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Neuropharmacological Studies of Phencyclidine (PCP)-Induced Behavioral Stimulation in Mice

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Abstract. A variety of drugs were screened to determine which were capable of blocking the behavioral stimulation produced in mice by acute administration of phencyclidine (PCP). Chlorpromazine and clozapine blocked PCP-induced stimulation, while haloperidol, reserpine, and alpha-methyl-p-tyrosine did not. The GABA receptor agonists imidazole acetic acid and muscimol blocked PCP, but other drugs that influence GABA, such as dipropylacetic acid, baclofen, and diazepam, were ineffective. Yohimbine and methysergide also blocked PCP in high dosages, but other drugs with comparable alpha-noradrenergic and serotonergic blocking properties (phentolamine, cyproheptadine, and cinnanserin) were ineffective. Cholinergic and anticholinergic drugs, beta-noradrenergic and opiate antagonists, and nonspecific sedatives and convulsants were also ineffective. These findings suggest that chlorpromazine, clozapine, yohimbine, and methysergide may share a property that is unlike their primary known modes of action on dopaminergic, alpha-noradrenergic, and serotonergic neurotransmitter systems, and that this property accounts for their ability to block PCP. However, the effectiveness of GABA agonists appears to be mediated through direct activation of GABA receptors. It is suggested that chlorpromazine and imidazole acetic acid should be considered as possible drug treatments for PCP toxicity.

Key words: Phencyclidine – Mice – Behavioral activity – Aminobutyric acid – Neuroleptics – Serotonin antagonists – Imidazole acetic acid – Muscimol – Yohimbine – Methysergide

Phencyclidine (phenylcyclohexyl piperidine, or PCP), a drug originally employed as a veterinary anesthetic, is now widely abused for its mind-altering effects posing an increasing public health problem. Prolonged toxic reactions to PCP ingestion, leading in many cases to hospital admissions for schizophrenia-like psychoses (Allen and Young 1978; Liden et al. 1975; Luisada 1978; Rainey and Crowder 1975; Showalter and Thornton 1977), are not uncommon. These toxic psychoses may last for as long as several weeks, probably due to accumulation of the drug in adipose tissue and brain (Mishra et al. 1979).

The toxic psychosis produced by PCP has been noted to be similar to acute schizophrenia in a number of respects such as its variable course and varied clinical picture which may include catatonic, hebephrenic, and paranoid features (Allen and Young 1978). Because of these similarities, PCP psychosis has been proposed as a drug model for acute schizophrenia (Allen and Young 1978; Meltzer et al. 1979). While an understanding of the neuropharmacology of PCP has potential implications for schizophrenia research and treatment, the mechanisms underlying this drug-induced psychosis are poorly understood. Moreover, the preferred pharmacological treatment for PCP psychosis is controversial, various authors advocating treatment with benzodiazepines (Liden et al. 1975; Showalter and Thornton 1977; Yesavage and Freeman 1979), haloperidol (Showalter and Thornton 1977), chlorpromazine (Luisada 1978), and reserpine (Meltzer et al. 1979).

The present study is an attempt to examine further the effects of pharmacological intervention on the behavioral stimulation produced by PCP. Specifically a variety of drugs were evaluated to determine which are capable of blocking PCP-induced stimulation of locomotor activity in mice (Chen et al. 1959). This behavior was chosen because locomotor activity is altered by a wide variety of drug classes. There were two purposes for this endeavor: (1) to identify agents capable of blocking the stimulant effects of PCP in mice, in the

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hope that this would contribute to the identification of drugs that could be used to treat PCP toxicity in man; (2) to compare drugs used in the treatment of schizophrenia with drugs that block PCP reactions in mice, to determine whether PCP-induced stimulation and schizophrenia are pharmacologically similar.

Materials and Methods

Animals. A total of 800 adult female Swiss-Webster mice were housed in groups of 4–8 and allowed free access to food and water. Animals were housed on a 12-h light cycle. Each mouse was used only once.

Drugs and Injection. Phencyclidine HCl [1-(1-phenylcyclohexyl)piperidine HCl], obtained from Philips-Roxane, Inc., St. Joseph, Missouri, was dissolved in normal saline in concentrations such that a volume of 10 ml/kg was administered by IP injection.

Other drugs used were dissolved in saline, except in a few cases where it was necessary to employ distilled water or saline slightly acidified with HCl as a vehicle. Drug solutions were made just prior to use, and administered IP in a volume of 10 ml/kg. Dosages were calculated as the salts.

Apparatus. The behavioral activity of each animal was measured in cylindrical Polystyrene jars 16.3-cm inside diameter by 23 cm high, which were placed on one of eight similar Motron-Produkter Co. activity meter units, using the horizontal photocell banks only. The apparatus was illuminated from above by dim red lights (Kodak No. 1A safelight filters).

Procedure. The general procedure was as follows: (1) Each mouse was given either a vehicle solution (normal saline, saline acidified pH 3–4 with HCl, or distilled water) or a solution of the drug being tested other than PCP. (2) The activity of each mouse was measured for 30 min. (3) The activity meters were turned off for 5 min, during which each animal was given a second injection; this second injection consisted of either a PCP solution or saline. (4) The activity of the animals was again measured for 30 min. The 30-min observation period was chosen arbitrarily, as the animals were generally stimulated by PCP for several hours.

For the first experiment, a PCP dose-response determination, 56 mice received an initial injection of saline, followed after 30 min by either saline or PCP in a dosage of either 0.625, 1.25, 2.50, 5.0, 7.5, 10.0 or 15.0 mg/kg.

For the remainder of the experiments, the animals were given either one of the drugs being tested (other than PCP) or vehicle for the first injection. All animals that received a drug for the first injection were given 5 mg/kg of PCP for the second injection. Of the animals that received vehicle for the first injection, half received PCP and half received saline for the second injection.

Testing was conducted during the 3rd to 7th of the 12-h light period. No masking noise was used, and the experimenter was in an adjacent room during testing. The only exceptions to this procedure were that reserpine and alpha-methyl-p-tyrosine were administered 24 h prior to testing. For the activity test, animals were given saline for the first injection and 5.0 mg/kg PCP for the second injection. Vehicle for reserpine and alpha-methyl-p-tyrosine was one part Tween 80 to nine parts 2% carboxymethylcellulose. Additional animals were given this vehicle 24 h prior to testing.

All animals receiving a given drug (other than PCP) were tested at about the same time, but the vehicle injections were distributed throughout the course of the experiments. Within these limitations, the animals were chosen randomly to receive each particular drug regime. With few exceptions (see Tables 1 and 2), at least six animals were tested for each dose of each drug.

Data Analysis. The data were collected every 10 min for the first and second 30-min periods of the activity tests, and examined in terms of (1) total activity during the first 30-min period, a measure of the effects of the drugs in the absence of PCP, and (2) the ratio of the total activity during the second 30-min period to the total activity during the first 30-min period, which was considered to be a measure of the degree of stimulation produced by PCP (stimulation ratio).

Data were analyzed statistically be means of one-way analysis of variance followed by Scheffe multiple comparisons. The null hypothesis was rejected at the 0.05 level.

Results

PCP produced a pronounced stimulation of locomotor activity in dosages of 5–15 mg/kg (Fig. 1). This effect, measured in terms of stimulation ratios, was similar when measured in terms of total activity during the second 30 min. The smallest dosage of PCP that produced large, consistent increases in stimulation ratios was 5.0 mg/kg; this dosage was therefore chosen for further study.

The stimulation ratios (mean ± SEM) for animals that received a vehicle followed by saline were as follows: (1) 0.51 ± 0.03 for saline followed by saline, (2) 0.53 ± 0.05 for distilled water followed by saline, and (3) 0.58 ± 0.08 for acidified saline followed by saline. For animals that received a vehicle followed by 5.0 mg/kg PCP, stimulation ratios were (1) 1.82 ± 0.12 for saline followed by PCP, (2) 1.79 ± 0.23 for distilled water followed by PCP, and (3) 2.01 ± 0.25 for acidified saline followed by PCP. The differences among the various drug vehicles were not statistically significant, and these groups were therefore combined for further analysis. Stimulation ratios for additional animals treated with Tween 80-carboxymethycellulose vehicle (used for reserpine) 24 h prior were similar (2.22

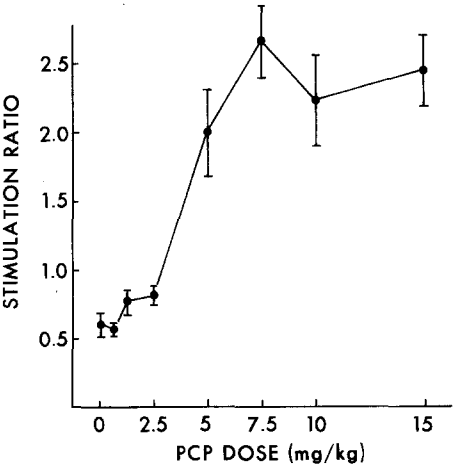

Fig. 1. Behavioral stimulation produced by PCP as a function of dose. Stimulation ratios (means ± SEM) are the ratios of behavioral activity after PCP administration to activity prior to the administration of PCP

Table 1. Drugs that blocked PCP-induced stimulation in mice

Drugs (source)	Dose (mg/kg)	*n*	Activity before PCP*	Stimulation ratios**
Vehicle	—	97	127 ± 4.2	1.85 ± 0.10
Chlorpromazine HCl	2.5	5	96 ± 17.5	1.34 ± 0.37
(Smith, Kline and French,	5	5	83 ± 16.1	0.23 ± 0.03[c]
Philadelphia, PA, USA)	10	6	19 ± 4.9[g]	0.30 ± 0.15[c]
	30	4	2 ± 1.4[g]	0.29 ± 0.24[c]
Clozapine	5	6	19 ± 7.0[g]	1.67 ± 0.28
(Sandoz, E. Hanover, NJ, USA)	10	6	16 ± 2.2[g]	0.72 ± 0.12[c]
Imidazoleacetic Acid	41	6	152 ± 11.9	1.49 ± 0.18
(Sigma, St. Louis, MO, USA)	82	10	61 ± 9.0[f]	0.55 ± 0.25[e]
	164	10	46 ± 9.9[g]	0.17 ± 0.14[f]
Methysergide maleate	5	6	178 ± 15.5[c]	1.69 ± 0.26
(Sandoz, E. Hanover, NJ, USA)	10	6	112 ± 26.1	2.34 ± 0.46
	20	6	60 ± 15.0[e]	0.94 ± 0.24[a]
	35	6	70 ± 7.5[d]	0.61 ± 0.15[c]
Muscimol	0.5	6	195 ± 28.1[c]	0.87 ± 0.45[b]
(Smith, Kline and French,	1.0	6	136 ± 21.6	0.72 ± 0.40[b]
Philadelphia, PA, USA)	1.5	6	120 ± 56.3	0.25 ± 0.17[e]
Yohimbine HCl	10	12	84 ± 11.9[c]	1.88 ± 0.35
(Sigma, St. Louis, MO, USA)	20	6	74 ± 5.3[e]	0.68 ± 0.15[d]
No PCP***	—	94	124 ± 4.7	0.53 ± 0.02

* Activity before PCP, after drug administration
** Stimulation ratios are the ratio of activity during the 30 min after PCP administration to the activity before PCP administration
*** Animals received vehicle followed (after 30 min) by saline
[a] $P < 0.10$; [b] $P < 0.05$; [c] $P < 0.02$; [d] $P < 0.01$; [e] $P < 0.005$; [f] $P < 0.001$ and [g] $P < 0.001$ as compared to vehicle

± 0.40). The ratios of the activity of all 97 PCP-treated animals to that of the 94 saline-treated animals for the first, second, and third 10 min of the 30-min testing period (2.90, 4.09, and 3.65, respectively) indicated that PCP was effective for the entire testing period.

Thus the overall mean (± SEM) stimulation ratio for animals that received a vehicle followed by saline was 0.53 ± 0.02, and for the animals that received vehicle followed by 5.0 mg/kg PCP, the mean stimulation ratio was 1.85 ± 0.09. A significant decrease in the stimulation ratio (as compared to the animals that received vehicle followed by PCP) was considered to be blocking of the PCP effect, while an increase in this ratio was considered to be potentiation of PCP.

Only a few drugs (chlorpromazine, clozapine, imidozole-4-acetic acid, muscimol, yohimbine, and methysergide) blocked the stimulant effects of PCP (Table 1). Benztropine (10 mg/kg) and quipazine (2.5 mg/kg) also slightly decreased the stimulation ratios (to 0.91 ± 0.12 and 1.01 ± 0.08; $t(100) = 2.13$, $P = 0.03$, and $t(101) = 2.08$, $P = 0.04$, respectively), but this was complicated by the fact that these drugs had stimulant effects of their own. Benztropine and quipazine did not, therefore, appear to 'block' the effect of PCP (Table 2).

The drugs found to be ineffective are listed in Table 2. It is noteworthy that several of these drugs have pharmacological effects in common with the effective drugs. Reserpine and alpha-methyltyrosine, which deplete presynaptic monoamine stores, as well as drugs such as chloral hydrate, propranolol, diazepam, picrotoxin, baclofen, and gamma-hydroxybutyric acid substantially enhanced the effects of PCP (Table 2).

Discussion

Pharmacological research on psychosis has generally focused on single neurotransmitter systems such as dopamine or serotonin. Our findings suggest that the psychotogenic effects of PCP, to the extent that they are related to behavioral stimulation in mice, are not mediated by a single neurotransmitter system. Chlorpromazine, clozapine, imidazole acetic acid, muscimol, methysergide, and yohimbine were the only drugs found to be capable of blocking PCP-induced stimulation. In general, other drugs with similar known actions on neurotransmitter systems were not effective; thus the effectiveness of chlorpromazine and clozapine does not seem to be related simply to decreases in

Table 2. Drugs that did not block PCP-induced stimulation

Drugs (source)	Dose (mg/kg)	*N*	Activity before PCP*	Stimulation ratios**
Vehicle	–	97	127 ± 4.2	1.85 ± 0.10
Arecoline (Sigma, St. Louis, MO, USA)	20	6	60.2 ± 10.1[f]	3.26 ± 0.71[e]
Baclofen	5	6	71.8 ± 18.4[c]	5.23 ± 2.40[e]
(Geigy, Summit, NJ, USA)	10	6	56.2 ± 14.3[e]	1.09 ± 0.44
	20	6	13.3 ± 1.99[g]	2.61 ± 2.50
Benztropine mesylate (Merck, Sharpe and Dohme, West Point, PA, USA)	10	5	291.2 ± 37.7[g]	0.91 ± 0.12[b]
Chloral hydrate	100	6	119.3 ± 19.2	2.68 ± 0.65
(Fisher, Pittsburgh, PA, USA)	200	6	26.0 ± 6.94[g]	19.27 ± 4.31[g]
Cinanserin HCl	8	6	117.2 ± 14.5	1.63 ± 0.31
(Squibb, Princeton, NJ, USA)	16	6	99.8 ± 9.1	1.74 ± 0.46
	48	6	34.0 ± 16.3[g]	4.54 ± 2.25[f]
Cyproheptadine	1.0	16	139 ± 14.8	1.54 ± 0.20
(Merck, Sharpe and Dohme,	1.8	14	114 ± 13.8	1.93 ± 0.30
West Point, PA, USA)	2.5	42	118 ± 11.8	2.00 ± 0.23
	3.5	4	176 ± 42.2[b]	1.70 ± 0.58
	5.0	11	65.5 ± 12.7[c]	3.85 ± 0.76[f]
	10.0	6	36.8 ± 6.6[f]	4.54 ± 1.01[g]
Diazepam	2.5	6	23.8 ± 5.61[g]	6.83 ± 2.14[a]
(Roche, Nutley, NJ, USA)	5	6	9.5 ± 4.00[g]	17.94 ± 10.75[g]
Diphenhydramine HCl	5	6	124.0 ± 33.8	2.56 ± 0.46
(Sigma, St. Louis, MO, USA)	15	4	90.0 ± 8.04	3.77 ± 0.43[f]
Diphenylhydantoin (Sigma, St. Louis, MO, USA)	20	6	101.3 ± 15.8	2.84 ± 0.33[c]
Dipropylacetic acid	100	5	159.6 ± 16.9	2.24 ± 0.43
(Abbott, North Chicago, IL, USA)	300	6	57.7 ± 8.55[e]	4.53 ± 1.00[g]
L-Glutamate diethyl ester HCl (Sigma, St. Louis, MO, USA)	480	6	47.0 ± 10.29[g]	3.16 ± 0.41[e]
Haloperidol	0.5	5	43.8 ± 10.40[f]	0.98 ± 0.39
(McNeil, Ft. Washington, PA, USA)	1.0	6	27.2 ± 6.30[g]	1.45 ± 0.39
	2.0	6	28.3 ± 10.70[g]	1.14 ± 0.45
L-Histidine HCl (Sigma, St. Louis, MO, USA)	1000	6	95.3 ± 17.4[a]	3.09 ± 0.40[e]
γ-Hydroxybutyric acid	200	6	35.7 ± 13.6[g]	5.78 ± 1.40[f]
(Sigma, St. Louis, MO, USA)	280	6	21.3 ± 5.09[g]	5.57 ± 2.82[f]
D,L-Isoproterenol sulfate	1	6	90.7 ± 15.0[a]	2.10 ± 0.23
(Sigma, St. Louis, MO, USA)	10	6	65.8 ± 12.6[e]	2.93 ± 0.70
	100	6	47.8 ± 11.4[f]	6.10 ± 3.29[f]
D,L-Alpha-methyl-para-tyrosine	125	6	134.0 ± 20.5	1.20 ± 0.15
(Sigma, St. Louis, MO, USA)	250	4	18.0 ± 9.98[g]	13.25 ± 4.35[g]
Naloxone HCl	1	6	143.5 ± 5.53	1.92 ± 0.39
(Endo, Garden City, NY, USA)	3	6	165.5 ± 15.0[a]	1.45 ± 0.19
	10	4	112.5 ± 20.2	3.93 ± 1.20[f]
	30	6	87.7 ± 18.5[a]	2.54 ± 0.46
Pentylenetetrazol (Sigma, St. Louis, MO, USA)	20	6	128.0 ± 21.3	1.32 ± 0.37
Phentolamine mesylate	5	6	132.3 ± 22.8	1.79 ± 0.15
(CIBA, Summit, NJ, USA)	10	6	100.7 ± 9.36	1.76 ± 0.30
	20	6	92.2 ± 15.4	1.94 ± 0.58
Picrotoxin	1	6	118.0 ± 6.89	1.32 ± 0.14
(Sigma, St. Louis, MO, USA)	2	6	47.8 ± 7.00[f]	5.17 ± 1.27[g]
Pilocarpine HCl	10	6	31.7 ± 2.38[g]	3.02 ± 0.51
(Sigma, St. Louis, MO, USA)	20	6	32.7 ± 7.88[g]	2.00 ± 1.27

Table 2. (Cont.)

Drugs (source)	Dose (mg/kg)	*N*	Activity before PCP*	Stimulation ratios**
Piperidine (Sigma, St. Louis, MO, USA)	60	6	31.2 ± 3.63[g]	6.75 ± 1.62[g]
D,L-Propranolol HCl (Sigma, St. Louis, MO, USA)	2.5	6	99.8 ± 9.38	2.07 ± 0.46
	10	6	152.2 ± 13.6	1.65 ± 0.15
	25	6	195.2 ± 23.3[e]	1.35 ± 0.11
	37.5	6	69.2 ± 12.1[c]	2.90 ± 0.74
	50	14	47.4 ± 8.22[f]	7.96 ± 2.46[f]
Quipazine (Miles, Elkhart, IN, USA)	2.5	6	184 ± 11.9[e]	1.01 ± 0.08[b]
Reserpine (Sigma, St. Louis, MO, USA)	5	6	18.8 ± 13.2[g]	1.92 ± 0.38
	15	6	4.83 ± 2.12[g]	22.64 ± 19.73[f]
Taurine (Sigma, St. Louis, MO, USA)	250	6	104.3 ± 21.3	2.41 ± 0.40
	450	6	129.3 ± 26.4	2.28 ± 0.34
Thiosemicarbazide (Sigma, St. Louis, MO, USA)	10	6	85.0 ± 11.8[b]	3.42 ± 0.91[e]
No PCP***	–	94	124 ± 4.7	0.53 ± 0.02

* Activity before PCP, after drug administration
** Stimulation ratios are the ratio of activity during the 30 min after PCP administration to the activity before PCP administration
*** Animals received vehicle followed after 30 min by saline
[a] $P < 0.10$; [b] $P < 0.05$; [c] $P < 0.02$; [d] $P < 0.01$; [e] $P < 0.005$; [f] $P < 0.001$ and [g] $P < 0.001$ as compared to vehicle

dopaminergic neurotransmission, because haloperidol, reserpine, and alpha-methyl-p-tyrosine were ineffective. However, because PCP-induced stimulation was not diminished following either alpha-methyl-p-tyrosine or reserpine, drugs which deplete intraneuronal catecholamines, this stimulation does not seem to be mediated by presynaptic monoaminergic elements. Yohimbine and methysergide were effective in high dosages, while other drugs with similar alpha-adrenergic and serotonergic blocking properties (phentolamine, cinanserin, and cyproheptadine) were ineffective. Cholinergic and anticholinergic drugs, beta-noradrenergic antagonists, an opiate antagonist, and nonspecific sedatives were also ineffective. It is also conceivable that unknown pharmacokinetic interactions contributed to some of the effects that were observed, although we have no evidence to support this possibility.

With respect to the gamma-aminobutyric acid (GABA) system, the findings appear somewhat more consistent. Both of the direct receptor agonists that were tested (imidazole acetic acid and muscimol; Enna and Snyder 1977; Haas et al. 1973; Naik et al. 1976) were effective. However, other drugs that indirectly promote GABA activity or interact with GABA (dipropylacetic acid, baclofen, diazepam; Simler et al. 1973; Naik et al. 1976; Costa and Greengard 1975; Mohler et al. 1978; Saito et al. 1975) were not effective. The contention that muscimol and imidazole acetic acid were acting through GABA receptors is supported by the differing chemical structures of the two compounds and their relative potencies, which was roughly consistent with their relative potency in displacing GABA binding (Enna and Snyder 1977).

The present findings could not have been predicted from the previously reported biochemical effects of PCP. PCP has potent cholinergic and anticholinergic effects (Maayani et al. 1974; Paster et al. 1974), displaces opiate, muscarinic, and nicotinic receptor binding (Kloog et al. 1979; Vincent et al. 1978), and inhibits catecholamine and serotonin uptake (Garey and Heath 1976; Smith et al. 1977), all in fairly low concentrations. Other biochemical effects of PCP have also been reported (Domino 1978; Johnson 1978). In the present study cholinergic, anticholinergic, opiate, catecholaminergic, and serotonergic drugs were not consistently effective. On the other hand, PCP has only minor effects on GABA metabolism (Leonard and Tongue 1970), yet GABA agonists were most consistently found to block PCP in the present study. Thus the known neurochemical effects of PCP do not, in themselves, appear capable of explaining the stimulatory effects of PCP.

There are also inconsistencies between the present findings and previous animal studies of pharmacological blockade of the behavioral effects of PCP; however,

these differences are generally consistent with procedural differences between studies. Dopaminergic antagonists such as pimozide and haloperidol (Finnegan et al. 1976; Martin et al. 1979; Murray and Honita 1979; Schlemmer et al. 1978), as well as alpha-methyl-p-tyrosine (Finnegan et al. 1976) have been reported to be effective. However, in each of these cases dopamine-specific tests such as rotational behavior and stereotypy have been employed. Similarly, when a serotonergic syndrome was studied (Martin et al. 1979), serotonergic antagonists were effective. Other studies have reported that physostigmine (Kanner 1975) and baclofen (Menon 1979) blocked PCP effects; however, the present study differs from these in that a ratio measure of stimulation was employed, thus providing a partial control for general sedation. Evaluation of our data in terms of total activity, without employing the ratio measure of stimulation, would also have led to the conclusion that pilocarpine, arecoline, haloperidol, reserpine (5 mg/kg), and baclofen (10 – 20 mg/kg) were effective (Table 2). Although the overall activity in these groups of animals was decreased, we concluded, because of the use of a ratio measure, that the stimulant effects of PCP were not diminished.

It is noteworthy that diazepam and haloperidol, the drugs most frequently recommended for use in treating PCP intoxication clinically (Liden et al. 1975; Showalter and Thornton 1977), were ineffective. The fact that diazepam is ineffective in animals has been previously reported (Menon 1979). This suggests that the clinical effects of these drugs may be related to either nonspecific sedation or effects of PCP not related to this animal model. Other clinicians report a strong preference for chlorpromazine in treating PCP toxicity (Luisada 1978; Luisada and Brown 1976), despite objections to its use related to possible interactive effects on blood pressure (Burns and Lerner 1976; Showalter and Thornton 1977; Yesavage and Freeman 1978). The present findings tend to support the use of chlorpromazine. Of the other drugs found to be effective in the present study, yohimbine and methysergide would not be clinically useful because of the high dosage required and their inherent toxicity. Muscimol has produced adverse behavioral effects in schizophrenics (Tamminga et al. 1978) and Huntington's disease patients (Shoulson et al. 1978) and would therefore probably not be useful in treating PCP intoxication. The possibility that imidazole acetic acid might be clinically useful merits further investigation. However, the applicability of the present findings to the treatment of humans depends on the validity of PCP-induced stimulation in mice as a model of PCP-induced psychosis in man. At most, locomotor stimulation in mice is likely to reflect only a part of the syndrome of PCP toxicity that is observed in humans.

There were significant differences between the drugs found to block PCP-induced stimulation and the drugs used clinically in schizophrenia. Clinically, haloperidol is about 50 times as potent as chlorpromazine on a mg/kg basis, while clozapine is between one and two times as potent (Wyatt 1976). We found haloperidol to be ineffective in dosages up to 2.0 mg/kg, while chlorpromazine completely blocked PCP-induced stimulation in dosages as small as 5.0 mg/kg, and clozapine at dosages of 10 mg/kg. On the basis of clinical potencies, relative to chlorpromazine, we would have expected haloperidol to be effective in dosages of 0.1 mg/kg and clozapine to be effective in dosages of, at the most, 5 mg/kg. Interestingly, propranolol in high dosages has been reported to be beneficial for schizophrenia (Yorkston et al. 1974), but potentiated PCP-induced stimulation, while muscimol, which has been reported to cause schizophrenia to become worse (Tamminga et al. 1978), was one of the few drugs that blocked PCP-induced stimulation.

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