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Phencyclidine: Behavioral and Biochemical Evidence Against the Anticholinergic Hypothesis

KENNETH M. JOHNSON

Department of Pharmacology and Toxicology
The University of Texas Medical Branch, Galveston, TX 77550

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JOHNSON, K. M. *Phencyclidine: Behavioral and biochemical evidence against the anticholinergic hypothesis.* PHARMAC. BIOCHEM. BEHAV. 17(1) 53–57, 1982.—Phencyclidine (PCP) is known to have anticholinergic effects in various *in vitro* test systems and to inhibit the binding of muscarinic antagonists to rat brain membranes. In order to verify the anticholinergic properties of PCP, its interaction with oxotremorine (OXO), a muscarinic agonist, was studied in mice. OXO (1 mg/kg) in combination with PCP (10 mg/kg) was lethal in 100% of the mice studied. The lethality of this combination was completely reversed by 3.3 mg/kg methyl atropine bromide (MA), a quarternary muscarinic antagonist. Therefore, PCP appears to act as a muscarinic agonist in some peripheral systems. The central interactions between PCP and OXO were studied in mice in which the preipheral effects of OXO were blocked by MA. In a test of motor performance, OXO potentiated the effect of PCP at one dose only. Contrary to the effects of PCP in other behavioral measures, no evidence for an anticholinergic effect of PCP was observed. The *in vivo* anticholinergic potential of PCP was estimated by adding a brain extract from PCP-treated mice to brain muscarinic receptors in the presence of ^{3}H-quinuclidinyl benzilate. These data suggested that PCP, after *in vivo* administration, does not attain a sufficient brain concentration to directly affect central muscarinic receptors. However, a direct action of PCP on peripheral muscarinic receptors was not discounted.

Phencyclidine   Phencyclidine metabolites   Muscarinic receptors   Phencyclidine lethality
Motor performance   Methyl atropine   Oxotremorine   Drug interactions

PHENCYCLIDINIE (1-(1-phenylcyclohexyl)piperidine, PCP) produces species-dependent alterations in behavior which range from psychomotor stimulant-like effects in rodents [6] to psychotomimetic effects in man [17]. The neurochemical mechanisms underlying this spectrum of activities are largely unknown at this time. However, pharmacological manipulation of PCP-induced turning behavior [15], locomotor activity [1], and stereotypic behavior [19] suggests that PCP may be an indirect dopaminergic agonist and/or cholinergic antagonist in the rodent. Because of the functional relationship between dopaminergic and cholinergic neurons in the basal ganglia it is very difficult to distinguish between these possibilities using these behaviors as the dependent variables [22].

At a biochemical level of analysis it has been shown that PCP inhibits dopamine (DA) uptake *in vitro* [11] and *in vivo* [24] and releases DA *in vitro* [9,25]. Also, PCP potentiates impulse-dependent release of DA *in vivo* [9,13]. The latter effect is common to the non-amphetamine stimulants, including amfonelic acid, methylphenidate, and cocaine. These data support the behavioral data which suggest that PCP is an indirect DA agonist. Evidence for the cholinergic properties of PCP are less consistent. PCP has been demonstrated to inhibit the actions of acetylcholine at nicotinic receptors in the frog rectus abdominus [20] and at muscarinic receptors in the guinea pig ileum [16]. PCP has also been shown to block the binding of a muscarinic antagonist to muscarinic binding sites in rat brain membranes [16]. It may also be important to note that at somewhat higher concentrations PCP inhibits peripheral and central acetylcholinesterase [16]. Although the *in vitro* effect of PCP on central muscarinic binding sites has been verified [26], preliminary studies have been reported that show an increase in the amount of a radiolabeled muscarinic ligand accumulated by the brains of PCP-treated rats after *in vivo* administration of both agents [4], suggesting that PCP can increase the affinity and/or the density of muscarinic receptors in the brain. In addition, PCP has been shown to mimic the effects of acetylcholine on cultured cardiac cells [10]. Behavioral studies have shown that mice rendered tolerant to PCP showed cross-tolerance with physostigmine and oxotremorine (OXO, a muscarinic agonist) on a test of motor coordination [21]. Finally, a study which used response rates of squirrel monkeys on variable-interval performance to evaluate PCP-atropine and PCP-physostigmine interactions concluded that atropine neither potentiated nor attenuated the effects of PCP, while physostigmine potentiated a low dose of PCP and partially blocked a higher dose of PCP [5].

These data led to the investigation of the effect of PCP on OXO-induced dopamine metabolism [14]. These experi-

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ments showed that certain combinations of PCP and OXO were lethal [14]. The study reported here further characterizes this effect and investigates the effects of OXO in combination with methyl atropine bromide (to counter the peripheral effects of OXO) on PCP-induced decrements of motor performance. I also measured the effects of PCP and two of its hydroxylated metabolites on the *in vitro* binding of a radiolabeled muscarinic ligand to its receptor and have used this assay to determine if PCP administration in behaviorally relevant doses attains a sufficient brain concentration to directly influence muscarinic receptors.

METHOD

Male ICR mice (Texas Inbred Mouse Co.) weighing 20–30 g were housed under a 12-hr light-dark cycle, six per cage, and had free access to food and water at all times prior to the experiment. All drugs (and saline vehicle) were administered subcutaneously in a volume of 1 ml/100 g body weight. After drug administration these mice were carefully observed for typical PCP-like behaviors as well as for signs of cholinergic stimulation such as salivation, lacrimation, defecation, Straub tail, and tremor. In Experiments in which lethality was measured I arbitrarily chose a 24 hr period of observation. In these experiments, however, all but two of the mice that died did so within 90 min after drug administration.

Forced, coordinated motor performance in mice was used as an index of PCP activity [2]. The apparatus used for testing this performance was essentially the same as that previously described [7] except that the squares of wire mesh were attached to individual ring stands with buret clamps. One mouse was placed on each screen, and the screen was rotated 180°. The mouse either fell off the screen, clung to the bottom, or climbed to the top. Twenty-four to 48 hr prior to the actual testing the mice were given a pretest trial. In the experiment reported here, only mice that were able to climb over the edge to the top of the screen within a 1.0-min period during the pretest were used. On the test day each mouse was administered either 0.9% NaCl or OXO 10 min prior to either 0.9% NaCl or PCP. Sixty min later each mouse was placed on the screen and the screen was inverted. The time each mouse stayed on the screen before falling off was recorded (1.0 min was recorded if the mouse climbed to the top before 1.0 min had elapsed).

The specific binding of ^{3}H-quinuclidinyl benzilate (^{3}H-QNB, 40 Ci/mmole, New England Nuclear) to rat cortical membranes was used to assess the interaction of PCP (and metabolites) with the muscarinic receptor. Binding was measured using minor modifications of a previously described method [28]. Male Sprague-Dawley rats (200–250 g, Holtzman Co.) were decapitated and their brains were removed and rinsed in ice-cold 0.9% NaCl. The appropriate areas were dissected and were immediately homogenized in 20 volumes of cold 50 mM sodium-potassium phosphate buffer (pH 7.4). The homogenate was then centrifuged at 1000 ×g and the crude nuclear pellet was discarded. The mitochondrial pellet was collected by centrifugation at 17,000 ×g and was resuspended in fresh buffer and frozen at −70°C. On the day of use it was thawed and 50 μl was added to 1.85 ml of 50 mM sodium-potassium buffer (the final protein concentration was about 100 μg/ml) Atropine sulfate (final concentration of 1 μM) or test drugs in varying concentrations or buffer was then added (50 μl) and preincubated at 22°C for 5 min prior to the addition (50 μl) of ^{3}H-QNB (0.2 nM). The incubation was continued for 60 min and the reaction was terminated by rapid vacuum filtration using Whatman GF/B glass fiber filters. The filters were air dried and radioactivity estimated by liquid scintillation spectrometry. Specific binding was defined at that displacable by 1 μM atropine sulfate. IC_{50} values for PCP and its metabolites were determined by plotting the percent inhibition obtained at at least five concentrations against the log of the concentration. The 50% inhibition point was determined by linear regression analysis.

This binding assay was modified slightly to allow an indirect estimation of the anticholinergic activity present in the brains of PCP and saline-treated mice, i.e., to determine if the concentration of PCP (and/or its metabolites) achieved after SC administration reached sufficient levels in the brain to inhibit ^{3}H-QNB binding to muscarinic receptors. In these experiments mice were administered either 0.9% NaCl, PCP (30 mg/kg), or atropine sulfate (7 mg/kg) as a positive control. The mice were decapitated at either 3, 10, or 30 min following drug administration. In order to minimize dilution of the brain PCP (or atropine) the brains were homogenized in only 2.5 volumes (about 1 ml) of 50 mM sodium-potassium buffer (pH 7.4). The homogenate was centrifuged at 20,000 ×g for 20 min and 0.9 ml of the supernatant (containing the extracted drug) was added to tubes containing 50 μl of a rat cortical membrane suspension (obtained as described above). ^{3}H-QNB (0.2 nM) was then added and incubated for 60 min at 22°C. Binding of ^{3}H-QNB to the rat cortical muscarinic receptors was estimated as described above. The buffer extracts from saline-treated mice showed significant inhibition of ^{3}H-QNB binding (as compared to buffer alone) which varied about 25% between experiments. Therefore, all data are reported as percent of values in control mice killed within each experiment.

In a preliminary experiment two mice were administered (SC) 4 mg/kg ^{3}H-PCP (New England Nuclear) and were decapitated 30 min later. The whole brain was homogenized in 50 mM sodium-phosphate buffer (pH 7.4) and centrifuged at 20,000 ×g. Radioactivity obtained in aliquots of the homogenate and the supernatant indicated an extraction efficiency of about 75%. Assuming that the brain contains about 75% water and taking the extraction efficiency and homogenization volume into account, the total "dilution factor" in these experiments is about 5.8. Therefore, a dose of 30 mg/kg (about fifteen times higher than that needed to significantly affect motor performance) was used in an attempt to overcome this factor.

The drugs used and their sources were as follows: PCP hydrochloride, 4-phenyl-4-piperidinocyclohexanol (4-OH cyclo PCP), and 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (4-OH pip PCP) were obtained from the National Institute on Drug Abuse; methyl atropine bromide, atropine sulfate, and oxotremorine were obtained from the Sigma Co. All drug doses are reported as either the free base or the salt form as listed above.

RESULTS

Initial experiments revealed that 0.5 mg/kg OXO produced tremor, salivation, Straub tail, lacrimation and decreased motor activity. Pretreatment (10 min) with 6 mg/kg PCP blocked none of these symptoms and markedly potentiated salivation and lacrimation. These mice were exopthalmic and had difficulty breathing. They were also immobile and showed complete loss of their righting reflex.

TABLE 1

EFFECT OF PCP AND OXOTREMORINE ALONE, AND IN COMBINATION, ON THE SURVIVAL OF MICE

Treatment	OXO (mg/kg)	PCP (mg/kg)	N	% Deaths
0.9% NaCl	—	—	10	0
Oxotremorine	0.3	—	10	0
Oxotremorine	1.0	—	10	0
Oxotremorine	3.0	—	6	0
Oxotremorine	5.5	—	8	38
Oxotremorine	10.0	—	7	100
Phencyclidine	—	10	10	0
Phencyclidine	—	30	10	0
Phencyclidine	—	50	6	17
Phencyclidine	—	65	6	50
Phencyclidine	—	80	6	83
OXO + PCP*	0.3	3	5	0
OXO + PCP*	0.3	10	5	0
OXO + PCP*	0.3	30	6	33
OXO + PCP*	1.0	3	5	20
OXO + PCP*	1.0	10	10	100
OXO + PCP*	1.0	30	10	100
NaCl + OXO + PCP†	1.0	30	10	100
MA + OXO + PCP	1.0	30	10	0
AS + OXO + PCP	1.0	30	10	0

*In groups which received both OXO and PCP, OXO was administered 10 min prior to PCP.

†Either methyl atropine bromide (MA) or atropine sulfate (AS) was administered 10 min prior to OXO at a dose of 3.3 mg/kg.

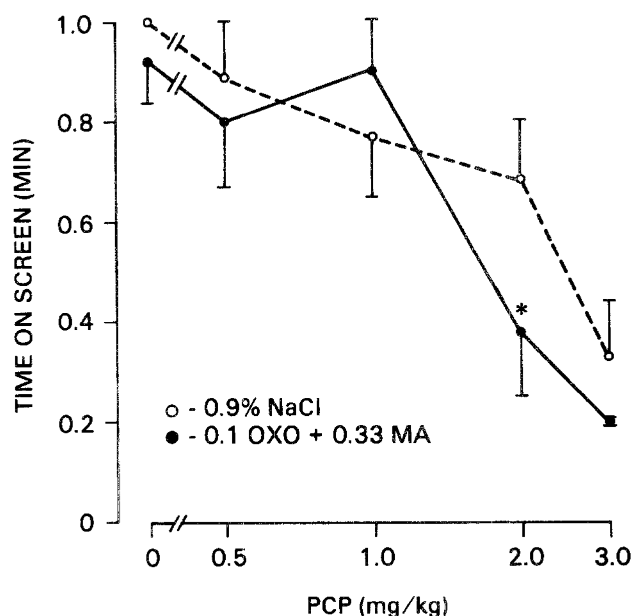

FIG. 1. The effect of saline or 0.1 mg/kg oxotremorine (OXO) and 0.33 mg/kg methyl atropine bromide (MA) 10 min prior to either saline or various doses of PCP on motor performance in mice. The mice were tested 60 min after PCP. There are eight mice per data point. *$p<0.05$ (Students' t-test).

However, treatment with either 1 mg/kg atropine sulfate or methyl atropine bromide (MA) 10 min after the PCP-OXO combination completely blocked the lacrimation, salivation, and exopthalmia.

This apparent potentiation of OXO by PCP (or vice versa) was quantified by administering PCP at doses of 0 (saline), 3, 10, and 30 mg/kg (5–10 mice/group) 10 min after either 0.3 or 1.0 mg/kg OXO and observing the mice for the subsequent 24 hr (Table 1). Two of six mice receiving 0.3 mg/kg OXO plus 30 mg/kg PCP died while ten of ten mice died that were administered either 10 or 30 mg/kg PCP in combination with 1.0 mg/kg OXO. Since the apparent LD_{50} for OXO is between 5.5 and 10 mg/kg (Table 1) and the LD_{50} for PCP is between 50 and 80 mg/kg (Table 1), the 100% lethality obtained with 1 mg/kg OXO plus 10 mg/kg PCP represents at least a five fold potentiation. Treatment with either 3.3 mg/kg atropine sulfate or MA (approximately equimolar with 1 mg/kg of OXO) 10 min prior to the administration of 1 mg/kg OXO plus 30 mg/kg PCP prevented death in ten of ten mice tested (Table 1).

It was noticed that the mice treated with MA prior to the OXO-PCP combination appeared to be less coordinated than mice treated with only an identical dose of PCP. In order to test the hypothesis that OXO potentiated the motor effects of PCP via a central mechanism, OXO was administered in combination (in the same syringe) with a 3.3 fold greater dose of MA (to block the peripheral effects of OXO) 10 min prior to either 0.9% NaCl or various doses of PCP. The effects of this pretreatment was compared with that of saline on the inverted screen test. Unfortunately, the OXO-MA combination was not without activity in this test. For example, mice administered OXO-MA at 0–0, 0.1–0.33, 0.2–0.66, 0.5–1.65, and 1.0–3.3 mg/kg remained on the inverted screen (1.0 min maximum) for periods of 1.0, 0.92±0.08, 0.47±0.16, 0.57±0.16, and 0.57±0.17 min, respectively, when tested 70 min after administration. Thus, only the lowest dose of OXO-MA tested (0.1–0.33 mg/kg) could be tested in combination with PCP without ambiguity.

The dose-response curves for both saline and OXO-MA pretreated groups are shown in Fig. 1. PCP clearly decreased performance in both groups of mice in a dose-responsive fashion. OXO-MA pretreatment significantly potentiated the decrease in performance of mice treated with 2 mg/kg PCP. Perhaps as important, is the observation that OXO-MA did not antagonize the effect of any dose of PCP studied.

In view of these results, and the apparent contradictory conclusion reached by several authors who observed anticholinergic effects of PCP *in vitro* [16, 20, 26], I wanted to determine the effect of *in vivo* PCP administration on ^{3}H-QNB binding. However, preliminary experiments in the rat showed that administration of 10 mg/kg PCP produced no detectable difference from controls in specific binding of ^{3}H-QNB to either hippocampal or cortical muscarinic receptor preparations. Since the membrane preparation procedure would wash out any unbound or loosely bound PCP, any detectable changes using this technique would have to be relatively permanent, i.e., the change would have to survive the homogenization procedure. In addition, inhibition of muscarinic receptor binding by soluble or loosely bound PCP would probably be undetectable using this method. Therefore, the approach described in the methods section was developed in order to be able to estimate whether or not PCP

TABLE 2

EFFECT OF 20,000 ×g MOUSE BRAIN SUPERNATANT ON ^{3}H-QNB BINDING IN RAT CORTICAL MEMBRANES

Treatment	dpm ^{3}H-QNB/mg protein (% control)* 3 min	10 min	30 min
Atropine Sulfate (7 mg/kg)	—	15.6 ± 2.3 (6)	18.8 ± 4.8 (4)
Phencyclidine (30 mg/kg)	92.1 ± 3.5 (6)	92.9 ± 3.9 (11)	105.5 ± 4.2 (8)

*Mice were treated with the indicated drug and decapitated at the indicated times. The data are presented as the % of the values (S.E.) obtained from mice similarly treated but decapitated immediately. (These values were not different from those obtained with a 30 min saline treatment.) One μM atropine sulfate added to an equal volume of buffer reduced the ^{3}H-QNB bound by greater than 98% in all experiments. The assays were carried out at 22°C in a volume of 1.0 ml containing approximately 100 μg protein and ^{3}H-QNB at approximately 0.2 nM.

achieved sufficient concentration in the brain to act in an anticholinergic fashion.

The results of these experiments are shown in Table 2. It can be seen that even after a very high dose of PCP, the brain extract from these mice did not contain sufficient PCP to inhibit the binding of ^{3}H-QNB to rat cortical muscarinic receptors. In comparison, a much lower dose of atropine sulfate resulted in a brain concentration sufficient to reduce ^{3}H-QNB binding by about 85%.

In *in vitro* experiments it was observed that the concentration of PCP required to inhibit ^{3}H-QNB binding to this membrane preparation by 50% was 6.7 μM (5.7–7.7 μM, 95% confidence intervals). In comparison, the IC_{50} values (and 95% confidence intervals) for atropine sulfate, 4-OH cyclo PCP, and 4-OH pip PCP were 0.65 nM (0.53–0.78 nM), 37 μM (29–46 μM), and 115 μM (89–148 μM), respectively.

DISCUSSION

The lethality experiments show a positive interaction between PCP and the muscarinic agonist OXO. The reversal of this effect by MA suggests a peripheral mediation of this phenomenon. From these experiments one cannot conclude either that PCP potentiates the lethality of OXO (3 mg/kg < LD_{50} < 10 mg/kg, Table 1) or that OXO potentiates the lethality of PCP (LD_{50}=63.5 mg/kg, 8 and Table 1). However, this point is relatively unimportant in comparison to the observation that PCP and OXO acted in an additive (or synergistic) manner rather than in an antagonistic fashion. A point of interest is the cause of death. The excessive salivation and breathing difficulty observed in these mice suggested that these mice died of asphyxiation. However, at this point this question remains unresolved.

The effects of PCP in combination with OXO-MA which were observed in the screen test (Fig. 1) suggest that the positive interaction observed in the lethality experiments may extend to include central mechanisms as well. However, the evidence for such a positive interaction in the CNS is not as clear as that in the periphery in that a significant difference between the saline and OXO-MA groups was observed only at 2 mg/kg PCP. Perhaps a less sensitive behavioral measure would allow better resolution of this putative postive central interaction.

On the other hand, the data obtained from the screen test argue strongly against an antagonistic relationship between PCP and OXO. Therefore, in this system, PCP apparently does not act as an anticholinergic as is commonly held for other systems such as those mediating turning behavior, stereotypic behavior, and locomotor activity. It should be reemphasized that these behaviors are not well suited for evaluating anticholinergic potential in the face of dopaminergic stimulation. On the other hand, it is impossible to refute evidence which suggests that PCP has anticholinergic properties in certain well-defined isolated organ systems [16,20]. In fact, our own studies have shown that PCP can block the OXO-induced increase in dopamine metabolism in the rat striatum [14]. This effect does not, however, require that PCP acts directly on muscarinic receptors to counter the OXO effect, e.g., propanolol also blocks the OXO-induced increase in rat brain dopamine metabolism [27].

The suggestion that, even after a large systemic dose, PCP does not reach sufficiently high levels in the brain to inhibit muscarinic receptors (Table 2) focuses attention on the question of PCP concentration in the brain after behaviorally relevant doses. Using ^{3}H-PCP this laboratory and others have suggested that peak levels of PCP (and metabolites) reach about 4 μM in the mouse brain after 7–8 mg/kg [12,16]. However, since both of the two hydroxy-PCP metabolites are much less potent than the parent, it is important to know the concentration of PCP itself. After administration of 3 mg/kg (IP) the peak concentration of PCP has been estimated to be about 1.5 μM in the mouse brain [18]. The estimated Ki value of PCP in binding to the muscarinic receptor site in mouse brain is 9.1 μM [16]. Assuming a muscarinic receptor density in the whole brain of 65 pmoles/g [28], competitive inhibition [16] and a K_D of 200 nM for acetylcholine binding to the muscarinic receptor [3], in order that 1.5 μM PCP produce greater than 20% inhibition, the concentration of acetylcholine would have to be less than 1 μM. The concentration of acetylcholine in various brain structures ranges from 15–60 μM [23]. Since PCP is evenly distributed throughout the major anatomical areas of the brain [12] and is not highly localized (63% is in the soluble microsomal supernatant and the rest is evenly distributed between the crude nuclear, myelin, and synaptosomal fractions) [12], it is unlikely that the behavioral effects of PCP in

the rodent are mediated by a direct inhibition of acetylcholine binding to muscarinic receptors.

Although our experiments suggest a central muscarinic agonist role for PCP, the same calculations force us to conclude that this effect is not mediated at the receptor level, but is probably an indirect effect mediated either through cholinergic regulatory systems, or through systems receiving cholinergic output. However, since PCP is found in many peripheral tissues in much higher concentrations than found in the brain [18], a direct cholinomimetic action of PCP at certain peripheral muscarinic receptors cannot be ruled out.

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