Pharmacology Biochemistry & Behavior, Vol. 20, pp. 559–566, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Effects of Mecamylamine, Nicotine, Atropine and Physostigmine on the Phencyclidine-Induced Behavioral Toxicity

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Received 21 January 1983

CHATURVEDI, A. K. *Effects of mecamylamine, nicotine, atropine and physostigmine on the phencyclidine-induced behavioral toxicity.* PHARMACOL BIOCHEM BEHAV 20(4) 559–566, 1984.—Phencyclidine (PCP) has multifaceted actions on the cholinergic functions, including interaction with the central and peripheral cholinergic receptors. Therefore, to evaluate the possible involvement of the nicotinic and muscarinic acetylcholine (ACh) receptors during the behavioral toxicity of PCP, influence of various cholinergic modifiers on the PCP-induced behavioral effects in male Swiss mice was studied. PCP-induced (45 μmol/kg, IP) behavioral toxicity (circular movements, side-to-side head movements, and hyperactivity leading to convulsions) was blocked by pretreating the animals with secondary- or tertiaryamino-cholinergic modifiers, mecamylamine (ME; 14.9 and 29.9 μmol/kg), nicotine (NI; 12.3 and 30.8 μmol/kg) and physostigmine (PH; 0.16 and 0.31 μmol/kg). NI at 1.5 μmol/kg significantly potentiated the PCP-induced convulsions. Atropine (AT; 14.4 and 28.8 μmol/kg) pretreatments shortened the onset of circular movements. The locomotor activity of PCP (16.4 μmol/kg) was blocked by ME, NI, and PH. AT at 7.2 μmol/kg significantly potentiated the PCP-locomotion by 62%. These observations indicated that the behavioral actions of PCP, at least in part, are mediated by the central nicotinic and muscarinic ACh receptors. The involvement of cholinergic receptors in conjunction with the dopaminergic actions of PCP during these behaviors also has been discussed.

Phencyclidine Behavioral toxicity Locomotor activity Cholinergic modifiers Mecamylamine Nicotine Atropine Physostigmine

PHENCYCLIDINE (PCP), an abused drug [35, 43, 44, 49], has been shown to produce psychomotor stimulant-like effects in rodents [13] and psychotomimetic effects in man [33]. In human, PCP intoxication is frequently characterized by an acute confusional state with disorientation and by motor ataxia and rigidity similar to the toxic effects induced by atropine and other anticholinergics [26,47]. Anticholinergic behavioral effects attributed to a central mechanism [22] and potentiation of the motor activity by atropine [2] also have been reported in the PCP-treated rats.

PCP possess similar electron charge distribution as actylcholine (ACh) in relation to the muscarinic receptor [34], and exhibits both central and peripheral antimuscarinic activity [5]. The antimuscarinic activity is evaluted by the ability of the drug to inhibit the muscarinic agonist-induced contractions of the longitudinal muscle of guinea pig ileum [6, 22, 31], and the [^{3}H] 3-quinuclidinyl benzilate (QNB) binding to muscarinic ACh receptors in rat cereberal cortex and brain stem and in the ileal longitudinal muscle [6,22]. The displacement of [^{3}H] QNB from its muscarinic receptor binding sites by PCP in rat brain membranes also has been reported [53–55]. Moreover, PCP has been demonstrated to inhibit the actions of ACh at nicotinic receptors in the frog rectus abdominus [42] and block the nicotinic ACh receptor-ion channel complex and neuromuscular transmission in the frog sartorius muscle [4, 5, 50]. Recently, an evidence for the specific involvement of the central muscarinic and nicotinic receptors in the lethality of PCP in mice has been reported from my laboratory [12]. In the study physostigmine, a tertiaryamino-cholinesterase (ChE) inhibitor, and mecamylamine, a secondaryamino-nicotinic receptor blocker at ganglia, were determined to decrease the lethality of PCP. The quaternaryammonium muscarnic agonists and ganglionic blocker were unable to alter the lethality, probably accounting for their poor ability to cross the blood brain barrier to provide protection against the PCP-induced death.

Despite these *in vivo* and *in vitro* studies indicating that the cholinergic neuron might be a site of action by PCP, the mechanism of action of the drug in the central nervous system (CNS) is complex and the understanding of the mechanism is rather limited [36]. Therefore, in order to better understand the pharmacological pertinence of the central effects of PCP on the cholinergic function, the influence of the secondaryamino- or tertiaryamino-cholinergic modifiers, i.e., mecamylamine (ME), nicotine (NI), atropine (AT) and physostigmine (PH), on the PCP-induced behavioral toxicity in mice is investigated. It is anticipated that the results from the study might be helpful in elucidating the possible role of central cholinergic involvement in the behavioral and toxic effects of PCP.

TABLE 1

EFFECTS OF CHOLINERGIC MODIFIERS ON THE PHENCYCLIDINE (PCP)-INDUCED BEHAVIORAL TOXICITY IN MICE†

Pretreatment		Behavioral Responses: Circular Movements (Mean ± S.E.)		Side-to-Side Head Movements (Mean ± S.E.)		Convulsions (Mean ± S.E.)	
Modifiers	Dose (μmol/kg, IP)	Response Onset Time (min)	Animals Showing Response (%)	Response Onset Time (min)	Animals Showing Response (%)	Response Onset Time (min)	Animals Showing Response (%)
Saline (control)	—	4.3 ± 0.2	97 ± 1	5.5 ± 0.2	89 ± 5	7.4 ± 0.4	65 ± 5
Mecamylamine (ME)	7.5	3.8 ± 0.3	98 ± 2	5.2 ± 0.4	85 ± 2	9.0 ± 1.5	60 ± 2
	14.9	5.4 ± 0.5*	97 ± 1	6.9 ± 0.5*	96 ± 4	10.0 ± 1.0*	15 ± 4*
	29.9	6.8 ± 0.5*	87 ± 7	9.1 ± 0.7*	77 ± 14	—	Nil
Nicotine (NI)	1.5	4.3 ± 0.3	94 ± 6	5.0 ± 0.3	98 ± 2	6.1 ± 0.5	85 ± 5*
	3.1	4.5 ± 0.4	97 ± 1	5.1 ± 0.2	90 ± 8	9.2 ± 1.2	70 ± 5
	12.3	6.3 ± 1.1*	60 ± 4*	9.7 ± 1.2*	80 ± 7	9.1 ± 1.8	35 ± 4*
	30.8	15.0 ± 2.0*	40 ± 10*	19.8 ± 2.0*	40 ± 10*	—	Nil
Atropine (AT)	7.2	4.6 ± 1.0	80 ± 12	5.3 ± 0.6	80 ± 10	6.5 ± 0.9	60 ± 6
	14.4	2.7 ± 0.3*	90 ± 6	3.2 ± 0.4	94 ± 2	7.6 ± 1.4	60 ± 8
	28.8	3.0 ± 0.1*	97 ± 2	6.7 ± 0.4	97 ± 2	7.4 ± 0.7	50 ± 5
Physostigmine (PH)	0.08	4.2 ± 0.3	97 ± 3	5.7 ± 0.3	97 ± 3	9.7 ± 0.9	55 ± 4
	0.16	4.0 ± 0.2	97 ± 3	5.4 ± 0.1	97 ± 3	12.1 ± 1.0*	26 ± 12*
	0.31	6.9 ± 0.7*	90 ± 4	9.8 ± 0.8*	95 ± 4	—	Nil

†Behavioral toxicity was produced by PCP at 45 μmol/kg, IP. The cholinergic modifiers were administered IP 15 min prior to the PCP administration. Circular movements, side-to-side head movements and convulsions occurring at this dose of PCP can easily be differentiated, and the onset time of these effects with respect to the PCP injection time can easily be recorded. At the selected doses, these modifiers did not produce any noticeable behavioral effects. Each value represents the mean ± S.E. of observations from a minimum of eight animals. Only animals showing the response are included in the mean onset data. A significant difference between a value and the corresponding control is designated by an asterisk. The control group animals were pretreated with saline (10 ml/kg, IP).

METHOD

Materials

Phencyclidine (PCP) hydrochloride was supplied by the National Institute on Drug abuse, Rockville, MD. Mecamylamine (ME) hydrochloride was kindly provided as a generous gift by Merck Sharp and Dohme Research Laboratories (West Point, PA). Nicotine (NI), atropine (AT) sulfate and physostigmine (PH) sulfate were purchased from Eastman Kodak Co. (Rochester, NY), Mallinckrodt Chemical Works (St. Louis, MO), and Sigma Chemical Co. (St. Louis, MO), respectively. Other chemicals used were of analytical grade and were purchased from commercial sources. All solutions were made in physiological saline (0.9% NaCl in deionized water). The solutions of the test agents were freshly prepared before use.

Animals

Male Swiss mice weighing 20–25 g used in this study were purchased from Laboratory Supply Co. (Indianapolis, IN). The animals were housed in cages of 11.5×7.5×5″ dimensions in groups of 5 in the centralized animal care facility, and allowed food and tap water ad lib. Two hr before the behavioral experiments, the mice were housed in the testing room in groups of 5 per cage under the controlled conditions and given free access to food and water.

Determination of the Effects of Cholinergic Modifiers on the Behavioral Toxicity of PCP

A dose of PCP for mice was determined and selected at which the behavioral toxic effects such as circular movements, side-to-side head movements and convulsions can be induced, and the onset of these effects can be easily differentiated and recorded. Mice, consisting of 10 in each group, were pretreated IP with the selective cholinergic modifiers at suitable doses (Table 1). Control group animals were pretreated with saline (10 ml/kg, IP). The doses for each modifier were selected from the information available in the literature [3, 7, 10, 11, 25, 32, 41]. At the selected doses, these agents did not produce behavioral effects similar to those observed with PCP alone. Fifteen min after the pretreatment, the animals were challenged by IP administration of the dose of PCP (45 μmol/kg). For observation, animals were housed in groups of 5 and were used only once. Every mouse in an observation group was challenged with the same dose of the same drug or combination of drugs. The drugs were administered to the group of animals at such different time intervals so that individual responses in each animal could be easily tracked. The observer was "blind" with respect to the treatment. Following the PCP administration, the mice were then observed for the occurrence of circular movements, side-to-side head movements, and hyperexcitability leading to intermittent jerks, episodes of tremulousness, and con-

TABLE 2

EFFECTS OF CHOLINERGIC MODIFIERS ON THE PHENCYCLIDINE (PCP)-INDUCED LOCOMOTOR ACTIVITY IN MICE

Pretreatment		Locomotor Activity† (counts/mouse/60 min) Saline		PCP (16.4 μmol/kg, IP)	
Modifiers	Dose (μmol/kg, IP)	Absolute Counts (Mean ± S.E.) (N)	Control (%)	Absolute Counts (Mean ± S.E.) (N)	Control (%)
Saline (control)	—	1490 ± 136 (26)	100	4182 ± 224 (24)	100
Mecamylamine (ME)	7.5	1106 ± 168 (6)	74	2295 ± 340* (9)	55
	14.9	1420 ± 451 (6)	95	2130 ± 408* (9)	51
	29.9	875 ± 114* (6)	59	1266 ± 219* (9)	30
Nicotine (NI)	1.5	1450 ± 199 (11)	97	3650 ± 278 (14)	87
	3.1	1534 ± 98 (12)	103	2774 ± 369* (15)	66
	12.3	1074 ± 149* (11)	72	2563 ± 316* (13)	61
	30.8	576 ± 103* (12)	39	1607 ± 370* (15)	38
Atropine (AT)	7.2	1935 ± 519 (6)	130	6782 ± 698* (6)	162
	14.4	2905 ± 564* (6)	195	4489 ± 670 (6)	107
	28.8	3703 ± 852* (6)	249	4328 ± 236 (6)	103
Physostigmine (PH)	0.08	2460 ± 339* (6)	165	3616 ± 808 (6)	86
	0.16	1143 ± 138 (6)	77	3064 ± 450* (6)	73
	0.31	995 ± 168* (6)	67	1549 ± 157* (6)	37

†The cholinergic modifiers were administered IP 15 min prior to the PCP administration. The locomotor activity in the groups treated only with saline (10 ml/kg, IP) or cholinergic modifiers was measured for 60 min after their administration, while with PCP group it was measured after the injection of PCP. Each value represents the mean ± S.E. of counts/mouse/60 min from a minimum of six animals. With certain groups, more than six animals were used for better statistical comparisons. Control experiments were run everyday. No significant change in the locomotor activity was observed between day-to-day control values. The numbers in parentheses (N) indicate the number of animals used for the particular observation. A significant difference between a value and the corresponding control is designated by an asterisk.

vulsions over a period of 30 min. The observed hyperexcitability appeared to be attributed to the PCP-induced increase in the locomotor activity. The time of the onset of these effects, persisting at least for 10–15 sec from the time of PCP injection, was noted for each mouse and the average was computed for each group. An episode of a spasm persisting for at least 5 sec was considered a threshold seizure. Transient intermittent jerks or episodes of tremulousness were not counted as seizure activity. Animals devoid of circular movements, side-to-side movements, and seizures during the 30 min observation period were considered to be protected from the PCP-induced behavioral effects. The number of animals exhibiting the effects in each group was recorded and presented as a percent activity.

Mice challenged with the 16.4, 45 and 89.3 μmol/kg IP doses of PCP exhibited a spectrum of behavioral effects (circular movements, side-to-side head movements, sniffing and excitement leading to convulsions). The lower dose only produced circular movements in 65% of the animals with 4.6 min onset time (data not shown). In addition to the circular movements, the 45 μmol/kg dose produced side-to-side head movements, sniffing and convulsions. The occurrence of the whole spectrum of the behavioral effects took an average of 7.4 min. The percentage and the onset time of these behavioral responses are summarized in Table 1. The dose, 89.3 μmol/kg in comparison to 45 μmol/kg, hastened the onset of the behavioral effects. It was determined that the behavioral effects produced by the dose, 45 μmol/kg of PCP, were comparatively easy to observe, distinguish and record. Furthermore, this dose of PCP produced submaximal convulsions in mice. Therefore, the dose, 45 μmol/kg of PCP, was selected for inducing the behavioral effects.

Measurement of the Locomotor Activity

Twelve animal activity cages, 31 cm in diameter with black walls, 21 cm high and grid floors, were used for the determination of the locomotor activity in mice. The interior of the cages was crossed by six photocell beams, interruption of which was additively recorded by electromechanical counters (Woodard Research Corp., Herndon, VA). The cages were covered with black cardboard sheets. Different groups of animals, each comprised of at least six mice, were intraperitoneally pretreated 15 min prior to the injection of PCP (16.4 μmol/kg, IP) with saline (10 ml/kg) or with various agents, namely ME, NI, AT, or PH. The doses of these modifiers are mentioned in the previous section and in Tables 1 and 2. The saline and the modifier controls also were run for the determination of the basal locomotor activity in these groups. Only one mouse in each activity cage was used. After the injection animals were kept in the cage and the activity meters were started immediately. Data were printed every 5 min, so that 60 min sessions were divided into 12

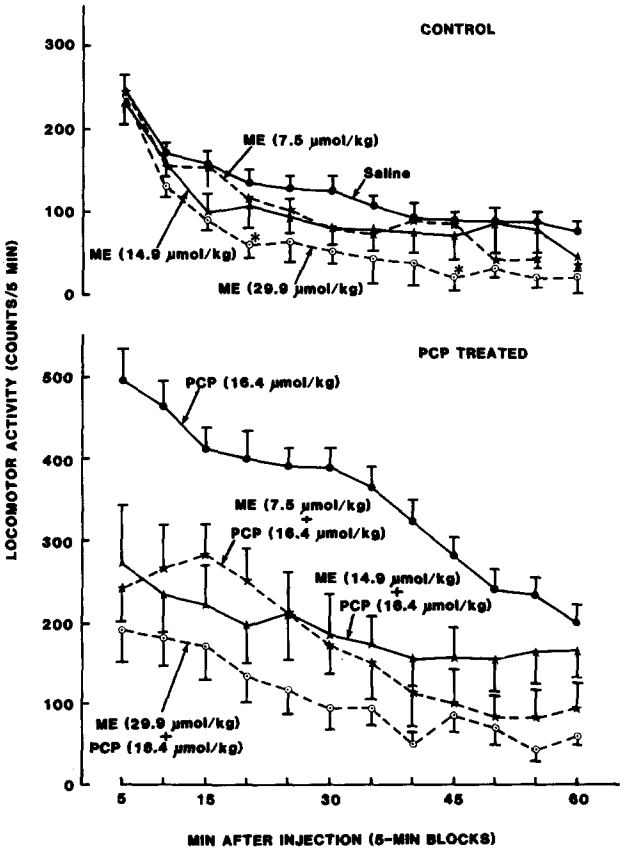

FIG. 1. Locomotor activity in mice after PCP and the influence of mecamylamine (ME). Each point depicts the mean±S.E. For detailed information about the number of animals used in each observation (N) see Table 2. *Top panel* (control), N=6–26. Asterisk denotes significant difference from the saline control. *Bottom panel* (PCP treated), N=9–24. There was statistically significant difference between the points of PCP vs. PCP and ME group, except the last three points of ME (14.9 μmol/kg) and PCP (16.4 μmol/kg) group where no such significant difference was noted.

5-min intervals. At the end of the session, total counts per mouse during the 60 min period also were noted.

Doses of 8.2, 16.4 and 32.8 μmol/kg of PCP were determined to be effective in producing locomotion in mice. The dose, 16.4 μmol/kg of PCP, produced a submaximal locomotion in mice and the maximum effects were over by about 60 min. At this PCP dose, a locomotor activity of 4182±224 counts/mouse/60 min was observed, which was 281% of the basal locomotion activity associated with the saline control group (Fig. 1; Table 2). There was a significant difference in the activity of the PCP treated group from the saline control at every 5-min interval point over the 60 min period. Both in the PCP treated and the control groups, the counts were initially higher and then gradually decreased during the observation.

Statistical Methods

Wherever possible, values are presented as the mean±S.E. of determinations. The statistical difference between means was determined by Student's *t*-test [23]. The difference between two means was considered significant with $p<0.05$.

RESULTS

Influence of Cholinergic Modifiers on the PCP-Induced Behavioral Toxicity

The behavioral responses of PCP were inhibited by the ganglionic blocker, ME, in a dose dependent fashion (Table 1). At 7.5 μmol/kg, ME did not alter the behavioral activities of PCP. However, at 14.9 μmol/kg it delayed the onset of the behavioral effects. At this dose of ME only 15% of the animals exhibited the convulsions whereas in the control group 65% of the animals responded. Similarly, the onset of circular movements and side-to-side head movements was further delayed in the animals pretreated with the higher dose (29.9 μmol/kg) of ME. At this dose, animals were completely protected against the convulsions produced by PCP. NI also influenced the PCP-induced effects. Small doses (1.5 and 3.1 μmol/kg) of NI did not significantly change the pattern of the behavioral effects. However, a significant increase in the convulsant activity of PCP was noted at 1.5 μmol/kg of NI dose (Table 1). On the other hand, NI at larger doses (12.3 and 30.8 μmol/kg) significantly delayed the onset of these effects, and protected the animals against the PCP-induced behavioral effects.

No change in the behavioral activities of PCP was observed in the animals pretreated with antimuscarinic agent, AT, at 7.2, 14.4 or 28.8 μmol/kg. Only the onset times for the circular movements in the groups pretreated with the last two doses of AT were significantly shortened by about 1.5 min.

Anti-ChE PH also exhibited influence on the PCP-induced behavioral effects. PH (0.08, 0.16, or 0.31 μmol/kg) protected the animals against the convulsions in a dose dependent manner (Table 1). The onset of convulsions was delayed by the PH pretreatment. PH at lower doses did not alter either the onset or the activities of circular movements and side-to-side head movements. However, delay in the onset of these two effects was noticed with the higher dose of PH (0.31 μmol/kg).

Influence of Cholinergic Modifiers on the PCP-Induced Locomotor Activity

Pretreatment with the ganglionic blocker, ME, (7.5, 14.9 or 29.9 μmol/kg) inhibited significantly the locomotor activity induced by 16.4 μmol/kg of PCP as assessed by the counts per mouse over a period of 60 min (Fig. 1, bottom; Table 2). The influence was dose related as 45, 49 and 70% inhibitions were noted with 7.5, 14.9 and 29.9 μmol/kg of ME, respectively (Table 2). At 7.5 and 14.9 μmol/kg doses, ME alone had no significant effects on the basal locomotor activity (Fig. 1, top). However, at the higher ME dose (29.9 μmol/kg), a 41% decrease in the basal locomotion over the 60 min period was distinguished (Table 2). The decline of activities of the saline control and ME, as well as PCP, and ME and PCP, were identical.

The inhibition of the PCP-induced locomotion by NI also was dose related. As seen in Fig. 2 (bottom), 12.3 and 30.8 μmol/kg of NI significantly inhibited the PCP-induced locomotion during the first 40 min period. Later during the rest of the 60 min observation period, the activities reached close to normal. In contrast, the lower doses, 1.5 and 3.1 μmol/kg, of NI failed to inhibit the locomotion induced by

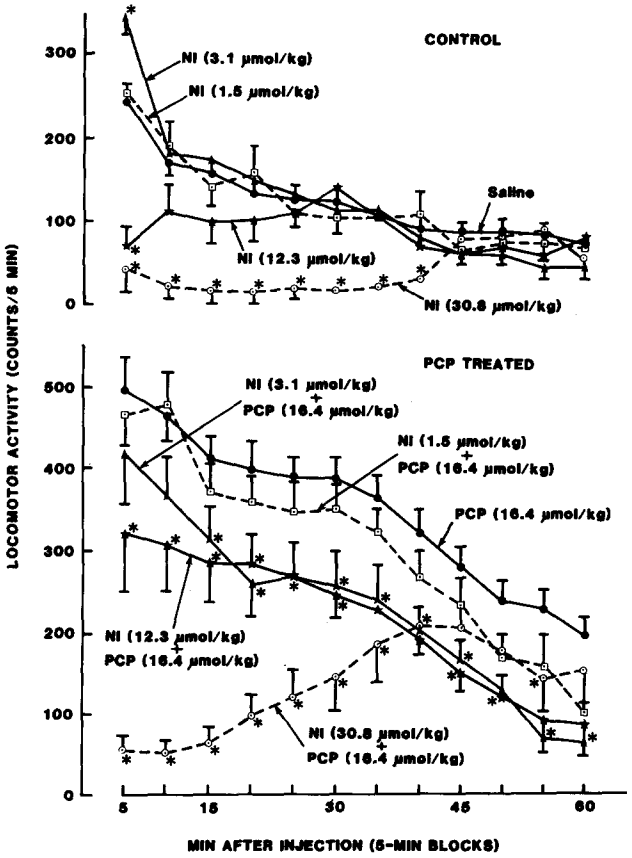

FIG. 2. Locomotor activity in mice after PCP and the influence of nicotine (NI). Each point depicts the mean±S.E. Refer to Table 2 for additional information about the number of animals (N) used for the observations. *Top panel* (control), N=11–26. A significant difference between the saline control vs. NI treated groups is indicated by an asterisk. *Bottom panel* (PCP treated), N=13–24. Asterisk denotes significant difference between PCP, and NI and PCP.

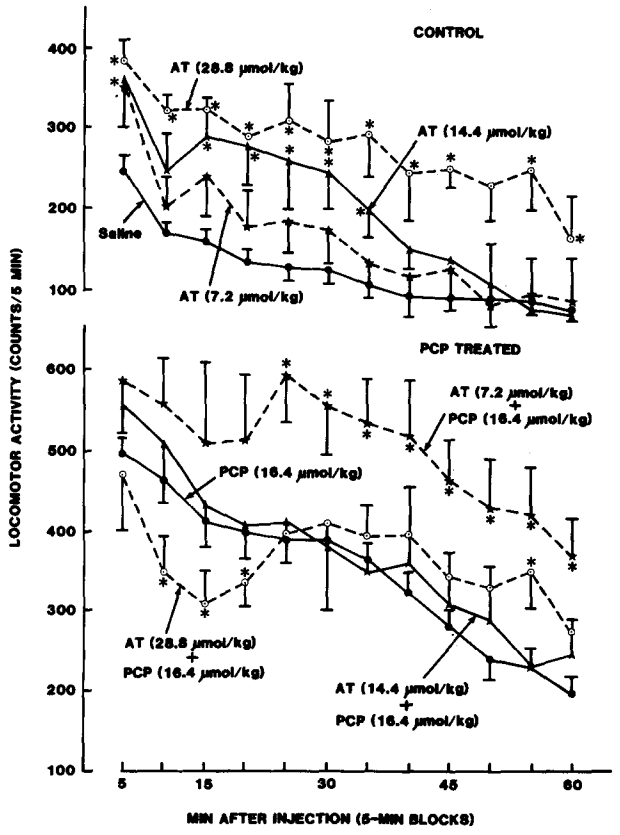

FIG. 3. Influence of atropine (AT) on the PCP-induced locomotion in mice. Points represent mean±S.E. Also refer to Table 2 for the details of the number of animals (N) used in the experiment. *Top panel* (control), N=6–26. *Bottom panel* (PCP treated), N=6–24. Asterisk denotes significant difference from the saline in the top panel, and from the PCP in the bottom panel.

PCP. Inhibitions of 13, 34, 39 and 62% in the total 60 min PCP-induced locomotor activity were observed at 1.5, 3.1, 12.3 and 30.8 μmol/kg doses of NI, respectively (Table 2). NI alone (1.5 and 3.1 μmol/kg) did not affect the locomotion when compared with the control group depicted in Fig. 2, top panel. However, at 12.3 or 30.8 μmol/kg NI dose, a significant decrease in the basal locomotor activity was observed (Table 2).

The patterns of the locomotor activity in saline control and AT groups, as well as in PCP, and AT and PCP groups, are illustrated in Fig. 3. The top panel of the figure depicts the effects of AT on the basal locomotor activity at various doses. AT at 7.2 μmol/kg did not significantly alter the basal activity when compared with the control group. However, at 14.4 and 28.8 μmol/kg, AT increased the total 60 min basal activity by 95 and 149%, respectively (Table 2). The decline in the activity of saline control and AT groups was parallel. The PCP-stimulated locomotion was altered by pretreating the animals with 7.2, 14.4 or 28.8 μmol/kg of AT (Fig. 3, bottom). As given in Table 2, the dose, 7.2 μmol/kg of AT, which alone does not alter the basal locomotor activity, significantly increased with PCP-induced locomotion from 4182±224 to 6782±698 counts/mouse/60 min. On the other hand, the AT dose (28.8 μmol/kg) which increased the basal activity by 149%, decreased the locomotion induced by PCP between the first 10 and 20 min periods, but later the activity reached normal. The 14.4 μmol/kg dose of AT, which increased the basal activity by 95%, did not significantly alter the pattern of the PCP-induced locomotion. The observed decrease in the locomotor activity of PCP by pretreating the animals with the higher dose of AT may actually reflect potentiation of the effect. Similar decrease in the activity also might be obtained by increasing doses of AT or PCP alone.

Pretreatment with the anti-ChE PH (0.08, 0.16, and 0.31 μmol/kg) decreased the PCP-induced locomotion in a dose related manner. As illustrated in Fig. 4, the three doses of PH inhibited significantly the locomotor activity during the first 20, 25 and 40 min periods, respectively. Later during the rest of the 60 min observation period, the locomotion reached close to normal. PH, at 0.16 and 0.31 μmol/kg, alone had no significant effect on the total 60 min basal locomotor activity, while at 0.08 μmol/kg PH increased the basal activity by 65% (Fig. 4, top; Table 2).

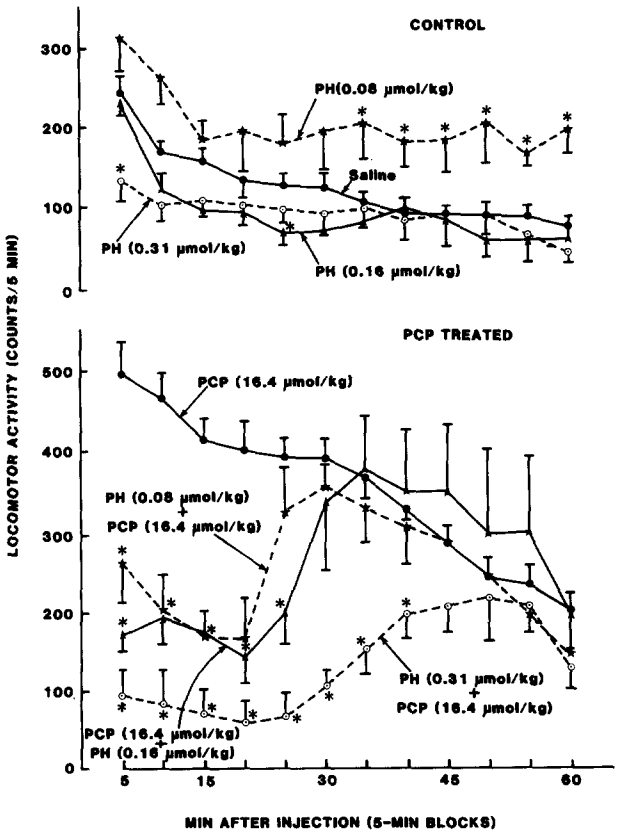

FIG. 4. Effect of physostigmine (PH) on the PCP-stimulated locomotion in mice. Each value is a mean from 6–26 mice. For details about the number of animals (N) used in the experiment refer to Table 2. Vertical bars represent S.E. A significant difference from the saline in the top panel, and from the PCP in the bottom panel is denoted by an asterisk.

DISCUSSION

The study revealed that the central nicotinic and muscarinic ACh receptors play a part during the exertion of PCP-induced behavioral toxicity in mice. This is supported by the ability of secondary and tertiaryamino-cholinergic modifiers, ME, NI, AT and PH, to modulate the behavioral effects (Tables 1 and 2). Quaternaryammonium and sulfonium compounds, i.e., muscarinic agents, 5-methylfurmethide [41] and 0-ethylcholine [10–12], and nicotinic ACh receptor blockers at ganglia, hexamethonium and trimethaphan, were not as effective in significantly altering the PCP-induced circular movements, side-to-side head movements and convulsions (data not given). These observations could account for the higher potential of secondary- or tertiaryamino-compounds than that of quaternaryammonium or sulfonium agents to cross the blood brain barrier thus influencing the behavioral toxicity. The involvement of the central cholinergic receptors is in agreement with the results reported previously from my laboratory in which ME and PH were effective in protecting mice against the PCP-induced death, while quaternaryammonium cholinergic modifiers were unable to alter the death [12]. The central cholinergic mechanism of PCP is further supported by other investigations. PCP has been found to impair spatial alteration performance in rats through a central anticholinergic mechanism [22], and PCP-induced motor activity in rats has been found to be potentiated by atropine, but not by methylatropine [2]. Furthermore, the hyperactivity evoked by PCP in mice was reversed by a lypophillic anti-acetylcholinesterase (AChE), tacrine [34].

PCP exhibits both dopaminergic and anticholinergic properties [28,29]. It facilitates the release of dopamine (DA) [29], antagonizes the increased metabolism of rat striatal DA induced by oxotremorine [27] and inhibits the uptake of [^{3}H]-DA [18,51]. Furthermore, PCP-induced stereotypic behavior [40], circular movements [16, 17, 30] and locomotor activity [2] in rats can be modulated by cholinergic and dopaminergic modifiers. These studies support the view that the anticholinergic property of PCP in conjunction with its dopaminergic activity play a crucial part in the behavioral and toxic effects of PCP. However, due to the functional relationship between cholinergic and dopaminergic neurons it is rather hard to differentiate the influence of these neurons in these behaviors [46]. For example, it would be difficult to evaluate anticholinergic activity of PCP in the presence of its ability to increase the release of DA, since dopaminergic agonists reduce striatal ACh turnover and inhibit the cholinergic interneurons' firing [46]. In spite of such complex mechanism(s), it can be rationally inferred that the enhancement in the cholinergic and/or the decrement in the dopaminergic activity should decrease the behavioral effects of PCP, while the effects should be induced by inhibiting the cholinergic and/or increasing the dopaminergic activity.

Even though the involvement of other neurotransmitter systems is associated with the effects of PCP [37,44], the present data, at least in part, can be interpreted on the conception of the mediation of the dopaminergic and cholinergic systems in the PCP-induced behaviors. The ability of ME to reduce the behavioral effects of PCP might be attributed to its capability to block the release of DA mediated through the central presynaptic nicotinic receptors [15, 19–21, 24, 38, 39, 56, 57] thus overpowering the PCP-induced increase in DA levels [18, 27, 29, 51]. NI in the concentration range of 10^{-3}M to 10^{-6}M has been determined to be effective in releasing DA from rat striatal slices [21,56]. Therefore, it is more likely that the potentiation of PCP-induced convulsions at a lower dose of NI could be related to such NI-induced release of DA. Since the pharmacology of the central nicotinic receptors is somewhat similar to the ganglion [1, 8, 14, 38, 58], the potentiation of the PCP-induced convulsions at a lower dose of NI and the blockade of the PCP-evoked behavioral effects by NI at higher doses may presumably be analogous to the biphasic action of NI at autonomic ganglia where NI at smaller concentrations produces ganglionic stimulation while at larger concentrations ganglionic depression. However, it appears that such blockade is attributed to the property of NI other than DA releasing [21,56]. This could be the result of the interaction of NI with the inhibitory nicotinic ACh, non-cholinergic nicotinic and mixed nicotinic muscarinic receptors of the CNS [15, 39, 48] in a complex fashion leading to the biphasic effects. Overall, it may simply be the result of the stimulation of the CNS at a lower dose of NI and the depression of the CNS at larger doses in a biphasic dose dependent manner. The observed effects of ME and NI also could be associated with the action of PCP at the nicotinic ACh receptor-ion channel complex level [4, 5, 50].

Because of the anticholinergic property associated with

PCP [2, 5, 22, 31, 53–55], ACh or muscarinic agents should decrease and atropine-like agents should enhance the effects of PCP. In the study, a similar observation was noted where PH treatment protected the animals against the PCP-stimulated convulsions and locomotion, and AT shortened the onset time of the circular movements (Table 1) and enhanced the locomotor activity of PCP (Fig. 3; Table 2). These findings conclude that the anticholinergic property of PCP plays a part in the PCP-stimulated behaviors. This could possibly be in conjunction with the dopaminergic property of PCP [28,29]. The conclusion is in agreement with previous studies where PCP-induced turning behavior in rats can be antagonized by inhibiting DA synthesis, blocking DA receptors and stimulating muscarinic receptors and potentiated by anticholinergic agents [2, 6, 16, 17, 30]. Furthermore, oxotremorine-induced increase in the rat striatal DA metabolism was blocked by PCP [27]. As in the present study, anti-ChE agents have been determined to be effective in diminishing the behavioral effects of PCP, such as the reversal of the PCP-induced hyperactivity in mice by tacrine [34] and the partial antagonism of PCP by PH on the variable-interval performance in squirrel monkey [9]. It appears that the PH-pretreatment possibly increases the local concentrations of ACh by inhibiting ChE thus protecting the animals against the antimuscarinic property of PCP. In addition to the interaction of such ACh with the muscarinic receptors, the probability of its interaction with the nicotinic receptors also exist which could enhance the release of DA [15, 19, 38, 39] leading to the potentiation of the PCP-induced behaviors. However, the lack of such potentiation by PH indicates that the stimulation of muscarinic receptors by ACh, i.e., decrease in the anticholinergic property of PCP, presumably dominates over the stimulation of nicotine receptor during the behavioral toxicity of PCP. The *in vitro* AChE inhibitory property of PCP [34,45] itself also may contribute towards its behavioral toxicity. However, this is not of concern since PCP at 179 μmol/kg, IP, a dose higher than that was used in the present study, does not produce inhibition of mouse brain ChE [12]. The data from the AT and PH experiments support the anticholinergic property of PCP. This is in agreement with the anticholinergic behavioral effects during the PCP-intoxication [2, 26, 27] and the PCP's antimuscarinic activity observed with the isolated tissue preparation and QNB binding studies [5, 6, 22, 31, 53–55].

In addition to multifaceted effects on the cholinergic functions and indirect dopaminergic property [28,29], PCP interacts with other neurotransmitter systems [37,44] and possibly with its own receptors [52,59]. Consequently, all the effects of PCP could not be completely reversed by only cholinergic modifiers. However, some of the behavioral toxic effects of PCP could be reduced by centrally-acting ganglionic blockers, ChE inhibitors or muscarinic agents.

ACKNOWLEDGEMENTS

The study was supported by USPHS NIH Grant DA No. 024-54 from the National Institute on Drug Abuse. The author is very appreciative for the excellent technical assistance of Mr. Brian Nesemeier. I am also grateful to N. G. S. Rao, Ph.D., Professor of Toxicology, for providing valuable advice and research facility throughout the period of this study. The author is indebted to Ms. Janna Unverzagt for her excellent secretarial assistance in typing this manuscript.

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