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NEUROPHARMACOLOGY OF PHENCYCLIDINE: Basic Mechanisms and Therapeutic Potential

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INTRODUCTION

Phencyclidine [1-(1-phenylcyclohexyl)piperidine hydrochloride, or PCP] was developed about 30 years ago by Parke, Davis & Company as an anesthetic agent. In monkeys and humans PCP was analgesic and caused a state of dissociative anesthesia with little cardiorespiratory depression (1). Unfortunately, it proved to be psychotomimetic in humans and produced an unacceptable incidence of prolonged postanesthetic emergence reactions ranging from blurred vision to confusion and proprioceptive hallucinations (2). Although PCP was eventually approved as a veterinary anesthetic, its psychoactive properties precipitated its withdrawal from clinical use in the mid-1960s. Ketamine, a related arylcycloalkylamine, is less potent and shorter-acting than PCP (3) and is still used as a short-acting dissociative anesthetic in humans.

Because of its ease of synthesis and its reported psychotomimetic properties, PCP appeared in the mid-1960s in San Francisco as the PeaCe Pill. However, as its psychoactive properties showed marked individual differences, it quickly earned a bad reputation on the street among the hallucinogen connoisseurs of the day, and its use fell out of favor. In fact, until the late 1970s PCP was largely misrepresented as more "acceptable" halluci-

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nogens such as "synthetic Δ^9-tetrahydrocannabinol (THC)," lysergic acid diethylamide (LSD), and mescaline. During this time and continuing through the 1980s, a significant number of people made PCP their drug of choice, and today in some urban settings in the United States its abuse is rivaled only by that of crack cocaine.

The continued abuse of PCP obviously represents a national health concern and has prompted a significant amount of research into its biological mechanisms of action. This research has also been prompted by the notion that the psychotomimetic properties of PCP cause a pathologically relevant schizophreniform psychosis in humans (4–6). Although PCP-induced psychotic episodes often resolve spontaneously as the drug is eliminated, many require extended hospitalization and antischizophrenic medication (7). There is also evidence that PCP abuse can lead to later schizophrenic episodes (8), suggesting that PCP can actually precipitate a latent psychosis. Nevertheless, the observation that acute reactions to PCP are often diagnosed in emergency room settings as acute paranoid schizophrenia attests to the relevance of PCP psychosis as a model for schizophrenia.

A great deal of the early animal research focused on monoamines, particularly dopamine (DA), and on related behaviors such as locomotor activity and stereotypy (9, 10). Following the reports in 1979 from two independent laboratories that [^{3}H]PCP binds to a saturable, proteinaceous site in brain membranes (11, 12), considerable effort was directed toward finding correlations between the behavioral effects and the binding affinity of several classes of compounds, principally the arylcycloalkylamines, *sigma* benzomorphans, and substituted dioxolanes. A very highly significant correlation was found between the affinity for the [^{3}H]PCP-binding site and a number of the behavioral effects of compounds in these classes. In fact, the correlation between binding and the discriminative stimulus properties of these drugs (13) is primarily responsible for the acceptance of the binding site for [^{3}H]PCP as a relevant receptor.

The understanding of the mechanism of action of PCP was greatly enhanced when Lodge and co-workers observed that PCP and ketamine selectively reduced the excitatory actions of glutamate on spinal neurons that were mediated by the *N*-methyl-D-aspartate (NMDA) receptor subtype (14, 15). In the last 5 years or so, research on the excitatory amino acid receptors has mushroomed, and this has been particularly true of the NMDA receptor (16, 17). Thus, our knowledge of one of the most important actions of PCP has increased at an equal rate. Because the NMDA receptor is now known to be intimately involved in synaptic transmission, seizure induction, long-term potentiation induction, excitotoxicity, ischemic brain damage, and perhaps neuronal plasticity, growth, and development, the therapeutic potential of drugs acting at the PCP binding site within the NMDA complex has attracted renewed interest in the pharmacology of PCP.

Inasmuch as our laboratory has most recently been concerned with the function and regulation of the NMDA/PCP receptor/ion channel complex, this review focuses primarily on this aspect of PCP pharmacology and its relevance to the behavioral and potential therapeutic effects of PCP. However, it is virtually certain that all the behavioral effects of PCP are not due simply to its interaction with the NMDA-operated ion channel. Therefore, PCP interactions with other pertinent neurotransmitters and ion channels also will be reviewed. More detailed information on the chemistry, metabolism, and general pharmacology of PCP can be found in the proceedings of three workshops organized by Domino and colleagues (18–20) and in two monographs edited by the National Institute on Drug Abuse staff (21, 22). In addition, there are two fairly extensive 1987 reviews on PCP (23, 24).

EVIDENCE FOR PCP RECEPTORS

A saturable, proteinaceous, high-capacity site that binds [^{3}H]PCP with modest affinity (K_D = 200 nM) was found in rat brain membranes by two independent groups in 1979 (11, 12). The pharmacologic specificity of this site was originally found to be unique in that only drugs from the arylcycloalkylamine and psychotomimetic benzomorphan classes were able to displace [^{3}H]PCP from its binding site (11, 12). The apparent affinities of these drugs were highly correlated with their ability to inhibit rotarod performance, which suggests that this binding site might be a physiologically relevant receptor (25).

The list of drugs with moderately high affinity for the [^{3}H]PCP-binding site now has been expanded to include some substituted dioxolane dissociative anesthetics (26), benz[*f*]isoquinolines (27), dihydropyridine calcium channel antagonists (28), noncompetitive antagonists of the nicotinic receptor-associated sodium channel (29), and the potassium channel antagonist 4-aminopyridine (30). The behavioral effects of the first three classes mentioned above have been studied extensively by using animals trained to discriminate between the interoceptive cues produced by PCP and salinc. Thesc and the arylcycloalkylamine class share discriminative stimulus properties with PCP (31–34). Moreover, the structure-activity relationships (SAR) of the discriminative stimulus properties of these drugs is parallel to the SAR determined by using displacement of [^{3}H]PCP from brain membranes (25, 35). This correlation and the pharmacologic specificity of the discriminative stimulus properties of PCP convinced most investigators in this area that the [^{3}H]PCP-binding site is the recognition site of an important receptor, which was referred to most commonly until about 1987 as the PCP/*sigma* receptor.

The use of the term *sigma* derived from the observation that *N*-allylnormetazocine (NANM) or SKF 10,047, originally described as the prototypic agonist for *sigma* opiate receptors (36), is one of the benzo-

morphans with PCP-like discriminative stimulus properties (32, 33). Inasmuch as the original observations on most of the naloxone-reversible actions of NANM have been refuted (37) and opiate antagonists have little or no effect on PCP-induced behavioral patterns (37), it is likely that the behavioral effects shared by PCP and opiates such as NANM are mediated through nonopiate receptors. Thus, the term PCP/*sigma* receptor was incorrect in that it implied a nonexistent opiate connection.

This matter became even more complicated with the discovery of a naloxone-insensitive site with a high affinity for the (+) isomers of several benzomorphans, including both *sigma* and *kappa* opiates (38–42). A similar but not identical site was also described by using either [^{3}H]NANM or [^{3}H]ethylketocyclazocine in the presence of opiate-blocking agents (43, 44). Both sites are now referred to as the *sigma* site. These sites also have a high affinity for di-*o*-tolylguanidine (DTG) (45) and the dopamine agonist (+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine (3-PPP) (41); these radiolabeled ligands are now most commonly used in the study of the *sigma* site. Certain antipsychotics such as haloperidol and more novel, putative antischizophrenic agents such as BMY 14802 also have nanomolar affinity for the *sigma* site (46). PCP, substituted dioxolanes, and the (−) benzomorphan isomers have low-micromolar affinity for this site (47).

In addition to the apparent differences in pharmacologic specificity that can be inferred from the above description, data from autoradiographic and developmental studies clearly show that the sites labeled with [^{3}H]DTG, (+)-[^{3}H]3-PPP, or (+)-[^{3}H]NANM are distinct from those labeled with [^{3}H]N-(1-[2-thienyl] cyclohexyl)3,4-piperidine ([^{3}H]TCP) (48–50). These and other considerations led the attendees at the second United States-French-sponsored International Seminar on Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology in Ann Arbor, MI in 1987 to adopt a distinct nomenclature for PCP and *sigma* receptors (51).

Although there is now general acceptance of distinct PCP and *sigma* sites, there is still considerable debate on whether these sites represent true receptors. As is discussed in detail below, almost all of the sites labeled with [^{3}H]TCP appear to be located deep within an ion channel regulated by one of the several specific receptors for the excitatory amino acids glutamate and aspartate. Binding of PCP blocks ion flux through this channel. Thus, if PCP is a functional antagonist of this receptor, is it proper to refer to its binding site as a receptor? Receptors are generally thought to consist of a recognition site and an associated signal transduction mechanism leading to alterations in either membrane potential or concentration of second messenger molecules. As PCP binding per se is not known to do either of the above, it may have been premature to designate the glutamate receptor-associated PCP binding site as a receptor unto itself.

The status of the *sigma* receptor is even less secure, as there are no known

biological effects that are completely correlated with *sigma* site binding affinity. It has been proposed that the psychotomimetic properties of *sigma* benzomorphans were mediated by the *sigma* site, but drug discrimination studies with (+)-NANM were inconclusive (52, 53), perhaps because of the modest selectivity of (+)-NANM for the *sigma* site relative to the PCP site. More recently it was shown that rats trained to discriminate saline from (+)-pentazocine (a more selective *sigma* drug) generalized completely to (+)-NANM, but only partially to PCP (54). Although this may suggest that the discriminative stimulus properties of (+)-NANM are mediated by the *sigma* site, (+)-3-PPP neither mimics nor blocks the discriminative stimulus properties of (+)-NANM (55). The fact that haloperidol and other agents, such as rimcazole, with putative antischizophrenic activity have affinity for the *sigma* site has been used to suggest that these agents are *sigma* antagonists, whereas those with psychotomimetic properties, such as (+)-pentazocine and (+)-NANM, are *sigma* agonists. In fact, haloperidol has been shown to block (+)-NANM discrimination (53), and rimcazole has been shown to block (+)-NANM-induced excitation of ventral tegmental DA neurons (56). However, this hypothesis has not been tested with DA antagonists without *sigma* affinity. Recently, in binding stdies with (+)-[^{3}H]3-PPP it was shown that *sigma* binding is GTP-regulated and that subchronic treatment with either rimacazole or DTG upregulated *sigma* binding-site density (57). Consistent with the identity of these drugs as antagonists, GTP had no effect on the displacement of (+)-[^{3}H]3-PPP by rimcazole, DTG, or haloperidol, whereas the displacement curves for (+)-NANM and cyclazocine were significantly right shifted. However, DTG does not antagonize (+)-NANM discrimination, as would be expected, but in fact mimics its discriminative cue (S. Holtzman, personal communication). Further discrepancies in the agonist/antagonist hypothesis come from experiments in which DTG, haloperidol, and (+)-NANM microinjected into the red nucleus have qualitatively identical effects on head and neck posture (58). To briefly summarize, there are several intriguing aspects of *sigma* "receptor" pharmacology, including some not discussed here, such as the strong similarity to the antitussive-related dextromethorphan-binding site (59, 60). However, they have not been extensively characterized, and the lack of consistency between paradigms, particularly involving putative agonists and antagonists, casts doubt on the relevance of the *sigma* binding site as it is now defined.

INTERACTIONS WITH MONOAMINERGIC AND CHOLINERGIC TRANSMITTER SYSTEMS

Dopamine

There is considerable evidence that PCP has amphetaminelike behavioral properties, particularly in rodents. Because PCP induces in some people a

psychosis that resembles paranoid schizophrenia, the effects of PCP on DA biochemistry and DA-mediated behaviors have received much attention. These areas have been reviewed recently by Meltzer et al (61), Johnson et al (10, 62, 63), and Balster (64).

PCP is known to competitively inhibit the uptake of [^{3}H]DA into rat striatal slices (65) and synaptosomes (K_i = 0.1 μM) (66, 67). At somewhat higher concentrations, PCP is also able to enhance the spontaneous efflux of preloaded [^{3}H]DA from synaptosomes (68, 69) and slices (70). PCP is approximately equipotent with amphetamine as an uptake blocker (70) but is about 10 times less potent as a releasing agent (68–70).

Similarities between PCP and nonamphetamine stimulants have been noted by investigators who showed that although PCP alone had no effect on striatal DA turnover, it augmented the enhanced utilization of DA produced by haloperidol (71, 72). This effect was blocked by γ-butyrolactone or baclofen, which suggests that it is dependent on nigrostriatal impulse flow. This effect of PCP is also characteristic of methylphenidate and amfonelic acid, but not amphetamine (73).

In contrast to the studies cited above, in which PCP alone had no effect on DA turnover, other evidence suggests that PCP does alter DA metabolism in vivo. It has been shown that PCP inhibits striatal tyrosine hydroxylase activity in vivo (71), perhaps as a transsynaptic compensatory response to DA release and blockade of DA reuptake. Furthermore, in vivo dialysis showed that PCP dose dependently increased striatal extracellular DA levels (74).

Electrophysiologic studies of the DA system also support the hypothesis that PCP releases DA in vivo. Inhibition of caudate neurons by local application of PCP was antagonized by neuroleptics and reduced in rats pretreated with either reserpine or 6-hydroxydopamine, which suggests that the effect of PCP was presynaptic (75). Also, a biphasic effect on A_9 and A_{10} DA cells was observed, with low doses of PCP increasing the firing rate and higher doses decreasing the firing rate (76, 77). Only the high-dose effect was blocked by haloperidol. Both enantiomers of NANM increased the firing rate in A_9 and A_{10} neurons. Interestingly, the common effect of PCP and NANM was the nondopaminergic, rate-increasing effect (76).

In addition to the similar effects of PCP on A_9 and A_{10} neurons, there are data that support the involvement of brain areas receiving A_{10} projections in the mechanism of PCP. For example, PCP increases the concentration of DA metabolites in the frontal cortex (78) and enhances DA release from slices of the nucleus accumbens (S. M. Jones, unpublished observations). Also, PCP-induced locomotor activity in rats can be dramatically reduced by bilateral 6-hydroxydopamine lesions of the nucleus accumbens (79).

As detailed below, the dopaminergic effects of PCP are probably not mediated by the PCP receptor described above. Two studies examined the effects of the enantiomers of the 3-methylpiperidine derivative of PCP

(PCMP) and found that the behaviorally active (+) isomer was more potent than the (−) isomer in inhibiting prolactin release (80) and in inhibiting the firing of caudate neurons (75). SAR studies of the inhibition of synaptosomal DA uptake by PCP-like drugs have been examined in two studies. In the first, PCP and eight arylcycloalkylamine analogs were tested, and their 50% inhibitory concentrations (IC_{50} values) were highly correlated ($r = 0.93$) with their IC_{50} values for inhibition of [^{3}H]PCP binding (81). In the second, this correlation for arylcycloalkylamines was verified but was found not to extend to either the substituted dioxolanes or psychotomimetic *sigma* benzomorphans with PCP-like behavioral activity (82). In a similar series of experiments, it was shown that neither striatal DA release in vitro nor haloperidol-induced DA metabolism in vivo by 13 PCP-like drugs was correlated with their affinity for the [^{3}H]PCP-binding site (83).

In summary, PCP inhibits striatal DA reuptake, facilitates its release, and subsequently affects its synthesis and metabolism in the rodent. These effects are correlated with electrophysiological effects in nigrostriatal and mesolimbic DA pathways and are probably related to behavioral effects such as enhanced locomotor activity and stereotypy (61). However, behavioral properties of PCP, such as its discriminative stimulus properties, which are shared by drugs from the psychotomimetic benzomorphan class and the dissociative anesthetic dioxolane class, are probably not mediated by these dopaminergic mechanisms. In addition, the effects of PCP itself on dopaminergic neurotransmission probably do not involve the PCP receptor, but could involve the *sigma* receptor (84), and may well be dependent on binding to the DA uptake carrier. In this regard, it should be noted that PCP analogs with a high affinity for the uptake carrier and a very low affinity for sites labeled with [^{3}H]PCP (85) are now available; conversely, MK801 has a high affinity for the PCP site and is a very weak inhibitor of DA transport (86). Thus, it should be possible to delineate the contributions of these mechanisms to specific behaviors.

Norepinephrine

On the basis of observations of locomotor stimulant and anticonvulsant properties of PCP, Chen and coworkers (3) proposed a central adrenergic mechanism for PCP. More recently it has been shown that performance in an avoidance-escape task that was dependent on brightness discrimination was impaired by PCP, ketamine, and dexoxadrol but not by levoxadrol (87). The effects of PCP on brightness discrimination (and locomotor activity between trials) were blocked by specific α_1 antagonists and by an α_2 agonist.

The effect of PCP on brain norepinephrine (NE) synthesis and metabolism is uncertain. Levels of NE have been reported to be unchanged by PCP in mouse forebrain (72) and guinea pig forebrain and brain stem (88) but to be

decreased in rat whole brain (89). Phencyclidine has been demonstrated to decrease the apparent synthesis of NE at the level of tyrosine hydroxylase (90), an effect thought to be consistent with the observation that PCP decreases the firing rate of noradrenergic cell bodies in the locus ceruleus (91). Both of these effects may well be secondary, compensatory responses to the ability of PCP to block NE reuptake competitively and to enhance its release (66, 67).

At the electrophysiological level, PCP has been shown to produce effects in the cerebellum and hippocampus that are consistent with its ability to enhance the synaptic concentration of NE. Pressure injection of PCP, ketamine, and PCMP depressed the spontaneous firing rate of cerebellar Purkinje cells (92, 93). This effect was stereoselective (92), was reversed by neuroleptics and lithium (93), and was absent in rats whose noradrenergic input had been destroyed by 6-hydroxydopamine (93). Similar effects have been observed in hippocampal CA_1 pyramidal cells (94, 95). Thus, although there is not a consensus (96, 97), NE appears to play a role in the pharmacology of PCP.

Acetylcholine (ACh)

Pharmacologic manipulation of PCP-induced locomotor activity, stereotypy, and turning behavior suggested that PCP has anticholinergic properties in addition to its indirect dopaminergic properties (98, 99). Interestingly, PCP also appears to have cholinomimetic properties in several behavioral paradigms (19, 86). Consistent with this, PCP has been shown to be a weak inhibitor of acetylcholinesterase and of binding to the muscarinic ACh receptor (100–102). However, comparison of these activities of PCP with those of two PCP metabolites and the enantiomers of NANM suggested that neither of these activities was correlated with either rotorod activity or the discriminative stimulus properties of PCP (102, 103).

PCP has also been shown to interact with the nicotinic receptor in various muscle and electric organ membrane preparations. It does not bind to the ACh recognition site of the nicotinic receptor but does bind to the ionic channel associated with it in the electric organ of *Torpedo ocellate* (104). However, structure-activity relationships among the benzomorphans suggest that this action is not behaviorally relevant in mammals (105).

Serotonin

PCP and ketamine have several pharmacologic effects that potentially could be mediated by serotonin (5-HT), including analgesia, hallucinations, stereotypy and sedation. Several biochemical studies have implicated 5-HT in the actions of PCP. The most clear-cut effect of PCP and ketamine is that they are potent inhibitors of 5-HT uptake into synaptosomes from rat cortex (67). Both drugs also reduce the turnover of 5-HT (106–108), perhaps as a com-

pensatory response to reduced 5-HT uptake. Reduced 5-HT turnover is also correlated with a reduced firing rate of some raphe neurons (91). Acute but not chronic administration of PCP increases cortical 5-HT levels in mouse brain (110). Similarly, the decrease in 5-HT turnover observed in rat forebrain following acutc PCP administration was not observed following 14 daily administrations (106). This apparent tolerance may be related to the finding that chronic but not acute PCP administration resulted in significant reduction of the density of 5-HT_2-binding sites in rat cortex (110). On the basis of studies of the effects of sulfhydryl-modifying reagents and PCP on [^{3}H-]PCP and [^{3}H]ketanserin binding, Nabeshimi et al have proposed that PCP and 5-HT_2 receptors overlap and, furthermore, that the effects of high-dose PCP on head twitch involve the direct activation of 5-HT_2 receptors (111).

INTERACTIONS WITH THE NMDA RECEPTOR-IONOPHORE COMPLEX

As Monaghan et al pointed out in their recent review (16), the effects of excitatory amino acids such as glutamate and aspartate are mediated through at least five different receptor subtypes. Three are well known and have been defined by antagonist pharmacology and the distinct depolarizing actions of selective agonists (kainate, quisqualate, and NMDA). The fourth appears to be an inhibitory autoreceptor, selectively activated by L-2-amino-4-phosphonobutyrate (AP4). AP4 has been demonstrated to inhibit synaptic activation of dentate granule cells (112), olfactory cortex (113), and hippocampal CA3 cells (114). The fifth receptor subtype appears to activate an oscillating Cl^- current (115) that may be mediated by inositol triphosphate (IP_3) (116). This response is blocked by pertussis toxin (117). Glutamate and quisqualate, but not kainate, NMDA, or AP4, increase inositol phosphate formation (118–120) via a mechanism that is insensitive to the quisqualate antagonists joro spider toxin (121) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (122). This unusual profile is amplified by the finding that the traditional quisqualate receptor agonist, AMPA, does not increase phosphatidylinositol turnover and further by the observation that quisqualate-induced inositol phosphate formation is blocked by AP4 (119).

The NMDA receptor mediates ion flux through a channel permeable to Na^+, K^+, and Ca^{2+}. Ion flux is voltage dependent and gated by Mg^{2+} and PCP, which act at distinct sites within the channel itself. An additional role for divalent cations has been illustrated by the voltage-independent inhibition of NMDA by Zn^{2+}. Glycine also modulates channel activation by NMDA agonists and may be required for the expression of receptor function. Recent work has also shown that polyamines act on presumably intracellular sites to regulate both glycine binding and channel activation. In addition, both the

NMDA and glycine receptor recognition sites may exist in agonist- and antagonist-preferring conformations, and the receptor state may be regulated by the relative concentrations of glutamate, glycine, and polyamines in the synapse. Thus, the actions of PCP in this complex are dependent on the degree of activation of the ion channel, which, in turn, is dependent on the relationship among at least five other receptors or binding sites. Thus, understanding the mechanism of action of PCP requires an understanding of the various components of the component and how they regulate to one another. An overview of the state of knowledge of this rapidly changing field of investigation is given below.

The NMDA Recognition Site

[^{3}H]glutamate has been widely used to specifically label each of the glutamate receptors, including the NMDA subtype (123). More selective NMDA agonists and antagonists have also been used to label the NMDA receptor, but their use has been somewhat limited by their relatively poor affinity. That is, the agonists [^{3}H]D-2-amino-5-phosphonopentanoate (D,AP5)[^{3}H]NMDA (124) and the antagonists L[^{3}H]-2-amino-7-phosphonoheptanoic acid (126, 127), and [^{3}H]-3-((+)-2-carboxypiperazin-4-yl)propyl-1-[^{3}H]phosphonic acid ([^{3}H]-CPP) (128, 129) have equilibrium dissociation constants in the 200–2000 nM range. However, a recently synthesized piperidine analog of CPP, *cis*-4-phosphonomethyl-2-piperidinecarboxylic acid (CGS 19755), appears to be a selective and more potent NMDA antagonist (K_i against [^{3}H]CPP = 50 nM) (130), and early indications are that [^{3}H]CGS 19755 is the best radioligand available at this time, at least for the antagonist preferring state of the NMDA receptor (see below).

Despite its lack of selectivity, L-[^{3}H]glutamate is still the agonist of choice for studies of the NMDA recognition site. Depending on the membrane preparation (and perhaps the extent to which endogenous glutamate and aspartate are removed), NMDA-displaceable L-[^{3}H]glutamate binding varies between 25 and 90% of the total binding and has a K_D between 50 and 200nM (131–135). Recently a high affinity (K_D = 36 nM) NMDA-displaceable L-[^{3}H]glutamate-binding site constituting about 85% of the total binding in an easily prepared buffy coat membrane preparation was described that can also be used for the study of [^{3}H]TCP and [^{3}H]glycine binding (136).

Monoghan et al have studied the autoradiographic distribution of [^{3}H]CPP-binding sites and NMDA-sensitive [^{3}H]glutamate-binding sites and have found their distribution to be heterogeneous (137). NMDA-sensitive L-[^{3}H]glutamate binding was relatively higher than [^{3}H]CPP binding in the striatum and relatively lower in portions of the thalamus and cortex. Interestingly, glycine increased [^{3}H]glutamate binding but decreased [^{3}H]CPP binding. These data led Monaghan et al to postulate that NMDA receptors

exist in both agonist- and antagonist-preferring states and that glycine may convert the antagonist-preferring state to the agonist-preferring state. The existence of agonist- and antagonist-preferring states finds precedence in the γ-aminobutyric acid ($GABA_A$) receptor complex (138). This has also been supported by recent studies showing that agonists have a greater relative affinity for sites labeled by [^{3}H]glutamate, whereas antagonists have a higher relative affinity for [^{3}H]CPP-labeled sites (139). These authors have postulated that the charge properties of the ω-phosphono group confer both the antagonist properties and the unique binding profile of the α-amino-ω-phosphono carboxylic acid antagonists such as D-AP5, CPP, and CGS 19755. The physiological significance of agonist- and antagonist-preferring states of the NMDA receptor and their purported regulation by glycine is unclear, but in the presence of an endogenous excitatory amino acid antagonist such as kynurenic acid (140), the glycine-induced conversion of antagonist- to agonist-preferring state could play a significant role in NMDA receptor function.

The PCP-Binding Site

Lodge and coworkers first demonstrated that PCP and the dissociative anesthetic ketamine blocked NMDA-induced depolarization of spinal neurons while having no effect on either kainate- or quisqualate-induced depolarization (14, 15). This finding was seminal to the development of modern research on the mechanism of action of PCP. This observation has been repeated many times with several different systems. There are no reports of failure of PCP to selectively block NMDA responses, be they depolarization of cortical (141, 142) or hippocampal (143, 144) neurons, induction of Ca^{2+} or Na^+ flux (145, 146), or induction of neurotransmitter release (147–150). The K_i for PCP as an NMDA antagonist is in the 50–100 nM range.

The mechanism by which PCP inhibits NMDA-mediated responses is noncompetitive with respect to NMDA (142, 148, 149, 151). The block also exhibits voltage and use dependence (152–157). For example, using whole-cell patch clamp techniques in dissociated cultures of mouse hippocampal neurons, Mayer et al have reported that NMDA-activated channels have a mean open time of 5–6 ms (155). In contrast to the rapid onset blockade caused by the competitive antagonist AP5 (which had no effect on mean open time), ketamine produced a slowly developing reduction in mean channel open time (from about 6 to 3 ms). This presumably reflects the high probability that open channels will be blocked by ketamine before they would normally close. The recovery from ketamine antagonism is also very slow and dependent on the presence of NMDA, suggesting that ketamine can enter the open channel and be trapped unless NMDA agonists are available to reopen the channel (155, 156). This use dependence has also been noted for other

PCP-like ligands including cyclazocine and MK-801 (158). Interestingly, use dependence was greatest for MK-801, followed by PCP and cyclazocine, and then by ketamine, which showed very little use dependence in a cortical wedge preparation. The reason for these differences is unclear, but it may be related to the size and relative flexibility of the molecules; c.g. MK-801 is a rigid, planar, three-ring structure with a nitrogen bridge oriented perpendicular to the central ring, whereas ketamine is a flexible, bicyclic structure.

A drug that exhibits substantial use dependence relative to its onset of action could conceivably be used clinically as a "prodrug," in that its antagonistic effects would not be realized until endogenous NMDA agonists opened the channel-binding site. This possibility has been examined in vivo by using rat spinal cord neurons (158). However, in this model the onset of block by intravenous MK-801 was not altered by iontophoretic application of NMDA, although the rate of recovery from MK-801 block was enhanced by NMDA application. This suggests that there may be enough endogenous NMDA tone in vivo to allow MK-801 to immediately act as an open-channel blocker or that MK-801 may gain access to its channel-binding site by rapidly diffusing through the membrane lipid bilayer.

Studies of the voltage dependence of the NMDA block by PCP and ketamine have provided additional evidence for the channel localization of the PCP-binding site (153, 155, 156, 159). In cultured hippocampal cells, blockade of NMDA responses is much greater at hyperpolarized membrane potentials (−60 to −70 mV) than at more depolarized potentials, and virtually no block is seen at holding potentials greater than +30 mV. Equilibrium analysis of the ketamine block at −60 mV revealed a K_i of 1.5 μM, whereas the K_i at +40 mV was calculated as 49 μM (155). Using these data, Mayer et al (155) calculated that the fraction of the membrane electric field that influences ketamine binding is close to 1.0. This suggests that the ketamine-binding site is deep within the channel, close to the cytoplasmic surface of the membrane. The voltage dependence of the binding also partially accounts for the accelerated rate of recovery from MK-801 block observed in cells held at +30 mV (159).

Together, the voltage-and use-dependent open-channel block (and unblock) may contribute to the pharmacological uniqueness of the various drugs that act at the PCP site. It appears that voltage and use dependence may be independent properties, although this has not been well studied. For example, the ketamine block is clearly voltage dependent and is similar to PCP in this regard (153), but it shows relatively little use dependence (158). However, MK-801 blockade shows little voltage dependence during its onset, but the recovery of blockade in the presence of NMDA does show marked voltage dependence (159). Interestingly, MK-801 shows greater use dependence than

PCP and considerably greater use dependence than ketamine (158). The relative importance of these two properties is difficult to assess, but its significance can be understood by realizing that they tend to offset each other in a functional sense. That is, inhibition of NMDA responses by PCP is dependent on the presence of an NMDA agonist, but NMDA also depolarizes the membrane, effectively decreasing the effect of a given concentration of PCP. Therefore, a compound that exhibits high use dependence relative to voltage dependence might be a more selective and potent NMDA antagonist than one that shows low use dependence but high voltage dependence.

The voltage-dependent properties of PCP blockade of the NMDA receptor-ionophore complex could also contribute to the uniqueness of PCP pharmacology in a way that is interdependent with the selectivity of endogenous excitatory amino acids for the several receptor subtypes. That is, because glutamate can act at kainate, quisqualate, and NMDA receptors, its ability to depolarize the cell membrane through quisqualate or kainate receptors would theoretically partially negate the effects of PCP-like compounds acting at NMDA receptors. However, aspartate, and particularly homocysteic acid, may have more selectivity for NMDA receptors. Thus, we would predict that PCP is a more potent antagonist of homocysteic acid than of glutamate responses. If so, this is important because these amino acids probably mediate synaptic transmission in independent neuronal pathways, thus affording an additional mechanism for PCP selectivity.

The localization of the PCP-binding site within the NMDA receptor-ionophore complex has received considerable support from binding studies. Initially, it was reported that the specific binding of [^{3}H]TCP was reduced by progressively washing brain membranes and that this reduction could be reversed by adding glutamate back to the medium (160). Subsequent studies demonstrated an excellent correlation between the potency of ligands in activating NMDA receptors and in increasing [^{3}H]TCP or [^{3}H]MK-801 binding in well-washed membranes (161, 162). This relationship was further strengthened by reports showing that NMDA receptor antagonists inhibited [^{3}H]TCP and [^{3}H]MK-801 binding (163–166).

In addition, autoradiographic studies of [^{3}H]TCP together with NMDA-displaceable [^{3}H]glutamate, [^{3}H]CPP, or [^{3}H]AP5 binding in brain slices have shown a very high degree of colocalization of NMDA receptor sites and PCP-binding sites (137, 167–169). Binding of ligands to both sites was highest in the stratum radiatum and stratum oriens of hippocampal area CA1, followed by the dentate gyrus, entorhinal cortex, and layers I and II of the somatosensory and motor cortex (137, 168). Intermediate binding was found in the olfactory region, amygdala, thalamus, lateral septum, hippocampal area CA3, and caudate nucleus. Approximately 10% or less of the binding found in area CA1 was in the globus pallidus, medial septum, habenula,

hypothalamus, diagonal band, and cerebellum. The granule cell layer of the cerebellum was the only area reported to be discordant in binding of the two ligands (168).

The mechanism by which NMDA agonists selectively stimulate ligand binding to the receptor-ionophore complex has not been completely resolved. Initial studies suggested that glutamate and NMDA increased either the affinity (161, 164, 165, 170) or the apparent site density (165) for [^{3}H]TCP or [^{3}H]MK-801 binding. Subsequently, it was determined that the time required for either ligand to reach true equilibrium in highly washed membranes (nominally free of glutatmate) was 5–24 h, depending on the ligand used and the thoroughness with which the membranes were washed (171–174). Thus, earlier studies with shorter incubation times were actually conducted at 50–70% of true equilibrium; this made inferences from these experiments difficult. More recent studies have suggested that glutamate and other NMDA agonists increase the rates of both association and dissociation of [^{3}H]TCP (171, 172) or [^{3}H]MK-801 (173, 175) without altering the equilibrium dissociation constant (172, 173). Although it has been stated that the equilibrium K_D is similar to the kinetically determined K_D (172), closer examination of the kinetic data (171) suggest that both association and dissociation are multiphasic; this makes the K_D determined by assuming classical bimolecular kinetics somewhat difficult to interpret. This is further complicated when considered in the light of the effects of glycine on channel kinetics (see below).

Nevertheless, the data thus far have been widely interpreted in a manner consistent with open-channel block by PCP-like ligands. That is, the increase in the rates of binding and unbinding induced by NMDA agonists is due to an increase in the fraction of time the channel-binding site is accessible to [^{3}H]TCP or [^{3}H]MK-801. This is supported by the observation that NMDA antagonists such as AP5 decrease the rates of association and dissociation (171, 172, 175). Thus, there appears to be overwhelming evidence that NMDA agonists regulate the binding of PCP-like ligands to the channel-binding site by increasing channel opening, but whether or not channel opening is also associated with a conformational change in the PCP-binding site [also suggested by electrophysiological studies (155)] is still a matter of debate, which will be settled only when the role of glycine in facilitating the actions of NMDA agonists is understood.

At this time, very little is actually known about the structure of the NMDA receptor-ionophore complex. Radiation inactivation analysis has indicated that the sites labeled with [^{3}H]TCP, [^{3}H]glutamate (NMDA specific), and [^{3}H]glycine have molecular masses in the range of 115–125 kDa (176). Curiously, the site labeled with [^{3}H]CPP appears to have a molecular mass of 209 kDa. This suggests that the recognition sites for NMDA and glycine are

part of the same protein that constitutes the channel-binding site for PCP, but that CPP may bind to a distinct but tightly coupled protein (176). Receptor solubilization studies also suggest that the NMDA-, glycine-, and PCP-binding sites are tightly coupled, as the binding of [^{3}H]TCP and [^{3}H]MK-801 to a solubilized protein is enhanced by NMDA agonists, glycine, and divalent cations (177, 178). Furthermore, injection of crude poly(A)$^+$ mRNA from rat brain into *Xenopus* oocytes results in the expression of a cation channel opened by NMDA agonists (in the presence of glycine) and blocked by PCP, MK-801, and Mg^{2+} (179–181). The NMDA complex is expressed by mRNA in the range of 4.2–7.7 kb, which suggests that the complex consists of several homologous subunits that might be encoded by mRNAs of different lengths, presumably because of differences in the lengths of untranslated regions (181). It seems likely that advances in knowledge of the molecular biology of this complex will occur soon. It will be most interesting to see whether the widely anticipated similarities with other receptor-operated ion channels become a reality.

The Glycine Receptor

In studies of the effects of excitatory amino acids on cultured neurons, Johnson & Ascher (182) observed that glycine potentiated the effects of NMDA in a strychnine-insensitive manner. The effects of glycine were mimicked by D-serine and D-alanine and were completely blocked by NMDA antagonists, which suggests that glycine was acting through a unique receptor to facilitate, or perhaps to permit, the actions of NMDA. Patch clamp analysis revealed that the primary effect of glycine was to increase the frequency of channel opening without changing the channel open time or channel conductance (182); this suggests that glycine could regulate transitions to states that are intermediate between binding NMDA agonists and ion channel gating (183). Consistent with this, Javitt & Zukin have presented a model based on near-equilibrium binding of [^{3}H]MK-801, which suggests that glycine converts a glutamate-associated, closed conformation of the channel (with a low affinity for [^{3}H]MK-801) to a high-affinity, open conformation (184).

Another prominent effect of glycine appears to be a reduction in the rapid desensitization of NMDA receptors (183). In experiments in which the ambient glycine concentration was minimized, no NMDA response could be obtained; this suggests an obligatory role for glycine (179). However, Mayer et al have pointed out that these measurements were made under conditions inadequate to detect rapid changes in receptor gating and that therefore the apparent requirement for glycine may in part be due to the ability of glycine to retard the rate of receptor desensitization (183).

The strychnine-insensitive glycine receptor has been studied by using [^{3}H]glycine binding (185, 186) and autoradiography (187). The glycine

receptor has a K_D of about 250 nM for [^{3}H]glycine. The relatively high concentrations reported for cerebrospinal fluid (188) suggest that this receptor may be normally saturated. This is supported by the relatively low-affinity transport systems for glycine in the forebrain (189) and by the lack of effect of exogenously applied glycine on NMDA responses in cortical wedges (190, 191). However, a recent study has found that iontophoretic application of glycine selectively facilitated NMDA responses in neocortical neurons (192). Thus, the saturation of glycine receptors may vary widely and may be dependent on the particular synapse. There may also be pathological conditions in which the local glycine concentration is abnormal, thereby adversely affecting normal synaptic transmission mediated by NMDA receptors.

The structural requirements for activation of the glycine receptor have been determined by measuring the effects of glycine and various analogs on [^{3}H]TCP binding under nonequilibrium conditions (193). The rank order potency for simple amino acids is as follows: glycine = D-serine > D-alanine > L-serine >L-alanine = L-valine >> D-valine. This rank order was found to correlate precisely with affinity for the site labeled with [^{3}H]glycine (193). Comparison with other analogs including cysteine (194), phenylalanine, GABA, β-alanine, glycine methyl ester, glycinamide, and *N*-methyglycine revealed a strict structural specificity involving virtually all aspects of the glycine molecule (174, 193). One of the more interesting series of compounds tested thus far involves ring substitutions of the α-carbon of glycine. The cyclopropyl-substituted analog, 1-aminocyclopropane-1-carboxylic acid, is a partial glycine agonist with a K_i in the range 50–100 nM (195, 196). The cyclobutyl analog, 1-aminocyclobutane-1-carboxylic acid, is a competitive antagonist with a K_i of about 20 μM (197). The cyclopentyl analog, 1-aminocyclopentane-1-carboxylic acid or cycloleucine, is a weak competitive antagonist with a K_i of about 600 μM (198). Higher-order analogs such as the cyclohexane and cycloheptane derivatives were found to be without agonist or antagonist activity (K. M. Johnson, unpublished observations). Thus, this series includes both agonist and antagonist compounds, with the conversion of one to the other being the result of enlarging the ring by a single methylene unit from cyclopropyl to cyclobutyl (197).

Recently, another cyclic glycine analog, 1-hydroxy-3-aminopyrolid-2-one (HA-966), was reported to antagonize NMDA-induced depolarization in a manner that was reversible by glycine (190). This compound inhibits [^{3}H]glycine binding with a K_i of about 5 μM and has no effect on the NMDA recognition site at concentrations up to 100 μM (L. D. Snell & S. M. Jones, unpublished observations). HA-966 is remarkably similar in structure to D-cycloserine, a moderately potent glycine agonist (199), again suggesting that relatively minor structural changes in cyclic glycine analogs can convert an agonist into an antagonist (174).

Kynurenic acid is a well-known, rather nonselective antagonist of NMDA,

kainate, and quisqualate receptors. The 7-chloro derivative of kynurenic acid is a potent (K_i = 0.5 μM) and selective glycine antagonist acid (191). Kynurenic acid also inhibits [^{3}H]glycine binding, but is about 75-fold less potent and 70-fold less selective (relative to the NMDA receptor) than 7-chlorokynurenic acid (191). Interestingly, comparisons with HA-966 suggest that 7-chlorokynurenic acid may be an inverse agonist rather than a simple antagonist (200). Recently, indole-2-carboxylic acid and its 5-chloro derivative have been reported to be selective but somewhat less potent glycine antagonists (201). Finally, CNQX and two of its derivatives have been shown to be almost as potent glycine antagonists as 7-chlorokynurenic acid, but they are not nearly as selective, as they interact with the kainate and quisqualate receptors with similar affinity (202, 203).

Interactions between the Glutamate and Glycine Receptors

Kessler et al (204) reported that NMDA agonists slightly increased [^{3}H]glycine binding (by 10–20%) and that NMDA antagonists reduced binding by up to 80%; the effects of both agonists and antagonists were mediated via changes in B_{max}. Furthermore, the inhibitory effects of AP5 on [^{3}H]glycine binding were reversed by glutamate. Nguyen et al, using quantitative autoradiography, also observed similar effects of agonists and antagonists on [^{3}H]glycine binding (205). Interestingly, glycine and serine were observed to increase NMDA-specific [^{3}H]glutamate binding, whereas kynurenate inhibited NMDA-specific [^{3}H]glutamate binding in a glycine-reversible manner (204). Autoradiographic data have also been reported showing that glycine dose-dependently enhanced [^{3}H]glutamate binding to NMDA receptors (205). These preliminary reports were the first to suggest reciprocal regulation between these two receptors.

It was recently reported that cycloleucine produced a maximal 40% inhibition of NMDA receptor binding that was completely reversed by 10 μM glycine (206). Conversely, the 50% inhibition of [^{3}H]glycine binding caused by the selective NMDA antagonist CPP was reversed by both L-glutamate and L-homocysteate (206). Furthermore, the inhibition of [^{3}H]glycine binding by CPP was mediated by an apparent reduction in the number of glycine sites, and, conversely, the increase in NMDA-specific [^{3}H]glutamate binding caused by 10 μM glycine was associated with a 50% increase in the apparent number of NMDA receptors (L. D. Snell & K. M. Johnson, unpublished observations). These data suggest that the number of sites available for binding either NMDA agonists or glycine is allosterically regulated by occupancy of the other receptor.

More recently, Monaghan et al have reported that glycine and D-serine increase NMDA-displaceable [^{3}H]glutamate binding, but decrease both [^{3}H]CPP and [^{3}H]AP5 binding (137). On the basis of these data and the

observation that glycine alters the regional autoradiographic distribution of [^{3}H]CPP, these authors postulated that the NMDA receptor exists in agonist- and antagonist-preferring states and that glycine shifts the equilibrium between them from antagonist- to agonist-preferring state. This is consistent with the findings described above (in which glycine increased the NMDA receptor density) if the high-affinity NMDA-sensitive [^{3}H]glutamate site (K_D = 36 nM) detected in this assay is selective for the agonist-preferring state. However, the data are also consistent with a recent report in which glycine increased NMDA-sensitive binding via a change in K_D from 140 to 100 nM (207). The source of these discrepancies is unclear at present. Nevertheless, a reciprocal interaction between the NMDA and glycine receptors could provide a very effective means of both amplifying and dampening the signal that controls channel opening, depending on the relative concentrations of glycine, glutamate, and antagonist.

Role of Divalent Cations

Magnesium and other divalent cations were shown several years ago to inhibit [^{3}H]PCP binding, with IC_{50} values of approximately 100 μM (208). Because Mg^{2+} is now known to block conductance activated by NMDA agonists in a voltage-dependent manner (209, 210) and because PCP blockade of NMDA responses also shows voltage-dependent characteristics (153, 154), the effect of Mg^{2+} on specific [^{3}H]TCP binding was determined. Surprisingly, it was found that Mg^{2+} stimulated basal [^{3}H]TCP binding in a concentration-dependent manner, with a maximal threefold increase occurring at 1 mM (163). At concentrations greater than 1mM, binding was inhibited. This biphasic effect was also characteristic of the other divalent cations tested, although the maximal effect and the maximally effective concentration were reduced in the following order: $Ba^{2+} > Mg^{2+} > Ca^{2+}$, Mn^{2+}, $Co^{2+} > Ni^{2+}$ (163, 174). Although Ni^{2+} had only a slight stimulatory effect, it was quite effective as an inhibitor, inhibiting binding even below control levels at 1 mM. Even more striking were the effects of Cd^{2+} and Zn^{2+}, which had no capacity to stimulate binding, but were capable of potently inhibiting [^{3}H]TCP binding to almost undetectable levels (174).

The relationship between the effect of these ions on [^{3}H]TCP (or [^{3}H]MK-801) binding and their effect on physiological responses to NMDA is not clear, but several correlations are apparent. First, Zn^{2+} is the most potent inhibitor of [^{3}H]TCP binding and of NMDA-induced depolarization and toxicity (211, 212). Furthermore, since Zn^{2+} blockade of the NMDA response shows little voltage dependence relative to Mg^{2+} (211), there may be a correlation between voltage-dependent blockade and the ability to stimulate [^{3}H]TCP binding. However, the relationship between the ability to stimulate PCP receptor binding and channel permeability is less clear. Ba^{2+} and Ca^{2+}

can effectively carry current through the NMDA-activated channel, but Mg^{2+} and Mn^{2+} are only poorly permeable (213). As the stimulatory effect of Mg^{2+} on binding is converted to an inhibitory effect upon addition of NMDA and glycine (163, 174), the apparent poor correlation between binding effects and permeability may be due to the concentrations of glutamate and glycine chosen for study. Reynolds & Miller (214) have studied this phenomenon thoroughly and have found that the potency of inhibition of [^{3}H]MK801 binding is markedly affected by glutamate and glycine, producing a 33- to 1.6-fold leftward shift (in the order given) for Mg^{2+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Ca^{2+}, and Ni^{2+} and a slight rightward shift for Cd^{2+} and Zn^{2+}. This confirms that the first group of ions, which block NMDA responses in a voltage-dependent manner, can be distinguished in binding assays from the latter group, which act in a voltage-independent manner to block NMDA. Nevertheless, there is still not a clear correlation between channel permeability and the effects of these ions on binding, regardless of the conditions under which they are studied.

Several reasons may account for the poor correlation between these two parameters. First, there are species and tissue differences between the electrophysiological (213, 215) and binding (163, 174, 214) studies. Second, the binding studies are conducted with what are presumably completely depolarized membranes, and thus these results cannot be rigorously compared with those of studies of intact polarized cell membranes. Third, it is clear that we do not yet understand either the topographical or functional relationship between the PCP site and the voltage-dependent site for Mg^{2+}. Similarly, we do not understand the relationship between channel permeability and affinity for the voltage-dependent divalent cation site. Finally, some workers have observed that Mg^{2+} increases the affinity of [^{3}H]glycine for its receptor (202, 216), thereby further compromising our ability to make correlations between divergent experimental models. Further development in understanding the role of divalent cations in the regulation of the NMDA ionophore, and hence in the pharmacology of PCP, may require the advent of ligands with affinity for the Mg^{2+} and Zn^{2+} sites.

Role of Polyamines

Putrescine is derived from the decarboxylation of ornithine. This divalent diamine is metabolized to the triamine spermidine, which, in turn, is converted to spermine, a primary amine with the structure H_2N-$(CH_2)_3$-NH-$(CH_2)_4$-NH-$(CH_2)_3$-NH_2. Ransom & Stec reported that spermidine and spermine, but not putrescine, increased [^{3}H]MK-801 binding by a mechanism that was enhanced by both glutamate and glycine and blocked by NMDA antagonists (217). This suggested that certain polyamines may modulate NMDA receptor function through an intracellular mechanism. This finding became

more intriguing with the preliminary report that the effects of NMDA on Ca^{2+} flux and neurotransmitter release were blocked by an irreversible inhibitor of ornithine decarboxylase (ODC) in a manner reversible by addition of putrescine (218). Furthermore, these investigators also reported that NMDA produced a rapid, transient increase in ODC activity. Together, these data suggest that the actions of NMDA may be partially mediated by spermidine and/or spermine.

As of this writing, the effect of NMDA on ODC activity and the effect of ODC inhibition on NMDA responses have not yet been confirmed, but the effects of spermine and spermidine on [^{3}H]MK-801 binding have been confirmed (I. J. Reynolds, personal communication). Studies using [^{3}H]TCP binding have extended this finding to several synthetic polyamine analogs in an effort to determine the structural requirements for this unique modulatory site (219). It was found that the number of nitrogen atoms in the polyamine backbone plays a major role in determining the efficacy of receptor activation and that the number of methylene groups separating the nitrogens is a major determinant of affinity. Furthermore, it was determined that several diamine analogs, including putrescine, antagonize spermidine-induced [^{3}H]TCP binding in a manner consistent with a noncompetitive mechanism (A. I. Sacaan & K. M. Johnson, unpublished observation). Since the metabolism of putrescine to spermidine and spermine is reversible, these data imply that the regulation of polyamine metabolism could be intimately involved in a complex regulation of NMDA receptor function. Recently, it has been reported that SL 82,0715 and ifenprodil may be antagonists at this polyamine site (220), but Reynolds & Miller recently concluded that ifenprodil is a noncompetitive antagonist at this site (221). Ifenprodil is about 100-fold more potent than putrescine, and possibly more so, depending on the concentration of glutamate and glycine (221). Ifenprodil is of additional interest in this context because of its neuroprotective effects in focal cerebral ischemia (222).

Further complexity is suggested by preliminary studies of the effect of polyamines on [^{3}H]glycine binding (223). These experiments revealed that spermine enhanced [^{3}H]glycine binding by increasing the binding affinity threefold. Interestingly, the structural requirements for activating the glycine receptor were completely different from those for activation of the NMDA ionophore, suggesting at least two independent sites for polyamine modulation of the NMDA receptor-ionophore complex. It was found that the spermine-induced change in glycine receptor affinity was selective for agonists; i.e. spermine shifted the IC_{50} for displacement of [^{3}H]glycine by glycine and D-serine threefold to the left, but had no effect on the displacement by the antagonists 7-chlorokynurenic acid or cycloleucine (223). This suggests that the glycine receptor may exist in agonist- and antagonist-preferring conformations. We suggest that this effect of spermine may be important phys-

iologically in regulating the effects of an endogenous antagonist, such as kynurenic acid.

BEHAVIORAL AND POTENTIAL THERAPEUTIC CORRELATES OF NMDA ANTAGONISM

Behavior

As can be discerned from the foregoing discussion, PCP affects several neurotransmitter systems in addition to the excitatory amino acids. Thus, it is probably unreasonable to think that any behavior affected or induced by PCP is the result of a single mechanism. Nevertheless, because of the potential therapeutic benefits that could be derived via an antagonism of NMDA receptor function (see below), it is important to ask which, if any, of the known behavioral effects of PCP could be mediated by this mechanism.

With regard to unconditioned behaviors in rodents, PCP produces amphetaminelike stereotyped behavior (224, 225), ipsilateral rotation in rats with lesions in the substantia nigra (98), and increased locomotor activity (226–229). There is, however, no consensus about which neurochemical mechanisms may mediate these behaviors. Although several studies point to a role for DA (230, 231), it is by no means conclusive that this neurotransmitter underlies all PCP-induced behaviors. In increased locomotor activity, the ability of neuroleptics to antagonize PCP are less well correlated with their potency as pure DA receptor blockers than with their efficacy at blocking both dopaminergic and serotonergic receptors (232, 233). Also, there is at least one report of 5-HT_2 receptor mediation of PCP-induced locomotion (234). Finally, PCP-induced rotation may involve actions at nondopaminergic sites (235) or may not be dependent on DA at all (62, 82, 83, 236).

Despite the diverse nature of PCP behavioral effects, there is evidence that the interaction of PCP with a specific PCP receptor can account for its discriminative stimulus properties (35) and for the production of stereotypy (225), ataxia (12, 208, 225), and turning behavior in rats with unilateral 6-hydroxydopamine lesions on the substantia nigra (62, 82). If the PCP receptor is coupled to the NMDA receptor as proposed, each of these behaviors might be expected to be produced by inhibition of NMDA.

Consistent with this hypothesis, MK-801, a noncompetitive NMDA antagonist, increased the locomotor activity in mice pretreated with reserpine and α-methyl-*p*-tyrosine (237). Furthermore, this stimulation was not blocked by haloperidol. The competitive antagonist CGS 19755 increased locomotor activity and produced side-to-side head movement, a stereotypic behavior widely reported for PCP (238). Systemic administration of the potent NMDA antagonist CPP produced a PCP-like behavioral syndrome in mice, consisting of circling behavior, head movements, and ataxia (239). In the only study to

directly compare the overt behavioral effects of AP5 with those of PCP (240), i.c.v. administration of AP5 produced locomotion, sniffing, swaying, and falling that was more similar to the effects produced by PCP and ketamine than by stimulants or sedatives.

In rats, intrastriatal injections of AP5 and kynurenate produce a specific behavioral syndrome of continuous and intensive upward sniffing (241, 242). Although similar to the sniffing produced by systemic amphetamine, the AP5 action differed in that it did not induce gnawing, biting, or licking. Unilateral injection of AP5 into the substantia nigra pars compacta resulted in contraversive turning behavior (243) similar to that observed following unilateral PCP injections into this area (236). Bilateral injection of AP5 into the mesencephalic DA cell bodies of the ventral tegmental area or substantia nigra pars compacta enhanced motor activity (242). Interestingly, the bilateral application of these antagonists to the substantia nigra pars reticulata causes sedation (243). This may be related to the ataxia-producing effects of PCP and other NMDA antagonists. This notion is supported by the report that local infusion of the NMDA antagonist AP7 into the ventromedial nucleus of the thalamus can produce a reversible akinesia resembling PCP ataxia in rats (244, 245).

Although the most prominent effect of PCP in rodents is amphetaminelike stereotyped behavior and hyperactivity, the most pronounced effect of PCP in pigeons is catalepsy (3), and, again, PCP-like drugs within and outside the arylcycloalkylamine class show the same selectivity and stereoselectivity in the production of this behavior as they do for the PCP receptor (31, 246). Koek et al have demonstrated that AP5 will produce a PCP-like catalepsy following icv or systemic administration (240). Furthermore, the catalepsy-inducing activity resides almost exclusively in D-AP5 (247), paralleling the stereoselectivity of this isomer as an NMDA receptor antagonist in vitro (248). The rank order potency of other excitatory amino acid antagonists to produce PCP-like catalepsy also agrees well with the in vitro potency of these compounds as NMDA antagonists (247).

To date, the strongest evidence that the binding site for PCP in the brain is a physiologically relevent receptor has come from the correlation between the affinity of PCP-like drugs for this site and their ability to generalize to the discriminative stimulus effects of PCP (13, 35). The discriminative stimulus effects of PCP are very distinct from those of other psychoactive drugs, and animals trained to discriminate between PCP and saline do not generalize stimulus control by PCP to cholinergic, dopaminergic, serotonergic, GABAergic, or opioid drugs (249–251). Furthermore, discriminative stimulus properties of PCP-like drugs are similar in rats (250), pigeons (252), and monkeys (253, 254). It might be expected, therefore, that NMDA receptor antagonists will provide a PCP-like discriminative stimulus cue.

However, in rats trained to discriminate between PCP and saline, systemi-

cally administered AP7 failed to elicit responding on the PCP lever, and CPP produced only a partial generalization to PCP (255). Similarly, only partial generalization to PCP was observed with a recently characterized competitive antagonist, NPC 12626 (256). As with CPP, partial PCP-like effects were seen only at doses that decreased response rates. Similar rates have recently been obtained in monkeys trained to discriminate ketamine. In these experiments, CGS 19755 failed to produce ketamine appropriate responding (257). These experiments were particularly interesting because ketamine and CGS 19755 antagonized the rate-decreasing effects of systemically administered NMDA.

These data strongly suggest that the subjective effects of competitive antagonists in humans will be different from those of the noncompetitive antagonists such as PCP, ketamine, and MK-801. Nevertheless, it is important not to overlook the strong similiarities between PCP and competitive antagonists on motor activity, coordination, catalepsy, and learning (258). Thus, although the subjective effects of competitive NMDA antagonists may be different from those of PCP- and MK-801-like compounds, that is not to say they will be pleasant or even tolerable. Until this class of drugs is tested in humans, we will not know their subjective effects, but it could be predicted that they will have other side effects similar to those of PCP.

Anticonvulsant Properties

The anticonvulsant properties of both PCP and the related anesthetic ketamine were first described 30 years ago. In the initial description of the pharmacology of PCP, it was reported that PCP is effective at suppressing electrically or pentylenetetrazol (PTZ)-induced tonic extensor seizures in mice (3). However, PCP is only weakly effective at blocking caffeine-induced seizures and is ineffective against seizures produced by strychnine. PCP is also effective at blocking audiogenic seizures and electroshock seizures, but not clonic seizures induced by PTZ (259). Ketamine is also effective at antagonizing electroshock-induced seizures in mice, but its effects appear more rapidly and are briefer than those of PCP (260, 261).

ANTICONVULSANT ACTIVITY IN VARIOUS SEIZURE MODELS PCP blocks seizures in several rodent seizure models, including maximal electroshock (234, 262–264), penicillin (265), and mercaptopropionic acid (266), as well as the tonic seizures produced by PTZ (66–269). PCP increases the threshold for seizures produced by flurothyl in rats (270). Ketamine inhibits audiogenic seizures in epilepsy-prone rats (271); it has been reported to block seizures in epileptic patients (272), although others have reported that it enhanced seizures in epileptic patients (273).

Both PCP and ketamine have been reported to block seizures in kindled rats (274–276). These effects may be due to the ability of PCP and ketamine to

increase the threshold for after-discharge production (277, 278) or decrease the after-discharge duration (274). However, other studies have reported that PCP had minimal effects on fully kindled seizures but retarded the development of kindling (279). PCP and ketamine are more effective at blocking kindled cortical seizures than kindled amygdaloid seizures (280). Ketamine has also been reported to prevent the development of amygdaloid kindling (276), and decrease after-discharge duration during cortical kindling (280).

STRUCTURE-ACTIVITY RELATIONSHIPS Anticonvulsant effects have also been described for compounds from several structurally diverse groups which exhibit affinity for the PCP-binding site. In 1979 Cowan et al (281) reported that NANM and cyclazocine produced dose-related anticonvulsant effects against flurothyl-induced seizures in rats. In contrast, the benzomorphan *sigma* agonist pentazocine had proconvulsant effects. Pentazocine and cyclazocine, as well as morphine and other opioids and opioid peptides, blocked tonic seizures produced by maximal electroshock (282). Cyclazocine also blocked PTZ- (267) and penicillin- and strychinine-induced seizures in rabbits (283).

Hayes & Balster found that PCP, ketamine, NANM, etoxadrol, and (−)-2-methyl-3,3-diphenyl-3-propanolamine ((−)-2-MDP) prevented PTZ-induced tonic seizures, with potencies that correlated with their potencies in drug discrimination models (268). Levoxadrol and (+)-2-MDP, which do not exhibit PCP-like activity, were ineffective.

Thus, the results of these studies suggest that the anticonvulsant effects of PCP and several other compounds are mediated via the NMDA-associated PCP site. However, the anticonvulsant effects of PCP and these other compounds occur at doses that produce ataxia and other side effects, which may limit their use as clinical anticonvulsants.

Several laboratories have compared the effects of PCP with structural analogs of PCP, in an attempt to determine the mechanism by which PCP exerts its diverse effects. Ketamine, PCP, and several structural analogs of PCP examined by Mattia and co-workers (262) were all anticonvulsant against electroshock-induced seizures at behaviorally equivalent doses, but in other assays the anticonvulsant and behavioral effects were not well correlated. Rogawski et al (263) tested various PCP analogs for anticonvulsant activity. They found that phencylcyclohexamine (PCA) and *trans*-(*R*)-3-methyl-PCA had similar potency but less toxicity than PCP against maximal electroshock–induced seizures. *m*-Nitro-PCP and *trans*-(*S*)-3-methyl-PCA were less potent anticonvulsants, but were also less toxic, resulting in an increased therapeutic index.

NMDA ANTAGONISM AND ANTICONVULSANT ACTIVITY Leander et al reported that PCP-like drugs and MK-801 were anticonvulsant against

maximal electroshock in mice, with potencies that correlated with their ability to block NMDA lethality (264). These studies suggested that the anticonvulsant effects of these drugs were related to their ability to bind to the PCP receptor and block NMDA-mediated responses. However, Rogawski et al found that several PCP analogs were anticonvulsant against maximal electroshock–induced seizures, but this effect was not necessarily related to their ability to displace [^{3}H]TCP binding (263). Many of the studies suggesting that anticonvulsant activity is related to NMDA antagonism have examined the structurally dissimilar MK-801, which was reported to potently antagonize seizures produced by bicuculline and electroshock (284). Because haloperidol and α-adrenoceptor blockers reduced the anticonvulsant effects of MK-801, Clineshmidt et al concluded that MK-801 actions were at least partially catecholaminergically mediated (284). However, it is now known that MK-801 has high affinity for the PCP site labeled with [^{3}H]TCP (86, 164), and it is possible that the anticonvulsant effects are due to this interaction. Alternatively, because both PCP and MK-801 inhibit the uptake of [^{3}H]NE (86), it is possible that this characteristic also contributes to anticonvulsant activity.

Several laboratories have found that MK-801 inhibits the development of amygdaloid kindling in rats (285–287). However, MK-801 has been reported to be both effective (288) and ineffective (285) in blocking fully kindled seizures.

Ketamine, MK-801, PCP, and AP7 increased the threshold for inducing spreading depression in the rat cortex, as well as reducing the propagation velocity and the duration of ionic changes produced during spreading depression (289). Both competitive and noncompetitive NMDA antagonists block "low Mg^{2+} epileptogenesis" in the CA1 region of hippocampal slices (290). Dextromethorphan prevented the development of amygdaloid kinding in rats by decreasing the after-discharge duration and seizure intensity (291). In fully kindled rats, dextromethorphan decreased seizure intensity, with no effect on after-discharge duration. However, dextrorphan was incapable of blocking fully kindled seizures (292). It appears that, like MK-801, dextrorphan is more effective at preventing the development of kindled seizures than blocking fully kindled seizures. PCP, as well as competitive NMDA antagonists, blocked an NMDA-mediated synaptic response in amygdala slices from kindled rats (293).

Dextromethorphan and its metabolite, dextrorphan, have been shown to block NMDA-mediated depolarizations (294, 295). Ferkany et al found that dextromethorphan, PCP, ketaminc, MK-801, CPP, and AP7 block NMDA-induced convulsions (296). Dextromethorphan was less potent than dextrorphan in blocking epileptiform activity induced by Mg^{2+}-free buffer in guinea pig neocortical slices (294). Dextrorphan has low affinity for [^{3}H]dextromethorphan sites, but does interact with PCP-binding sites (297).

Tortella & Musacchio (298) found that dextromethorphan and carbetapentane block maximal electroshock–induced seizures in rats and potentiate the anticonvulsant effects of phenytoin, suggesting that the anticonvulsant effects are due to effects at the [^{3}H]dextromethorphan site. A more recent study by Tortella et al (289) found that dextrorphan blocked maximal electroshock–induced seizures, but did not potentiate the effects of phenytoin. Therefore, the anticonvulsant effects of dextromethorphan may be mainly due to interaction with the [^{3}H]dextromethorphan site, but the anticonvulsant effects of dextrorphan appear to be mediated by antagonism of NMDA receptors.

It has been determined that the potency of PCP-like drugs as NMDA antagonists correlated with their ability to block epileptiform activity in Mg^{2+}-free medium (300). The potency of *sigma* or dextromethorphan ligands did not correlate with their affinities at the *sigma* or dextromethorphan sites, respectively. This profile of action was indistinguishable from that of competitive NMDA antagonists, yet different from other anticonvulsants. In summary, PCP and PCP-like compounds share the ability to antagonize seizures produced by a variety of methods. It also appears that this ability may be related to the ability of ligands for the PCP-binding site to antagonize NMDA-mediated responses. However, it is possible that other characteristics of PCP-like compounds also contribute to anticonvulsant activity.

Neuroprotective Properties

Although excitatory amino acids play a major role as excitatory neurotransmitters, there is substantial evidence that suggests that the excessive release of these amino acids in the central nervous system can have detrimental results. Glutamate, NMDA, kainate, ibotenate, quinolinate, and quisqualate are all neurotoxic in vivo and in vitro at high concentrations, with rank order potencies identical to their potency at producing depolarizing responses. It has been proposed that the excessive release of endogenous excitatory amino acids in certain conditions such as seizures, anoxia, hypoglycemia, and stroke could be the causal factor in neuropathology. In several conditions such as Alzheimer's disease, Huntington's disease (302), or ischemia (303), the pathology is localized to areas of the brain receiving glutamatergic innervation, and there is a corresponding loss of glutamate receptors (303). In fact, transection of glutamatergic innervation of the hippocampal CA1 area can protect this area from ischemic damage (303, 304).

In 1984, Rothman reported that the excitatory amino acid antagonist γ-D-glutamylglycine blocked glutamate- or aspartate-induced necrosis as well as anoxic neuronal death of cultured hippocampal neurons (305). Intrahippocampal injections of AP7 was also reported to prevent the development of ischemic damage due to carotid artery occlusion in rats (306) or to hypoglycemic coma (307). Since that time, work by many laboratories has

shown that excitatory amino acid antagonists, particularly NMDA antagonists, can reduce neurotoxicity produced by various neuropathological conditions.

PCP-like compounds also block neurotoxicity, perhaps by antagonism of NMDA-mediated events. Choi et al (308) found that ketamine, AP7, and kynurenate attenuated glutamate-induced neurotoxicity in cultured cortical neurons, whereas quisqualate or kainate receptor antagonists were ineffective. These experiments indicate that glutamate-induced cell death in cortical culture is predominantly mediated by NMDA receptors. In addition, delayed administration of AP5 also attenuated cell death. Because NMDA antagonism blocked late neuronal cell loss, with less effect on earlier events such as neuronal swelling or glutamate neuroexcitation, it was suggested that the ultimate loss of neurons is due to activation of NMDA receptors (and subsequent calcium influx), whereas earlier toxicity may be mediated by other receptor subtypes (309). It was also reported that TCP and MK-801 protected against glutamate neurotoxicity in cortical and hippocampal cell cultures (309). Olney et al found that PCP, ketamine, SKF 10,047, pentazocine, Mg^{2+}, AP5, and AP7 selectively blocked NMDA-induced neurotoxicity in the chicken embryo retina (310). The order of potency of the noncompetitive antagonists (PCP > ketamine > SKF 10,047 > pentazocine) is the same as their affinity for the PCP site of the NMDA receptor-ionophore complex. The noncompetitive NMDA antagonists were totally selective for NMDA-induced necrosis, but the competitive NMDA antagonists could partially block necrosis produced by kainate. It was subsequently found that MK-801 noncompetitively blocked NMDA-induced toxicity in the chicken retina (311). The neurotoxicity produced by the endogenous NMDA agonist homocysteic acid was also antagonized by Mg^{2+}, AP5, PCP, ketamine, SKF 10,047, and pentazocine (312). It has also been reported that PCP, MK-801, SKF 10,047, and pentazocine (with rank order potencies identical to their affinities for the PCP site) blocked NMDA- and quinolinate-induced neurotoxicity in cortical neuronal cultures, with no effect on kainate or quinolinate neurotoxicity (313). The antagonism by PCP appeared noncompetitive. These compounds also attenuated hypoxic neuronal injury at the same concentrations and in the same order of potency.

Ketamine prevents anoxia-induced necrosis of hippocampal neurons (314). Similarily, it was reported that hypoxia or cyanide-mediated neurotoxicity in cortical culture was antagonized by the NMDA antagonists AP5, AP7, PCP, and SKF 10,047 and the nonselective antagonist kynurenate, but not by kainate or quinolinate antagonists (315). In vitro, AP5 and MK-801 enhanced the recovery of dentate granule cells or CA1 pyramidal cells following a 5- or 10-min period of anoxia (316, 317).

The ability of PCP-like compounds to readily gain access to the brain has led many researchers to investigate the possibility that these compounds are

especially useful at blocking neuropathology produced by various models of ischemia. The most popular models for global ischemia are carotid occlusion in the rat, or, more often, because of its incomplete circle of Willis, the gerbil. Focal ischemia is most often studied in the cat or rat following cauterization of the medial cerebral artery. In models of global forebrain ischemia, systemic administration of ketamine (318, 319), PCP (320), or MK-801 (321, 322) has been reported to protect against ischemia-induced necrosis, particularly in areas rich in NMDA receptors, such as hippocampal area CA1 (320, 323). Ketamine is generally regarded to be less effective than either PCP or MK-801, perhaps because of its shorter duration of action (323, 324). MK-801 also has been reported to be effective in attenuating necrosis produced by focal ischemia in both the rat (325) and the cat (326). Of particular clinical interest is the reported ability of MK-801 to prevent degeneration in the striatum and hippocampus following intracerebral administration of NMDA or quinolinate (327). This is significant because of the protection afforded by MK-801 even when administered 2–5 h after the excitotoxin.

Losses in binding sites labeled with [^{3}H]TCP (329), [^{3}H]MK-801 (329), [^{3}H]glutamate (NMDA specific) (330), and [^{3}H]AMPA (330) have been reported to occur days to weeks after various forms of ischemic insult. Furthermore, the losses in hippocampal and cortical NMDA and PCP receptors produced by global ischemia in the gerbil were prevented by treatment with the competitive antagonist CGS 19755 (331). These data support the notion that cells vulnerable to damage possess quisqualate receptors in addition to NMDA receptors and that antagonism of NMDA receptors can prevent ischemia-induced degeneration.

In summary, the biology of excitotoxicity and its role in neuronal degeneration in disease or following ischemic or hypoglycemic insult are not completely understood, but the NMDA receptor-ionophore complex appears to be a key player. Thus, NMDA antagonists, including those with actions at the PCP site, may have a future in prophylaxis and therapy in certain situations. In this regard, it has recently been noted that acute and chronic PCP and MK-801 administration caused a self-limiting pathomorphological reaction in specific neurons of the posterior cingulate and retrosplenial cortices of rats (332). Nevertheless, it is entirely conceivable that in situations of acute trauma (333) or stroke, the potential therapeutic benefit of PCP-like drugs may outweigh concerns about their psychotomimetic and other self-limiting side effects.

CONCLUSIONS

It is striking to us that research on a drug of abuse with potential implications for the etiology of schizophrenia has played a significant role in the develop-

ment of agents with potential in the therapy of epilepsy and stroke. Whether the therapeutic potential of PCP and related compounds will be realized depends to a considerable extent on whether the psychotomimetic, reinforcing, and therapeutic properties of these drugs are based on common mechanisms. Although it seems relatively certain that the anticonvulsive and neuroprotective effects are the results of blockade of ionic conductance through the NMDA-operated ion channel, the molecular basis of the psychotomimetic and reinforcing properties of PCP remain speculative. Thus, additional work on these aspects of PCP pharmacology will be required to determine whether these "side effects" will be separable from the therapeutic effects.

No other receptor complex, including the $GABA_A$-operated Cl^- channel, can lay claim to either a larger number of modulatory sites or a greater richness of modulatory mechanisms than have been promised by recent research in this area. In addition to providing an intellectual playground for pharmacologists, this complexity provides an opportunity to subtly control receptor function, possibly according to therapeutic demands, that would not be possible by simple interference with transmitter binding to its recognition site. In addition to the voltage- and use-dependent nature of the blockade by PCP-like drugs mentioned above, the possibility that the makeup and organization of NMDA receptor complexes vary regionally also affords an opportunity for more selective modulation of receptor function. Thus, the possibility of selectively targeting specific pathways for therapeutic intervention is exciting and should be a fruitful area of future research.

Whether PCP research has supported the utility of PCP intoxication as a model for schizophrenia is unclear at this time, but it now seems possible to at least partially test the hypothesis. That is, if the ability of PCP to block the NMDA ionophore has anything to do with its ability to mimic certain aspects of schizophrenia, NMDA and glycine agonists should be able to ameliorate some of the symptoms of schizophrenia. Furthermore, this research may suggest a dysfunction in schizophrenia in transmission through the glutamatergic corticostriatal pathway, which could ultimately adversely affect the ability of the thalamus to function as a filter for sensory input to the cortex (334). The indirect dopaminergic effects of PCP would also adversely affect striatopallidal input to the thalamus. Perhaps this is why sensory isolation is such an effective treatment of PCP intoxication.

A final word on areas of future research also involves up-regulation of NMDA receptor function. If PCP administration produces memory loss and schizophreniform psychosis, it is possible that NMDA or glycine agonists improve memory in certain situations, and they may even be able to reduce the signs of PCP intoxication by enhancing the rate of dissociation from the channel-binding site. The possibility of excitotoxicity with agonists may limit this approach, but it is our opinion that further research in this area could pay

huge benefits in the therapy of a wide variety of diseases with both genetic and environmental etiologies.

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