Phencyclidine

Physiological Actions, Interactions with Excitatory Amino Acids and Endogenous Ligands

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Abstract

Phencyclidine (PCP) produces many profound effects in the central nervous system. PCP has numerous behavioral and neurochemical effects such as inhibiting the uptake and facilitating the release of dopamine, serotonin, and norepinephrine. PCP also interacts with sigma, mu opioid, muscarinic, and nicotinic receptors. However, the psychotomimetic effects induced by PCP are believed to be mediated by specific PCP receptors, where PCP binds with greater potency than sigma compounds. Electrophysiological, behavioral, and neurochemical evidence strongly suggests that at least some of the many PCP actions result from antagonism of excitatory amino acid-induced responses via PCP receptors. The recent isolation and partial characterization of the alpha and beta endopsychosins and the identification of other endogenous ligands for the PCP and sigma receptors, is another promising area of research in the elucidation of the physiological role of an endogenous PCP and sigma system.

Index Entries: Phencyclidine; sigma opioids; excitatory amino acids; receptors; schizophrenia; NMDA; peptides.

Introduction

Phencyclidine [1-(1-phenylcyclohexyl) piperidine], angel dust, whack, PCP] was synthesized in 1957 by the Parke Davis Pharmaceutical Company. PCP was originally developed as a general anesthetic because it produces anesthesia with analgesia, but with minimal cardiorespiratory depression. However, in clinical trials PCP was found not only to be a good anesthetic, but also to produce post-anesthetic hallucinations that could last more than 12 h in about 30% of patients (Greifenstein et al., 1958). Therefore, clinical use of PCP in humans was discontinued. PCP was later approved for use as a veterinary anesthetic, and subsequently an analog of PCP, ketamine, was approved for use in humans because it is a general anesthetic with psychotomimetic side effects that were not as long in duration as those of PCP.

Much of what is known about the effects of PCP in humans is a result of the fact that PCP is a drug of abuse. Although PCP first appeared "on the street" in the 1960s in San Francisco as the PeaCe Pill, PCP did not become popular until the 1980s. Today PCP is the second most popular drug of abuse in the US and the most commonly abused drug on the east and west coasts and in major cities of the US. The reason for the popularity of PCP is not clear, but in part is caused by the fact that PCP is easy to synthesize and produces euphoria, excitation, and feelings of tranquility. But PCP can also produce dysphoria, violent aggressive behavior, and a psychosis very similar to schizophrenia.

There has been considerable research on the mechanism of action of PCP in an attempt not only to understand its actions, but also to find a selective antagonist for use in cases of PCP intoxication. The similarity between the symptoms of schizophrenia and PCP-induced psychosis (Luby et al., 1959; Randrup and Munkvad, 1974; Cohen et al., 1960; Allen and Young, 1978) suggests that PCP would be a better drug model of psychosis than the currently used agents, such as amphetamines. This similarity also suggests that PCP interacts with an endogenous system that is involved in the pathogenesis of schizophrenia. The results of these studies are reviewed in this paper.

General Actions of Phencyclidine

Behavioral Effects

The cognitive effects of PCP in humans vary according to the dose ingested. At low doses, below 5 mg, PCP may produce stimulation, euphoria, confusional states, and memory im-

pairment (Luby et al., 1959; Burns and Lerner, 1976; Fauman and Fauman, 1981). At moderate doses of 5–10 mg, symptoms include conceptual disorganization, delusions, stereotyped movements, and violence. At higher doses, the most common symptoms include delusions, hallucinations, mutism, violence, and extreme agitation. Although a typical PCP "high" lasts 4–6 h, and normal cognitive states are generally reached 24–48 h later (Burns and Lerner, 1976), some individuals experience long-lasting effects. Much larger doses of PCP produce convulsions and respiratory depression that can be fatal.

The behavioral effects of PCP appear to be mediated through various neurotransmitter systems in the CNS, as indicated by pharmacological management strategies. Physostigmine has been used successfully in mild cases of intoxication to counteract the anxiety, tension, excitement, and suspiciousness (Price and Giannini, 1985), indicating that at low doses the effects may be mediated primarily through cholinergic pathways. Symptoms of hallucinations, delusions, paranoia, and confusion can be treated with neuroleptics; halperidol appears to be the most effective, indicating the dopaminergic system involvement in these behavioral effects (Price and Giannini, 1985). The opioid meperidine has also been used for severe intoxication (Price and Giannini, 1985). However, there is no one specific or very effective antidote at present.

PCP also produces a dose-dependent behavioral profile in animals, in some ways similar to that induced by other psychotomimetic drugs. Low doses of PCP increase locomotor activity (Kesner et al., 1981; Pryor et al., 1977), and interfere with cognitive processes, such as memory of previously learned responses (Adey and Dunlap, 1960; Brown and Bass, 1976; Domino et al., 1965; Aguayo et al., 1982), and consolidation of information learned under the influence of the compound (Handelmann et al., 1987). Higher doses produce ataxia (Chen et al., 1959), disruption of motor reflexes (Kesner et al., 1981), and stereotyped behavior, consisting of head weaving, rearing, nondirected mouth movements, and circling (Murray and Horita, 1979; Contreras et al., 1986; Marwaha, 1982). The stereotyped behavior can be blocked by neuroleptic drugs, such as haloperidol and chlorpromazine (Murray and Horita, 1979), suggesting that the behavior is mediated by central dopaminergic mechanisms. PCP-induced behavioral effects in animals may therefore be a useful pharmacological model for psychosis in humans.

Peripheral Effects

In addition to effects on the central nervous system, PCP has peripheral actions. PCP intoxication results in hypersalivation, sweating, increased blood pressure, and increased heart rate. The increase in blood pressure and heart rate are believed to be mediated by a PCP receptor mechanism, because this effect is produced by only one of the stereoisomers of a PCP analog (Bayorh et al., 1983). PCP also produces cerebrovascular spasms (Altura et al., 1983). It is not known whether these effects are mediated solely by a strictly peripheral mechanism or by actions on the brainstem or spinal cord.

Other peripheral effects of PCP include muscle rigidity, which may be mediated by an interaction with nicotinic receptors or with calcium channels (Bolger et al., 1986a). PCP has also been shown to inhibit contractions of smooth muscle, such as the guinea-pig ileum (Gintzler et al., 1982), and to depress humoral and cellular immune responses in vitro (Khansari, 1984).

Neurochemical Effects

PCP has been shown to interact with several receptors, ion channels, and most neurotransmitter systems. In addition to interactions with specific receptors for PCP, PCP can interact with

mu opioid and cholinergic receptors. This interaction with mu opioid receptors may account for the analgesic action of PCP (Vincent et al., 1978).

PCP also interacts with the cholinergic system, in particular cholinergic receptors. Behaviorally active doses of PCP do not affect the brain concentration of acetycholine (ACh) (Leonard and Tonge, 1970; Domino and Wilson, 1972), but may potentiate the actions of released ACh by competitively inhibiting butyrylcholinesterase and acetycholinesterase (Becker, 1969; Maayani et al., 1974). PCP also acts as a very weak muscarinic antagonist (Weinstein et al., 1973; Kloog et al., 1977; Vincent et al., 1978; Aronstam et al., 1980) and a noncompetitive inhibitor at the nicotinic receptor (Haring and Kloog, 1984; Heidmann et al., 1985; Oswald et al., 1984). At the nicotinic receptor, the binding of PCP is saturable and protein-dependent with a K_d of about 6 μM. The PCP binding to the nicotinic receptor is not at the site of labelling by [^{3}H]-alpha bungarotoxin nor [^{3}H]-ACh, but PCP does inhibit the binding of [^{3}H]-perhydrohistrionicotoxin([^{3}H-]-H12-HTX) (Albuquerue et al., 1980a). However, there are reported differences in the binding of [^{3}H]-PCP and [^{3}H]-H12-HTX (Eldefrawi et al., 1980). Photoaffinity labeling studies with ligands related to either HTX or PCP label different subunits of the nicotinic receptor (Oswald and Changeux, 1981; Kaldany and Karlin, 1983). It has been suggested that this variability may result from binding to an area accessible to all subunits (Changeux et al., 1984) A kinetic analysis of the inhibition of acetylcholine-induced ion flux in membrane vesicles was consistent with a model in which PCP interacts with all active forms of the acetylcholine channel in a preformed site not dependent on the opening of the channel. It is suggested that other functionally diverse, noncompetitive inhibitors of acetylcholine also bind to this site (Karpen and Hess, 1986). However, the interaction between PCP and the nicotinic receptor probably does not mediate any of the psychotomimetic effects of PCP, because there are different structure–activity requirements for inducing psychotomimetic effects and interacting with the nicotinic receptor (Eldefrawi et al., 1982a).

PCP and its analogs have been shown to interact with other ion channels. PCP selectively blocks a voltage-gated, non-inactivating potassium channel with potencies that correlate with the ability of these compounds to bind to the PCP receptor. The order of potency for blocking potassium flux was also reported to be consistent with that for in vivo psychotomimetic activity (Albuquerque et al., 1981). Blockade of the potassium channel and subsequent alteration of calcium entry may explain neurotransmitter release stimulated by PCP (Bartschat and Blaustein, 1986). Not only do potassium channel blockers inhibit the binding of [^{3}H]-PCP, but also azido-PCP covalently labels polypeptides of molecular weights identical to subunits of the voltage-gated potassium channel (Sorensen and Blaustein, 1986). Interestingly, PCP has also been found to block myocardial potassium and calcium channel currents (Hadley and Hume, 1986).

Another ion channel affected by PCP is the calcium channel. PCP, analogs of PCP, and HTX alter the binding of dihydropyridine calcium antagonists (Bolger et al., 1986a) and an acylating derivative of PCP irreversibly enhances the binding of calcium antagonists (Bolger et al., 1986b). Conversely, calcium antagonists were found to inhibit the binding of [^{3}H]-PCP in rat brain (Quirion and Pert, 1982), crayfish muscle (El-Fakahany et al., 1984), and *Torpedo* electric organ (Epstein and Lambert, 1984). However, the ability of verapamil analogs to inhibit the binding of [^{3}H]-PCP was not stereoselective (Eldefrawi et al., 1982b).

It is possible that effects of PCP on neurotransmitter release may be explained by the PCP interaction with the acetylcholine receptor ion channel, because Takeda et al. (1986) found that ketamine inhibited the functional coupling be-

tween nicotinic receptors and voltage-dependent calcium channels. In addition, it has been postulated that the increase seen in neurotransmitter levels may be indirect and a result of action of PCP on potassium channels altering the entry of calcium (Bartschat and Blaustein, 1986).

Although PCP has been reported to induce the release of numerous neurotransmitters including histamine (Itoh et al., 1985), GABA (Nabeshima et al., 1981), and acetylcholine (Benishin, 1986), few studies have differentiated between the effects on the release of neurotransmitters and the uptake of neurotransmitters. PCP has been found to increase the release of dopamine (Ary and Komiskey, 1982; Vickroy and Johnson, 1982) and acetylcholine (Leventer and Johnson, 1983) in superfused preparations; however, PCP is a competitive inhibitor of the uptake of norepinephrine, dopamine, tyramine, and 5-hydroxytryptamine (O'Donnell and Wanstall, 1968; Garey and Heath, 1976; Smith et al., 1977; Bowyer et al., 1984). PCP has also been found to increase release of norepinephrine and 5-hydroxytryptamine in studies measuring the metabolites of these neurotransmitters (Tonge and Leonard, 1970, 1972; Nabeshima et al., 1983). These effects on neurotransmitters are not limited to PCP, but are found to occur after use of ketamine, an analog of PCP (Sung et al., 1973).

There are numerous behavioral studies that suggest that many of the neurochemical effects may play a role in mediating the behavioral effects of PCP. The ability of PCP analogs to inhibit dopamine uptake has been found to correlate both reasonably well (Vignon and Lazdunski, 1984) and poorly (Snell et al., 1984) with their ability to inhibit the binding of [^{3}H]-PCP. Also, PCP produced ipsilateral rotation in rats with unilateral 6-hydroxydopamine lesions (Fessler et al., 1979), suggesting a presynaptic effect of PCP on dopaminergic neurons. In addition, PCP-induced stereotyped behavior is antagonized by dopaminergic antagonists and serotonergic antagonists (Martin et al., 1979; Murray and Horita, 1979). Electrophysiological studies have shown that the ability of PCP and its analogs to inhibit the firing rate of cerebellar Purkinje neurons correlates well with their relative potency on the rotarod (Marwaha et al., 1981). This inhibition is caused by a potentiation of adrenergic release of norepinephrine, which suggests that PCP-induced ataxia is mediated at least in part by presynaptic effects of PCP on adrenergic neurons.

PCP produces a variety of other effects, such as inhibition of monoamine oxidase activity (Usdin and Usdin, 1961), stimulation of 5-hydroxytryptamine decarboxylase (Leonard and Tonge, 1970) and tyrosine hydroxylase activity (Vickroy and Johnson, 1981), binding to melanin (Misra et al., 1979), inhibition of some protein synthesis (Deutsch, 1984; Koul et al., 1986), and uncoupling of oxidative phosphorylation (Lees, 1962, 1968).

Receptors for Phencyclidine and Related Compounds

Evidence for Multiple Binding Sites

Specific binding sites for PCP have been shown to exhibit reversible, saturable, and high affinity binding of [^{3}H]-PCP (Vincent et al., 1979; Zukin and Zukin, 1979). The binding of [^{3}H]-PCP was rapidly inactivated by heat and by proteases, indicating that the binding was to a protein (Vignon et al., 1982). Furthermore, binding to the site labeled by [^{3}H]-PCP was stereoselective (Quirion et al., 1981b) and had a unique distribution in the central nervous system (Quirion et al., 1981a; Contreras et al., 1986a).

There is still some controversy concerning the number of receptors for phencyclidine and related compounds. Originally, it was believed that PCP and sigma opioids (opioids that produce psychotomimetic efffects), exert common psychotomimetic effects through a common

receptor. Like PCP, sigma opioids such as *N*-allylnormetazocine (SKF 10,047) and cyclazocine produce psychotomimetic effects in humans (Haertzen, 1974). Similarly, in drug discrimination paradigms, PCP or ketamine generalize to the drug stimulus of many sigma opioids (Teal and Holtzman, 1980; Shearman and Herz, 1982; Shannon, 1983), and conversely, sigma opioids generalize to PCP or ketamine (Holtzman, 1980; Shannon, 1981; Brady et al., 1982). Furthermore, PCP inhibits the binding of [^{3}H]-cyclazocine and vice versa (Zukin and Zukin, 1981). However, it is more likely that there are at least two different binding sites, because of numerous reports indicating distinct PCP and sigma receptors. There are differences in the structure-activity requirements for binding of PCP, *N*-allylnormetazocine, and dexoxadrol (Su, 1982; Martin, 1984; Tam, 1985; Contreras et al., 1987; Itzhak, 1987), and differences in the distribution of binding sites labeled by PCP and sigma opioids (Largent et al., 1984; Pilapil et al., 1986; Gundlach et al., 1985; Contreras et al., 1985). Also, it was shown that haloperidol and chlorpromazine only inhibit the binding of sigma opioids and not those of PCP (Tam, 1983; Tam and Cook, 1984). The consensus is that PCP receptors are defined by a rank order of potency where TCP, PCP, and and dexoxadrol are more potent than (+)SKF 10,047; haloperidol and (-) butaclamol are inactive. The sigma receptor, which has been called the high affinity SKF 10,047 site, the haloperidol-sensitive site, or the sigma receptor, is defined by a rank order of potency where haloperidol, (-)butaclamol and (+) SKF 10,047 are more potent than PCP.

Physiological Relevance of Receptors

The physiological relevance of the PCP receptor is supported by studies showing the ability of PCP analogs to inhibit the binding of [^{3}H]-PCP correlates with their ability to produce ataxia (Vincent et al., 1978; Contreras et al., 1986b), stereotyped behavior (Contreras et al., 1986b), and to mimic the PCP-like stimulus in drug discrimination paradigms (Shannon, 1981). An analog of PCP that acylates PCP receptors in vitro (Rafferty et al., 1985) and in vivo (Contreras et al., 1986d) was found to selectively antagonize PCP-induced stereotyped behavior and ataxia in rodents (Contreras et al., 1986d), and PCP-induced inhibition of neuronal firing in the caudate (Contreras et al., 1986c) and cerebellum (Wang et al., 1987). So far, there is only one relatively selective ligand for the PCP receptor, MK-801, which potently inhibits binding of [^{3}H]-TCP and weakly inhibits binding of [^{3}H]-SKF 10,047 (Loo et al., 1987). MK-801, like PCP, produced stereotyped behavior and ataxia (Contreras et al., 1987b). These studies indicate that the PCP receptor mediates, at least in part, PCP-induced stereotyped behavior, ataxia, inhibition of spontaneous firing of cerebellar and striatal neurons, and activity in drug discrimination paradigms.

It has been more difficult to demonstrate a physiological role for the sigma receptor. Part of the difficulty in determining whether there were separate sigma and PCP receptors was due to the lack of selective ligands for sigma receptors. Until recently, the only selective ligands for sigma receptors were haloperidol (Tam, 1985; Contreras et al., 1987a), (+)3-(3-hydroxyphen-y1)*N*-(1-propyl)-piperidine ([+]3-PPP) (Gundlach et al., 1985; Contreras et al., 1985), and (–)butaclamol (Tam, 1985). Haloperidol is not the ideal tool to study sigma receptors in vivo because haloperidol binds to both dopamine and sigma receptors. The use of (–)butaclamol in behavioral studies is limited because of its poor solubility. (+)3-PPP, believed by many to also be a presynaptic dopaminergic receptor agonist, has been shown to generalize to SKF 10,047 stimulus in drug discrimination paradigms (Steinfels et al., 1987). Better tools for the study of sigma receptors may be 1,3-di-*o*-

tolylguanidine (DTG) (Weber et al., 1986), BMY-14802-1 (Taylor and Dekleva, 1987), cinuperone (HR-375) (Su, 1986), and rimcazole (BW234U) (Ferris et al., 1986), which appear to selectively interact with sigma receptors and not PCP receptors. DTG and (+)3-PPP appeared behaviorally to be sigma agonists because they produced stereotyped behavior, and ataxia (Contreras et al., 1987). These results suggest that there are two receptors, a PCP and a sigma receptor, that can mediate similar behavioral effects in the rat.

The finding that haloperidol and chlorpromazine bind to the sigma receptor (Tam, 1983; Tam and Cook, 1984) suggests that these neuroleptics may be effective antipsychotic drugs by acting as antagonists at both PCP and sigma receptors. Thus, there may be a role not only for the PCP receptor, but also for the sigma receptor in schizophrenia.

Interaction with Excitatory Amino Acids

Electrophysiological Evidence for an Interaction

PCP and other sigma compounds have been reported to have many electrophysiological actions. For example, in the hippocampus alone, phencyclidine has been reported to increase and decrease the spontaneous discharge rates of neurons, decrease the population spike, decrease the population EPSP (excitatory post synaptic potential), decrease inhibition, raise after discharge thresholds, block induction of long-term potentiation (LTP), and to reduce glutamate-induced excitation.

Lodge and Anis (1982) were the first to show that PCP can block increases in neuronal discharge induced by excitatory amino acids. Moreover, this blockade is selective for excitation induced by excitatory amino acids which act at the *N*-methyl-D-aspartate (NMDA) receptor. PCP-like compounds do not block excitation induced by excitatory amino acids acting at the kainate (KA) or quisqualate (QA) receptor. Given that PCP will block an action of NMDA, at least four questions immediately arise: How widespread is this effect; how specific is it for the PCP or sigma receptor; what is the mechanism of this effect; and how many of the other actions of PCP-like compounds can be explained by antagonism of the actions of NMDA? Lodge et al. have reported that PCP and related compounds block the discharge rate induced by NMDA in unidentified dorsal horn interneurons (Lodge and Anis, 1982; Berry et al., 1984a; Church et al., 1985), on Renshaw cells in cat, and rat in vivo (Lodge et al., 1982; Berry et al., 1983b; Anis et al., 1983a; Berry et al., 1984a), and frog motorneurons in vitro (Lodge et al., 1984). The blockade of NMDA-induced excitation has also been shown in neurons in dissociated mouse spinal neurons (Honey et al., 1985; Blake et al., 1986), in the rat medulla, and in rat cortical slices (Thomson et al., 1985a; Harrison and Simmonds, 1985; Thomson et al., 1985b). The blockade of NMDA-induced excitation on several neuronal types in different regions of the CNS in several species suggests the effect is generalized to most cells that have NMDA receptors.

The specificity of the antagonism of NMDA-induced excitation has been approached in a number of studies. The first question is whether the interaction of PCP with mu opioid receptors plays a role in antagonism of NMDA-induced excitation. Other compounds active at the mu opioid receptor, such as naloxone and levorphanol (Anis et al., 1983b; Lodge et al., 1984; Church et al., 1985), and opioids interacting with the kappa opioid receptor, such as ethylketocyclazocine, U-50, 488, and tifluadom, do not antagonize the actions of NMDA in a selective manner (Parsons et al., 1986; Berry et al., 1984b). In contrast, dextrorphan, the stereoisomer of levorphanol, which is inactive as an analgesic, selectively antagonizes the electrophysiological effects of NMDA and is seven times more potent than levorphanol (Church et al., 1985). Thus,

only the opioids that interact with PCP and sigma receptors, such as dextrorphan and cyclazocine, are able to selectively antagonize NMDA-induced excitation.

Another question is whether compounds structurally diverse from PCP, but sharing the ability to bind to the PCP and sigma receptor, can antagonize NMDA-induced excitation. Some dioxolanes, such as etoxadrol and dexoxadrol, that potently bind to the PCP receptor and induce PCP-like stereotyped behavior and ataxia, selectively reduce NMA (*N*-methyl-D,L-aspartate)-induced excitation. The (–)-isomer of dexoxadrol, levoxadrol, is much less potent in inducing PCP-like effects (Berry et al., 1984a). Another structurally dissimilar compound, 2-methyl-3,3-diphenyl-3-propanolamine, and, in particular, the (–)-isomer, is a selective antagonist of NMA-induced excitation (Blake et al., 1986). In addition, some benz(f)isoquinolines, such as LY154045, have actions similar to PCP and other sigma compounds. LY154045 selectively antagonizes NMA-induced excitation, but the behaviorally inactive analog, LY154005, is inactive (Berry and Lodge, 1984).

Further support for a role of the PCP receptor in mediating the antagonism of NMDA is provided by the finding of similar stereoselectivity in binding to the PCP receptor and antagonizing NMDA-induced excitation. The (+)-isomer of ketamine, the behaviorally active isomer, is 2.5–3 times more potent than (–)-ketamine (Lodge et al., 1982). *Cis*-*N*-(1-phenyl-4-methyl-cyclohexyl) piperidine (GK5) is more potent than the trans-enantiomer (GK4) (Berry et al., 1983). In addition, (+)-*N*-(1-phenylcyclohexyl)-3-methylpiperidine (PCMP) is more potent than (–)-PCMP (Berry et al., 1983). (–) Cyclazocine, a sigma compound, is twice as potent as the (+) isomer (Lodge et al., 1984). Both isomers of SKF-10,047 selectively antagonize NMDA-induced excitation, but the (+)-isomer appears slightly more potent (Berry et al., 1984b). In each case, the more potent isomer in antagonizing NMDA-induced excitation is also the more potent isomer in the PCP radioreceptor assay and in behavioral assays.

The next question is whether only PCP or both PCP and sigma receptors mediate the antagonism of NMDA. MK-801, which selectively binds to PCP receptors and not to sigma receptors, is a potent NMA antagonist (Wong et al., 1986). Haloperidol, which selectively binds to the sigma receptor versus the PCP receptor, does not antagonize NMA-induced excitation, but this finding may be because haloperidol is an antagonist at the sigma receptor. Thus, it is clear that antagonism of NMDA-induced excitation is mediated largely by PCP receptors, with involvement of the sigma receptor questionable.

Behavioral Evidence for an Interaction

In addition to the electrophysiological and biochemical studies, there are behavioral studies indicating an interaction between PCP and excitatory amino acids. Similarities between the behavioral effects of competitive NMDA-antagonists, such as 2-amino-5-phosphonopentanoate (AP5) and 2-amino-7 phosphonoheptanoate (AP7), and PCP-like compounds support the hypothesis that many of the behavioral effects of PCP are mediated in part through NMDA-receptor mediated transmission. PCP and AP7 have similar anticonvulsant properties; both antagonize chemically induced (Croucher et al., 1982; Hayes and Balster, 1985) and electroconvulsant shock-induced seizures (Leccesse et al., 1986; De Sarro et al., 1985) in mice. APH and ketamine have also been shown to antagonize NMDA-induced seizures in mice (Cruczwar and Meldrum, 1982; Amrick et al., 1986). Additionally, PCP and AP7 blocked biting and scratching behavior in mice induced by intrathecal injection of NMDA, suggestive of antinociceptive activity (Aanonsen and Wilcox, 1986).

If the behavioral actions of PCP are in part a result of antagonism of NMDA receptor-mediated transmission, then competitive NMDA antagonists should induce PCP-like behaviors. PCP produces certain characteristic behaviors in animals, including catalepsy and stereotyped behavior in pigeons (Koek et al., 1984) and stereotyped behavior and ataxia in rats (Sturgeon, 1979, Contreras et al., 1986a). The ability of PCP analogs to produce these behaviors correlates with their potency in inhibiting binding of [^{3}H]-PCP (Contreras et al., 1986a). Recently, AP5 has been shown to induce PCP-like catalepsy and stereotyped behavior in pigeons in a time and dose dependent manner following either icv or im administration (Koek et al., 1986a; Koek et al., 1986b). Two other NMDA selective antagonists, AP7 and CPP, produce PCP-like stereotyped behavior and ataxia in rats (Bernard and Bennett, 1986; Compton et al., 1987). AP7 afforded this behavioral response in a stereoselective and time-dependent manner consistent with concentrations in the cerebrospinal fluid (Compton et al., 1987). These results indicate that PCP-like compounds and competitive NMDA antagonists (e.g., AP5, AP7, CPP) produce similar behaviors in rats and pigeons, which supports a NMDA receptor-mediated mechanism in the behavioral effects induced by PCP.

Competitive NMDA antagonists have been tested for their ability to produce a PCP-like cue in discriminative stimulus paradigms in pigeons and rats. AP5 produced PCP-appropriate responses in pigeons at doses similar to that used to induce catalepsy (Koek et al., 1986). Comparable results were obtained with AP7 in rats trained to discriminate PCP from saline (Willetts et al., 1986). In these experiments, AP7 administered icv shared some discriminitive stimulus properties with systemically administered PCP. These results are, again, consistent with antagonism of the NMDA receptor as involved in mediating many of the behaviors induced by PCP.

Neurochemical Evidence for an Interaction

Ketamine (Johnston and Lodge, 1983) and PCP (Snell and Johnson, 1985) have been shown to antagonize NMDA-stimulated release of ACh from cortical tissue. The NMDA subclass of excitatory amino acid receptors appears to mediate the excitatory effects of glutamate on striatal cholinergic interneurons. The order of potency of agonists, the magnesium sensitivity, and the antagonism by 2-amino-5-phosphonovalerate of the calcium-dependent and tetrodotoxin-(TTX)-sensitive L-glutamate-stimulated release of ACh (Lehmann and Scatton, 1982) are characteristics of the NMDA receptor. PCP and PCP-like drugs stereospecifically antagonize the stimulation of ACh release by NMDA. This inhibition does not appear to be competitive (Snell and Johnson, 1985). There is a good correlation between the ability of these drugs to interact with the PCP receptor and their ability to inhibit NMDA-induced release of ACh (Snell and Johnson, 1986). PCP does not antagonize the release of ACh stimulated by kainate or quisqualate (Snell and Johnson, 1986) and the PCP inhibition of NMDA-stimulated ACh release is not reversed by haloperidol (Snell and Johnson, 1985), which indicates that antagonism of NMDA-induced release of ACh is mediated by the PCP receptor and not the sigma receptor.

Glutamate stimulates dopamine release in the striatum in a calcium-dependent and TTX-insensitive manner (Roberts and Anderson, 1979) that can be antagonized by PCP (Snell and Johnson, 1985). Although PCP and PCP-like drugs are less potent at blocking NMDA-stimulated release of dopamine than at antagonizing NMDA-stimulated release of ACh, there is also a good correlation between the ability of these compounds to interact with the PCP receptor and their ability to inhibit NMDA-induced release of dopamine (Snell and Johnson, 1986).

Other interactions between PCP and NMDA were found in studies, showing that PCP selectively and noncompetitively antagonized the NMDA -stimulated efflux of sodium-22 (Pullan and Hood, 1987).

Additionally, PCP has been shown to antagonize NMDA-mediated excitotoxicity in the chick retina (Olney et al., 1986). The anti-ischemic effect of PCP-like compounds and competitive NMDA antagonists has also been documented (Olney et al., 1986). Both MK801 and CPP [3-(2-carboxypiperazin-4-yl)propyl-L-phosphonic acid], a competitive NMDA antagonist, have been shown to afford some cellular protection following bilateral carotid occlusion in the gerbil (Foster et al., 1986; Gerhardt et al., 1986), and AP7 (2-amino-7-phosphonoheptanoate), a competitive NMDA antagonist, has been shown to protect against ischemic damage in the rat (Simon et al., 1984).

The possibility that the interaction between NMDA and PCP is at the level of the receptor has been explored. It is clear that PCP does not act at the NMDA recognition site because PCP does not inhibit binding of [^{3}H]-glutamate (Fagg, 1986; Monahan and Michel, 1987), nor do ligands for the NMDA receptor inhibit binding of [^{3}H]-PCP (Monahan and Michel, 1987). This finding is consistent with the finding that PCP is a noncompetitive antagonist of NMDA-induced excitation.

It is possible there is an interaction between PCP and NMDA receptors. This possibility is supported by the striking similarity in distribution of PCP and NMDA receptors (Maragos et al., 1986). It is clear that PCP does not affect the binding of ligands to the NMDA receptor (Monahan and Michel, 1987). In contrast, under conditions that remove glutamate from the membrane preparations, the affinity of the PCP receptor for [^{3}H]-TCP decreased, but returned to control levels by the addition of glutamate (Loo et al., 1986). This effect of glutamate is presumably caused by an interaction with the NMDA receptor, because the effect of glutamate could be attenuated by AP7 (Loo et al., 1986).

In support of a complicated interaction between PCP and NMDA receptors, it has been shown that metaphit pretreatment for 24 h produces a decrease in the number of PCP receptors, but increases the activity of NMDA receptors (Compton et al., 1987c). In contrast, acute treatment with metaphit has no effect on the number of NMDA receptors, but still decreases the number of PCP receptors. A similar type of interaction is seen in studies examining the flux of sodium-22. Again, metaphit pretreatment 24 h prior to the study results in potentiation of NMDA-induced efflux of sodium-22, but in vitro metaphit had no significant effect on the actions of NMDA (Pullan et al., 1987).

Possible Mechanism of Interaction

It is clear that there is an interaction between PCP and NMDA receptors, but the form of this interaction is not clear. Any model must be able to account for not only a mechanism for an interaction between PCP and NMDA, but also voltage- and agonist-dependence and use-dependent unblockade. Voltage-dependence refers to the fact that the ability of magnesium and PCP to antagonize NMDA-responses occurs only when the membrane is hyperpolarized, and the extent of antagonism depends on the degree of hyperpolarization (Honey et al., 1985). Agonist-dependence refers to the fact that PCP only acts as an antagonist following cotreatment with an NMDA-like agonist (Wong et al., 1983). Also, the extent of agonist dependence varies depending upon the PCP-like ligand (Wong et al., 1983). Use-dependent unblockade refers to the situation where an NMDA-like agonist must be added to remove the PCP-induced blockade (MacDonald and Miljkovic, 1986).

PCP noncompetitively inhibits the actions of NMDA (Harrison and Simmonds, 1985; Lodge et al., 1985; Pullan et al., 1987), but does not inhibit binding of NMDA (Monahan and Michel, 1987). Thus, PCP does not compete with NMDA for the NMDA receptor. A modification of this theory is that the interaction is a simple,

mutual allosteric interaction. There is evidence demonstrating an effect of NMDA on the affinity of the PCP receptor, but there is no evidence of an effect of PCP on the affinity of the NMDA receptor (Monahan and Michel, 1987). Thus, the interaction is not a mutual allosteric interaction.

Another possibility is that PCP is an open channel blocker, such as magnesium (Mayer and Westbrook, 1985). The presence of voltage- and agonist-dependent interactions often indicates that the antagonist acts by blocking the ion channels, like an intrachannel plug (Honey et al., 1985). This theory implies that the active site of the PCP receptor is within the channel. If the active site of the PCP receptor is within the channel, then metaphit might be expected to induce long-term antagonism of NMDA by acylating the PCP receptor. In fact, after a short period of time, metaphit had no effect on NMDA-induced efflux of sodium, and after a longer period of time potentiated the NMDA-induced efflux of sodium (Pullan et al., 1987). It has also been shown that magnesium and ketamine act at diffferent sites (Harrison and Simmonds, 1985; Lodge et al., 1985). Thus, it is unlikely that PCP acts by simply blocking the ion channel associated with the NMDA receptor.

Other models explaining the interaction between PCP and NMDA are much more complicated. These models take into account that it is also possible for voltage-dependence to be caused by an effect on an element outside of the NMDA receptors/channel complex that is sensitive to changes in voltage, such as the phospholipid bilayer. Agonist-dependence could also be caused by a change in the conformation of the PCP receptor that is consistent with the ability of NMDA to increase the affinity of the PCP receptor for PCP-like ligands.

Since one of the purposes of models is to provide the framework for further experiments to prove or disprove them, we would like to suggest two alternative models. Instead of a fully occluded ion channel, as an intrachannel binding site implies, a partially occluded receptor could explain the electrophysiological and neurochemical data. In this model, NMDA modifies the conformation of the receptor channel that in some way makes the active site of the PCP receptor more accessible. When the NMDA agonist dissociates, the conformation of the receptor channel returns to the control state where the active site of the PCP receptor is not accessible. This would trap the PCP-like compound in the active site. Thus, only after another NMDA agonist modifies the conformation would the PCP-like agonist be capable of dissociating from the PCP receptor. This model has the advantage that it explains use-dependent unblockade.

An alternative is that the ion channel associated with the PCP and NMDA receptor exists in an active, inactive, and desensitized state. An NMDA agonist changes the conformation of the receptor/channel complex, which converts the ion channel into an active state and increases the affinity of the PCP receptor for PCP agonists. Then the PCP agonist in turn induces a conformational change, converting the ion channel into a desensitized state. The conversion of the desensitized state into an active state would require an association of a NMDA agonist. This model would explain use-dependent unblockade and induction of NMDA receptors by metaphit.

Most of these models rely upon the ability of the NMDA receptor to modify the conformation of the PCP receptor and the NMDA-associated ion channel. These models also rely upon the ability of PCP to alter the conformation of the ion channel. The fact that PCP does not appear to alter the conformation of the NMDA receptor does not indicate that the PCP-receptor interaction is unable to modify the conformation of the ion channel. This lack of mutual allosteric interaction is not uncommon; one example is the interaction between GABA and picrotoxin at the GABA receptor/channel complex. GABA modulates the binding of picrotoxin, but picrotoxin does not appear to affect the binding of

GABA (Leeb-Lundberg and Olsen, 1980; Ticka and Olsen, 1979). It is interesting to note that picrotoxin has also beeen called a channel blocker.

Endogenous Ligands for PCP and Sigma Receptors

The characterization of specific PCP and sigma receptors raised the possibility that there might be an endogenous ligand for PCP and/or sigma receptors. This is particularly interesting in light of the profound behavioral effects of PCP and the production of a schizophrenic-like psychosis. Thus, some disturbance in an endogenous PCP system in the CNS might be involved in the pathogenesis of schizophrenia. Characterization of endogenous ligands for the PCP and sigma receptor will also help in the understanding of the physiological role of an endogenous PCP and sigma system.

Alpha and Beta Endopsychosin

A factor isolated from porcine brain, alpha-endopsychosin, inhibited the binding of [^{3}H]-PCP in a concentration-dependent manner (Quirion et al., 1984; DiMaggio et al., 1986; Contreras et al., 1986c). This PCP-like activity, which inhibited binding of [^{3}H]-PCP, did not inhibit the binding of [^{3}H]-dihydromorphine, [^{3}H]-D-ala^2-D-leu^5-enkephalin, [^{3}H]-ethylketocyclazocine, [^{3}H]-diazepam, or [^{3}H]-neurotensin. These results indicate that the PCP-like material is specific and selective for PCP receptors, since binding of the radioligands for the mu, delta, and kappa opioid and the benzodiazepine and neurotensin receptors was unaffected by the alpha-endopsychosin. Similarly, no inhibition of the binding of [^{3}H]-haloperidol was apparent with this same active material.

The distribution of the PCP-like activity was determined and found to roughly parallel the distribution of PCP receptors (Quirion et al., 1984). The highest concentration of alpha-endopsychosin was found in the hippocampus and cortex, while lesser amounts were found in the striatum, and very little in the brainstem and cerebellum.

An aliquot of the PCP-like activity was tested to determine whether it could induce PCP-like electrophysiological effects (Quirion et al., 1984). On hippocampal and cortical cells, the alpha-endopsychosin mimicked the actions of PCP; PCP inhibited spontaneous cortical and hippocampal cell firing, as did the PCP-like material. Chromatographic fractions that did not possess PCP-like activity in the radioreceptor assay had no effect on spontaneous neuronal activity.

Similarly, using a behavioral paradigm where unilateral injection of PCP into substantia nigra induces contralateral turning in rats, PCP-like fractions also mimicked the actions of PCP, producing contralateral turning (Quirion et al., 1984). Once again, chromatographic fractions inactive in the radioreceptor assays elicited no response in this test.

To study the nature of the PCP-like factor, the effect of various enzymes on the PCP-like activity was examined (Quirion et al., 1984). The potency of the PCP-like activity was markedly reduced following incubation of sample with pronase, carboxypeptidase A, and trypsin. No significant change in activity was seen following incubation of active fractions with alpha-chymotrypsin. Also, the ability of the PCP-like fractions to inhibit the binding of [^{3}H]-PCP was not attenuated following incubation with boiled enzymes. These data indicate that the endogenous material is a protein or a peptide with few aromatic amino acids. Spectroscopic methods confirmed this finding because no absorbance bands were seen when the sample was scanned at 280 and 254 nm (Contreras et al., 1987).

Studies using gel filtration and SDS gel electrophoresis were carried out to determine the relative size of alpha-endopsychosin (Quirion

et al., 1984). PCP-like active fractions were chromatographed over columns of Sephadex G-10, G-25, and G-50, and aliquots of collected fractions were assessed for their ability to inhibit the binding of [^{3}H]-PCP. Results indicated that the endogenous PCP-like material has a mol wt of about 3000. In contrast, studies using SDS gel electrophoresis show two distinct bands migrating with marker proteins at mol wt of 13,000 and 3000, respectively (John Bishop, personal communication).

When alpha-endopsychosin has been purified, there are three peaks of absorbance at 214 nm (DiMaggio et al., 1986). An aliquot of the most active material was hydrolyzed in acid and the amino acid composition was determined using OPA detection. It was apparent that the peptide contained approximately 26 amino acids, in close agreement with the molecular weight predicted by Sephadex gel filtration studies. *N*-terminal analysis revealed that the peptide was blocked at this site. The nature of this blockade is yet to be determined. Studies are under way to determine the amino acid sequence of the peptide.

Another peptide, beta-endopsychosin, isolated from porcine brain selectively inhibited the binding of [^{3}H]–(+)SKF 10,047 and not that of [^{3}H]-PCP (Contreras et al., 1986c). A partial sequence for this peptide was determined and the synthetic peptide fragment inhibited only the binding of [^{3}H]–(+)SKF 10,047 in a concentration-dependent manner (DiMaggio et al., 1987).

Other Endogenous Ligands

Several other groups have reported evidence for endogenous ligands for PCP and sigma binding sites. One group reported the isolation of an endogenous ligand that inhibits NMDA-induced release of acetylcholine (Sircar et al., 1986). In a recent paper, Zukin and coworkers (1987) have shown that, in rat striatal slices, this endogenous ligand for the PCP binding site partially purified from bovine hippocampi, stimulated spontaneous acetylcholine efflux, inhibited NMDA-stimulated acetylcholine release, stimulated basal dopamine release, and inhibited NMDA-stimulated dopamine release.

Isolations of endogenous ligands for the sigma binding site have been reported by other groups. Su and coworkers (1986) have isolated two endogenous ligands having apparent molecular weights of 10,000 and 4000, as determined by gel filtration studies. These ligands inhibited the binding of [^{3}H]-(+)SKF 10,047 in a concentration dependent manner, but did not inhibit the binding of [^{3}H]-PCP. These ligands appear to be peptides, since protease treatment abolished the ability of these ligands to inhibit the binding of[^{3}H]-(+)SKF 10,047. The binding of [^{3}H]-ethylketocyclazocine, [^{3}H]-naloxone, and [^{3}H] D-ala-D-leu-enkephalin was not inhibited by the endogenous factor, evidence of considerable specificity. A second group (Sonders et al., 1986) has isolated a compound that is not protease sensitive but also binds selectively to the sigma site.

Summary

Since the synthesis of PCP in the late 1950s, much behavioral, neurochemical, and electrophysiological data has been gathered in an attempt to understand the effects and the mechanism of action underlying the effects of PCP. It is not surprising that a drug like PCP, which has numerous and profound physiological and behavioral effects, has many different types of interactions in the nervous system. PCP interacts with sigma receptors, enzymes, and neurotransmitter release and uptake. The role of these interactions in the behavioral effects of PCP remains to be elucidated. There is also an abundance of data suggesting an important role for the PCP receptor in mediating some of the behavioral actions of PCP. A question is whether the PCP receptors are linked to a potassium

channel, the ion channel associated with nicotinic receptors, or the ion channel associated with the NMDA receptor. Another possibility is that PCP receptors are not all associated with the same ion channel. Thus, it will be important in the future to determine whether there is any situation where the actions of PCP can be clearly dissociated from those of the NMDA receptor.

The development of selective and potent agonists and antagonists for the PCP and sigma receptors will be important in delineating the function of each receptor. A promising area of research into the physiological relevance of endogenous PCP and sigma systems is in the isolation and characterization of endogenous ligands for the PCP and sigma receptors. The finding that the highest density of PCP receptors and the highest concentration of alpha-endopsychosin is in the cortex and hippocampus, and the ability of PCP to produce a schizophrenic-like psychosis suggests that pathologies of an endogenous PCP-like system may be involved in cognitive dysfunctions such as psychoses.

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