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Phencyclidine-Induced Rotational Behavior in Rats with Nigrostriatal Lesions and its Modulation by Dopaminergic and Cholinergic Agents [1]

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FINNEGAN, K. T., M. I. KANNER AND H. Y. MELTZER. *Phencyclidine-induced rotational behavior in rats with nigrostriatal lesions and its modulation by dopaminergic and cholinergic agents.* PHARMAC. BIOCHEM. BEHAV. 5(6) 651–660, 1976. – The peripheral administration of the psychotomimetic drug phencyclidine (1-(phenylcyclohexyl) piperidine hydrochloride) (PCP) induces a dose-related ipsilateral rotation in unilateral substantia nigra electrolytically-lesioned rats. The intensity of this rotation can be modulated by administration of various dopaminergic and cholinergic agents. Injection of alpha-methylparatyrosine methylester (125 mg/kg) or haloperidol (1 mg/kg) inhibited the ipsilateral circling behavior. Pimozide (1 mg/kg) also inhibited the rotation, but to a lesser extent. The injection of the anticholinergic agent trihexyphenidyl (5 mg/kg) potentiated, and the cholinomimetic drug arecoline (5 mg/kg), depressed the rotation induced by PCP (7.5 mg/kg). It is probable that PCP possesses significant dopaminergic and anticholinergic properties. The capacity of PCP to induce rotation in this model may be related to its effects on dopaminergic and cholingergic neurons in the rat striatum. Thus, PCP may induce rotational behavior by potentiating dopaminergic transmission, by blocking cholinergic activity, or both; both of these effects have been demonstrated to be important in the generation of circling behavior in rats with nigrostriatal lesions.

Rotational model Phencyclidine Dopamine Acetylcholine

PHENCYCLIDINE (1-(phenylcyclohexyl) piperidine hydrochloride) (PCP) is a potent psychotomimetic agent in man [48]. The neurochemical effects of PCP are not well defined, but both behavioral and biochemical studies suggest that it may interact with dopaminergic (DA), cholinergic (Ach), noradrenergic (NE) and serotonergic (5HT) systems. In the rat, injection of PCP produces dose-dependent hyperactivity [14], stereotyped behavior including repetitive side-to-side movements of the head, and turning in a unilaterally-lesioned substantia nigra rat [40]. The PCP-induced locomotor stimulation and hyperactivity can be modified by pharmacological pretreatments which interact with the dopaminergic, noradrenergic, and cholinergic systems [41]. PCP significantly decreases the whole brain NE in the rat [47], and blocks its reuptake in adrenergic postganglionic nerve terminals [56]. It inhibits the accumulation of H^3-NE from cortical slices [16]. PCP produces an increase in the concentration of normetanephrine and 3-methoxytyramine, suggesting an increased release of catecholamines, or blockade of their reuptake [36]. Smith *et al.* [63] found that PCP in a rat caudate synaptosomal preparation is a more potent blocker of DA uptake than is d-amphetamine.

In the periphery, it has been reported that PCP possesses anticholinergic properties at muscarinic sites in a guinea pig ileum preparation in vitro, and in the iris of rabbits, mice and guinea pigs in vivo [49]. These anticholinergic effects are about three orders of magnitude less potent than atropine. Under different conditions, however, PCP has been shown to be a reversible, competitive inhibitor of acetylcholinesterase (Ki = 10^{-7} to 10^{-5} M, dependent on source of enzyme), leading to a relative increase in acetylcholine [49].

It is not clear to what extent the peripheral anticholinergic properties of PCP may be generalized to central nervous system effects. However, the degree of interaction between various PCP derivatives and muscarinic receptors, as measured by quantum mechanical techniques, reveals a high correlation between the potency of these derivatives as peripheral competitive anticholinergics, and as central psychomotor stimulants [50]. PCP significantly accelerates the depletion of brain Ach after the administration of hemicholinium-3, suggesting increased Ach turnover [25]. PCP-induced anesthesia and hyperactivity in guinea pigs may be blocked by the cholinesterase inhibitor tacrin (9-amino-1,2,3,4,-tetrahydro-acridine), a report also consistent with a central anticholinergic mechanism of action of PCP.

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PCP increases whole-brain 5HT while simultaneously decreasing 5HIAA levels [68], although this effect appears to be strain specific [69]. Additionally, PCP inhibits the uptake of 5HT in a crude synaptosomal preparation of rat brain [63].

A behavioral method for monitoring the effects of drugs on the nigrostriatal dopaminergic system in the rat has been described by Ungerstedt and others [15, 70, 71]. Degeneration of the nigrostriatal system is associated with disturbance of motor function both clinically and experimentally [37, 42, 60]. By lesioning the corpus striatum or the dopaminergic pathway unilaterally, it is possible to create an experimental situation in which pharmacologically-induced dopamine release may occur on only one side [7, 70, 72]. The resulting imbalance in dopamine is revealed behaviorally as a mild asymmetry in posture.

These characteristic postural asymmetries can be potentiated into active turning by various drugs or combinations of drugs that selectively increase or decrease dopaminergic or cholinergic activity [4, 6, 21, 53]. Following a unilateral 6-hydroxydopamine-induced lesion of the substantia nigra, the peripheral administration of dopamine-like agents causes either ipsilateral or contralateral turning. The difference in the direction of rotation is hypothesized to result from the development of a denervation-induced postsynaptic supersensitive dopamine receptor, and differences in pre- versus postsynaptic activity of the administered drug. Thus, drugs having an indirect mode of action, such as amphetamine or the combination of reserpine plus nialamide [13,33] cause active rotation towards the lesioned side (ipsilateral rotation). Administration of apomorphine, thought to interact directly with post-synaptic dopamine receptors [8,26] results in rotation away from the lesioned side (contralateral rotation).

Following unilateral electrolytic lesions of the substantia nigra, however, all dopamine-like agents, irrespective of their pre- or postsynaptic mode of action, cause ipsilateral circling ([23]; Finnegan, Kanner and Meltzer, unpublished observations). Additionally, it has been reported that after asymmetric lesions of the raphe nucleus, these agents induce contralateral rotation [22]. Thus, the direction of rotation induced by a dopamine-like agent may not permit the distinction between increased dopaminergic activity via pre- or postsynaptic mechanisms. Nevertheless, this simply observed, easily quantified behavior, which has been experimentally linked to imbalances in the functional activity of striatal dopamine and acetylcholine, does provide a model for monitoring the effects of various pharmacological agents on dopaminergic, cholinergic, and perhaps serotonergic activity.

To investigate whether PCP interacts with the dopaminergic and cholinergic systems as manifested by turning behavior, we conducted pilot studies which indicated that phencyclidine produced ipsilateral turning in rats with unilateral electrolytic substantia nigra lesions. Here we present data on the systematic study of this phenomenon including a dose-response function for PCP and results of our attempts to modulate the rotation with various pharmacological agents. A preliminary report has been published elsewhere [40].

METHOD

Animals

Male Sprague-Dawley rats (Sprague-Dawley, Madison, Wisconsin) weighing 150 ± 5 g at the time of surgery were used. They were housed individually in a temperature-controlled colony on a 12 hr light-dark cycle (7 AM lights on) with free access to Purina laboratory chow and tap water throughout the course of the experiments, except during testing sessions.

Surgical Procedure

At the time of surgery rats were anesthetized with sodium pentobarbital (Nembutal) (40 mg/kg, IP). The animals were placed in a Kopf stereotaxic instrument and were prepared with unilateral electrolytic lesions of the substantia nigra on the animal's left side, according to the atlas of Konig and Klippel [44]. The following coordinates and current parameters were used: AP – 2.4, L – 1.6, and H – 2.6; 1 ma for 10 sec, anodal current. The lesioning electrode was stainless steel insulated with teflon except for 0.5 mm at the tip. After surgery the rats were returned to individual cages in the colony. One week to 10 days later behavioral testing was begun.

Histology

After the experiments were completed, the animals were decapitated and the brains were removed from the calvaria and stored in 10% Formalin. The brains were sliced with a cryostatic microtome and sections were stained with cresyl violet. Tissue damage common to all effective lesions included that of the substantia nigra, pars compacta and pars reticulata, and almost always portions of the adjacent medial lemniscus and formatio reticularis. Occasionally, the lesioned area included the red nucleus or the crus cerebri, or both.

Drug Preparation

A fresh solution of phencyclidine (Sernyl) (Bio-Ceutic Laboratories, St. Joseph, MO) was prepared daily in sterile physiological saline. All injections were intraperitoneal (IP).

EXPERIMENT 1

Procedure

On each test day a rat was placed in a Plexiglas bowl (17.4 cm deep, 36.5 cm in dia.) and allowed to habituate to the testing situation for 15 min. Rats were injected with saline and two days later with PCP (5 mg/kg). After PCP, 5 mg/kg, or saline, the rat's behavior was observed for 1 hr. General posture, ataxia, headshaking, and turning were evaluated for 1 min every 5 min for the first 20 min after injection and then for 1 min every 10 min for the duration of the experiment. A paired t-test for statistical significance [27] between saline and PCP responses was carried out on the data at each interval.

Results

Immediately after surgery the rats exhibited the postural asymmetry typically seen after unilateral substantia nigra lesions [7,70]. Spontaneous ipsilateral turning was occasionally observed in the first few days following surgery but this subsided as the animals recovered.

Rotational behavior produced by PCP is presented in Fig. 2. After saline, virtually no rotational behavior or other abnormal behaviors were observed. Approximately 5 min after PCP administration, increased locomotor activity was

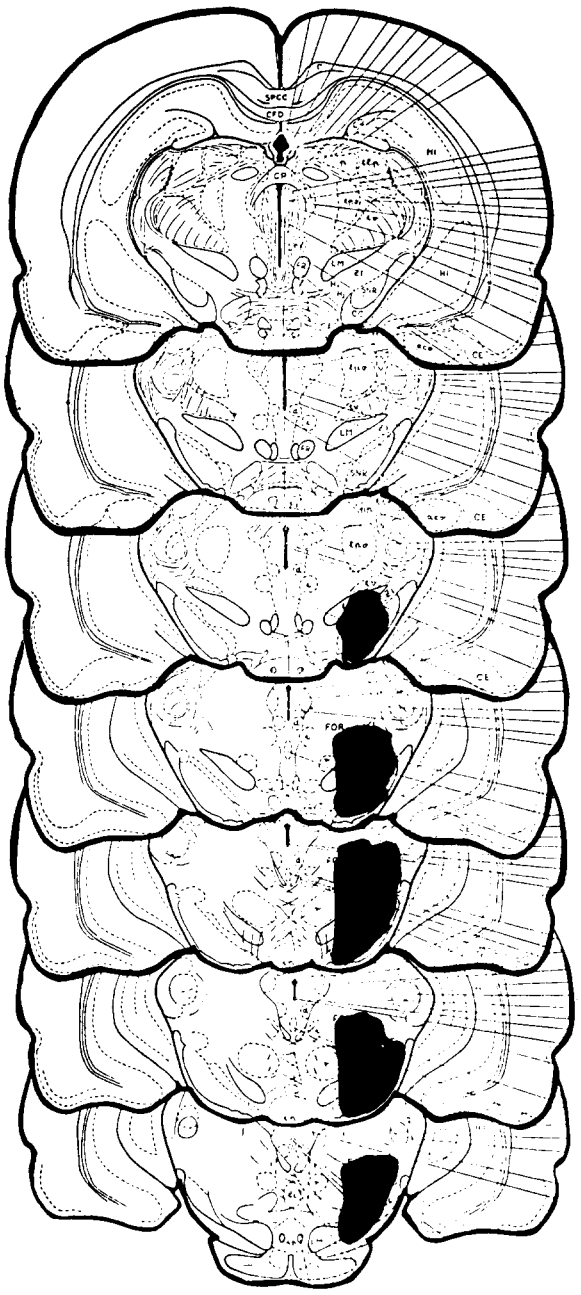

FIG. 1. A representative unilateral lesion of the substantia nigra, as adapted from atlas of Konig and Klippel [40].

observed in all rats. Only 1 out of 6 of the unilaterally lesioned rats exhibited the characteristic side-to-side headshaking produced by PCP in normal rats. Ipsilateral rotation developed in all 6 rats studied. Only sporadic contralateral turns were noted. The rate of ipsilateral turning reached a peak 10 min after PCP, after which time the rats began to exhibit some signs of ataxia. The rate of turning decreased over the next 60 min and returned to baseline at 90 min. In contrast, the time course of amphetamine-induced rotation is quite different. Rotation peaks at 30–40 min after amphetamine, with the effects lasting for approximately 3 hr [15,70].

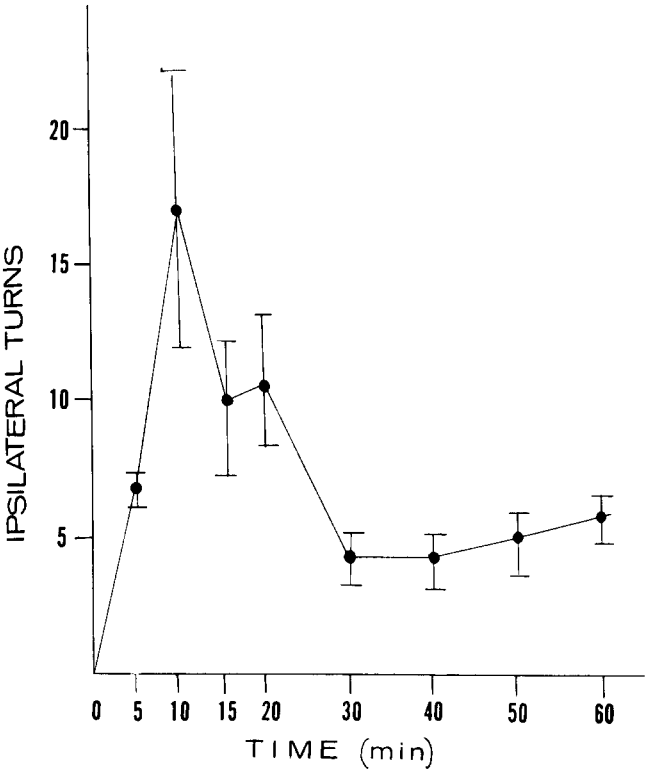

FIG. 2. Rotational behavior produced by PCP in the unilaterally lesioned substantia nigra rat. Turns were counted for 1 min every 5 min for the first 20 min and for 1 min every 10 min for the duration of the experiments.

EXPERIMENT 2

To further characterize the effect of PCP in producing rotation, a dose-response study was carried out. The doses chosen for study were 0.5, 1.0, 2.5, 3.5, 5.0, 7.5, 10.0, 15.0 and 25.0 mg/kg. Half of the rats were given the doses in ascending order and half in descending order. The behavioral testing was identical to that in Experiment 1 with one day intervening between drug injections.

Results

Data are presented in Fig. 3 and 4. The effect of PCP on the intensity of turning behavior was dose-dependent. PCP, 5–15 mg/kg, produced strong ipsilateral rotation which reached a peak within 10 min of administration. No significant differences in rotation were noted between groups administered PCP on the ascending or descending regimens, indicating that tolerance is probably not a compounding factor on this dosage schedule. Many of the unilaterally lesioned animals did not show the characteristic headshaking response produced by administration of PCP to normal rats at all doses tested. Slight ataxia was observed in all animals starting at the 5 mg/kg dose. This impairment in coordination increased with dose, and at 15–25 mg/kg, interefered severely with the turning response. Despite the severe ataxia, the characteristic postural asymmetries described above (head and tail deviated towards the lesioned site) continued to be noted at the higher drug doses, but the gross impairment in motor function resulted in low rates of rotation.

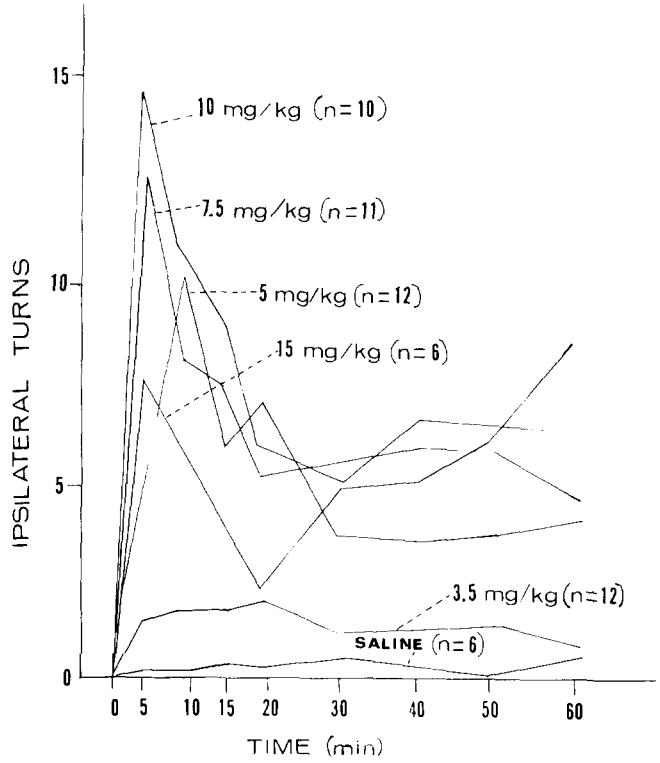

FIG. 3. The effects of various doses of PCP on rotational behavior. Turns were counted for 1 min every 5 min for the first 20 min and for 1 min every 10 min for the duration of the experiment.

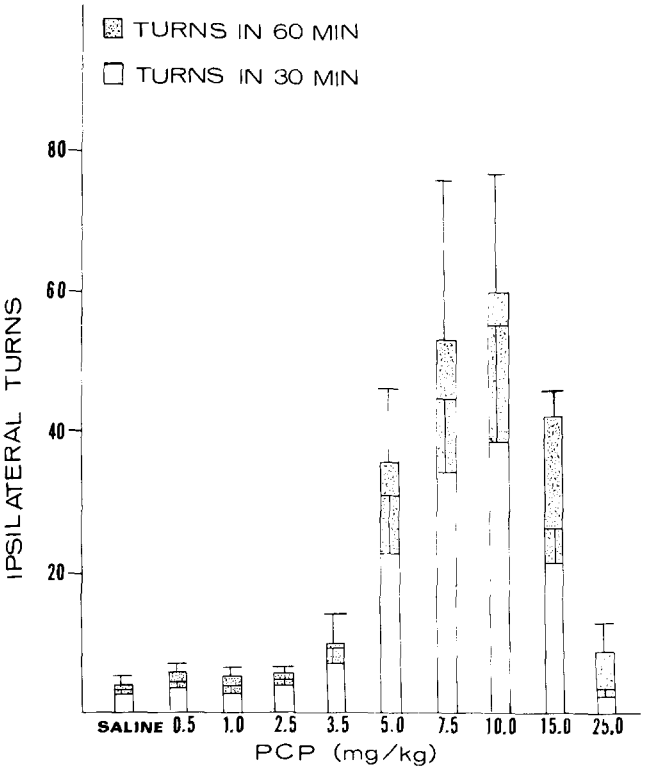

FIG. 4. The cumulative number of turns during observation periods of 30 and 60 min for data presented in Fig. 3.

EXPERIMENT 3

In rats which have sustained a unilateral substantia nigra lesion, considerable evidence indicates that imbalances in dopaminergic and cholinergic activity between the bilaterally represented corpus striati mediate the turning response to amphetamine [5, 21, 54, 70]. To ascertain the role of dopamine and acetylcholine in PCP-induced turning, various pharmacological agents were administered in conjunction with PCP in an attempt to modulate the rotation. In this series of experiments, the dose of PCP used was increased to 7.5 mg/kg, as it had been demonstrated in Experiment 2 that this was the most effective dose in eliciting turning.

Animals

Rats with unilateral substantia nigra lesions were prepared as in the above experiments. Following postoperative recovery, a test dose of PCP, 7.5 mg/kg, was given to identify rats which demonstrated a consistent turning response.

Drugs

The following drugs were dissolved in sterile physiological saline and injected intraperitoneally in the doses indicated: alpha-methylparatyrosine methyl ester, Sigma Chemical Co. (125 mg/kg); haloperidol (Haldol), McNeill Chemicals (1 mg/kg); arecoline, Sigma Chemical Co. (5 mg/kg); trihexyphenidyl (Artane), Lederle Chemical Co. (5 mg/kg). Pimozide, Janssen Pharmaceutical Co. (1 mg/kg and 2 mg/kg), was dissolved in .1 M tartaric acid.

Recording of Rotational Behavior

In this series of experiments, the rotational behavior was automatically recorded in a modified version of the rotometer designed by Barber [10]. The modified design was less complex and more economical to construct (Finnegan and Kubos, unpublished design). By way of a harness and thin wire, the rat was connected to the geometric center of the hemisphere (17.4 cm deep, 36.5 cm diameter). Because of the spherically-shaped surface, the rat could move about comfortably with little interference from the recording apparatus. Each full left and right turn was recorded on tape on separate channels with an Esterline-Angus Event Recorder (Esterline-Angus Co., Indianapolis, IN).

Procedure

On each test day the rat was placed in the Plexiglas bowl and given 15 min to habituate to the test situation. On Day 1, the rat was injected with saline at a time appropriate for the test drug used on Day 3, and then administered PCP. Day 2 was a rest day. On Day 3 the rat was injected with a combination of test drug and PCP. Rotational behavior was measured for one hour after injection of PCP.

Data Analysis

Although the rotometer printed a minute by minute record of the direction and intensity of turning, it was decided to continue selecting every fifth minute as a representative interval in which turns were scored. Not only did this facilitate data analysis, but also this manner of reporting the data was compatible with that of Experiments

TABLE 1

	N	Ipsilateral Turns in 30 Min: AMPT Alone (N=5)	Saline + PCP	AMPT + PCP	Signif.	Ipsilateral Turns in 60 Min: AMPT Alone (N=5)	Saline + PCP	AMPT + PCP	Signif.
$\bar{X}$	12	0.5	67.9	40.0	$p<0.05$	0.75	115.2	65.0	$p<0.05$
S.D.		± 0.57	± 36.1	± 30.0		±0.50	± 69.0	± 46.8	

Data are presented for the following experiment:

Day 1: Saline $\xrightarrow[\text{hrs}]{4}$ PCP Day 3: AMPT $\xrightarrow[\text{hrs}]{8}$ AMPT $\xrightarrow[\text{hrs}]{4}$ PCP

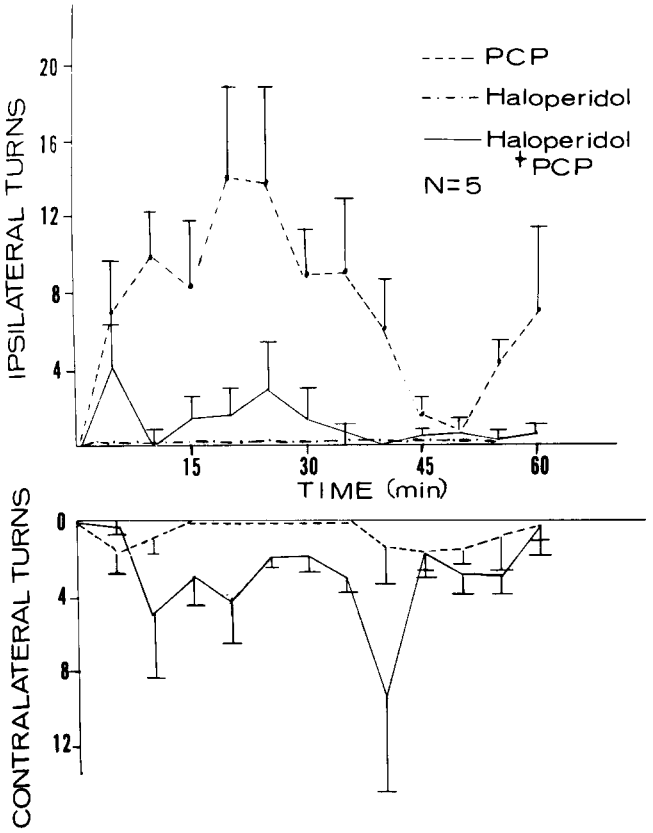

FIG. 5. The effects of haloperidol (1 mg/kg) administered 5 min prior to PCP (7.5 mg/kg). Turns were counted for 1 min every 5 min.

1 and 2. A correlation between the number of turns in the interval selected and those 1 min intervals on either side of it revealed similar rates of turning ($r = 0.842$, $p<0.01$). Thus, turns were scored every fifth minute and data is reported as the mean number of turns in six 1-min intervals in 30 min and the twelve 1-min intervals in 60 min. Tests of significance were performed with a paired data Student t-test [27].

Results

1. Tyrosine hydroxylase inhibition. Two injections of alpha-methylparatyrosine methylester (AMPT) (125 mg/kg) were administered 12 hr and 4 hr before the injections of phencyclidine. The direction and intensity of the resulting rotational behavior was then recorded for 1 hr following administration of PCP. The data are presented in Table 1. AMPT produced a 58.9% decrease at 30 min ($p<0.05$) in PCP-induced ipsilateral rotation. Administration of AMPT alone caused no significant turning in either direction.

2. Dopamine receptor blockade. (a) Haloperidol (1 mg/kg IP) was administered 5 min before injection of PCP. The data are presented in Fig. 5. Haloperidol (1 mg/kg), inhibited the ipsilateral turning induced by PCP, and potentiated contralateral rotation. Although injection of haloperidol alone caused no turning, it did produce a contralateral asymmetry with respect to body and limb position. (b) Pimozide (1 mg/kg, IP) was administered 15 minutes before PCP. The data are presented in Table 2. Pimozide (1 mg/kg) produced a significant decrease in ipsilateral turning elicited by PCP ($p<0.05$, 1 tailed-test), although two of the rats showed an increase in ipsilateral turning at this dose. At 2 mg/kg of pimozide, there was no significant alteration in PCP-elicited rotation. Injection of pimozide alone (1 mg/kg) caused no turning.

3. Cholinergic agents. (a) Trihexyphenidyl (5 mg/kg, IP) was administered 15 min before the injection of PCP. The data are presented in Table 3. A small, but statistically significant, potentiation of PCP rotation was observed at 30 minutes ($p<0.05$). However the potentiation was not nearly so evident at 60 min. and failed to reach the 0.05 level of significance at this time interval. Injection of trihexyphenidyl alone caused no rotation. (b) Arecoline (5 mg/kg, IP) was given 15 min before the injection of PCP, and the rotational behavior observed. The data are presented in Table 4. Arecoline produced a significant decrease in rotation when given in conjunction with PCP. When given by itself, however, no rotation was noted.

DISCUSSION

A behavioral method for monitoring the functioning of the extrapyramidal motor system in the rat has been described by Ungerstedt and others. Unilateral substantia nigra lesions result in an ipsilateral decrease of dopamine (DA) in the corpus striatum [7]. Characteristic postural asymmetries resulting from the subsequent imbalance of DA between corpus striati are thought to be potentiated into active rotation by the augmentation of DA transmission in the remaining intact striatum, or by direct stimulation of the supersensitive denervated receptor [70].

TABLE 2

	N	Ipsilateral Turns in 30 Min: Pimozide alone (N=5)	Saline + PCP	Pimozide + PCP	Significance
$\bar{X}$	9	0	67.5	36.5	$p<0.05$
S.D.		0	± 25.3	± 40.7	(one-tailed test)

Data are presented for the following experiments:
Day 1: Saline $\xrightarrow[\text{min}]{15}$ PCP Day 3: Pimozide $\xrightarrow[\text{min}]{15}$ PCP

A large body of evidence has demonstrated that a balance between Ach and DA is important in many of the behaviors believed to be under the control of the extrapyramidal system, including turning. Anticholinergic agents, such as atropine, produce a contralateral rotation when injected unilaterally into the caudate-putamen or globus pallidus, while intrastriatal application of cholinomimetic agents, such as arecoline, cause ipsilateral turning [21]. In a rat with a 6-hydroxydopamine-induced unilateral lesion of the substantia nigra peripheral administration of scopolamine causes ipsilateral circling, and this rotation is blocked by pretreatment with haloperidol or AMPT [53,71].

Similiarly, cholinergic drugs can modulate the intensity and duration of amphetamine-induced stereotyped behavior, a behavioral syndrome believed to be directly mediated by DA release [28, 43, 62]. Some researchers consider circling behavior to be a form of stereotypy [55]. Amphetamine-induced stereotyped behavior is potentiated by anti-cholinergic agents, and inhibited by cholinomimetic drugs [9,43].

The production of catalepsy is a CNS phenomena that has been experimentally linked to decreased DA activity [67,75], in all probability the striatum being the neuroanatomical locus responsible for its induction [20,29]. Haloperidol-induced catalepsy is potentiated by arecoline. The cataleptic effects of the two drugs alone, or in combination, are blocked by atropine.

More recently, biochemical data from animal experiments have been accumulating in support of a recipricol link between DA and Ach in the striatum. Agents that increase DA activity by acting pre-synaptically (e.g., amphetamine, amantadine), or postsynaptically (e.g., apomorphine, piribedil), display the common feature of increasing the concentration of striatal Ach [17, 18, 35, 46]. Conversely, antipsychotic drugs induce a decrease in the concentration of striatal Ach [51]. This decrease is not due to their concomitant anticholinergic properties, but rather their ability to block DA receptors [61]. These changes in the concentration of striatal Ach have been related to utilization of the transmitter, i.e. a decrease in the concentration of striatal Ach is indicative of increased cholinergic neuronal activity, and vice versa [30, 45, 65].

On the other hand, administration of centrally acting cholinergic drugs has been shown to influence the turnover of striatal DA. Systemic injection of atropine decreases the content of homovanillic acid (HVA) in the striatum without affecting the concentration of DA [11,58] and delays the disappearance of endogenous cerebral DA after AMPT [5]. Administration of cholinomimetics, such as

TABLE 3

	N	Ipsilateral Turns in 30 min: Trihexyphenidyl alone (N=6)	Saline + PCP	Trihexyphenidyl + PCP	Signif.	Ipsilateral Turns in 60 min: Trihexyphenidyl alone (N=6)	Saline + PCP	Trihexyphenidyl + PCP	Signif.
$\bar{X}$	6	4.05	30.0	49.5	$p<0.05$	5.0	70.0	96.6	n.s.
S.D.		± 4.03	± 16.6	± 11.0		± 4.8	± 44.9	± 24.5	

Data are presented for the following experiments:
Day 1: Saline $\xrightarrow[\text{min}]{15}$ PCP (7.5 mg/kg) Day 3: Trihexyphenidyl (5 mg/kg) $\xrightarrow[\text{min}]{15}$ PCP (7.5 mg/kg)

TABLE 4

	N	Ipsilateral Turns in 30 Min: Arecoline alone (N=6)	Saline + PCP	Arecoline + PCP	Signif.	Ipsilateral Turns in 60 Min: Arecoline alone (N=6)	Saline + PCP	Arecoline + PCP	Signif.
$\bar{X}$	6	0.50	81.4	46.4	$p<0.02$	0.66	153.4	82.8	$p<0.01$
S.D.		± 0.83	± 29.7	± 31.8		± 0.81	± 44.6	± 39.9	

Data are presented for the following experiments:
Day 1: Saline $\xrightarrow[\text{min}]{15}$ PCP (7.5 mg/kg) Day 3: Arecoline (5 mg/kg) $\xrightarrow[\text{min}]{15}$ PCP (7.5 mg/kg)

arecoline, nicotine, oxytremorine, and physostigmine, cause an increase in striatal HVA [19,51]. Moreover, the increase in HVA induced by both neuroleptics and cholinomimetic agents can be blocked by atropine.

There is abundant evidence, then, that striatal function is regulated by a reciprocal balance between DA and Ach in the striatum. Using this behavioral model in which the nigro-striatal pathway is unilaterally destroyed by electrolytic lesion, we have found that PCP causes, as does amphetamine or apomorphine, a dose-responsive ipsilateral rotation. However, a comparison of the duration and intensity of turning elicited by PCP and amphetamine, coupled with attempts to modify the PCP-induced rotation by injection of various pharmacological agents, has revealed considerable difference between the two drugs.

In our studies, depletion of norepinephrine and dopamine by AMPT led to a 41% decrease ($p<0.05$) in PCP-induced rotation. In contrast, AMPT reduced amphetamine-elicited rotation to 10% of control values [70,73]. Similar decreases in amphetamine-induced turning are also obtained for the catecholamine receptor blockers haloperidol, spiroperidol [70] and pimozide (Finnegan, Kanner and Meltzer, unpublished observations). Although we observed a decrease in PCP-induced rotation after haloperidol similar to that seen with amphetamine-elicited circling behavior, administration of pimozide (1 mg/kg) reduced PCP-induced turning by only 54% ($p<0.05$); and at 2 mg/kg an even smaller effect was noted. As reported by other researchers investigating circling behavior after amphetamine, the inhibition of PCP-induced ipsilateral circling by haloperidol is accompanied by an increase in contralateral turns [5].

In our findings, the anticholinergic agent trihexyphenidyl potentiated and the cholinomimetic arecoline depressed the turning induced by PCP. These findings are in keeping with other reports concerning the interaction of cholinergic agents with the rotation observed after administration of amphetamine, as well as the research discussed above regarding the reciprocal role of Ach and DA in controlling extrapyramidal motor function. Physostigmine inhibits and the anticholinergic agents scopolamine and procyclidine potentiate amphetamine-induced ipsilateral circling in unilateral electrolytically lesioned rats. The potentiation caused by procyclidine could be abolished by AMPT [52,53].

The inhibition of PCP-induced turning by AMPT, coupled with the decrease in rotation after haloperidol and pimozide, indicates that dopaminergic activity is important in the generation of rotational behavior by this drug. However, the fact that we were able to obtain only a 40% decrease in PCP induced turning with AMPT, along with the smaller inhibition observed after pimozide, suggests that PCP is interacting with more than one CNS neurotransmitter system. The stereotypy and hyperactivity induced by PCP in rats is most likely the resultant of a complex interaction between dopaminergic and cholinergic systems within the striatum.

This conclusion is in agreement with other research. PCP causes a significant accleration in the depletion of brain DA after alpha-methylmetatyrosine (MMT) [47], an agent that depletes DA from the neuronal storage granules by replacing it with metaraminol, the metabolite of MMT [3]. This suggests that PCP increases DA turnover although the data must be interpreted with caution as a similar effect after AMPT was not observed. PCP produces an increase in the concentration of the COMT products, normetanephrine and 3-methoxytryamine, suggesting increasing catecholaminergic release or reuptake blockade [36]. PCP is a more potent blocker of DA uptake than is d-amphetamine in a rat caudate synaptosomal preparation [63]. Such a mechanism would serve to increase the local concentration of DA at the post-synaptic receptor.

It is well documented that PCP possesses significant peripheral anticholinergic properties [49, 59, 74]. Additionally, a strong correlation between psychotomimetic activity and anticholinergic potency has been observed with various drugs [1, 2, 12, 74]. PCP is a potent psychotomimetic and thus may possess significant central anticholinergic potency. It is probable that these central anticholinergic properties activate the striatum in such a manner as to cause rotation, probably by removing a cholinergic excitation.

The hypothesis that PCP possesses both anticholinergic and dopaminergic properties accounts for the relatively small decreases in PCP-induced rotation after AMPT or pimozide. We have previously cited the evidence that peripheral administration of anticholinergic drugs induces ipsilateral rotation in rats with unilateral substantia nigra lesions [53,71]. Under those experimental conditions in which any PCP effect on dopaminergic transmission is diminished (by the catecholamine synthesis inhibitor AMPT; or the dopamine receptor blocker pimozide), the significant rates of turning we observed can be attributed to the anticholinergic actions of PCP. The borderline significance of the inhibition seen with pimozide at 1 mg/kg, and the lack of significant inhibition at 2 mg/kg, may be accounted for by just such a mechanism. This hypothesis also accounts for the limited effectiveness of cholinomimetic drugs in decreasing the intensity of the PCP-induced rotational response.

Other work suggests that serotonin (5HT) may be important in modulating the direction and intensity of circling behavior. After an asymmetric lesion of the medial raphe nucleus, peripheral administration of drugs that stimulate dopaminergic activity (such as amphetamine, apomorphine, amantadine) results in a contralateral rotation irrespective of the drug's pre- or postsynaptic activity [22,23]. Rotation could also be induced by administration of quipazine, a drug thought to act on 5HT systems [34]. This circling behavior could be blocked by cyproheptadine, but not haloperidol [24].

Although this evidence would argue for the notion that 5HT is important in the neural control of the mechanisms governing turning behavior, it is probable that 5HT is not a relevant factor in the rotation seen with unilateral electrolytic lesions of the substantia nigra. The direction and intensity of the circling response to amphetamine was found to be the same in animals sustaining both a unilateral substantia nigra and a raphe lesion, as compared to those animals sustaining a unilateral substantia nigra lesion alone [52]. Furthermore, injections of para-chlorophenylalanine (PCPA), resulting in a 90% depletion of cerebral 5HT, or administration of the 5HT precursor, 5-hdyroxytryptophan did not modify the rotation seen with amphetamine in unilateral electrolytically-lesioned substantia nigra animals. Moreover, the ipsilateral turning observed with amphetamine in substantia nigra animals was shown to add or substract with the raphe-induced circling, dependent upon whether the location of the lesions were on the opposite or same side [22]. These results suggest that the rotation induced by substantia nigra and raphe lesions are indepen-

dent of each other. Hence, the rotation induced by substantia nigra lesions would be insensitive to any 5HT properties a drug might possess. Although there is some evidence that PCP interacts with central 5HT mechanisms [68], it is not yet clear what role 5HT mechanisms play in PCP-elicited rotation in rats with unilateral electrolytic substantia nigra lesions.

Although our observations were consistent under a given set of conditions with respect to the direction of the turning response, some variation in the magnitude of individual responses was noted. Several researchers have recently demonstrated that rotation may occur in normal, unlesioned rats following administration of a variety of amphetamine-like compounds although at much lower rates [31, 32, 36, 37]. The preoperative predisposition to turn can influence the intensity of the circling behavior after surgery, and it is therefore important that the preoperative direction and magnitude of rotation be considered in the interpretation of postsurgical rotational studies. The data we report here were obtained before the importance of such considerations became evident. It is probable that some of the variability of our results may be attributed to preoperative differences in turning behavior.

It has been hypothesized that excessive dopaminergic activity can produce an altered state of consciousness that can appear clinically indistinguishable from paranoid schizophrenia [64]. Additionally, a strong correlation between psychotomimetic activity and anticholinergic potency has been observed with various drugs [1, 2, 12, 74]. The studies reported here, which add to the evidence for an effect of PCP on dopaminergic and cholinergic transmission, may be taken as support for the notion that altered states of consciousness are related to changes in the functional activity of these neurotransmitters.

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