European Journal of Pharmacology, 44 (1977) 113—119

COMPARATIVE EFFECTS OF HALLUCINOGENIC DRUGS ON ROTATIONAL BEHAVIOR IN RATS WITH UNILATERAL 6-HYDROXYDOPAMINE LESIONS

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Received 29 December 1976, revised MS received 15 March 1977, accepted 24 March 1977

M.E. TRULSON, A.D. STARK and B.L. JACOBS, *Comparative effects of hallucinogenic drugs on rotational behavior in rats with unilateral 6-hydroxydopamine lesions*, European J. Pharmacol. 44 (1977) 113—119.

The dopaminergic actions of various hallucinogenic drugs were assessed by examining their effects on turning behavior in rats with unilateral 6-hydroxydopamine lesions of the nigro-striatal pathway. LSD (0.1 and 0.2 mg/kg) produced strong contralateral turning, indicating that it is a potent dopamine receptor agonist, while BOL (5 mg/kg), a non-hallucinogenic congener of LSD, was found to be a weak dopamine receptor agonist. STP (2 and 5 mg/kg) and mescaline (50 and 100 mg/kg) produced significant ipsilateral turning, indicating that these compounds have a moderate dopamine-releasing action. DMT (10 and 20 mg/kg) and 5-M-DMT (0.75 and 1.25 mg/kg) produced weak ipsilateral turning, which was not significantly different from that produced by the non-hallucinogenic compounds tryptamine (40 mg/kg) or scopolamine (0.25 mg/kg). Psilocin (1—20 mg/kg) produced no significant turning in either direction. These data, in conjunction with previous studies, indicate that while inactivation of the brain serotonin system may be a necessary and sufficient condition for hallucinogenesis, the ability to activate dopamine receptors may be an important factor in determining the potency of hallucinogens.

Hallucinogenic drugs Rotational behavior Dopamine Drug potency

1. Introduction

The finding that lysergic acid diethylamide (LSD) has a powerful depressant action on serotonin-containing midbrain raphe neurons led to the hypothesis that the psychological and perceptual effects of LSD are due to its inactivation of the central serotonin system (Aghajanian et al., 1968). Subsequently, several other hallucinogens, including mescaline, STP, psilocin and DMT, were found to depress raphe neuronal activity as well (Aghajanian et al., 1970; Aghajanian and Haigler, 1975). Thus, a common property of many hallucinogenic drugs is their ability to inactivate the brain serotonin system. Furthermore, the relative potency of these hallucinogens in depressing the activity of raphe neurons generally parallels their potency on psychological and perceptual measures in humans (Snyder et al., 1967; Wolbach et al., Szara, 1970). Together, these studies suggest that the efficacy of a drug in producing an hallucinogenic experience may be a function of the drug's effect on raphe neurons.

Recently, however, several studies have demonstrated that LSD also acts as a direct agonist on central dopamine receptors. Following unilateral destruction of the nigro-striatal dopamine system, compounds which either directly stimulate postsynaptic dopamine receptors or increase synaptic dopamine content produce unilateral turning (Anden et al., 1966; Ungerstedt, 1971a,b; Ungerstedt and Arbuthnott, 1970; Von Voigtlander and Moore, 1973). The directionality of the turning is dependent upon whether the test compound acts pre- or post-synaptically. Compounds which release presynaptic stores of dopamine, such as amphetamine, produce turning in the direction ipsilateral to the lesion due to the greater release of dopamine

on the intact side as compared to the denervated side. Whereas, compounds which directly stimulate postsynaptic dopamine receptors, such as apomorphine, produce turning in the direction contralateral to the lesion due to denervation supersensitivity on the lesioned side (Ungerstedt, 1971a,b; Von Voigtlander and Moore, 1973). The fact that LSD produces contralateral turning in 6-OHDA lesioned rats and that this effect is abolished by dopamine receptor blocking agents is evidence that LSD acts directly on postsynaptic dopamine receptors (Pieri et al., 1975). In addition, LSD has been shown to bind to dopamine receptors using neurochemical measures (Burt et al., 1976), and to activate a dopamine-sensitive adenylate cyclase as well (Von Hungen et al., 1975). Furthermore, recent electrophysiological evidence from our laboratory (Christoph, Kuhn and Jacobs, in preparation) has shown that LSD depresses the activity of dopamine-containing neurons in the pars compacta of the substantia nigra.

In the present study, we utilized the unilateral turning model to examine the relative efficacy of several hallucinogens to either release brain dopamine or to act as a direct dopamine agonist. These studies suggest that although a dopaminergic effect is not a necessary property of hallucinogenic drugs, the ability to activate dopamine receptors may be an important factor in determining the potency of hallucinogenic drugs.

2. Materials and methods

Male Sprague—Dawley rats (250—350 g) were pretreated with pargyline HCl (25 mg/kg, i.p.) 30 min prior to receiving unilateral intracerebral injections of 6-hydroxydopamine (6-OHDA) to destroy catecholaminergic nerve terminals in the nigro-striatal pathway. The rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic instrument with the bite bar 4.0 mm below the interaural line. Injection of 4 μl of 6-OHDA hydrobromide (6 μg of base in 4 μl of sterile saline containing 0.2 mg/ml ascorbic acid) was performed over a 15 min period. The 6-OHDA solution was delivered by a microsyringe through a 32-gauge cannula whose tip was placed at AP + 7.3, ML + 2.5, and DV − 6.9 from dura. Following injection, the cannula remained at the injection site for 5 min to allow for diffusion. After removing the cannula, the wound was sutured and an antibiotic (Bicillin, 60,000 units, i.m.) was administered. Behavioral testing was not begun until at least two weeks post-surgery.

Rotational behavior was measured using the method of Ungerstedt (1971a). Animals were placed in black hemispheric bowls (35 cm in diameter and 18 cm in depth) with sawdust covering the floor. The bowls were housed in a room with overhead fluorescent illumination and 70 dB masking noise. A rotary disc above the bowl was connected to the rat by attaching a stiff wire extending from the swivel post in the disc to a rubber band placed around the rat's midsection. Complete 360° turns in both the clockwise and counter-clockwise directions closed a microswitch placed in close proximity to the rotating disc and the number of turns in either direction were automatically counted. Subjects were habituated to the test chamber for 15 min and then a 15 min baseline of rotational activity was recorded. The test drug was then administered and the number of turns per 15 min for 1 h post-injection were recorded. When the effects of pharmacological blocking agents were examined, a 15 min baseline of rotational activity following administration to the blocking agent was recorded prior to injection of the test drug.

The following drugs were administered: d-amphetamine sulfate (0.2, 0.5 and 1.0 mg/kg, as salt), apomorphine HCl (0.2 mg/kg), BOL (2-bromo-d-lysergic acid diethylamide bitartrate, 0.5, 2.0 and 5.0 mg/kg), DMT (N,N-dimethyltryptamine-HCl, 1.0, 5.0, 10.0 and 20.0 mg/kg), STP (2,5 dimethoxy-4-methylamphetamine HCl, 0.1, 0.5, 2.0 and

5.0 mg/kg), LSD (d-lysergic acid diethylamide bitartrate, 0.05, 0.1 and 0.2 mg/kg), mescaline (3,4,5-trimethoxy-phenethylamine HCl, 20.0, 50.0 and 100.0 mg/kg), 5-M-DMT (5-methoxy-N,N-dimethyltryptamine HCl, 0.25, 0.75 and 1.25 mg/kg), methysergide (n-methyl-d-lysergic acid butanol amide, 1.0 and 5.0 mg/kg), psilocin (4-hydroxy-N,N-dimethyltryptamine HCl, 1.0, 5.0, 10.0 and 20.0 mg/kg), scopolamine HBr (0.25 mg/kg), spiroperidol (0.25 and 0.5 mg/kg), and tryptamine (3-(2-aminoethyl)-indole HCl, 20.0 and 40.0 mg/kg). All substances were dissolved in saline and injected intraperitoneally in a volume equal to 1—2 ml/kg of body weight.

Evaluation of the statistical significance of the differences in the data between experimental and control conditions was made using one-way analysis of variance (ANOVA), followed by Dunnett's tests. All analyses were performed on the number of net turns (contralateral minus ipsilateral) per 5 min occurring between 0 and 45 min post-injection.

At the completion of the study, 6-OHDA-lesioned rats were randomly selected for monoamine assays. Norepinephrine, dopamine and serotonin in the corpus striatum were measured using a method developed by Jacobowitz and his colleagues, which we have previously described (Jacobs et al., 1977a). Monoamine values were not corrected for recoveries which were as follows: norepinephrine, 96.4 ± 2.5%; dopamine, 94.9 ± 2.9%; and serotonin, 95.6 ± 1.9%.

3. Results

Rats with unilateral 6-OHDA lesions showed a slight tendency to turn ipsilaterally when injected with saline (x = 0.5 net turns per 5 min). Administration of apomorphine (0.2 mg/kg) produced turning in the direction contralateral to the lesion (23.3 ± 2.9 net contralateral turns per 5 min, $p < 0.01$ as compared to saline vehicle). LSD also produced contralateral turning in these rats ($p = 0.002$, ANOVA). A dose of 50 μg/kg of LSD was ineffective in producing turning, while each of the higher doses produced a significant effect (24.1 ± 7.3 and 36.6 ± 10.7 net turns per 5 min for the 100 and 200 μg/kg doses, respectively). Thus, LSD appears to be slightly more potent than apomorphine in eliciting contralateral turning. The LSD-induced turning was blocked by pretreatment with spiroperidol (0.25—0.5 mg/kg). BOL, a non-hallucinogenic congener of LSD, also consistently produced significant contralateral turning ($p = 0.013$, ANOVA), but was much less effective (table 1): a dose of 5 mg/kg of BOL produced only 8.2 ± 3.4 net contralateral turns per 5 min. The time course for drug-induced rotational behavior was very similar following apomorphine, LSD or BOL: the rats turned at a relatively constant rate for the first 30 min post-injection, and showed a sharp decrease in rotation rate during the final 15 min period. None of the 3 drugs produced any other marked behavioral changes.

Administration of amphetamine produced turning in the direction ipsilateral to the lesion ($p < 0.001$, ANOVA). Doses of 0.2 and 0.5 mg/kg of amphetamine produce small, non-significant turning, while a dose of 1.0 mg/kg produced 15.9 ± 2.0 net ipsilateral

TABLE 1

Hallucinogenic drugs which produce contralateral turning.

Drug	n	Dose (mg/kg)	Net contralateral turns per 5 min ± S.E.M.
Apomorphine	12	0.2	23.3 ± 2.9 [3]
LSD [2]	7	0.05	0.3 ± 0.6
		0.10	24.1 ± 7.3 [3]
		0.20	36.6 ± 10.7 [3]
BOL [1]	9	0.5	0.0 ± 0.3
		2.0	4.4 ± 2.0
		5.0	8.2 ± 3.4 [3]

[1] $p < 0.05$, ANOVA.
[2] $p < 0.01$, ANOVA.
[3] Significantly different from saline control, $p < 0.05$, Dunnett's test.

turns per 5 min (table 2). STP and mescaline both produced significant ipsilateral turning ($p < 0.001$, ANOVA), with STP much more potent, requiring only 1/20 the dose of mescaline to produce the equivalent degree of turning (table 2). The amount of turning produced by 5 mg/kg of STP and 100 mg/kg of mescaline was approximately equivalent to that produced by 0.5—1.0 mg/kg of amphetamine. The STP-induced turning was blocked by pretreatment with spiroperidol (0.25 mg/kg). The time course for drug-induced rotational behavior showed some differences among drugs. Amphetamine produced relatively little unilateral turning during the first 15 min period, while the rate during the next 30 min was much higher and relatively constant. STP, on the other hand, produced the opposite pattern: the rate of unilateral turning was high and relatively constant during the first 30 min and decreased sharply during the final 15 min period. Finally, mescaline produced a relatively constant rate of turning throughout the 45 min observation period. None of the 3 drugs produced any other marked behavioral changes, with the exception of mild stereotyping (digging and sniffing) at the high dose of STP (5 mg/kg) and mescaline (100 mg/kg).

TABLE 2

Hallucinogenic drugs which produce ipsilateral turning.

Drug	n	Dose (mg/kg)	Net ipsilateral turns per 5 min ± S.E.M.
Amphetamine [3]	10	0.2	4.1 ± 1.5
		0.5	4.5 ± 1.3
		1.0	15.9 ± 2.0 [6]
STP [3]	10	0.1	1.6 ± 0.8
		0.5	4.3 ± 0.9
		2.0	5.9 ± 2.0 [4]
		5.0	8.4 ± 1.2 [5]
Mescaline [3]	11	20	2.0 ± 0.9
		50	7.2 ± 2.2 [4]
		100	8.9 ± 2.1 [5]
DMT [2]	9	1	0.6 ± 0.7
		5	1.6 ± 0.3
		10	2.4 ± 0.8
		20	2.3 ± 0.7
5-M-DMT [2]	9	0.25	1.0 ± 0.8
		0.75	2.8 ± 1.1
		1.25	3.1 ± 1.1
Tryptamine [1]	10	20	0.4 ± 0.2
		40	1.3 ± 0.4 [4]
Psilocin	9	1	1.1 ± 0.3
		5	2.8 ± 1.4
		10	2.5 ± 0.6
		20	0.9 ± 1.6
Methysergide	7	1	1.1 ± 0.3
		5	0.7 ± 0.5
Scopolamine	6	0.25	4.6 ± 3.2 [4]

[1] $p < 0.05$, ANOVA.
[2] $p < 0.01$, ANOVA.
[3] $p < 0.001$, ANOVA.
[4] Significantly different from saline control, $p < 0.05$, Dunnett's test.
[5] $p < 0.01$, Dunnett's test.
[6] $p < 0.001$, Dunnett's test.

Significant ipsilateral turning also occurred following administration of DMT ($p < 0.01$, ANOVA), 5-M-DMT ($p < 0.01$, ANOVA), and tryptamine ($p < 0.05$, ANOVA). The turning produced by these tryptaminergic drugs was, however, of a very small magnitude (1—3 net ipsilateral turns per 5 min). The time course for drug-induced rotational behavior was very similar following DMT, 5-M-DMT and tryptamine. The greatest amount of ipsilateral turning following each drug occurred during the first 15 min period post-injection, and steadily decreased during the next 30 min. None of the 3 drugs produced any other marked behavioral changes, with the exception of a mild serotonergic syndrome (tremor, head-weaving, forepaw-treading) (Trulson et al., 1976; Trulson and Jacobs, 1976; Jacobs, 1976) at the high doses of 5-M-DMT (0.75, 1.25 mg/kg).

Psilocin and methysergide both produced ipsilateral turning of the same order of magnitude (1—3 net turns per 5 min) as the tryptamine drugs, but analyses of variance revealed no significant effect in either case ($p > 0.1$). Neither of these two drugs produced any notable behavioral changes. Administration of

TABLE 3

Effect of unilateral (left side) brain injections of 6-OHDA on striatal monoamine levels (x ± S.E.M.), in μg/g tissue.

	DA	NE	5-HT
Right striatum	5.172 ± 0.340	0.340 ± 0.016	1.691 ± 0.078
Left striatum	0.448 ± 0.223 [1]	0.075 ± 0.020 [1]	1.632 ± 0.087
Depletion	(91.3%)	(77.9%)	(3.5%)

[1] $p < 0.001$ (2-tailed *t*-tests, comparing right and left sides, n = 6).

scopolamine (0.25 mg/kg) also produced a small amount of ipsilateral turning (4.6 ± 3.2 net turns per 5 min), which was approximately evenly distributed across the 45 min observation period. Injection of 6-OHDA into the nigrostriatal pathway produced marked reductions in the levels of dopamine (−91.3%) and norepinephrine (−77.9%) in the left striatum, and no change in striatal serotonin levels (table 3).

4. Discussion

The present data indicate that dopamine receptor stimulation, although not crucial to the hallucinogenic activity of drugs, may be an important factor in determining their potency. This is based on evidence that while the most potent hallucinogens activate dopamine receptors, as evidenced by their ability to elicit strong unilateral rotation and for this effect to be reversed by dopamine receptor blockade, other less potent hallucinogens have either no dopaminergic activity or at best a weak one.

LSD is the most potent of the hallucinogens, producing profound psychological and perceptual changes in humans in doses of less than 1 μg/kg (Abramson et al., 1955; Isbell et al., 1956). In the present study, LSD (0.2 mg/kg) was found to be more effective than an equivalent dose of apomorphine in producing contralateral turning in rats with unilateral 6-OHDA lesions (table 1). This confirms a previous report by Pieri et al. (1975), and suggests that LSD is an extremely potent dopamine receptor agonist. BOL, a non-hallucinogenic congener of LSD, also produces significant contralateral turning in high doses, but the effect is much smaller than that observed with LSD. The relative ineffectiveness of BOL as an hallucinogen is apparently due to its weak effect in inactivating the central serotonin system (Aghajanian et al., 1970).

The second most potent hallucinogen, STP, produces behavioral changes in humans in doses of approximately 50 μg/kg (Snyder et al., 1967). In the present study, STP produced significant ipsilateral turning at doses of 2 and 5 mg/kg (table 2). The ipsilateral turning is the result of the dopamine-releasing action of STP (Vrbanac et al., 1975). Mescaline also releases dopamine from presynaptic stores (Leonard and Tonge, 1969), and produces ipsilateral turning in rats with unilateral 6-OHDA lesions (table 2). Mescaline is much less potent than STP, however, producing significant ipsilateral turning only in doses of 50 and 100 mg/kg. In humans, mescaline is effective in doses of approximately 2—5 mg/kg (Wolbach et al., 1962). The amount of turning produced by STP and mescaline is equivalent to that produced by 0.5—1.0 mg/kg of amphetamine, indicating that these compounds have a moderate dopamine-releasing action.

DMT, which is effective in humans in doses of 0.5—1.0 mg/kg (Szara, 1970), produced a small degree of ipsilateral turning at doses of

10 and 20 mg/kg (table 2). Similarly 5-M-DMT, which is reportedly hallucinogenic in humans (Gessner, 1970), produced a small amount of ipsilateral turning at doses of 0.25—1.25 mg/kg. These relatively small effects of DMT and 5-M-DMT are probably not important for their hallucinogenic potency, since tryptamine (40 mg/kg) and scopolamine (0.25 mg/kg) produce a similar degree of ipsilateral turning (table 2). These latter two compounds are both non-dopaminergic and, more importantly, non-hallucinogenic, but stimulate general locomotor activity. Thus, the small amount of unilateral turning following all four of these drugs (1—3 net turns per 5 min) may reflect increases in general arousal or locomotor activity, rather than a dopamine releasing action.

The psilocin data indicate that stimulation of dopamine receptors is not a necessary factor in determining the potency of hallucinogens since psilocin is effective in humans in relatively low doses (50—100 μg/kg) (Wolbach et al., 1962), but does not elicit significant unilateral turning in rats with 6-OHDA lesions (table 2). Similarly, high doses of methysergide are reportedly mildly hallucinogenic (Hale and Reed, 1962), but do not elicit unilateral turning. It is important to note that, while both LSD and psilocin are effective in inactivating the serotonin system (Aghajanian and Haigler, 1975), LSD is a much more potent hallucinogen. This latter fact may be due to the potent dopamine-agonistic effect of LSD.

While the present results, demonstrating that BOL, mescaline and DMT produce significant unilateral turning, are at variance with a similar previous study which reported that all of those compounds were ineffective (Pieri et al., 1975), it should be noted that the two studies employed different dose levels of the test drugs.

In conclusion, the present data indicate that while inactivation of the brain serotonin system may be a necessary and sufficient condition for hallucinogenesis (Aghajanian et al., 1968, 1970; Aghajanian and Haigler, 1975), the ability to activate dopamine receptors may be an important modulatory factor determining the potency of hallucinogens. This hypothesis also receives support from recent studies in our laboratory, utilizing the behavioral measures in the cat which are a specific reflection of the activity of LSD and related hallucinogens (Jacobs et al., 1976, 1977b). LSD and STP were found to be much more behaviorally potent than psilocin, DMT, and mescaline, as well as producing their effects in significantly lower doses (Jacobs, Trulson, Stark and Christoph, unpublished observations).

Acknowledgement

This research was supported by grants MH 23433 and MH 13445 from the National Institute of Mental Health.

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