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Discriminative Stimulus Properties of Phencyclidine (PCP)-Related Compounds: Correlations With ^{3}H-PCP Binding Potency Measured Autoradiographically

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KOZLOWSKI, M. R., R. G. BROWNE AND F. J. VINICK. *Discriminative stimulus properties of phencyclidine (PCP)-related compounds: Correlations with ^{3}H-PCP binding potency measured autoradiographically.* PHARMACOL BIOCHEM BEHAV **25**(5) 1051–1058, 1986.—Several PCP analogs, the putative PCP agonist MDP, and the sigma receptor agonists SKF-10,047 and dexoxadrol were tested for their ability to substitute for PCP in animals trained to discriminate PCP from saline. The potencies of these compounds in substituting for PCP in the behavioral task correlated with their abilities to inhibit the specific binding of ^{3}H-PCP to rat hippocampal sections measured autoradiographically, which occurred at a single class of sites with an affinity of 85 nM and a capacity of 2646 fmol/mg protein. In addition to this specific binding, an additional nonspecific but displaceable fraction of total ^{3}H-PCP binding was present. These results suggest that the specific ^{3}H-PCP binding site measured in the hippocampus may be the type of binding site which mediates the behavioral effects of PCP and related compounds. Therefore, measurement of the inhibition of ^{3}H-PCP binding at this site might aid in the search for PCP antagonists.

Phencyclidine (PCP) Drug discrimination ^{3}H-PCP binding Autoradiography

THE mechanism by which the dissociative anesthetic phencyclidine (PCP) produces its psychotropic effects is of considerable interest in view of the fact that PCP can induce a state in humans that resembles endogenous psychosis [26,39]. Thus, elucidation of this mechanism might provide insights into the causes of schizophrenia. Another reason for interest in the mechanism of action of PCP stems from the high level of abuse of PCP [3,47]. Understanding the mechanism of action of this drug could lead to better treatment of PCP intoxication and toxicity.

Many attempts to explain the mechanism of action of PCP have focused on its interactions with established neurotransmitter systems in the brain. These interactions include increased release and attenuated reuptake of monoamine neurotransmitters [12, 15, 18, 50], blockade of cholinergic receptors and inhibition of acetylcholinesterase [5, 23, 29, 52], and binding to ion channels [2, 4, 6, 22, 37]. The idea that the psychotropic effects of PCP are mediated by these interactions is suggested by the observation that some of the behavioral effects of PCP, such as stereotypy and hypermotility, are modulated by aminergic and cholinergic agonists and antagonists [1, 30, 34, 48].

However, PCP has other effects which are relatively specific to itself and related compounds. For example, the discriminative stimulus properties of PCP are not mimicked by cholinergic, monoaminergic, GABAergic or opioid drugs, nor by ion channel blockers [9, 40, 42]. More importantly, the psychotropic effects of PCP differ from those produced by dopaminergic or serotonergic drugs [27,46]. These effects suggest that PCP may also act at relatively specific sites within the brain. This idea has been supported by several studies demonstrating specific PCP binding in brain tissue [17, 36, 53, 54]. However, there still exist disagreements concerning the parameters of this binding interaction such as the affinity of binding and the number of types of sites. These discrepancies may be related to the difficulty in performing homogenate binding assays using ^{3}H-PCP due to the labelling of clearly non-physiological sites, such as glass filters, unless exotic chemicals are added to the incubation mixture [17, 18, 33].

The present study represents an attempt to determine the behavioral relevance of PCP binding sites in the brain. The abilities of PCP analogs and related compounds, as well as sigma agonist agents, to substitute for PCP as a discriminative stimulus were compared with their potencies as inhibitors of ^{3}H-PCP binding in the hippocampus of the brain measured by an autoradiographic technique. If ^{3}H-PCP binding in hippocampus occurs at sites that are relevant to the behavioral effects of PCP, then these activities should be correlated.

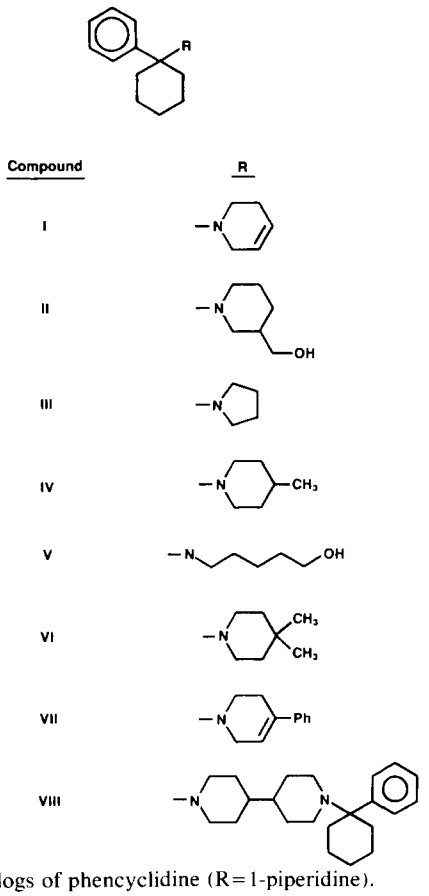

FIG. 1. Analogs of phencyclidine (R=1-piperidine).

TABLE 1

GENERALIZATION TO THE DISCRIMINATIVE STIMULUS PROPERTIES OF PCP COMPARED TO THE INHIBITION OF SPECIFIC ^{3}H-PCP BINDING BY PCP ANALOGS, AND PCP AND SIGMA AGONISTS

Compound	Inhibition of Specific ^{3}H-PCP Binding (IC_{50}, nM)	ED_{50} for PCP-Like Discrimination (mg/kg)
PCP	42	0.55
Sigma agonists		
Dexoxadrol	25	1.68
(+) SKF-10, 047	180	NT*
(−) SKF-10,047	1100	NT
(±) SKF-10,047	1200	2.74
Levoxadrol	8000	>100†
PCP mimetics		
(−) MDP	8.0	2.13
Tiletamine	9.4	0.46
Ketamine	35	2.20
(+) MDP	180	> 10
PCP analogs		
(+) PCMP	52	0.65
(±) PCMP	71	1.65
I	86	0.38
II	100	1.04
III	140	< 3.2
(−) PCMP	1100	11.4
IV	1200	5.37
V	>1100	> 10
VI	5000	> 10
VII	5000	> 10
VIII	>5000	> 10

*Not tested.
†">" indicates 50% generalization not achieved at the dose indicated.

METHOD

Generalization Training

Fifty adult, male Sprague-Dawley rats (Charles River, 200–250 g) were housed individually, with water freely available. Purina rat chow was fed after each experimental session and on weekends in quantities adjusted to maintain their weights between 270 and 350 g throughout the experiment. Training and testing sessions were conducted in 10 identical isolated Colbourn operant chambers equipped with two levers mounted on either side of a motor-driven dipper. Reinforcement consisted of 3 second presentations of 0.2 ml of a commercial liquid diet food (Carnation Slender) diluted 1:1 with water. Reinforcement contingencies and data recording were performed using a Rockwell AIM 65 microcomputer. The procedure was based on the two lever fixed ratio 10 drug-discrimination protocol first described by Colpaert *et al.* [11]. At 30 minutes prior to the 15 min session, PCP HCl (1.0 mg/kg) or vehicle (5% EtOH; 95% water) was administered SC in a volume of 1.0 ml/kg. Depending on whether the rat received drug or vehicle, reinforcement was programmed exclusively on either the left or right lever, respectively. Sessions were conducted Monday through Friday under the alternating drug sequence used by Colpaert *et al.* [11]: drug-vehicle-vehicle-drug-drug and vehicle-drug-drug-vehicle-vehicle. To avoid the possibility that the correct lever for rats previously tested in the chambers could serve as an olfactory cue, the treatments on training days were alternated for successive groups (i.e., half the animals received vehicle and half received PCP). For each session, the number of responses emitted prior to receiving the first reinforcement was the measure of discrimination accuracy. Most rats were clearly discriminating the effects of PCP from vehicle within about 30 training sessions, as demonstrated by the animals emitting their first 10 responses on the appropriate lever in 8 out of 10 consecutive sessions.

Generalization Testing

In order to determine stimulus generalization profiles for different doses of PCP, various other drugs, and drug interactions with PCP, twice weekly (Wednesdays and Fridays) tests were interposed between PCP (1.0 mg/kg) and vehicle maintenance sessions. Experimental treatments were given in the same EtOH:water vehicle described above in a volume of 1 ml/kg. Unless noted otherwise, all treatments were given SC 30 min prior to a 15-min session. The reinforcement scheduling procedure was changed on experimental test days as follows: the first reinforcement was programmed after 10 responses were emitted on either lever. The lever on which 10 responses were first accumulated defined the animal's "choice" for that test treatment. If it was the left lever, the animal was said to have selected the drug side, indicating generalization of the treatment to the PCP training condition;

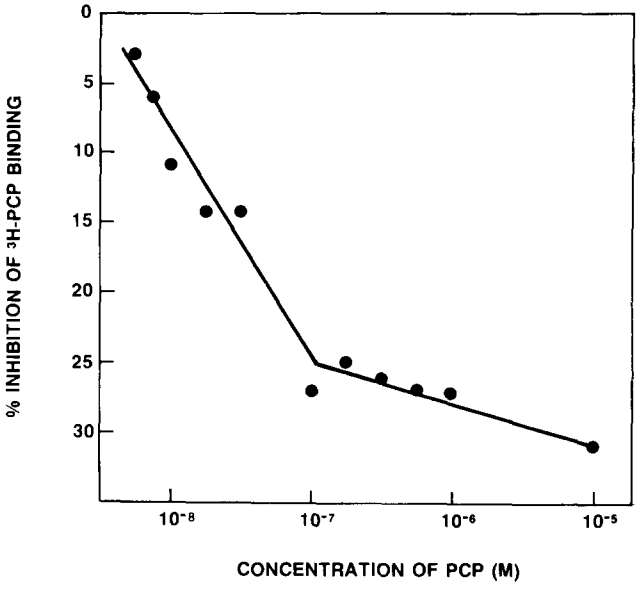

FIG. 2. Representative binding inhibition experiment using a 5 nM concentration of ^{3}H-PCP and increasing concentrations of unlabeled PCP.

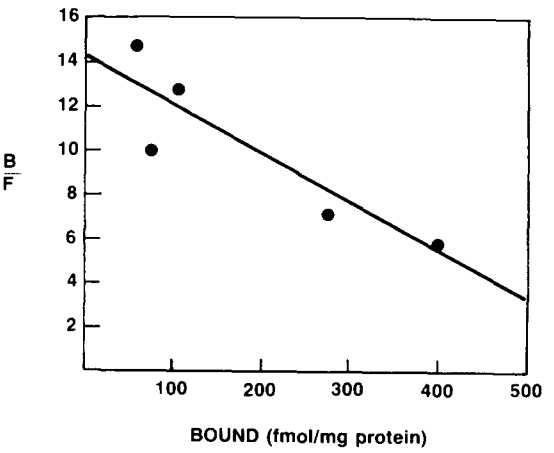

FIG. 3. Scatchard plot of a representative saturation binding experiment using 1 to 100 nM ^{3}H-PCP.

if it was the right lever, the animal was said to have selected the vehicle side, indicating non-generalization of the treatment to the PCP training condition. Following the first reinforcement on experimental treatment days, subsequent reinforcements were given on a FR10 schedule for responses on either lever. Doses of test compounds (N=10/treatment) were administered in a randomized design based on previous findings in rats trained to discriminate higher doses of PCP [9]. Generalization tests were performed using a number of compounds, including PCP analogs [1-(-1-phenylcyclohexyl)-3-methyl-piperidine; PCMP and I-VIII; Fig. 1], structurally related compounds (ketamine, tiletamine), and other sigma receptor agonists (dexoxadrol and SKF-10,047). In all cases, doses high enough to produce either 90 to 100% generalization or behavioral toxicity (defined as half the animals failing to emit at least 20 responses during the 15 min session) were tested. The percentage of animals choosing the lever previously paired with PCP was used for ED_{50} determinations based on probit analysis.

Measurement of ^{3}H-PCP Binding

Male Sprague-Dawley rats (250–300 g) were decapitated, and their brains rapidly removed and frozen in isopentane chilled to −20°C. Brain sections 20 μm in thickness were prepared the same day using a cryostat. The sections were dried overnight in a dessicator at 4°C, and then transferred to a freezer at −40°C. The brain sections were used within 1 week. Measurement of 3H-PCP binding was performed in a manner similar to that described by Quirion *et al.* [36]. The sections were brought to 4°C on ice and then preincubated for 15 min in ice cold 5 mM Tris-HCl buffer (pH 7.4) containing 50 mM NaCl, which was changed once. Following the preincubation, the sections were transferred to 5 mM Tris-HCl buffer (pH 7.4) containing ^{3}H-PCP. Where indicated, this incubation mixture also contained unlabeled PCP or other compounds being tested for their ability to inhibit ^{3}H-PCP binding. The sections were incubated at 4°C for two hours followed by six, 5 sec rinses in ice-cold 5 mM Tris-HCl buffer (pH 7.4). Following the rinses, the sections were rapidly dried under a stream of air and placed in contact with a sheet of tritium sensitive film (Ultrofilm, LKB). After 10 to 14 days, the film was developed and the binding quantified using a computerized image analysis system (Quantimet 900, Cambridge Instruments). Plastic standards containing 14C (Amersham), which had been calibrated to tritium in the laboratory were used in the quantification. The calibration was performed by exposing the plastic standard together with reconstituted tissue sections containing known amounts of tritium to the film for 10 to 14 days. The relationship between concentration of radioactivity and optical density was linear in the optical density range employed (>0.5). The protein content of whole brain sections was measured by the method of Lowry [25]. The protein contained in the hippocampal region was calculated by multiplying the protein in the whole section by the fraction of the area of the section represented by the hippocampus.

The binding data were analyzed using the LUNDON-1 computerized curve-fitting program. Qualitative pictures of the distribution of specific binding were prepared by subtracting an image of non-specific binding which had been transformed (linearized) to show density of binding sites from a similar image of total binding using a computerized image analysis system (Spatial Data Systems model 850). The contrast of the subtracted image was enhanced by spanning the range of densities between the darkest area and the background with the full range of grey levels from black to white. [Piperidyl-3,4-3H(N)]-phencyclidine (43.5 to 49.0 Ci/mmol) was purchased from New England Nuclear. SKF-10,047 was supplied by NIDA and dexoxadrol by The Upjohn Company. All other compounds were synthesized by one of us (F.J.V.).

RESULTS

Discriminative Stimulus Properties of PCP

Consistent with previous findings, all 50 rats learned to discriminate the effects of PCP from saline as evidenced by all emitting greater than 90% treatment-appropriate responses during maintenance sessions throughout the study. Dose-response and time-course analysis revealed an ED_{50}

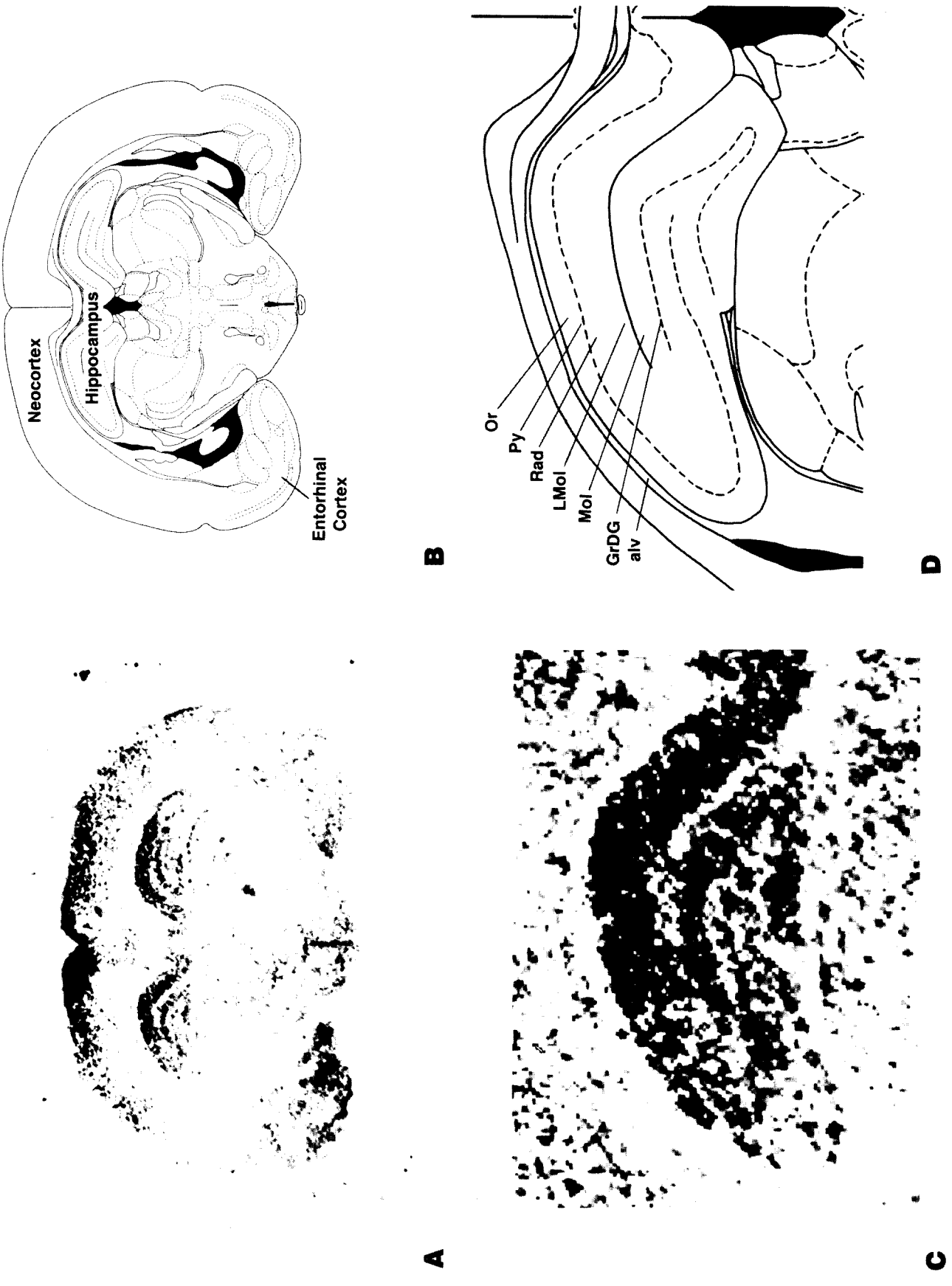
Neocortex
Hippocampus
Entorhinal Cortex
B
Or
Py
Rad
LMol
Mol
GrDG
alv
D
A
C

TABLE 2
INHIBITION OF SPECIFIC ^{3}H-PCP BINDING BY AMANTADINE AND VERAPAMIL

Compound	Concentration	% Inhibition of Specific Binding
Amantadine	10 nM	40
	100 nM	35
	500 nM	59
	1000 nM	40
	5000 nM	43
Verapamil	5000 nM	52

for PCP of 0.55 mg/kg and a tl/2 of 120 min. The PCP analogs tested for generalization (Fig. 1) all contained modifications of the piperidinyl moiety of PCP. These substitutions either did not change, or lowered the potency of these compounds in substituting for PCP (Table 1). Replacement of the piperidine group with a tetrahydropyridine (I) or a pyrrolidine ring (III), or methyl (PCMP) or methanol (II) substitutions at the 3 position on the piperidine ring resulted in either no change or up to a 5-fold decrease in potency. A number of substitutions at the 4 position on the piperidine or tetrahydropyridine ring (IV, VI, VII, VIII) caused a much greater decrease in potency. Likewise, the known PCP metabolite, V, in which the piperidinyl moeity was replaced with an aminopentanol group [10], was much less active than PCP. The putative PCP agonist 2-methyl-3,3-diphenyl-3-propanolamine (MDP) also substituted for PCP. Generalization to the PCP cue was stereoselective with dexoxadrol, (−)MDP and (+)PCMP being more potent than levoxadrol, (+)MDP and (−)PCMP, respectively.

Characteristics of ^{3}H-PCP Binding

Binding of ^{3}H-PCP (5 nM) was measured in the hippocampus of rat brain sections because this area contains a high density of binding sites [54]. The binding to the hippocampal region could be inhibited by adding excess unlabeled PCP. The inhibition curve was biphasic with the steepest part of the curve occurring at concentrations between 10 and 100 nM PCP (Fig. 2). The fraction of total ^{3}H-PCP binding inhibited by a concentration of 500 nM of unlabeled PCP was 21%. The binding of ^{3}H-PCP was inhibited by an additional 10% as the concentration of unlabeled PCP was raised to 10 μM, however, the slope of this part of the inhibition curve was very shallow. High concentrations (1 to 10 μM) of the structurally unrelated PCP agonists SKF-10,047 and dexoxadrol inhibited approximately the same amount of total ^{3}H-PCP binding as the 500 nM concentration of PCP (16.3±0.9 and 19.7±6.1%, of total binding, respectively; mean±s.e. of 3 assays). Thus, the initial, steep portion of the PCP inhibition curve produced by concentrations of PCP up to 500 nM appeared to represent specific PCP agonist binding. The IC50 value for inhibition of specific ^{3}H-PCP binding, defined as that inhibited by a 500 nM concentration of unlabeled PCP, by PCP was 44±14 nM (mean±s.e. of 11 experiments). Scatchard plots obtained from saturation experiments using concentrations of ^{3}H-PCP ranging from 1 to 100 nM (Fig. 3) were linear and gave a Kd value of 85±15 nM, in approximate agreement to that obtained from the inhibition experiments, and a Bmax value of 2646±65 fmol/mg protein (mean±s.e. of 3 experiments).

The distribution of specific ^{3}H-PCP binding sites in the hippocampus was visualized by digitally subtracting the linearized autoradiographic image of non-displaceable binding from that of total binding as described in the Method section. The highest densities of binding sites were located in the stratum oriens, stratum lacunosum moleculare and dentate gyrus, while the CA3 region of the hippocampus had a very low density of binding sites (Fig. 4).

Pharmacology and Behavioral Significance of 3H-PCP Binding

Specific 3H-PCP binding was inhibited by several of the PCP analogs (PCMP and I–IV), the PCP-like dissociative anesthetics, ketamine and tiletamine, the putative PCP agonist MDP, the sigma receptor agonist SKF-10,047 and the stereoisomers of dioxadrol (dexoxadrol and levoxadrol) (Table 1). Furthermore, there was a significant correlation between inhibition of specific 3H-PCP binding and PCP-like discriminative effects for all compounds tested, $r(10)=0.73$, $p<0.05$.

Specific 3H-PCP binding was stereoselective, with dexoxadrol, (−)MDP, (+)PCMP and (+)SKF-10,047 being more potent binding inhibitors than their stereoisomers levoxadrol, (+)MDP, (−)PCMP, and (−)SKF-10,047, respectively. This was the same pattern of stereoselectivity found in the generalization of the enantiomers of dioxadrol, MDP and PCMP to the PCP cue. In addition, this same stereoselectivity has been reported in the abilities of the isomers of SKF-10,047 to substitute for PCP as a discriminative stimulus [7, 41, 43].

Compounds that label opiate, cholinergic, aminergic or purinergic receptor binding sites did not inhibit specific 3H-PCP binding. Thus, naloxone (μ opiate antagonist), atropine (muscarinic cholinergic antagonist), apomorphine (dopamine agonist), chlorpromazine (D1 and D2 dopamine antagonist), spiroperidol (D2 dopamine antagonist), 2-chloroadenosine (A1 purinergic agonist), and clonidine (alpha adrenergic agonist) were all inactive at doses of up to 5 μM. Interestingly, specific 3H-PCP binding was inhibited by verapamil and amantadine, drugs that act on ion channels (Table 2). However, even at a high dose (5 μM) these compounds produced only about a 50% inhibition of specific binding. In the case of amantadine, this inhibition appeared to be maximal, since increasing the concentration from 10 nM to 5 μM produced no further increase in the amount of inhibition.

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FIG. 4. Regional distribution of specific ^{3}H-PCP binding in the hippocampus. A. Digitally subtracted and enhanced image of specific ^{3}H-PCP binding (see the Method section for details). The dark area in the cingulate cortex is a subtraction artifact caused by tissue damage. C. Enlargement of the hippocampal area in "A." B and D. Brain atlas planes for comparison with autoradiographs (redrawn from Paxinos and Watson [35]).

The small additional amount of ^{3}H-PCP binding inhibited by concentrations of PCP between 500 nM and 10 μM did not appear to represent binding at a specific site. Thus, it was almost completely inhibited by a 5 μM concentration of each of the pharmacologically unrelated compounds apomorphine, 2-chloroadenosine, propranolol, naloxone or verapamil, and to a lesser extent by spiroperidol and chlorpromazine. Furthermore, examination of its distribution in autoradiographs revealed that, unlike specific ^{3}H-PCP binding, it was uniform throughout the hippocampus, a property not characteristic of specific binding sites [14], although the low ratio of this fraction of the binding to total binding could have obscured subtle regional differences in distribution. Therefore, this fraction of the total ^{3}H-PCP binding appears to be displaceable but nonspecific. Amantadine produced an interesting effect by increasing the size of the displaceable, nonspecific fraction of the binding.

DISCUSSION

The results of the present study suggest that specific ^{3}H-PCP binding sites with the characteristics of those present in the hippocampus may mediate the behavioral effects of PCP-related compounds. Thus, the affinities of PCP analogs and related compounds in inhibiting specific ^{3}H-PCP binding were correlated with their potencies in mimicking the discriminative stimulus properties of PCP.

The drug discrimination paradigm was chosen as an indicant of PCP agonist behavioral activity, because it effectively distinguishes PCP-related compounds from compounds with other pharmacological activities. Thus PCP and its analogs, as well as compounds related to PCP by similar physiological effects, such as other sigma agonists [8, 20, 21, 24, 31, 51], are active in this test, while unrelated compounds from several pharmacological classes are inactive [7, 9, 40–42]. The measurement of binding to tissue sections combined with autoradiography was deemed superior to conventional homogenate techniques because it made possible the examination of the distribution of ^{3}H-PCP binding sites within the hippocampus. This information is important because ^{3}H-PCP has exhibited displaceable binding which was clearly not associated with neurotransmitter receptors (i.e., to glass filters), suggesting that PCP binding sites in brain might be artifacts [28]. The present results indicate that specific ^{3}H-PCP binding had a distinct regional distribution within the hippocampus, being densest in the stratum oriens, stratum lacunosum moleculare and dentate gyrus, and sparse in the CA3 region. This non-uniform distribution argues against this site being an artifact [14]. A similar distribution of the binding of the PCP analog ^{3}H-N-(1-[2-thienyl]cyclohexyl)piperidine (TCP) in the hippocampus has been shown semiquantitatively [44]. A disadvantage of the use of the autoradiographic technique was that the ratio of specific to total binding was less than that obtained with conventional homogenate techniques [17, 33, 53, 54]. It was also less than that achieved in another autoradiographic study, although this may have been due to differences in the type of tissue used [36].

While there was an overall correlation between the abilities of compounds to substitute for PCP in the discrimination paradigm and their affinities for the ^{3}H-PCP binding site, some compounds (e.g., (−)MDP and tiletamine) were much less effective as discriminative stimuli for PCP than would have been predicted on the basis of their binding potencies. This discrepancy may simply reflect the poorer absorptions, higher rates of metabolism or lower central nervous system penetrabilities of these compounds, thus giving them relatively poorer *in vivo* activities relative to their *in vitro* potencies than the other compounds. Alternatively, these compounds may possess mixed agonist/antagonist properties.

A single type of specific ^{3}H-PCP binding site was identified in the hippocampus in agreement with several other studies employing brain tissue [16, 36, 53, 54]. In some of these studies, the affinity of the site was lower than that measured in the present study, however this discrepancy may be due to differences in the types of buffers used [53,54]. However, other investigators have found an additional, low affinity binding site for ^{3}H-PCP in whole rat brain or cortex homogenates by saturation analysis [17,33]. We also noted that presence of low affinity of ^{3}H-PCP binding, defined as the fraction of total ^{3}H-PCP binding not inhibited by a 500 nM concentration of PCP, but inhibited by a 10 μM concentration. However, it appeared that this binding was nonspecific, since it could be inhibited by several pharmacologically distinct ligands. Furthermore, it was not regionally localized within the hippocampus, but rather was uniformly distributed, a property not characteristic of a homogeneous population of receptor binding sites [14]. Therefore, the present results suggest that the low affinity binding site identified in other studies should be reevaluated to make sure that it does not also represent nonspecific ^{3}H-PCP binding. The nature of the displaceable but nonspecific ^{3}H-PCP binding observed in this study is not known. It may represent the combined low affinity binding of ^{3}H-PCP to a number of receptors, since PCP has been shown to be a weak inhibitor of cholinergic, opioid and purinergic binding [5, 9, 19, 52].

The specific ^{3}H-PCP binding site may also mediate the behavioral effects of other sigma agonist compounds, since SKF-10,047 and dexoxadrol were also potent inhibitors of high affinity ^{3}H-PCP binding in the hippocampus. Furthermore, the relative potencies of PCP and SKF-10,047 as binding inhibitors were similar to their relative abilities to stimulate sigma receptors measured behaviorally and physiologically [51]. Other studies have shown that sigma agonists also inhibit ^{3}H-PCP binding in homogenates of rat and human brain, and in rat olfactory bulb sections [17, 36, 45, 54].

The present results may help to clarify the previously reported interactions of the ion channel blockers verapamil and amantadine with ^{3}H-PCP binding [13, 37, 38]. We found that both of these compounds inhibited specific ^{3}H-PCP binding. However, the behavioral relevance of this interaction is unclear, since amantadine does not support PCP-like responding in the discrimination paradigm, nor did it act as an antagonist [9]. Verapamil may possess some PCP agonist properties, since it potentiates some of the effects of PCP on radial arm maze performance [32]. Since neither compound, at the doses tested, produced a total inhibition of binding, it may be that they interact with only a subset of the high affinity ^{3}H-PCP binding sites, and that this subset is not, by itself, able to mediate all of the behavioral effects of PCP. These drugs had differing effects on the displaceable but nonspecific fraction of ^{3}H-PCP binding. Verapamil also inhibited this fraction of ^{3}H-PCP binding while amantadine increased the size of this fraction. The enhancement of ^{3}H-PCP binding by amantadine has been previously reported [38]. Our demonstration that this enhancement may reflect an increase in nonspecific ^{3}H-PCP binding casts doubt on its role in mediating the behavioral effects of PCP.

The results of this study also support the claim that (−)MDP possesses PCP-like properties. It has been reported that (−)MDP produces PCP-like responding in rats in drug or brightness discrimination tasks, and causes anesthesia in monkeys [49]. Our results confirm that (−)MDP can support PCP-like responding in a drug discrimination task and go on to show that (−)MDP inhibits specific ^{3}H-PCP binding, similarly to other PCP agonists.

In conclusion, our results suggest that specific ^{3}H-PCP binding sites such as those present in the hippocampus may mediate the behavioral effects of PCP. Therefore this site may be useful in the search for PCP antagonists for use in the treatment of PCP-induced psychosis, and possibly also the endogenous psychosis which PCP intoxication mimics.

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