necessary for, the expression of the seizure generating activity. Thus, in these situations NMDA antagonists may raise the threshold for, but not prevent, seizures.

The mechanisms by which NMDA receptors contribute to interictal and ictal-like activity is described in detail in section V B. In brief, if the quisqualate receptor mediated EPSP is prolonged by, for example, a depression of GABA-mediated inhibition, then cells will remain depolarized for a sufficiently long time for the neurotransmitter to appreciably activate the NMDA receptor system. Since the NMDA receptor-mediated EPSP has a long duration and increases in size with membrane depolarization it will promote repetitive firing. In this manner NMDA receptors may contribute to abnormal activity at an epileptic focus. High frequency discharges, from such a focus, will provide favourable conditions for

activity of the NMDA receptor system in target neurones, and hence NMDA receptors may contribute to the spread of epileptic activity from the focus.

Although NMDA antagonists are undoubtedly anticonvulsant, they are perhaps of greater potential as antiepileptogenic drugs, where they may be able to prevent the changes in the brain that predispose the area to seizure activity. The logic of this potential therapeutic strategy is the known role of NMDA receptors in synaptic plasticity (i.e., LTP and kindling, see sections VI A) and the finding that NMDA antagonists are potent anti-epileptogenic agents in experimental models of epilepsy (755).

A major potential problem with the use of NMDA antagonist as either anticonvulsant or antiepileptogenic agents is the likelihood of unacceptable side-effects with chronic administration. NMDA receptors are important in synaptic transmission in many pathways in the brain, and in a form of synaptic plasticity that underlies certain forms of learning and development (see sections V and VI). Whether the therapeutic advantages will outway the side-effects will need to be determined during clinical trials.

B. Neuronal death

There has been considerable interest in the mechanisms by which excitatory amino acids can cause cell death. The so-called excitotoxic hypothesis (572) suggested that cell death is essentially due to excessive excitation. Early studies were particularly concerned with the mechanisms by which kainate kills neurones (278, 296), but its precise mode of action has remained elusive. Once again, the development of selective NMDA antagonists has diverted attention to the role of this receptor in excitotoxicity and has led to important advances in the understanding of mechanisms involved in neuronal death.

NMDA antagonists offer protection against neuronal cell death in models of ischaemia (660), hypoglycaemia (747), and trauma (238). Consequently, there has been considerable interest in the potential use of NMDA antagonists as neuroprotective agents in, for example, stroke, cardiac arrest and traumatic injury. Of major significance was the finding that MK-801 can offer neuroprotection when given to gerbils up to 24 h after an ischaemic insult (299). Competitive NMDA antagonists are also effective if given after the ischaemia (81, 514). This means that NMDA receptor-mediated mechanisms responsible for cell death occur for considerable periods of time after the initial insult. Consequently, acute therapies may be efficacous if given shortly after cardiac arrest, stroke, or traumatic injury. The therapeutic time-window for administering an NMDA antagonist post-insult is shorter in rats than in gerbils (514) and has not yet been established in man.

The mechanism of NMDA receptor-mediated cell death has been extensively studied by Garthwaite and colleagues using rat cerebellar slices and by Choi and associates using cultures of mouse neocortical neurones. In both types of preparation, it is established that Ca^{2+} is the major ion involved in causing NMDA- and glutamate-induced toxicity (109–111, 282, 287). Although Cl^- fluxes have also been implicated in NMDA-induced cell death (600, 622), this seems to be peculiar to tissue culture and caused by the unrestricted swelling of cells (283, 291). The mechanism of NMDA receptor-mediated cell death seems to be an extension of the mechanism by which this receptor is involved in physiological processes. Thus, the potency of NMDA at killing granule cells and intracerebellar nucleus neurons is potentiated in Mg^{2+}-free medium or by depolarization in Mg^{2+}-containing medium. Depolarization alone by 50 mM K^+, which would be expected to lead to entry of Ca^{2+} via voltage-gated channels, was not toxic (284). It is reasonable to suppose that cell death ensues when entry of Ca^{2+} through NMDA channels is in excess of that which can be maintained at low levels by sequestration and pumping mechanisms. If Ca^{2+} remains elevated for too long it could lead to over stimulation of, for example, proteases and phospholipases with destructive results.

NMDA antagonists offer protection against hypoxic/hypoglycaemic-induced neuronal death and irreversible synaptic impairement in brain slices and cell cultures (113, 302, 303, 624). These models are now being used for the preliminary screening of new anti-ischaemic agents.

Quisqualate also causes neurodegeneration. In the hippocampus this "dark cell degeneration" resembles the pathology following periods of cerebral ischaemia or seizure activity (286). In hippocampal slices from young rats, quisqualate kills cells in the order CA3 > CA1 > dentate gyrus. The toxicity is not dependent on either Ca^{2+} or Cl^- and is not blocked by NMDA antagonists. CNQX has complex effects on the neurotoxicity. If present during the exposure to quisqualate it is ineffective; however, if added immediately after the exposure to quisqualate it offers protection (285). It is possible, therefore, that quisqualate neurotoxicity involves mechanisms that use, firstly, metabotropic (since these are CNQX-resistant) and, secondly, conventional (i.e., CNQX-sensitive) quisqualate receptors.

There has been considerable speculation that excitotoxic mechanisms may be involved in neurodegenerative diseases. For example, in Alzheimer's disease an early symptom is the inability to learn new information and a common pathology is a marked loss of pyramidal cells in the hippocampus. It might be more than coincidence that hippocampal neurones retain high densities of NMDA receptors throughout life. The nature of the excitotoxins, if any, in these various conditions is unknown but they could have one of two origins, exogenous or endogenous.

It has been suspected for some time that ODAP that occurs in the chick pea (*Lathyrus sativus*) is responsible

for the neurodegenerative condition known as lathyrism (737). This toxin may work through an excitotoxic mechanism involving non-NMDA, possibly quisqualate receptors (105). More recently, Spencer and Nunn and their colleagues, have shown that a structurally related toxin β-*N*-methylamino-L-alanine (BMAA), which is found in the seed of *Cycas circinalis*, may be responsible for the degenerative condition known as the amyotrophic lateral sclerosis (ALS)-parkinsonism-dementia of Guam. This toxin produces neurodegeneration in monkeys (677) and toxicity in culture in a manner that can be prevented by NMDA antagonists (621). These findings raise the possibility that exogenous excitotoxins may be responsible for the more common neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS). Alternatively, the excitotoxin in these more common disorders may be endogenous. For example, quinolinate has been suggested to be an endogenous agent that could be responsible for Huntington's disease (50), and abnormalities in glutamate metabolism or transport could lead to excitotoxic effects of the natural transmitter in ALS (596).

IX. Concluding Remarks

The last decade has seen considerable advances in the knowledge and understanding of the role of excitatory amino acid receptors in the vertebrate central nervous system. This has come about largely because of the discovery of selective antagonists and the developing concept of multiple types of excitatory amino acid receptor.

The first useful antagonists were for the NMDA receptor and as a consequence, and since NMDA itself is a highly selective agonist, most is known about this receptor subtype. NMDA gates a high conductance cation selective ion channel which is blocked in a voltage-dependent manner by divalent ions, such as Mg^{2+}, and dissociative anaesthetics, such as PCP. Activation of the NMDA receptor requires the presence of glycine. However, since very low amounts of glycine are required the physiological significance of this site, if any, is unclear. Another important property of this system is that the NMDA channel is permeable to Ca^{2+}.

The NMDA receptor serves two main, inter-related functions in the brain. It is involved in synaptic transmission and in a form of plasticity that may underlie important forms of learning and development. Two features of the NMDA receptor system are important in understanding its role in synaptic transmission; the voltage-dependence conferred by Mg^{2+} and the slow time-course of the NMDA receptor-mediated EPSP. As a consequence the NMDA receptor system is particularly influenced by synaptic inhibition, which acts to maintain cells in a hyperpolarized state. Synaptic activation of the NMDA receptor system occurs when synaptic inhibition is depressed, in particular during high frequency transmission. The entry of Ca^{2+} through NMDA channels is believed to be of fundamental importance in synaptic plasticity. Uncontrolled entry of Ca^{2+} through this system is likely to be a major cause of several acute and chronic neuropathologies.

Many drugs, including dissociative anaesthetics and tricyclic antidepressants, can block NMDA channels. Since the ability of a range of drugs to block NMDA-induced response correlates with their ability to cross-discriminate with PCP and to displace binding to "PCP receptors," it has been suggested that the NMDA receptor system may mediate the psychotomimetic effects of PCP and hence that the NMDA receptor system may be involved in schizophrenia. More recent studies have shown that ethanol, over a dose-range that produces intoxication, depresses NMDA receptor-mediated responses in hippocampal neurones (469, 470) (and see ref. 453). It is likely that more drug interactions with the NMDA receptor system will be found in the future. Other areas of potential interest include polyamines, gangliosides, and adenosine.

The other major excitatory amino acid receptor for which a function is established is the one often called the quisqualate receptor, which is best characterized by its activation by AMPA and blockade by CNQX. This receptor is likely to be responsible for all fast amino-acid-mediated EPSPs in the vertebrate central nervous system. Recent evidence suggests that an NMDA receptor-initiated, kinase-mediated process may lead to an increase in quisqualate receptor function and that this might underlie increases in synaptic efficacy.

Other excitatory amino acid receptors exist, but in the absence of selective antagonists little is known about their function. A kainate receptor might be specifically associated with certain fibre tracts (e.g., hippocampal mossy fibres and dorsal root C-fibres), and an L-APB receptor with different presynaptic terminals (e.g., lateral perforant pathway in the dentate gyrus) and a metabotropic glutamate receptor may be involved in PI hydrolysis and Ca^{2+} mobilization, particularly during development. Yet other affects of excitatory amino acids, such as the potentiation in culture of whole cell responses to GABA (679), have been described, but how these relate to any of the above receptors is unclear.

An area not discussed in this review since it is still in its infancy is the molecular biology of excitatory amino acid receptors. In this respect, however, it is worth noting that a kainate receptor (310), the metabotropic glutamate receptor (692) and the NMDA receptor (438, 451, 722) have been expressed in *Xenopus* oocytes. Progress is also being made in the solubilization of excitatory amino acid receptors (e.g., 756). This is likely to be a major growth area in the near future. Another area that might develop in the future is the properties and functional significance of excitatory amino acid receptors on glial cells (see, e.g., 720).

In summary, the explosion of interest in excitatory

amino acid receptor research has led to many important and interesting findings. There are, however, many more important questions that remain only partly answered and probably many more surprises ahead.

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