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MODULATION OF GLUTAMATE RECEPTORS: MOLECULAR MECHANISMS AND FUNCTIONAL IMPLICATIONS

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INTRODUCTION

The concept that excitatory amino acids (EAA) function as neurotransmitters mediating neuronal excitation is now well established. Their receptors are among the most abundant in the mammalian central nervous system. Recent progress in the understanding of EAA receptors has been summarized in several review articles that focus on the selectivity of agonists and competitive antagonists for the particular subclasses of EAA receptors (1–4), noncompetitive EAA receptor antagonists (5), anatomical organization of EAA receptors in the CNS (6), characteristics of ionic channels associated with EAA receptors (7, 8) and the role of EAA receptors in synaptic plasticity (9), long-term potentiation (10), and neurotoxicity (11).

The current classification of EAA receptors, originating mostly from iontophoretic and radioligand-binding studies, is based on ligand selectivity in distinguishing receptors for N-methyl-D-aspartate (NMDA), kainate, quisqualate, and 2-amino-4-phosphonobutyrate (APB) (3). Among endogenous compounds, L-glutamate seems to activate all of the above receptors, although other compounds found in the brain tissue, such as L-aspartate, L-homocysteate or N-acetyl-aspartylglutamate, may activate particular EAA receptor subtypes (3).

Although the activity of glutamate receptors may be regulated by mechanisms controlling the release and reuptake of the transmitter (12), an increas-

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ing body of evidence indicates that the control of glutamatergic transmission may be realized at the postsynaptic site of transmitter action. Here, several levels of control may be envisaged: (*a*) endogenous compounds binding to the primary transmitter recognition site may interfere in a competitive manner; (*b*) other compounds may bind to sites distinct from the primary recognition site (allosteric sites) and induce a positive or negative modulation of the affinity of transmitter recognition sites; (*c*) modulators may also affect the efficiency of coupling between the transmitter recognition site and the effector mechanism; (*d*) in the case of ionotropic receptors noncompetitive antagonists may bind within or in the proximity of ionic channels and inhibit ion fluxes. Thus, receptor function depends on dynamic interactions between primary transmitter recognition and modulatory sites that affect the coupling and effector mechanisms responsible for signal transduction. Changes in these interactions may underlie the mechanisms of synaptic plasticity and the impairment of receptor function in various neuropathologies.

This review describes the various molecular mechanisms participating in signal transduction at EAA receptors and focuses on the evidence pointing to the existence of multiple modulatory sites within the receptor domains, on their mutual interactions, and their role in the control of receptor function. Included is a demonstration that the modulation of EAA receptors observed in vitro relates to the involvement of these receptors in various aspects of brain function and pathology.

Mechanisms of Signal Transduction at Glutamate Receptors

In functional terms, a neurotransmitter receptor may be defined as a complex protein structure located in the neuronal membrane that recognizes a specific transmitter molecule and transduces the incoming message into changes of membrane potential and/or synthesis of intracellular messenger molecules. On this basis, ionotropic and metabolotropic transmitter receptors can be distinguished (13). In the former, the transmitter recognition site is coupled either directly or indirectly to an ionic channel and its activation results in channel opening and increased ion fluxes across the neuronal membrane. In metabolotropic receptors, the transmitter recognition site is coupled, often through GTP-binding proteins, to a membrane-bound enzyme that catalyzes the formation of single or multiple second messengers. In some cases these two categories cannot be clearly distinguished; the opening of receptor-operated Ca^{2+} channels, for instance, will trigger a cascade of intracellular messages caused by activation of many Ca^{2+}-dependent enzymes.

IONOTROPIC GLUTAMATE RECEPTORS The development of new electrophysiological techniques, especially single channel recording in cultured neurons, allowed it to be established that glutamate activates cationic channels with multiple conductance levels (14, 15). These channels can be further

distinguished since NMDA preferentially activates channels with large (40–50 pS) conductance levels (16), while kainate and quisqualate activate those of low (5–15 pS) conductance (17). However, each of these agonists can activate additional conductances resembling those induced by the other agonists. These observations led to two hypotheses; either there is only one glutamate receptor channel complex able to assume different conductance states depending on the agonist (14), or three distinct receptors are coupled to a similar ionic channel with multiple conductance states (14, 15). The ionic properties of the NMDA and non-NMDA (kainate and quisqualate) channels can be distinguished. While all glutamate-activated channels are permeable to Na^+ and K^+ ions (18), those activated by NMDA also allow Ca^{2+} fluxes (19–21). The NMDA channel can also be distinguished from non-NMDA channels on the basis of its modulation, (described below). However, at the present time single channel recordings do not permit a clear distinction between kainate and quisqualate receptors.

Ionotropic glutamate receptors can be studied with the use of biochemical techniques. The use of Ca^{2+}-sensitive dyes (21, 22) showed that the activation of NMDA receptors evokes an increase in intracellular Ca^{2+} concentration. The studies of $^{45}Ca^{2+}$ influx in cultured cerebellar granule cells showed an increased Ca^{2+} entry induced by the activation of NMDA and kainate but not quisqualate receptors (23, 24). Kainate does not induce Ca^{2+} currents when measured by electrophysiological techniques (17). This apparent discrepancy could be explained by a presynaptic localization of kainate receptors (25). The responses to NMDA and kainate could be distinguished by their different sensitivity to the action of competitive and noncompetitive antagonists (24, 26). The use of primary cultures of granule cells allowed us to establish that the enhanced Ca^{2+} entry due to NMDA receptor activation leads to several intracellular metabolotropic responses. These include the activation of guanylate cyclase resulting in increased formation of cGMP (27), release of arachidonic acid (28), translocation and activation of protein kinase C (29) and increase in the expression of *c-fos* proto-oncogene (30). Among these responses kainate receptors strongly enhance cGMP formation (27).

METABOLOTROPIC GLUTAMATE RECEPTORS Glutamate metabolotropic receptors are coupled to phospholipase C located within the neuronal membrane. Their stimulation increases the hydrolysis of membrane phosphoinositides (PI) (13, 31–34). This leads to the formation of two distinct second messenger molecules: inositol-1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DG) (35–37). IP_3 acts at an intracellular receptor located on the endoplasmic reticulum and increases the intracellular Ca^{2+} concentration, which may lead to the activation of a variety of Ca^{2+}-dependent processes (38). DG, in the presence of Ca^{2+} and phosphatidylserine, facilitates the activation of protein kinase C (39).

The classification of metabolotropic glutamate receptors is not clear. It has been difficult to correlate the pharmacology of PI hydrolysis stimulation with receptor subtypes established in radioligand-binding assays and electrophysiological studies (1, 3). In cultured cerebellar granule cells, two subtypes of metabolotropic glutamate receptors were identified—G_{P1} and G_{P2} (13). The former are activated by glutamate, aspartate and NMDA, and are inhibited by the same competitive and noncompetitive antagonists as the ionotropic NMDA receptors (24, 40, 41), while the latter are activated by glutamate and quisqualate and are insensitive to NMDA receptor antagonists (24, 40, 41). Moreover, G_{P2} receptors are inhibited by pertussis toxin, which indicates that a GTP-binding protein is involved in the coupling between the recognition site and phospholipase C (42). Pertussis toxin also inhibits the increase in chloride conductance evoked by glutamate and quisqualate in *Xenopus* oocytes injected with rat brain mRNA (34). However, this electrophysiological response is secondary to the activation of a metabolotropic receptor coupled with PI hydrolysis.

The pharmacological profile of glutamate receptors stimulating PI hydrolysis in slices from several brain areas differs from that seen in cultured neurons. In newborn rats, glutamate, aspartate, quisqualate, and ibotenate strongly enhance PI hydrolysis (33). These responses decline during postnatal development (33) but reappear in adult animals after specific lesions of glutamatergic pathways (43). This stimulation is not activated by NMDA and is resistant to PCP and APV inhibition, although it is antagonized by APB (33, 43).

Modulators of NMDA Receptor Activation

All electrophysiological and biochemical responses induced by NMDA receptor agonists are inhibited by several competitive antagonists. Among the most selective are 2-amino-5-phosphono-valeric (APV) and 2-amino-7-phosphonoheptanoic (APH) acids (44–46), and the newly developed more potent analogs 3-(2-carboxy-piperazin-4-yl)propyl-1-phosphonic acid (CPP) (47, 48) and cis-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755) (49). Here, we focus on the modulation of NMDA receptor responses by agents acting at sites distinct from the primary transmitter (agonist) recognition site. These include the inhibition by Mg^{2+} and Zn^{2+}, noncompetitive inhibition by phencyclidine (PCP)-like compounds and the enhancement of responses by glycine.

MAGNESIUM The ability of Mg^{2+} ions to inhibit depolarizations induced by NMDA receptor agonists was first demonstrated in isolated spinal cord preparations (50). Studies of cultured neurons using voltage-clamp and patch-clamp techniques showed that this inhibition is noncompetitive and voltage-dependent (16, 18, 51–53). This implies that at physiological concentrations

(about 1mM) Mg^{2+} blocks the NMDA receptor-coupled ion channel, but a high-frequency stimulation may induce a neuronal depolarization sufficient to reduce the Mg^{2+} block (54). The blocking effect of Mg^{2+} was also shown in biochemical studies of NMDA receptor-mediated intracellular events. In cultured neurons, Mg^{2+} inhibits Ca^{2+} influx (21, 22, 26), cGMP formation (27), and arachidonic acid release (28) induced by NMDA receptor agonists. In all cases the inhibition caused by Mg^{2+} was selective for responses elicited by the agonists of the NMDA receptor, but not by kainate or quisqualate.

Mg^{2+} was also found to inhibit PI hydrolysis induced by NMDA receptor agonists in cerebellar granule cells (41), while the effect of quisqualate was unchanged. Such a response, therefore, is either secondary to an initial opening of NMDA receptor-coupled ionic channels, or the metabolotropic NMDA receptor (G_{PI}) has a site where Mg^{2+} can bind and induce a noncompetitive receptor inhibition. That metabolotropic and ionotropic NMDA receptors are distinct may be supported by the finding that micromolar concentrations of Ni^{2+} and Co^{2+} enhance PI hydrolysis induced by NMDA receptor agonists, but not by quisqualate (26, 55). This stimulation is antagonized by Zn^{2+} and Cu^{2+}, but not by 1 mM, Mg^{2+}, or Ca^{2+}. At millimolar concentrations, Ni^{2+} and Co^{2+} show an inhibitory action similar to Mg^{2+}, as it was also reported for the inhibition of NMDA-induced ion currents (18, 53). Even though the mechanism and significance of the potentiation caused by Ni^{2+} and Co^{2+} is unknown, the inability of Mg^{2+} to inhibit this effect indicates an action at a separate site that may contribute to the modulation of metabolotropic NMDA responses in the presence of Mg^{2+} ions.

ZINC Recently, Zn^{2+} was reported to attenuate the depolarization of cortical neurons induced by NMDA receptor agonists (56), as well as NMDA-induced neurotoxicity (57). Since Zn^{2+} failed to reduce postsynaptic responses to kainate and quisqualate, its action was selective for NMDA receptors. Also in hippocampal neurons, Zn^{2+} was shown to induce a noncompetitive inhibition of NMDA responses, which, unlike that of Mg^{2+}, was voltage-independent (58). This suggests that Zn^{2+} acts at a site distinct from Mg^{2+}, probably outside the ion channel. Its role in modulating the activity of NMDA receptors is unclear, but it should be noted that Zn^{2+} was found in the terminals of hippocampal excitatory mossy fibers, from where it can be released by a depolarizing stimulus (59–61), possibly together with glutamate.

PHENCYCLIDINE Neuronal excitation induced by NMDA, but not by kainate and quisqualate, is reduced by dissociative anesthetics such as ketamine and PCP (62, 63), by *sigma* opiates N-allylnormetazocine (SKF10,047) and cyclazocine (64), and with even higher potency by a newly developed compound (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine

maleate (MK-801) (65, 66). Since these compounds act at a site distinct from the NMDA recognition site (63, 67), they have been classified as noncompetitive NMDA antagonists. Their action is voltage-dependent appearing at negative membrane potentials and displays use-dependence, signifying that both the inhibition and the recovery from inhibition are facilitated in the presence of a NMDA receptor agonists (68, 69). PCP-like compounds have therefore been concluded to bind within the NMDA receptor channel, causing a blockade of the open channel.

The noncompetitive antagonism of NMDA-induced responses was also shown in biochemical studies. PCP inhibits NMDA receptor-stimulated Ca^{2+} influx, cGMP accumulation, PI hydrolysis (24) and arachidonic acid release (28) in cultured neurons, as well as $^{22}Na^{+}$ flux in rat hippocampal slices (70). In vivo, PCP and analogs inhibit the NMDA-induced accumulation of cGMP in rat and mouse cerebellum (71, 72). In slices from various brain regions, PCP-like compounds antagonize NMDA receptor-stimulated release of neurotransmitters, such as acetylcholine, dopamine, norepinephrine, and GABA (72–76).

GLYCINE In cultured mouse brain neurons, glycine facilitates depolarization induced by NMDA and glutamate without affecting kainate- and quisqualate-induced currents (77). This effect is not inhibited by strychnine, hence is not mediated by the strychnine-sensitive inhibitory receptor (78, 79). Similar effects of glycine were seen in rat cortical, cerebellar (80), and hippocampal (81) neurons. Electrophysiological recordings from *Xenopus* oocytes injected with brain mRNA showed a potentiation by glycine of expressed NMDA receptors (82, 83). In biochemical studies glycine potentiates Ca^{2+} influx into cultured neurons induced by NMDA receptor agonists (84, 85). It also enhances NMDA-induced $^{22}Na^{+}$ flux (96) and the release of norepinephrine, acetylcholine, and dopamine (87) from brain slices. In vivo studies have shown glycine able to enhance the accumulation of cGMP in rat cerebellum induced by NMDA (71).

The modulatory actions of glycine can be mimicked by D-serine and D-alanine, while the L-enantiomers are much less potent (85). Studies of aspartate-induced Ca^{2+} influx in cultured neurons showed that in Mg^{2+}-free conditions glycine increases the potency but not the efficacy of agonist action (85). Since the action of glycine is visible only in the presence of NMDA receptor agonists, glycine may be regarded as a positive allosteric modulator of NMDA receptors.

Recognition Sites for Modulators of NMDA Receptors

PHENCYCLIDINE BINDING SITES Radioligand-binding studies have demonstrated the presence in the brain of high-affinity saturable and stereoselective binding sites for [^{3}H]PCP (88–90). However, [^{3}H]PCP labels at least two sites

that have been recently classified on the basis of relative agonist affinity as PCP and *sigma* receptors (91). The *sigma* sites are sensitive to haloperidol and can be labeled preferentially with [^{3}H]SKF 10,047 (92). The most selective ligand of the *sigma* site is 1,3-di(2-tolyl)guanidine (DTG) (93). PCP sites are those associated with NMDA receptors and can be labeled with higher selectivity and affinity by the thienyl PCP analog [^{3}H]TCP (94) and the most potent and selective ligand [^{3}H]MK-801 (65, 95–97). The physiological significance of the PCP recognition sites was documented by the discovery of an endogenous brain peptide, α-endopsychosin (98), that inhibits [^{3}H]PCP binding and shows a brain distribution similar to PCP receptors. In functional tests, this peptide mimics the electrophysiological and behavioral effects of PCP (98).

GLYCINE BINDING SITES In the CNS [^{3}H]glycine binds to two classes of unrelated recognition sites. The first represents the inhibitory glycine receptor antagonized by strychnine (78, 79). The second class of sites is not inhibited by strychnine, but is displaced stereoselectively by D-serine and D-alanine (99, 100). These sites are related to the NMDA receptor complex.

The strychnine-insensitive binding of [^{3}H]glycine in rat forebrain membranes is competitively inhibited by kynurenic acid (101, 102). This acid, known to reduce nonselectively EAA-evoked neuronal excitations (103, 104), inhibited competitively responses mediated by kainate and quisqualate in rat spinal cord, while causing a noncompetitive block of depolarizations induced by NMDA (105, 106). However, this latter effect might be due to a competitive antagonism of glycine action. At higher concentrations, kynurenic acid may also inhibit directly [^{3}H] glutamate binding (102) and attenuate NMDA receptor-mediated responses in both a competitive and noncompetitive manner (105, 107), thus showing a poor selectivity for the modulatory glycine site.

A variety of compounds were studied for a possible antagonism at the glycine binding site. Cycloleucine, with a relatively low potency, displaces glycine binding and antagonizes glycine-induced stimulation of TCP binding (108). Another compound, 1-hydroxy-3-aminopyrrolidone-2 (HA-966) initially reported as a noncompetitive NMDA antagonist (109), was found to antagonize competitively the facilitation by glycine of NMDA-induced depolarizations (110). An analog of kynurenate—7-chlorokynurenic acid—was described as the most potent inhibitor of [^{3}H]glycine binding and of glycine-enhanced NMDA responses in rat cortical slices (111). All these compounds can thus induce a noncompetitive inhibition of NMDA-evoked responses by counteracting the positive modulatory action of glycine. Since in vivo, as well as in most experimental conditions, a certain concentration of endogenous glycine is present, the action of these compounds will result in a negative modulation of NMDA receptors. This modulation may be significant in vivo

because the presence of kynurenic acid has recently been demonstrated in the mammalian brain (112) and apparently increases with age (113).

COLOCALIZATION OF NMDA, PCP, AND GLYCINE BINDING SITES The evidence for a common localization of NMDA, PCP, and glycine recognition sites may be derived from anatomical studies. The brain distribution of NMDA sites has been determined by quantitative autoradiography using either [^{3}H]glutamate binding, displaced by NMDA (114–116), or competitive NMDA receptor antagonists [^{3}H]APV (117) and [^{3}H]CPP (118, 119). The highest density of NMDA-sensitive binding sites is found in strata oriens and radiatum of the hippocampal area CA1, followed by area CA3 and dentate gyrus, as well as in the superficial layers of cerebral cortex, striatum, dorsolateral septum, and amygdala. An almost identical distribution was reported for [^{3}H]TCP binding sites (120–122) and high correlation coefficients were obtained in studies comparing the localization of NMDA and PCP recognition sites (118, 123).

The distribution of [^{3}H]glycine binding sites in the CNS seems to be complementary rather than parallel to the binding of [^{3}H]strychnine that labels the inhibitory glycine receptor (79, 124, 125). Strychnine-sensitive glycine receptors predominate in the spinal cord and brain stem, while those insensitive to strychnine are distributed similarly to NMDA sites (126). Recent autoradiographic studies show a high correlation of [^{3}H]glycine binding with NMDA, MK-801, and TCP binding sites (127), a finding that supports the colocalization of all three recognition sites.

A different type of evidence for the colocalization of NMDA, PCP, and glycine sites may be derived from studies with *Xenopus* oocytes (82, 83). The injection of brain mRNA causes the expression of functional NMDA receptors sensitive to inhibition by PCP and potentiation by glycine. Moreover, in PCP receptors solubilized from rat forebrain membranes [^{3}H]TCP binding is regulated by the ligands of NMDA recognition sties (128) providing direct evidence for the localization of recognition sites on the same protein complex.

All NMDA receptors may not contain PCP recognition sites. In the rat cerebellum a low density of [^{3}H]TCP binding sites contrasts with a relatively high number of NMDA recognition sites (118, 123). However, this discrepancy may be attributable to a lower affinity of PCP sites in this brain region and not to their absence, since in the cerebellum PCP antagonizes NMDA-induced norephinephrine release (129) and cGMP accumulation (71, 72).

Modulatory Interactions between Recognition Sites of the NMDA Receptor Complex

PCP-like drugs and glycine modulate NMDA-sensitive receptors acting at distinct recognition sites similarly distributed throughout the brain. This may

suggest that NMDA, PCP, and glycine recognition sites are located within the same supramolecular receptor complex and interact allosterically in controlling the NMDA receptor function. This hypothesis was tested in radioligand-binding studies where mutual interactions between recognition sites could be expected.

NMDA-PCP INTERACTIONS The agonists of NMDA receptors enhance the binding of PCP-like ligands (96, 130–132), while competitive NMDA receptor antagonists such as APV inhibit this binding in a noncompetitive manner (24, 96, 132, 133). Glycine does not seem to directly affect [^{3}H]TCP (134) or [^{3}H]MK-801 (84, 135) binding, but does enhance the action of NMDA receptor agonists. This is supported by the finding that CPP, a selective NMDA receptor antagonist, abolishes MK-801 binding stimulated by glycine without interacting with the glycine recognition site (102). Glutamate and glycine increased the affinity of the PCP recognition site (84, 136, 137), although the number of binding sites also reportedly rose (133). These discrepancies were clarified by kinetic studies (137–139) showing that at equilibrium the specific binding of [^{3}H]TCP or [^{3}H]MK-801 is not affected by glutamate or glycine. However, glutamate and glycine increase both the association and dissociation rates of PCP receptor ligands, which may appear as a change of receptor affinity in nonequilibrium conditions. These findings indicate that allosteric interactions between the NMDA and PCP recognition sites are lacking and that the agonists and antagonists of the NMDA recognition site affect the binding of PCP-like drugs by controlling their access to the binding site located inside the channel. This mechanism also explains the absence of PCP effects on [^{3}H]glutamate binding (140, 141).

GLYCINE-NMDA INTERACTIONS The stimulatory action of glycine on NMDA receptor responses may result from direct interactions of their recognition sites. In brain membranes, glycine and D-serine increase NMDA-sensitive [^{3}H]glutamate binding (142) and change the affinity but not the number of binding sites (143). This change in affinity explains the observed effect of glycine on the potency of NMDA receptor agonists to increase Ca^{2+} influx (84, 85), and ionic currents (144) in cultured neurons maintained in Mg^{2+}-free conditions. In the presence of Mg^{2+} glycine enables the action of NMDA agonists, namely increasing their maximal response (85, 144). In experiments using [^{3}H]TCP or [^{3}H]MK-801 binding as an index of NMDA receptor activation, increases in both efficacy (84, 145, 146) and potency (147) were reported. Since glutamate and glycine affect the time needed to reach the equilibrium of ligand binding to the PCP receptor (137–139), apparent changes of efficacy or potency may be observed in different experimental conditions.

Interactions between glycine and NMDA recognition sites appear to be reciprocal since, as shown by autoradiography, NMDA receptor agonists enhance while antagonists decrease [^{3}H]glycine binding (142). However, this has not been fully confirmed in binding studies in rat brain membranes, where glutamate had little effect while antagonists of NMDA sites only partially decrease [^{3}H]glycine binding (102; L. D. Snell, personal communication). It is possible that NMDA and glycine recognition sites interact in an allosteric manner, however a detailed analysis would be needed to confirm this hypothesis.

The presence of glycine is suggested not only to enhance but also to be essential for NMDA receptor activation (83). This assumption is based on studies in oocytes injected with mRNA, where in essentially glycine-free conditions NMDA-induced responses could be detected only after including exogenous glycine (83). However, the blockade of glycine recognition sites by kynurenic acid does not prevent the stimulation of [^{3}H]MK-801 binding by NMDA agonists (102). Instead, antagonists of NMDA recognition sites abolish the enhancement of [^{3}H]MK-801 binding by glycine. This may suggest a sequential mechanism where glycine enhances the interaction of glutamate with the NMDA recognition site which, in turn, gates the receptor-operated channel.

IONIC INTERACTIONS Mg^{2+} has a biphasic effect on the binding of ligands to the PCP recognition site. In concentrations up to 300 μM it enhances [^{3}H]TCP and [^{3}H]MK-801 binding, while concentrations above 1 mM cause inhibition (131, 137, 144, 148). This inhibitory effect seems related to the blockade of the channel (148). Glutamate increases the potency of Mg^{2+} to produce this effect (144), consistent with the use-dependency of the channel block. The stimulatory action of low Mg^{2+} concentrations may suggest the existence of additional Mg^{2+} binding sites. Mg^{2+} does not seem to affect the binding of [^{3}H]glutamate but does increase the affinity of [^{3}H]glycine binding in brain membranes (144, 149). A distinct Mg^{2+} site may therefore cause changes in the conformation of the receptor complex not related to channel blockade.

Zn^{2+} is the most potent cation inhibiting [^{3}H]MK-801 binding (148) and, in a manner similar to the competitive antagonist APV, reduces MK801 association and dissociation rates in the presence of glutamate (150). Thus, it may act by reducing the ability of agonists to open the NMDA receptor-coupled ion channels. Its site of action could be located in the proximity of the transmitter recognition site since Zn^{2+}, unlike Mg^{2+}, reduces the binding of [^{3}H]glutamate (140, 151).

MODELS OF THE NMDA RECEPTOR COMPLEX Analysis of interactions between the particular recognition sites of the NMDA receptor complex

allows two receptor domains that do not interact in an allosteric manner to be distinguished, although allosteric effects may in fact exist within each domain. The ionophore domain consists of the cationic channel and contains recognition sites for PCP and Mg^{2+}. These two sites may interact allosterically since Mg^{2+} was shown to increase the [^{3}H]MK-801 dissociation rate (150). The regulatory domain includes the NMDA recognition site, the positive modulatory site for glycine and, possibly, metal-binding sites for Mg^{2+} and Zn^{2+}. This receptor domain controls the opening of the channel and the access of ligands to recognition sites located within. This barrier-limited model (137, 138) accounts for the use-dependent action of PCP-like drugs and explains the inability of PCP to modify [^{3}H]glutamate binding.

Within the regulatory domain, NMDA and glycine recognition sites appear to interact allosterically, mutually controlling their affinities. The NMDA recognition site has been proposed to exist in two transitional states with different affinities for agonists and antagonists (152). The positive and negative modulation induced, respectively, by glycine and kynurenic acid could maintain the equilibrium between these two states. A recent finding that the glycine antagonist HA-966 increases [^{3}H]CPP binding in a glycine-sensitive manner supports this hypothesis (153). The modification of glycine and glutamate binding sites by Mg^{2+} and Zn^{2+} suggests the participation of these divalent cations in glycine-NMDA interactions, however, too little is known to propose their role in the model described.

Modulation of Non-NMDA Receptors

Studies of the kainate and quisqualate receptors in the CNS have been hindered by the lack of selective antagonists and thus their function and possible modulation still remain obscure. The recent discovery of two new quinoxalinediones with potent antagonistic actions at kainate and quisqualate, but not at NMDA, receptors (154) may stimulate research in this field. So far, the only modulatory effects reported are noncompetitive actions of quisqualate at the kainate receptor. In cerebellar granule cells, kainate strongly stimulates Ca^{2+} influx and cGMP accumulation (23, 27) and these actions are not sensitive to competitive or noncompetitive antagonists of NMDA receptors (13, 24). However, quisqualate potently and noncompetitively inhibits the kainate-induced stimulation (155–157), and may therefore act at separate recognition sites allosterically coupled to kainate receptors. Glutamate also inhibits the stimulation of cGMP formation by kainate when it is tested with high concentrations of APV to abolish the activation of NMDA receptors (155). Quisqualate inhibits [^{3}H]kainate binding in membranes prepared from granule cells and decreases both the affinity and the number of binding sites (13, 157).

Evidence from several lines of research indicates that the effect described above may have physiological importance. Quisqualate protects cerebellar

granule cells in culture from the excitotoxic activity of kainate (157, 158). It also inhibits the kainate-induced release of [^{3}H]D-aspartate from cerebellar granule cells, although this effect is complex inasmuch as quisqualate alone can cause some release (159). Quisqualate also inhibits whole-cell currents produced by kainate (160). In vivo, a pretreatment with quisqualate selectively prevents seizures evoked by injections of kainate into a rat brain epileptogenic zone—area tempestas (161).

The mechanism controlling these interactions is not yet understood. Kainate receptors may be located presynaptically and their activation may enhance glutamate release from nerve endings (25). However, an endogenous ligand for these receptors has not yet been identified. Could it be that the negative modulation of kainate receptors by quisqualate (and glutamate) represents a feedback mechanism whereby glutamate controls its own release?

Behavioral Expression of NMDA Receptor Modulation

PCP-like drugs antagonize the NMDA-induced responses by blocking the receptor-operated channel, and thus may be expected to produce behavioral responses similar to competitive NMDA receptor antagonists. In fact, behavioral profiles of PCP, MK-801, and APV studied in rats and pigeons are very similar and include stereotypy, ataxia, and catalepsy (162–165). The stereotypy induced by PCP-like drugs correlates with their potency to inhibit [^{3}H]PCP binding (166). Since PCP acts also at *sigma* receptors (167), their involvement in PCP-induced behavior should be considered. In fact, PCP, MK-801, and DTG (selective *sigma* receptor agonist) appear to produce similar behavioral effects (168). However, DTG seems to induce a different profile of sterotypy (flat body posture, back paddling, piano playing), and at high doses catalepsy but with no signs of ataxia, characteristic of NMDA receptor blockade (W. Danysz, unpublished observation).

Behavioral demonstration of the positive modulation of NMDA receptors by glycine meets several difficulties. One is the lack of selective glycine agonists resistant to the high-affinity uptake mechanism. Another is the anticonvulsant action of glycine at strychnine-sensitive receptors located in lower brain areas (124, 169) that may invalidate the use of convulsions as a behavioral model of NMDA receptor stimulation. These problems could be solved by the use of D-serine or D-cycloserine resistant to uptake and more selective for the strychnine-insensitive glycine receptor (85, 99, 170). Alternatively, strychnine may be used to mask the inhibitory glycine receptors (170a).

DRUG DISCRIMINATION Drug discrimination studies in rats (171) and pigeons (172) have demonstrated generalization between competitive (APV, APH) and noncompetitive (PCP, MK-801) NMDA antagonists. Both types

block NMDA-induced discriminative stimuli (173). However, recent data suggest only a partial generalization to APH and CPP in PCP-trained rats (174–176), usually accompanied by a decreased responding rate that suggests nonspecific actions. The lack of complete generalization between competitive and noncompetitive NMDA antagonists may arise from the reported effects of PCP, ketamine, and MK-801 on dopaminergic activity, not related to NMDA receptor blockade (177). It may be also due to the use-dependent character of the NMDA receptor block by PCP-like drugs, which is not shared by competitive antagonists (178). Drug discrimination experiments allow a clear distinction between PCP and *sigma* receptor stimulation, since no generalization to DTG was observed in PCP-trained rats (174). This supports the role of NMDA receptor complex in PCP discriminative cue.

SENSORY INPUT, AROUSAL, AND MOTIVATION Glutamate serves as a transmitter of primary afferent fibers in the dorsal horn of the spinal cord (179, 180) and may be involved in nociception (181, 182). In fact, NMDA, but not quisqualate or kainate, produce nociception when injected intrathecally into the lumbar spinal cord, this action being potently antagonized by PCP (181). However, in rats, PCP and MK-801 do not produce analgesia when injected systemically (181, 183, 184). On the other hand, NMDA may induce analgesia when injected into the periaqueductal grey (185). Thus, glutamate may have different functions at the various levels of nociceptive stimuli processing and the effects of systemically administered antagonists may represent the net action at different sites.

A role for glutamatergic transmission in sensory information processing is indicated by startle reflex experiments. A decreased response to auditory stimulus was found after injections of selective and nonselective NMDA receptor antagonists into the ventral nucleus of the lateral lemniscus (186). But APV may also produce EEG desynchronization indicating enhanced arousal (187) and PCP at low doses induces a similar effect in rats and monkeys (188, 189). Evidently, NMDA receptors play a role in sensory information processing and arousal mechanisms that may be of primary importance for the learning processes.

Glutamate receptors seem to be also involved in reinforcement mechanisms (190). Glutamate antagonists decrease the rate of self-stimulation responding upon injection into the ventral tegmentum area, the origin of mesocortical dopaminergic projections, suggesting an enhanced dopaminergic function (177, 190, 191). This may imply the participation of glutamate receptors in all motivation-dependent forms of behavior.

LOCOMOTOR RESPONSES Injections of NMDA, kainate, or quisqualate into the nucleus accumbens produce locomotor excitation, yet only the NMDA-

induced response is inhibited by APV and Mg^{2+} (192). The mechanism of action may involve a postsynaptic facilitation at the level of dopaminergic receptors rather than enhanced dopamine release (193). This experimental design represents a useful behavioral model to study the function of all three EAA receptor subtypes (193, 194). Moreover, the observed responses may reflect naturally occurring regulatory mechanisms since multiple EAA pathways project to this region (195). Turning behavior apparent after substantia nigra lesions represents another model to investigate the modulation of glutamate receptors. Ipsilateral turning induced by PCP-like drugs has been attributed to the inhibition of presynaptic NMDA receptors that in turn decreases acetylcholine release (74).

There is no direct evidence for the stimulatory action of glycine on NMDA receptor function expressed in motor responses. Glycine was shown to antagonize PCP-induced hyperactivity in mice (196), an effect that could be due to its action at the inhibitory strychnine-sensitive receptor since, in biochemical and electrophysiologial experiments, glycine fails to reverse PCP inhibition of NMDA receptors (80, 85).

CONVULSIONS Systemic or intracerebral injections of NMDA induce convulsions that can be blocked by competitive NMDA-receptor antagonists (197, 198). Also, PCP-like drugs completely antagonize NMDA-induced convulsions and lethality (199, 200). Irreversible blockade of PCP recognition sites by metaphit (201) induces audiogenic and/or spontaneous seizures (W. Danysz, unpublished observation), perhaps caused by the interference of metaphit with the inhibitory action of the endogenous ligand of PCP sites—α-endopsychosin (98). Injections of kainate appear to induce seizures that are not blocked by NMDA receptor antagonists, which suggest that kainate receptors are directly involved (202). Kainate-induced seizures may be blocked by low doses of quisqualate (161), supporting the possibility of a modulatory linkage between these two recognition sites. However, seizures induced by injections of kainate into deep prepiriform cortex are blocked by APH, a selective NMDA antagonist, and thus kainate may also act indirectly, releasing glutamate to activate NMDA receptors (203). The positive modulation by glycine of NMDA receptor-mediated convulsions has not been demonstrated until recently due to the simultaneous anticonvulsant action of glycine at strychnine-sensitive receptors. However, in mice pretreated with subconvulsive doses of strychnine, glycine enhances NMDA-induced convulsions (170a). The effectiveness of NMDA receptor antagonists in chemically induced seizures has raised the possibility of their application in the treatment of epilepsy in humans (204).

ANXIETY Moderate doses of NMDA injected intraventricularly in rats induce behavioral effects, including excitation, panic, escape reaction, jump-

ing, clonic convulsions, and, as the dose increases, tonic convulsions (W. Danysz, unpublished observations). Stimulation of excitatory amino acid receptors in the midbrain periaqueductal grey region produces defense reactions possibly related to increased anxiety (205). Anxiolytic effects have been observed after blockade of NMDA receptors with both PCP-like agents and competitive antagonists (206, 207). However, these compounds are much less potent than benzodiazepines in inducing anxiolytic effects and they are unlikely to find clinical application as anxiolytic agents (204).

Glutamate Receptors in Learning and Memory

The basic principle of learning is the ability to retain acquired information for further retrieval. The initial stage of this process may result from Hebb-type synaptic plasticity characteristic of NMDA receptor function (9). However, long-lasting fixation of these changes must involve molecular events that include the formation of intracellular second messengers, phosphorylation of specific proteins, and, possibly, the induction of regulatory genes. As discussed earlier, glutamate receptors can mediate all these processes.

Experimental data suggest that conditioning stimuli can increase glutamate receptor binding (208) and the responsiveness of hippocampal neurons to glutamate (209). Comparative studies of genetically diverse mice strains (210, 211) and lesion studies in rats (212) illustrate the importance of hippocampal afferent glutamatergic projections in spatial learning. Electrophysiological and biochemical studies of long-term potentiation and behavioral studies on pharmacological modulation of glutamatergic function strongly support the role of glutamate receptors in learning and memory.

LONG-TERM POTENTIATION Described initially in hippocampal neurons, long-term potentiation (LTP) refers to a phenomenon where a short high-frequency stimulation results in the strengthening of synaptic efficacy that may last for days and is widely regarded as a synaptic model of memory (10). The induction of LTP appears related to the activation of NMDA receptors, since it is blocked by competitive and noncompetitive NMDA-receptor antagonists including Mg^{2+} ions (213–216). NMDA receptor-independent forms of LTP have, however, also been observed (217). In the hippocampus the induction of LTP is accompanied by an increased release of glutamate, (218) which provides the occupation of NMDA recognition sites and a strong depolarization that neutralizes the voltage-dependent block of NMDA receptor-coupled channels by extracellular Mg^{2+} (10).

The induction and maintenance of LTP seems to involve the participation of several intracellular messengers. LTP is associated with enhanced entry of extracellular Ca^{2+}, increased phosphoinositide turnover (219) and is dependent on the formation of arachidonic acid metabolites (220). These systems may interact in the activation of Ca^{2+}-dependent enzymes such as

protein kinase C, Ca^{2+}-calmodulin-dependent kinase II and a Ca^{2+}-dependent protease (reviewed in 221) that may lead to genomic events such as *c-fos* induction (222).

Despite strong evidence for the primary role of NMDA receptors in LTP and learning, their activation may not be sufficient per se to trigger these phenomena (223). Recently the activation of quisqualate receptors was found to enable NMDA-induced LTP in hippocampal neurons (224). Hence, if LTP is the mechanism mediating synaptic plasticity during learning (10), as has been postulated, the modulation of several subtypes of glutamate receptors may be expected to affect learning and memory.

LEARNING AND NMDA RECEPTORS The first behavioral evidence linking NMDA receptors to learning was obtained in the water maze test where spatial learning in rats was disrupted by the intraventricular infusion of APV (214). The water maze learning is also disrupted by noncompetitive NMDA receptor antagonists PCP and MK-801 (207, 225). In other spatial learning tasks such as the radial maze, competitive and noncompetitive NMDA receptor antagonists act similarly (184, 226). These compounds also disrupt learning in the passive avoidance test that is not based on spatial cues (184). Among other types of learning, brightness discrimination in aversively motivated Y-maze test is disrupted by MK-801, APH, and CPP (227). In humans, the abuse of PCP produces anterograde amnesia (228) that could be related to NMDA receptor blockade.

Some evidence indicates that increased glutamatergic transmission may facilitate learning. Such an effect would be more difficult to demonstrate since an overstimulation of NMDA receptors may cause neuronal damage, and in consequence learning impairment (229, 230). However, post-training injection of either NMDA, kainate, or quisqualate can increase retention 24 hr later in T-maze avoidance task (231). Action at the glycine positive modulatory site of the NMDA receptor can facilitate learning. In fact, Milacemide (N-pentylglycinamide, glycine pro-drug) and D-cycloserine (putative glycine agonist) appear to enhance learning in the T-maze task (170).

LONG-TERM AND SHORT-TERM MEMORY An unresolved issue is whether the antagonism of NMDA receptors affects long-term memory (post-task memory processing) or is effective only during the acquisition phase. In the passive avoidance task both competitive and noncompetitive NMDA receptor antagonists produce anterograde, but not retrograde amnesia in rats, i.e. are effective only if administered before the training (149, 183, 184, 232). This, however, does not exclude the possibility that the NMDA antagonist-sensitive early phase of long-term memory formation is completed before the training is over. In appetitive T-maze learning, PCP and MK-801 fail to affect reversal (short-term memory), but disrupt the long-term memory of events learned

under the drug's effect (207, 233). In radial maze experiments, intraaccumbens injections of kynurenic acid disrupt reference (long-term) memory (234), while PCP and APV impair also the working memory (184, 226). However, this latter effect may be related rather to general disorientation than to a real disruption of working memory (235). A different type of long-term behavioral plasticity, early olfactory learning in rats, is also blocked by NMDA receptor antagonists (236). From such evidence NMDA receptor antagonists appear to affect the initial stage of long-term memory formation, rather than the short-term working memory.

NMDA RECEPTOR-INDEPENDENT LEARNING In spite of accumulating evidence involving NMDA receptors in learning, one should not generalize this phenomenon to all learning tasks and forms of memory. In the water maze task NMDA receptor antagonists apparently do not affect visual discrimination in spite of impaired spatial learning (214). A striking example is the demonstration that rats can associate unconditioned and conditioned stimuli when under deep ketamine anesthesia (237). Since ketamine noncompetitively blocks NMDA receptors, other mechanisms must be involved. Similarly, induction of LTP in hippocampal CA3 region is not blocked by NMDA receptor antagonists (217).

The role of non-NMDA glutamate receptors in learning has received less attention but they may be involved in some types of learning paradigms. In rats trained in spatial radial maze tasks, PI hydrolysis induced by ibotenate, acting possibly through APB-sensitive receptors, is enhanced (238). However, APB is ineffective in the passive avoidance paradigm (239). In the same test, CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), which is reportedly a potent antagonist of quisqualate and kainate receptors, (154) was found to disrupt passive avoidance learning, while the less selective GAMS (gamma-D-glutamylaminomethylsulfonic acid) was ineffective (239). However, GAMS was found to impair retention in T-maze learning if administered after the training (231).

A role for *sigma* receptors (sensitive to PCP but not coupled to NMDA receptor complex) in conditioned suppression of motility was also proposed (240). However, central injections of DTG, a selective agonist at *sigma* receptors, have no influence on passive avoidance learning (W. Danysz, unpublished observation). This suggests that *sigma* receptors are not involved in the amnesic action of PCP described in humans (228) and animals (184, 207, 226).

Glutamate Receptors in Neurodegenerative Diseases

ALZHEIMER'S DISEASE The evidence for glutamatergic dysfunction in Alzheimer's disease derives from studies indicating decreased [^{3}H]glutamate binding to NMDA and quisqualate receptors (241, 242), as well as decreased

[^{3}H]TCP binding (243) in the cortex and hippocampus. It appears that in many cases, changes in NMDA receptor density are not visible (244, 245) or become apparent only at late stages of the disease together with a general massive neuronal loss (246). A general decrease of NMDA and kainate receptor density has recently been reported in the elderly, especially pronounced in individuals with Alzheimer's disease symptoms (247). Strong evidence indicates the impairment of presynaptic glutamatergic mechanisms, such as the decrease in the number of [^{3}H]glutamate or [^{3}H]aspartate uptake sites (245, 248, 249) and perforant path degeneration in Alzheimer's disease (250).

Thus, decreases in NMDA receptor density seem not to occur at the early stages of Alzheimer's disease. However, NMDA receptors are particularly dense in hippocampal regions characterized pathologically by the formation of neurofibrillary tangles and neuritic plaques (244). The involvement of NMDA receptors in the early stages of the pathology may in fact be releated to their increased vulnerability to excitotoxic mechanisms (9).

HUNTINGTON'S DISEASE Afferent glutamatergic pathways have been implicated in degenerative changes in striatal neurons characteristic for Huntington's chorea (251). Decreases in glutamate uptake sites are found in patients suffering from this disease, and, as suggested, excessive accumulation of the transmitter may promote striatal lesions (252). Some evidence points also to the possible role of increased endogenous concentrations of quinolinic acid as the promoting factor in the pathogenesis of the disease (253, 254). Neuronal depolarizations induced by quinolinate are strongly antagonized by competitive NMDA antagonists (255, 256) suggesting their mediation by the NMDA receptor. Injections of quinolinic acid to the striatum cause a pattern of neuronal loss resembling that observed in Huntington's disease, but unlike that caused by injections of kainate or quisqualate (257). Moreover, a substantial, preferential loss of neurons rich in NMDA and PCP receptors was observed in putamen of Huntington's disease patients (258). Since APH can block neurotoxic effects of both NMDA and quinolinic acid (259), excitotoxic mechanisms activated by quinolinic acid, acting at the NMDA receptor, may possibly underlie the development of neuronal lesions in Huntington's disease.

ISCHEMIA The development of ischemic-hypoxic brain damage is associated with stroke, cardiac arrest, or mechanical brain injury. The mechanism involved seems to include the excessive accumulation of glutamate (260) followed by its excitotoxic action that causes neuronal cell death (261, 262). Some brain regions such as hippocampus and dorsolateral striatum that are enriched in EAA receptors are especially vulnerable to ischemic lesions

(263). Ischemic brain damage seems to be selective for neurons containing NMDA receptors since in the hippocampus ischemia decreases the number of NMDA-sensitive [^{3}H]glutamate (264) and [^{3}H]TCP binding sites (265). Studies of competitive NMDA receptor antagonists show that ischemia-induced hippocampal damage is reduced by prior local infusion of APH (266) or systemic administration of CPP or CGS 19755 (267). Similar protective effects were observed using systemic administration of the noncompetitive NMDA receptor antagonist MK-801 (66, 268).

Recent data point to the possibility that quisqualate receptors also may be involved in ischemic brain damage. The density of binding sites for a selective quisqualatc ligand [^{3}H]AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) was found to be decreased in the ischemic hippocampus (269). Moreover, biochemical experiments show that combined hypoxia-ischemia in 7-day old rats results in enhanced PI hydrolysis stimulated by quisqualate in hippocampal and striatal slices (270).

HYPOGLYCEMIA Neuronal damage in the rat striatum, resulting from insulin-induced hypoglycemic coma, can be prevented by prior administration of APH, a selective NMDA receptor antagonist (271). As in the ischemic-anoxic condition, hypoglycemia may impair the glutamate reuptake system, which results in an excessive accumulation and excitotoxic action of this amino acid (11).

NEUROTOXICITY The pathogenesis of the several neurodegenerative conditions described seems to involve a common mechanism. It may be initiated by excessive accumulation of glutamate or some other endogenous EAA, followed by its excitotoxic effect mediated mostly by NMDA receptors, resulting in neuronal death. The mechanism of this neurotoxicity has been studied in several in vitro systems, including neuronal cultures and slices of brain tissue. A prolonged activation of NMDA receptors may lead to two independent phenomena; NMDA-receptor induced depolarization, followed by passive Cl^- influx, entry of cations and increased water entry resulting in osmotic lysis of the cell (272, 273); and, secondly, the entry of Ca^{2+} ions through NMDA receptor-operated channels and a subsequent uncontrolled activation of intracellular Ca^{2+}-sensitive lipases and proteases (274). This second Ca^{2+}-dependent mechanism apparently is also involved in toxicity mediated by kainate receptors (275). The neurotoxic effects of NMDA receptor agonists, but not those induced by kainate, are prevented by the application of competitive and noncompetitive antagonists of NMDA receptors (66, 276–278). Glycine has been shown to enhance NMDA-induced toxicity (279), while Mg^{2+} has a reducing action (280, 281), in line with the known modulatory properties of the NMDA receptor-channel complex.

These findings have led to the proposal that the use of NMDA receptor antagonists, especially noncompetitive antagonists acting at the PCP recognition site, may be beneficial in the treatment of neurodegenerative disorders (204). However, a serious drawback are the psychotomimetic and other side effects associated with the systemic administration of these compounds. A new approach has emerged from the studies on the effects of gangliosides on EAA-induced cell death (282). These compounds, used in vitro in primary cultures of cerebellar neurons, prevent the neurotoxic effects of both glutamate and kainate. Their mechanism of action is related to a strong inhibition of EAA receptor-mediated translocation and activation of protein kinase C (29). These studies demonstrate that protein kinase C is an important link in the chain of events leading to EAA-induced cell death, and point to the therapeutic potential of gangliosides as drugs targeted not at the recognition sites of EAA receptors but at intracellular mechanisms of neurotoxicity.

Glutamate Receptors in Psychoses

The observation of decreased CSF levels of glutamate in schizophrenic patients has led to the hypothesis that impaired glutamatergic transmission may contribute to the pathogenesis of this disease (283). Findings that PCP, which inhibits NMDA receptors, produces psychotomimetic effects in humans similar to some symptoms of schizophrenia support this postulate (284). Since in animals PCP produces a wide range of behavioral effects, many of which can be blocked by neuroleptics, PCP-treated animals were proposed as a pharmacological model for psychosis in humans (285).

However, it should be stressed that the psychotomimetic actions of PCP-related drugs may be due to several mechanisms other than the antagonism of NMDA receptors. PCP interacts with dopaminergic, cholinergic, and serotonergic systems, and some of these effects may be mediated through haloperidol-sensitive *sigma* receptors, rather than through NMDA receptor-associated PCP binding sites [for discussion, see (286)]. Most significant are the antipsychotic effects of rimcazole, a drug that potently antagonizes *sigma* receptors (287).

According to a recent report, high doses of glycine are effective in some schizophrenic patients who do not respond to standard neuroleptic medication (288). Such treatment appears to correct the glycine deficiency caused by impaired activity of serine hydroxymethyltransferase found in schizophrenic and psychotic patients (289). Although there is no experimental evidence linking this therapeutic effect of glycine with its ability to induce a positive allosteric modulation of NMDA receptors, such a possibility cannot be excluded. Thus, the hypothesis that NMDA receptor hypofunction may be involved in human psychoses has not been disproved. Hence, the possible

therapeutic potential of drugs that enhance the function of NMDA receptors either by positive allosteric modulation or by inhibition of PCP-induced antagonism should be considered in treatment of human psychoses.

CONCLUSION

The studies of the last few years have demonstrated the universal role of excitatory amino acid receptors in almost every aspect of brain activity. Although the particular EAA receptor subtypes cannot yet be clearly correlated with specific functions, it seems that two features of EAA receptors may be essential for the diversity of their actions. The first is their ability to induce the formation of multiple intracellular messages that may be integrated with other incoming stimuli to produce distinct neuronal responses. This includes the possibility that several subtypes of glutamate-sensitive receptors may contribute to the generation of a specific response. The second feature is the control of EAA receptor activation by multiple positive and negative modulatory sites, for many of which endogenous ligands have been identified. This arrangement allows a level of precision and selectivity in the control of receptor function that cannot be paralleled by mechanisms regulating the release and inactivation of a transmitter.

These features of EAA receptors have significant implications for the strategies used to develop new pharmacological agents effective in the treatment of neurological disorders. It has been pointed out that drugs targeted at modulatory mechanisms, as opposed to those interfering directly with primary transmitter action, allow a subtle control of receptor activity, according to therapeutical needs, without producing a drastic impairment of receptor function and often without nonspecific side effects (290). The complex modulatory mechanisms and the multiple intracellular systems involved in the functioning of glutamate receptors offer the best opportunities for the design of such drugs.

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