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Effects of Phencyclidine (PCP)-Like Drugs on Turning Behavior, ^{3}H-Dopamine Uptake, and ^{3}H-PCP Binding

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JOHNSON, K. M. AND L. D. SNELL. *Effects of phencyclidine (PCP)-like drugs on turning behavior, ^{3}H-dopamine uptake, and ^{3}H-PCP binding.* PHARMACOL BIOCHEM BEHAV 22(5) 731–735, 1985.—In this study representatives from three chemical classes which are known to produce a phencyclidine (PCP)-like discriminative stimulus cue in rats were tested for their ability to inhibit synaptosomal uptake of ^{3}H-dopamine (^{3}H-DA) and to compete for a binding site labeled with ^{3}H-PCP. Although there was a good correlation between these two *in vitro* activities within the arylcycloalkylamine class (PCP, N-ethyl-phenylcyclohexylamine (PCE), and ketamine) it did not hold when representatives from the benzomorphans, N-allylnormetazocine (NANM), cyclazocine (CYCL), and ethylketocyclazocine (EKC), or a substituted dioxolane (etoxadrol) were included. At some dose each of these drugs with the exception of EKC also produced ipsilateral turning in rats with a unilateral 6-hydroxydopamine lesion of the substantia nigra. This effect was also not well correlated with inhibition of ^{3}H-DA uptake. However, a significant correlation was found to exist between turning behavior and affinity for the putative PCP/sigma receptor. The possibility that a non-dopaminergic mechanism involving the PCP/sigma receptor underlies the ability of these agents to induce turning behavior is discussed.

Phencyclidine Ketamine Cyclazocine N-Allylnormetazocine Ethylketocyclazocine Etoxadrol ^{3}H-Phencyclidine binding Dopamine uptake Turning behavior

PHENCYCLIDINE (1-(1-phenylcyclohexyl) piperidine, or PCP) almost certainly enhances CNS dopaminergic function when given to rats in doses (2.5–10 mg/kg) which causes stereotypic behavior [2, 21, 22] or ipsilateral rotation in animals with unilateral destruction of the nigro-striatal dopaminergic pathway [6, 7, 17]. Although the precise underlying biochemical mechanism(s) are not known, it has been inferred that these behavioral alterations are related to PCP's ability to block DA reuptake [8,28], or to facilitate DA release and synthesis [1, 29, 30], or to enhance impulse-dependent release and metabolism of DA [5,16]. The validity of this inference has not been stringently tested. Further, the role of DA in other PCP-induced behaviors is unknown [14].

This laboratory has recently sought to clarify the relationship between the discriminative stimulus properties of PCP [3, 12, 25] and its dopaminergic properties by determining the effects of several drugs which have PCP-like properties on DA release *in vitro* and DA metabolism *in vivo*. From these studies, we concluded that the discriminative stimulus properties of these agents are not related to either of the parameters measured [27]. Recently, a report appeared which showed that the inhibition of synaptosomal ^{3}H-DA uptake by a variety of arylcycloalkylamines including PCP was correlated with their ability to displace ^{3}H-PCP from the putative PCP/sigma receptor [31]. The present study was designed to verify and extend this observation to drugs from the benzomorphan and dioxolane classes which have been shown to compete with ^{3}H-PCP for its binding site [9, 33, 34] and to share discriminative stimulus properties with PCP [3, 4, 12, 25]. In addition, these drugs were tested in rats with a unilateral 6-hydroxydopamine (6-OHDA)-induced lesion of the nigrostriatal pathway. In this way, we sought to clarify the postulated role of the inhibition of DA reuptake in a behavioral assay which is predominantly dependent upon dopaminergic mechanisms [23].

METHOD

Male Sprague-Dawley rats (220–270 g) were obtained from Holtzman Co. (Madison, WI) and were housed in groups of four or five with food and water available continuously. Lights were on between 0600 and 1800 hr daily. Animals which were to be used for either the assessment of ^{3}H-DA uptake or ^{3}H-PCP binding were killed on the day of use by decapitation. The brains were rapidly removed and the appropriate area dissected, weighed, and placed in 9 volumes of ice-cold 0.32 M sucrose and homogenized in a glass grinding vessel with a teflon pestle (0.13–0.18 mm clearance) for uptake studies or using a Polytron (setting 6, 15 sec) for binding studies.

Synaptosomal Uptake of ^{3}H-DA

Striatal homogenates were centrifuged at 1,000× for 15 min. The P_1 pellet was discarded and the supernatant was centrifuged at 17,500×g for 20 min. The crude synaptosomal pellet (P_2) was resuspended in 40 volumes of ice-cold buffer (in mM: NaCl, 135; KCl, 4.5; $NaHCO_3$, 2.73; KH_2PO_4, 1.36; $MgCl_2 \cdot 6H_2O$, 1.4; $CaCl_2 \cdot 2H_2O$, 1.3; disodium EDTA, 0.134;

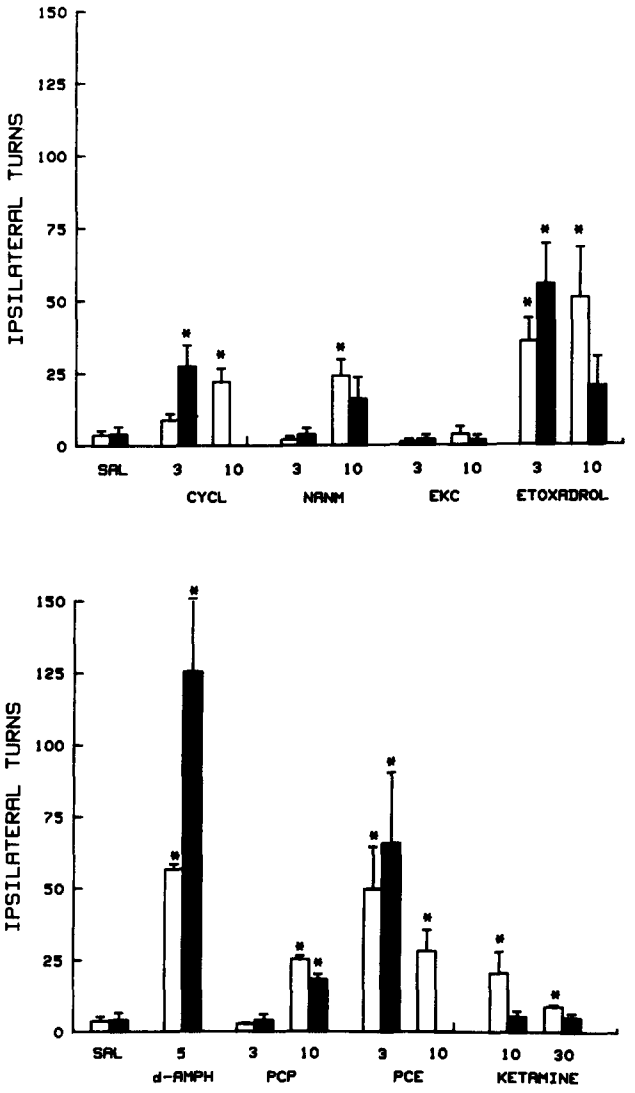

FIG. 1. Turning behavior induced by PCP-like drugs in rats with 6-OHDA lesions of the substantia nigra. Three to four rats were injected (IP) with the indicated dose (mg/kg) of each drug and placed in a stainless steel bowl 30 cm in diameter. The number of 360° rotations were counted in two time bins: 0–15 min post-injection (open-bars) and 16–30 min post-injection (closed bars). *$p<0.05$ as compared to saline.

ascorbic acid, 1.13; glucose, 11.0; and pargyline (an MAO inhibitor), 0.125) adjusted to pH 7.4. An aliquot of the tissue suspension (0.1 ml) was added to flasks containing the buffer and either a drug or appropriate vehicle (total volume 3.9 ml). After incubation for 5 min at 37°C in a shaking water bath, the reaction was started by adding 0.1 ml of dihydroxyphenylethylamine, 3,4-(ethyl-1-^{3}H(N)[(34.2 Ci/mmole, New England Nuclear) in a final concentration of 10 nM. After 5 min the uptake of ^{3}H-DA was stopped by the addition of 5 ml ice-cold buffer and immediate centrifugation at 17,500×g for 20 min. The pellet was washed once by resuspension in cold buffer and recentrifugation. The pellet was then digested in 0.2 N NaOH at 45°C, neutralized with 1 N HCl, and radioactivity estimated in an aliquot by liquid scintillation spectrometry. Uptake of ^{3}H-DA by passive diffusion was estimated in parallel experiments in which the tissue suspension was cooled to 2°C prior to the addition of ^{3}H-DA. This quantity was approximately 10–15% of the total uptake. High-affinity uptake was estimated by subtracting this value from the total. Each drug was tested in two to four independent experiments in which triplicates of at least four concentrations of drug were compared to vehicle. Where possible the concentration of drug which inhibited uptake by 50% (IC_{50}) and the 95% confidence intervals was estimated by linear regression analysis of the data plotted as the fraction of control uptake against the log of the concentration.

^{3}H-PCP Binding Assay

Rat forebrain homogenates were centrifuged at 1000×g for 15 min, the pellet discarded, and the supernatant centrifuged at 17,500×g for 20 min. The pellet was resuspended in cold 5 mM Tris-HCl (pH 7.4) and recentrifuged at 17,500×g. The pellet was finally resuspended in 5 mM Tris buffer at approximately 0.8 mg protein/ml. An aliquot of tissue homogenate (0.5 ml) was then added to tubes containing 10 or 100 nM phencyclidine, [piperdyl-3,4-^{3}H(N)] (43.5 Ci/mmole, New England Nuclear) in the presence and absence of 30 μM additional unlabeled PCP in a total volume of 1 ml and this mixture was incubated in a shaking ice bath at 2°C for one hr (previously determined to be suitable for attainment of equilibrium). The incubation was terminated by rapid filtration over GF/C filters (previously soaked in 0.025% polyethyleneimine to eliminate specific binding of ^{3}H-PCP to the filters). The filters were then rapidly washed twice with 5 ml of cold Tris buffer and then placed in scintillation vials to which 0.5 ml of water and 4 ml of Scintiverse 2 (Fisher Scientific) were added. After mechanical shaking for 30 min the radioactivity was estimated by liquid scintillation spectrometry. Internal standardization using ^{3}H-H_2O applied to the filters indicated a counting efficiency of 31%.

Displacement experiments with unlabeled PCP showed a maximal inhibition of 50–60% with a plateau beginning at 10–30 μM. Therefore, we have defined specific binding of ^{3}H-PCP as that which is displaced by 30 μM unlabeled PCP. Using this definition we obtained an IC_{50} of about 0.3–0.5 μM in all brain areas studied. In these experiments at least five concentrations of each drug were run in triplicate and the percent inhibition of specific binding of 10 or 100 nM ^{3}H-PCP was calculated. The log of the concentrations producing an inhibition between 10 and 90 percent were plotted against the percent of specific binding and an IC_{50} (with 95% confidence interval) was calculated using linear regression techniques.

Lesions of the Substantia Nigra

Male Sprague-Dawley rats were anesthetized with 40 mg/kg sodium pentobarbital and were subsequently injected intracerebrally with 8 μg of 6-OHDA (Aldrich) in 4 μl of saline containing 0.1% ascorbic acid. Unilateral injections were made on the left side of the brain through a 30 gauge needle attached to a 10 μl Hamilton syringe fixed to a stereotaxic surgery device. A syringe pump was used to make the injections at a rate of 0.33 μl/min. With the incisor and ear bars leveled, the stereotaxic coordinates for the needle placement in the substantia nigra were as follows: 4.2 mm P and 1.4 mm L from Bregma, and 8.0 mm below the skull surface. The rats were subsequently housed individually with unlimited access to food and water.

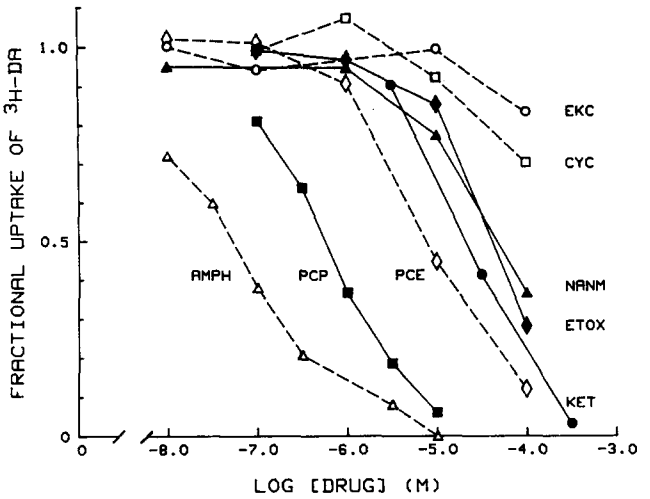

FIG. 2. The effect of PCP and various other compounds with proposed PCP-like activity on the high-affinity uptake of ^{3}H-DA into rat striatal synaptosomes. Each value represents the mean of 2–4 independent experiments in which triplicate determinations were made at each concentration.

Two weeks after surgery, the rats were placed individually in clear plastic hemispherical bowls. After a brief adaptation period they were injected (SC) with 0.05 mg/kg apomorphine HCl dissolved in 0.9% NaCl containing 0.2 mg/ml ascorbic acid. Each rat was then observed for three minute periods beginning at 15 min and 30 min post-injection. Only those rats that made at least 10 net contralateral turns (away from the lesioned side) in one of the observation periods were used in this study. On the average, subjects made about 30 net contralateral rotations in the three minute period 15 to 18 min post-injection. It has previously been shown that only rats with gross unilateral loss of dopaminergic neurons (as indexed by loss of tyrosine hydroxylase activity) exhibit contralateral rotation in response to apomorphine administration [11]. Thus, it is felt that the twelve animals used in this study had extensive loss of dopaminergic neurons on the left side of their brain.

Approximately six months later these animals (550–700 g) were again tested for rotational behavior. The rats were placed in a stainless steel hemispheric bowl (30 cm diameter) and after a 10 min habituation period, they were injected (IP, 1 ml/kg) with either saline or the test drug. They were then returned to the bowl and observed in 5 min bins for a total of 30 min. Only complete 360° rotations were counted. Although clockwise rotations (contralateral to the lesion) were subtracted from the total number of rotations to give the number of net ipsilateral rotations, no drug except ethylketocyclazocine (EKC) produced any contralateral rotations at all. In this paradigm, each of the twelve rats were tested with either saline or drug on four or five occasions spaced over a one month period. No animal was tested more than once with any drug. Each dosage was tested in at least three rats. These results were compared to saline injected controls by the use of the Mann-Whitney U test.

Drugs and Chemicals

The drugs in this study were obtained from the following sources: l-(l-phenylcyclohexyl) piperidine HCl (PCP) and (+)-amphetamine sulfate from Dr. Robert Willette of the National Institute on Drug Abuse (NIDA, Bethesda, MD); N-ethyl-l-phenylcyclohexylamine HCL (PCE), from Dr. Harlan E. Shannon (NIDA, Lexington, KY); N-allylnormetazocine (NANM) and ketocyclazocine (KC) from Dr. Robert L. Balster (Medical College of Virginia, Richmond, VA); etoxadrol HCl from Dr. Philip Von Voightlander (Upjohn, Kalamazoo, MI); cyclazocine (CYCL) and ethylketocyclazocine methanesulfonate (EKC) from Dr. A. E. Soria (Sterling-Winthrop Research Institute, Rensselaer, NY). All other drugs and chemicals were obtained from commercial sources. All drugs were used as their salts or bases as listed above and dissolved in 0.9% NaCl except CYCL and KC which were dissolved in a minimal volume of 0.2 N HCl and then diluted with 0.9% NaCl.

RESULTS

The effects of amphetamine, PCP, and several other drugs on rotational behavior are shown in Fig. 1. Amphetamine, at 5 mg/kg, produced vigorous ipsilateral turning in the first 15 min following injection. This was followed by an even higher turning rate in the next 15 min. PCP produced a dose related increase in turning as reported previously [6]. However, the effects of PCE and ketamine were related to dose in an inverse manner. This inverse dose-relationship was apparent in both 15 min periods shown in Fig. 1 and appeared to be due to a general motor incapacitation. With PCE, ipsilateral posturing was apparent, but hind limb coordination was grossly impaired. Ketamine, on the other hand, seemed to reduce turning more by virtue of its sedative effects. In fact, after either 50 or 100 mg/kg ketamine, the rats became totally akinetic within 5 min (data not shown). The effects of etoxadrol and CYCL were more similar to PCE than ketamine. In the second 15 min observation period, these drugs also produced an inverse dose-response. The effects of N-allylnormetazocine (NANM or SKF 10047) were similar to those of PCP, except that the latter drug was slightly more potent. Neither EKC nor KC at 5 mg/kg (data not shown) produced significant turning. The rats treated with EKC appeared "cataleptic" although this was not verified experimentally.

The effects of these drugs on high-affinity synaptosomal uptake of ^{3}H-DA are shown in Fig. 2. As expected, amphetamine and PCP were potent inhibitors of this process with IC_{50} values (95% confidence limits) of 0.06 (0.05–0.07 μM) and 0.58 (0.50–0.69 μM), respectively. PCE was moderately potent, with an IC_{50} value of 9.4 (6.0–15 μM). Ketamine, etoxadrol, and NANM were weak inhibitors with IC_{50} values of 24 (11–53 μM), 38 (13–115 μM), and 46 (17–124 μM), respectively. CYCL and EKC were extremely weak, producing minimal inhibition even at 100 μM.

The data in Table 1 are reflective of these drug's affinity for the PCP/sigma receptor as measured by competition with 100 nM ^{3}H-PCP for the binding site. The rank order potency was as follows: PCP $\geq$ etoxadrol $\geq$ PCE = CYCL $\geq$ NANM $\geq$ ketamine > KC > EKC. When the rank order potencies for each of the seven drugs which were tested in both *in vitro* assays were compared using Spearman's rank-order correlation test we found an insignificant correlation ($r=0.62$, $z=1.51, p>0.10$). These data were verified in a second experimental series in which these drugs were tested against 10 nM ^{3}H-PCP. Virtually identical results were obtained, with the only difference being that the rank order of ketamine and NANM were reversed (data not shown).

TABLE 1

DISPLACEMENT OF ^{3}H-PCP (100 nM) BINDING BY REPRESENTATIVES OF THE ARYLCYCLOALKYLAMINE, BENZOMORPHAN, AND SUBSTITUTED DIOXOLANE DRUG CLASSES

	IC_{50}, μM (95% Confidence Limits)	Relative Potency
PCP	0.44 (0.34–0.58)	100
Etoxadrol	0.63 (0.30–1.3)	70
PCE	1.1 (0.88–1.3)	40
CYCL	1.1 (0.76–1.5)	40
NANM	2.2 (0.64–7.8)	20
ketamine	3.2 (2.3 –4.4)	14
KC	8.9 (5.4 –15)	5
EKC	*	<2

*Maximal inhibition obtained was 45% at 30 μM.

DISCUSSION

Although we tested only three compounds from the arylcycloalkylamine series (PCP, PCE, and ketamine) these data would tend to confirm the study which showed that the ability of eight arylcyclohexylamines to inhibit ^{3}H-DA uptake and ^{3}H-PCP binding was strongly correlated [31]. However, our data also suggest that this correlation is not a general one in that the activities of representatives from other drug classes which have PCP-like behavioral properties are not correlated in these two *in vitro* measures. These data also extended our earlier observations which suggested that the ability of drugs with PCP-like discriminative stimulus properties to inhibit ^{3}H-PCP binding was not correlated with their ability to enhance ^{3}H-DA release from striatal slices or to increase haloperidol-induced DA metabolism [27]. Thus, we have found no apparent relationship between striatal dopaminergic function (as indexed by three biochemical parameters involving three levels of structural complexity) and either the affinity of these drugs for the PCP/sigma receptor or their reported ability to produce a PCP-like discriminative stimulus cue.

It might be reasonable to argue that one should not expect to see a correlation between striatal dopaminergic activity and a behavior which obviously requires the involvement of brain areas outside of the striatum. Thus, we cannot exclude the possibility that non-striatal dopaminergic mechanisms are involved in the production of interoceptive cues which rats perceive as PCP-like. Given that, we asked if the inhibition of striatal DA reuptake was correlated with the ability of these agents to cause rotational behavior, and, secondarily, whether turning behavior was possibly mediated by an action on the PCP/sigma receptor.

Although the nature of the turning data made it difficult to compare with the *in vitro* data, there does not appear to be a good correlation between turning and the inhibition of ^{3}H-DA uptake in the striatum. For example, etoxadrol and CYCL were at least as effective as PCP in inducing ipsilateral rotation but were much less potent than PCP as inhibitors of ^{3}H-DA uptake. Also, PCE was much more effective *in vivo* than would have been expected based on its ability to inhibit reuptake *in vitro*. Further, the concentrations of most of these drugs (ketamine, etoxadrol, NANM, and CYCL) required to produce significant inhibition ($\geq$10 μM) is probably greater than would be achieved after systemic administration.

Since these data along with our earlier observations [27] suggest that striatal dopaminergic mechanisms do not account for the effects observed or rotational behavior, other possible mechanisms need to be considered. Turning behavior, while largely dependent upon striatal dopaminergic mechanisms for producing postural asymmetries, has been reported to have a motor component associated with mesolimbic dopaminergic pathways, most notably those terminating in the nucleus accumbens [18,24]. A differential effect of the drugs tested in the present study on nonstriatal dopaminergic mechanisms may account for some of the quantitative and qualitative aspects of the turning behavior observed. There are also many potential non-dopaminergic mechanisms which could account for the weak ipsilateral turning observed in this study [23]. For example, several narcotic agonists and mixed agonist/antagonist drugs like buprenorphine and pentazocine cause ipsilateral turning. Also anticholinergics such as scopolamine and atropine induce turning toward the lesioned side. Although we have found that certain of these (including PCP and NANM) are probably not potent enough to block muscarinic cholinergic receptors directly after peripheral administration [13,15] we have recently discovered an indirect mechanism by which these agents can block striatal cholinergic transmission at much lower concentrations than required to block cholinergic receptors [26]. In that study we found that PCP, (−) CYCL, and NANM inhibited stimulated-ACh release from striatal slices with IC_{50} values of approximately 0.1, 0.3, and 1.0 μM, respectively. ACh release was stimulated in those experiments by N-methly-D-aspartate which is believed to act as an agonist at certain types of glutamate receptors [20,32]. Since the glutamatergic projection from the cortex is believed to provide the major excitatory input onto striatal cholinergic neurons [10,19], blockade of N-methyl-D-aspartate-induced ACh release suggests a feasible mechanism by which these drugs could cause ipsilateral turning behavior.

In conclusion, we believe that these data support the hypothesis that inhibition of DA reuptake is not necessarily associated with an action at the PCP/sigma receptor, and further, that this action does not underlie the complex behavioral effects of PCP (such as drug discrimination). In addition, we found that dopaminergic mechanisms are not even well correlated with the simpler rotational behavior caused by these drugs. We speculate that the effects of these drugs on turning may be better related to dopaminergic mechanisms in other brain areas associated with turning behavior or to non-dopaminergic striatal mechanisms.

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