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Hallucinogen-Induced Rotational Behavior in Rats

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Abstract. LSD, mescaline, and MDMT (5-methoxy-*N*,*N*-dimethyltryptamine) in normal rats induced dose-dependent rotation (circling behavior), which was consistent in direction from week to week (1 week separating hallucinogen administrations). The direction of LSD-induced rotation for individual animals was the same as amphetamine-induced, but not apomorphine-induced, rotation. Of the three postsynaptic serotonin antagonists (methysergide, cyproheptadine, and 2-bromo-LSD) tested, only methysergide induced rotation; this rotation was consistent in direction from week to week, and was in the same direction as LSD-induced rotation. L-LSD induced weak rotation and was approximately six times less potent than D-LSD. *p*-Chlorophenylalanine pretreatment increased the sensitivity to LSD, whereas α-methyl-*p*-tyrosine pretreatment blocked LSD-induced rotation. Simultaneous administration of LSD and amphetamine induced rotation significantly greater than amphetamine alone; a similar effect was observed with LSD plus scopolamine. However, apomorphine plus LSD induced rotation similar in magnitude to apomorphine alone. These results suggest that the mechanism by which hallucinogens induce rotation is consistent with an inhibitory action on the serotonin-containing midbrain raphe neurons. The inhibition of raphe neuronal firing could disinhibit nigrostriatal activity (possibly at the level of the substantia nigra). Methysergide-induced rotation could result from partial antagonism of postsynaptic serotonin receptors in the substantia nigra or striatum. The dopaminergic properties of LSD may attenuate rotation resulting from disinhibition of nigrostriatal activity by interacting with presynaptic nigrostriatal dopamine autoreceptors.

Key words: Rotational behavior – Hallucinogens – Serotonergic-dopaminergic interactions – LSD – Mescaline – Methysergide – Cyproheptadine – *p*-Chlorophenylalanine – Amphetamine – Scopolamine

Following unilateral lesions of the dopamine-containing nigrostriatal pathway, animals rotate, as is the case when administered amphetamine or apomorphine (Ungerstedt, 1971a; von Voigtlander and Moore, 1973b). Amphetamine induces rotation ipsilateral to the lesioned side, presumably through the release of dopamine from axon terminals in the intact striatum (Christie and Crow, 1971; Ungerstedt, 1971a; Ungerstedt and Arbuthnott, 1970; Von Voigtlander and Moore, 1973b). The direction of rotation induced by apomorphine, which directly activates postsynaptic dopamine receptors (Ernst, 1969), depends upon which striatum receives greater activation (Jerussi and Glick, 1975; Ungerstedt, 1971b; Von Voigtlander and Moore, 1973b). This, in turn, is related to where the nigrostriatal pathway is lesioned, how the lesion is made (i.e., by physical or chemical means), and to what extent postsynaptic denervation supersensitivity develops. What is clear from studies of rotation, both in lesioned animals and in intact animals receiving unilateral electrical or pharmacologic stimulation of the striatum (Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1969; Zimmerberg and Glick, 1974), is that the direction of rotation is always contralateral to the striatum with higher dopaminergic activity.

Using rats with unilateral chemically induced nigrostriatal lesions, Pieri et al. (1974) reported that D-lysergic acid diethylamide (LSD) induced rotation contralateral to the lesioned side. This suggested that LSD, like apomorphine, was a dopamine agonist on

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denervated, supersensitive striatal dopamine receptors. Pycock and Anzelark (1975), using a similar 6-hydroxydopamine model in mice, observed weak and inconsistent contralateral rotation following high doses of LSD (1 – 1.5 mg/kg, i.p.), although Trulson et al. (1977) confirmed Pieri et al.'s findings in rats.

LSD also interacts with a dopamine-sensitive adenylate cyclase (Von Hungen et al., 1974) and postsynaptic dopamine receptors (Bennett and Snyder, 1975; Burt et al., 1976) isolated from rat striatum. It functions as a partial dopamine agonist; stimulating the cyclase in the absence of dopamine, but inhibiting it in the presence of dopamine (Von Hungen et al., 1974).

LSD decreases the firing rates of serotonin-containing midbrain raphe neurons (Aghajanian, 1972) and the turnover of brain serotonin (Anden et al., 1968; Rosecrans et al., 1967). Both effects are apparently due to a direct action of LSD on raphe neurons rather than on neurons postsynaptic to the raphe (Haigler and Aghajanian, 1974a, b).

Recently it has been demonstrated that amphetamine or apomorphine will induce dose-dependent rotation in normal, intact rats (Jerussi and Glick, 1974, 1975), mice (Glick et al., 1977b), or gerbils (Jerussi and Glick, 1976a). This rotation, for individual animals, is stable in direction and magnitude when either drug is administered at weekly intervals. Amphetamine-induced rotation has been correlated with an intrinsic presynaptic asymmetry in nigrostriatal dopamine content (Glick et al., 1974; Jerussi and Glick, 1976b), whereas apomorphine-induced rotation has been attributed to an intrinsic asymmetry in postsynaptic dopamine receptor sensitivity (Glick et al., 1977b; Jerussi and Glick, 1975, 1976b). Since the same drugs that induce rotation in lesioned animals also do so in intact animals, the present investigation was undertaken to determine whether LSD, two other hallucinogens (mescaline and 5-methoxy-*N*,*N*-dimethyl tryptamine), and some nonhallucinogenic agents that interact with serotonergic mechanisms could induce rotational behavior in normal rats.

Materials and Methods

Female Sprague-Dawley albino rats ranging in weight from 230 – 300 g were used. The apparatus for measuring rotation was an automated rotometer (Glick et al., 1977b; Ungerstedt and Arbuthnott, 1970), which differentiates between complete 360° rotations and incomplete oscillatory turns. Full rotations to the left and right were separately totalled. The experimental procedure consisted of a 15-min habituation period, immediately followed by intraperitoneal administration of drug or vehicle and a 60-min testing period. Net rotations for the pre- and post-injection periods were determined by subtracting rotations in the nondominant direction from rotations in the dominant direction. Drugs were usually dissolved in physiologic (0.9%) saline and injected at a volume of 1 ml/kg. The following drugs were used: D-lysergic acid diethylamide tartrate (LSD); L-lysergic acid diethylamide tartrate (L-LSD); 2-bromo-D-lysergic acid diethylamide tartrate (2-bromo-LSD); mescaline HCl; 5-methoxy-*N*,*N*-dimethyltryptamine (MDMT); methysergide bimaleate; cyproheptadine HCl; *d*-amphetamine sulfate; apomorphine HCl; scopolamine HBr; D,L-alpha-methyl-*p*-tyrosine methyl ester HCl (AMPT); D,L-*p*-chlorophenylalanine methyl ester HCl (PCPA).

Dose-Response Relationships. Dose-response relationships were obtained for three hallucinogenic agents: LSD, mescaline, and MDMT; the nonhallucinogenic enantiomer of LSD, L-LSD; and the serotonergic antagonists 2-bromo-LSD, methysergide, and cyproheptadine. A dose-response relationship for LSD was also generated before and after pretreatment with the tryptophan hydroxylase inhibitor, PCPA.

Each point on a dose-response curve represents the mean net rotations of a separate group of animals for the 60-min interval immediately following administration of drug or vehicle. Analysis of variance (ANOVAR) and two-tailed *t*-tests were used for data analysis.

Consistency of Drug-Induced Rotation. The directional consistency of drug-induced rotation was determined (using chi-square analysis) by comparing the direction of net rotations for individual animals given the same or different drugs, with 1 week separating drug administrations. If rotation is a reliable behavioral index, then the same drug, given at the same dose to the same animal, should induce rotation in the same direction every week. Two rotation-inducing drugs with a common mechanism of action should cause the same animal to rotate in the same direction every week. However, two drugs that induce individual animals to rotate in the same direction need not do so through the same mechanism.

Pharmacologic Interactions: Effects upon Rotational Behavior. The drug interaction experiments were designed to elucidate the neurotransmitter systems subserving rotation induced by LSD. For each drug interaction experiment, the same group of animals was used throughout, so that each animal served as its own control. Two-tailed *t*-tests were used for data analysis.

Results

Dose-Response Relationships. LSD induced dose-dependent rotational behavior in normal rats (Fig. 1).

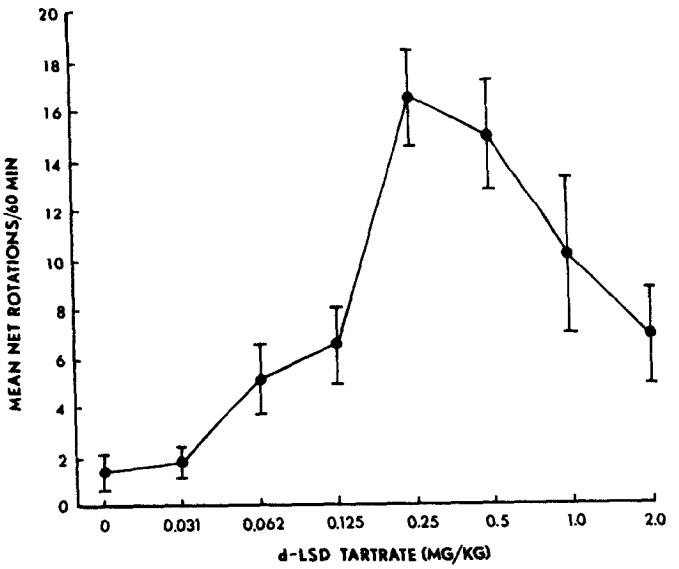

Fig. 1. Dose-response relationship for D-LSD-induced rotation (mean ± standard error)

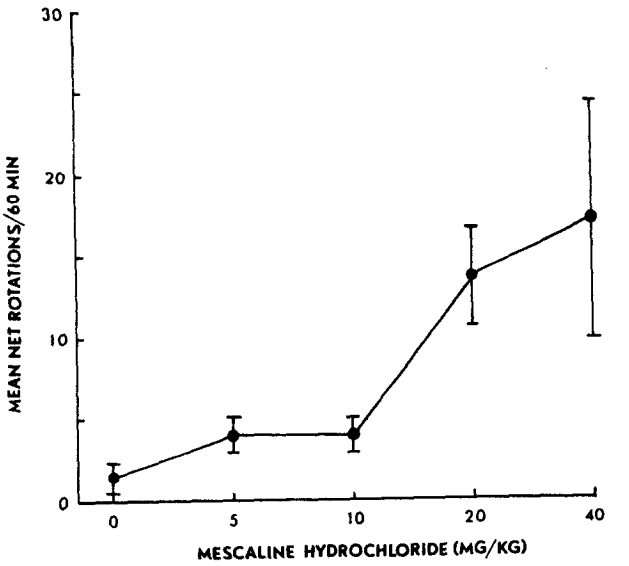

Fig. 2. Dose-response relationship for mescaline-induced rotation (mean ± standard error)

One-way ANOVAR indicated a significant drug effect ($P < 0.001$) and subsequent t-tests indicated that all doses greater than 0.31 mg/kg induced significant rotation ($P < 0.05$ to $P < 0.001$). The rotation induced by LSD in the dose range 0.062 – 0.5 mg/kg occurred without any other gross behavioral changes. However, at the highest doses of LSD (1 and 2 mg/kg) the animals exhibited a characteristic behavioral syndrome (aberrant behavior) consisting of shaking, piloerection, salivation, and marked splaying of the limbs (Dixon, 1968).

Dose-dependent rotational behavior was also induced by the methoxylated phenylethylamine derivative, mescaline (Fig. 2). One-way ANOVAR indicated that significant rotation was induced by 20 and 40 mg/kg doses ($P < 0.01$ and $P < 0.05$, respectively). Doses greater than 40 mg/kg were not administered since considerable aberrant behavior, similar to that observed with the highest doses of LSD, occurred at 40 mg/kg.

Figure 3 illustrates the dose-response relationship generated after the administration of MDMT. One-way ANOVAR revealed a significant drug effect ($P < 0.005$) and subsequent t-tests showed that significant rotation was induced by 1 and 2.5 mg/kg doses ($P < 0.005$ and $P < 0.01$, respectively). Following 2.5 mg/kg doses, the animals displayed considerable aberrant behavior, similar to that seen after high doses of LSD or mescaline.

Three serotonin antagonists, methysergide, cyproheptadine, and 2-bromo-LSD, were tested for the capacity to induce rotation. Neither cyproheptadine nor 2-bromo-LSD induced rotation at any of the doses

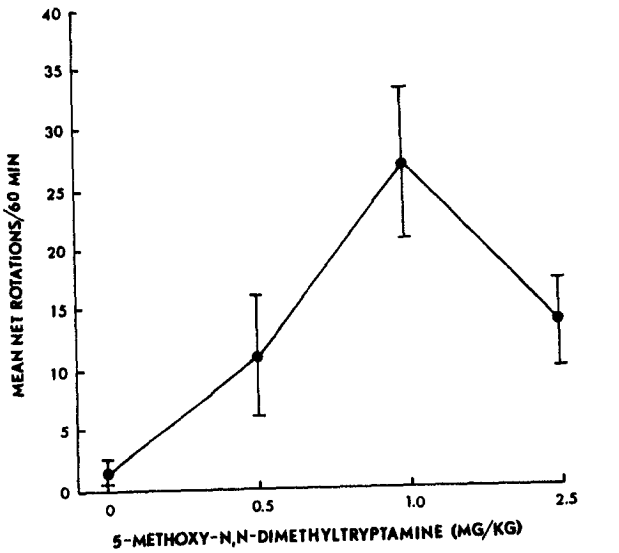

Fig. 3. Dose-response relationship for 5-methoxy-*N*,*N*-dimethyltryptamine-induced rotation (mean ± standard error)

tested. For methysergide, one-way ANOVAR revealed no significant drug effect. However, t-tests indicated that rotation induced by 10 mg/kg doses ($N = 8$) was significantly greater ($P < 0.005$) than saline-injected controls.

Rotation was also induced by L-LSD. One-way ANOVAR revealed a significant drug effect ($P < 0.05$) and subsequent t-tests indicated that the 0.5 mg/kg dose ($N = 6$) induced significant rotation ($P < 0.02$), although the magnitude was considerably less than after D-LSD.

Figure 4 illustrates the dose-response relationships for LSD-induced rotation both before (day 1), and after (days 8 and 15) PCPA treatment. Rats were tested with LSD on day 1, administered PCPA (300 mg/kg) on day 5, and retested on days 8 and 15. Three-way ANOVAR indicated a significant effect of dose ($P < 0.01$), time ($P < 0.05$), and PCPA treatment ($P < 0.05$). There was also a significant interaction between the dose of LSD and the PCPA treatment ($P < 0.05$); that is, the effect of PCPA depended upon the dose of LSD administered. Subsequent analysis with *t*-tests revealed that on days 8 and 15, only the 0.125 mg/kg dose induced rotation significantly greater than the day 1 control ($P < 0.05$) receiving a comparable dose of LSD.

Consistency of Drug-Induced Rotation. For all drugs tested twice at the same dose (LSD, 0.25 mg/kg, $N = 6$; mescaline, 20 mg/kg, $N = 11$; MDMT, 1.0 mg/kg, $N = 6$; methysergide, 10 mg/kg, $N = 7$), the direction of rotation was consistent ($P < 0.001$ – $P < 0.05$) and the mean net rotations were not significantly different from week to week. Since the direction of rotation was consistent for LSD, mescaline, MDMT, and methysergide, directional consistency was examined between these drugs ($N = 7-12$). Regardless of the order of administration, LSD, mescaline, MDMT, or methysergide induced rotation in the same direction ($P < 0.01$ to $P < 0.05$).

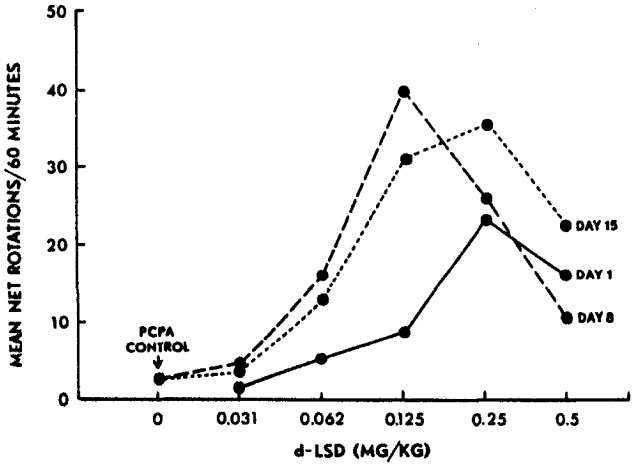

Fig. 4. Dose-response relationship for D-LSD-induced rotation, before (day 1) and after (days 8 and 15) treatment with *p*-chlorophenylalanine (300 mg/kg on day 5)

The direction of rotation induced by LSD was then compared to the direction of rotation induced by an indirectly acting dopamine agonist (amphetamine, 1 mg/kg, $N = 19$) and a directly acting dopamine agonist (apomorphine, 10 mg/kg, $N = 19$). The direction of LSD-induced rotation was the same as that induced by amphetamine ($P < 0.05$), but not the same as that induced by apomorphine.

LSD and AMPT Interactions. Pretreatment with the tyrosine hydroxylase inhibitor AMPT (administered 135 min prior to retest with LSD at a dose of 150 mg/kg) significantly reduced the magnitude of rotation induced by 0.25 mg/kg of LSD ($P < 0.005$, $N = 9$).

LSD-Amphetamine, LSD-Apomorphine, and LSD-Scopolamine Interactions. Table 1 summarizes these results. The first row gives the mean net rotations induced by LSD alone. In the second row the term (B) refers to the mean net rotations induced by the other drug used in that particular interaction experiment (i.e., amphetamine, apomorphine, or scopolamine) when administered alone. Combo (third row) refers to the mean net rotations induced by the simultaneous administration of 0.25 mg/kg of LSD and either 1 mg/kg of amphetamine, 10 mg/kg of apomorphine, or 1 mg/kg of scopolamine. The term (LSD) + (B) (fourth row) refers to the algebraic sum of the mean net rotations induced

Table 1. Amphetamine-, apomorphine-, and scopolamine-induced rotation; interactions with LSD-induced rotation

Drug treatment	*d*-Amphetamine + LSD ($N = 8$)	Apomorphine + LSD ($N = 6$)	Scopolamine + LSD ($N = 8$)
(LSD) (0.25 mg/kg)	18.2 ± 5.38	10.2 ± 3.21	8.8 ± 3.06
(B) Amphetamine (1 mg/kg) Apomorphine (10 mg/kg) Scopolamine (1 mg/kg)	20.1 ± 9.68	42.3 ± 14.56	38.6 ± 8.78
Combo	110.8 ± 38.17*	64.2 ± 25.76	69.9 ± 6.66***
(LSD) + (B)	31.1 ± 11.82	43.5 ± 13.10**	44.1 ± 10.19****

* Significantly greater than (LSD), (B), or Combo ($P < 0.05$)
** Significantly greater than (LSD) ($P < 0.05$)
*** Significantly greater than (LSD) or (B) ($P < 0.05$ and $P < 0.05$, respectively)
**** Significantly greater than LSD ($P < 0.01$)'
Mean net rotations were compared using two-tailed *t*-tests

by either drug alone, and was computed as follows: If an animal went in the same direction with LSD or (B), then the net rotations were added together; if an animal went in opposite directions, then the net rotations were subtracted. The algebraic sum takes into account the directions of rotation induced by (LSD) or (B) when administered alone, since they would be expected to add if in the same direction and subtract if in opposite directions.

For LSD-amphetamine interactions, the mean net rotations induced by the Combo were significantly higher than LSD ($P < 0.05$), amphetamine ($P < 0.05$), or (LSD) + (amphetamine) ($P < 0.05$). However, when (LSD) + (amphetamine) was compared to LSD or amphetamine alone, there were no significant differences ($P > 0.2$ and $P > 0.1$, respectively).

For the LSD-apomorphine interactions, analysis with paired t-tests revealed that the only means differeing significantly in magnitude were LSD compared to (LSD) + (apomorphine) ($P < 0.05$).

For the LSD-scopolamine interactions, the mean net rotations induced by the Combo were significantly higher than LSD ($P < 0.05$) or scopolamine ($P < 0.05$) alone. In addition, the mean net rotations induced by (LSD) + (scopolamine) were significantly higher than for LSD ($P < 0.01$), but not for scopolamine ($P > 0.2$).

Discussion

This investigation has demonstrated dose-dependent rotational behavior in normal rats induced by the hallucinogenic agents LSD, mescaline, and MDMT; the nonhallucinogenic enantiomer, L-LSD; and the serotonergic antagonist methysergide. Apparently, these agents interact with the nigrostriatal systems so that the intrinsic asymmetry in dopaminergic function is manifested as rotational behavior.

Since LSD induces contralateral rotation in unilaterally lesioned animals (Pieri et al., 1974; Trulson et al., 1977), and is a partial dopamine agonist at striatal dopamine receptors (Bennett and Snyder, 1975; Burt et al., 1976), LSD could be inducing rotation in normal rats by activating postsynaptic striatal dopamine receptors. However, the direction induced by LSD was not the same as that induced by apomorphine. Furthermore, LSD-induced rotation was antagonized by AMPT; this has not been observed for apomorphine-induced rotation in lesioned (Von Voigtlander and Moore, 1973b) or unlesioned (Jerussi and Glick, 1976b) animals.

The LSD-amphetamine and LSD-PCPA interactions and the directional consistency of the three hallucinogens suggest that nondopaminergic mechanisms are also involved. The mean net rotations following a combination of amphetamine (1 mg/kg) and LSD (0.25 mg/kg) were significantly greater than those observed with amphetamine alone. Comparison of the amphetamine-LSD combination with 93 rats administered with 1 mg/kg amphetamine (mean net rotations = 44.9), revealed that the combination exhibited significantly greater ($P < 0.001$; unpaired t-test) mean net rotations. Since this dose is at the peak of the dose-response relationship for amphetamine-induced rotation in normal rats (Jerussi and Glick, 1975), the additivity of rotation induced by amphetamine plus LSD suggests an interaction with at least two receptor systems.

The increase in rotation induced by an amphetamine-LSD combination could be due to amphetamine-induced increases in the release of nigrostriatal dopamine coupled with LSD-induced increases in the firing rates of nigrostriatal neurons. Indeed, Von Voigtlander and Moore (1973a) found that electrically induced increases in nigrostriatal firing rates increased amphetamine- or amantadine-induced release of ^{3}H-dopamine into the cerebral ventricles.

LSD also interacts with presynaptic autoreceptors apparently involved in the regulation of dopamine synthesis and release (Carlsson et al., 1976; Roth et al., 1975). Using functionally intact dopaminergic systems, Persson (1977) found that LSD or apomorphine antagonized the increase in L-dopa accumulation induced by gamma-butyrolactone (GBL). Since GBL blocks impulse flow in the nigrostriatal pathway (Roth et al., 1975), a dopamine agonist could only slow down dopamine synthesis by interacting with nigrostriatal autoreceptors. Thus, the apparent discrepancy between the rotatory actions of LSD in lesioned and unlesioned animals could be resolved as follows: In animals with unilateral lesions of the nigrostriatal pathway little dopamine would be released in the denervated striatum so that the dopamine agonist properties of LSD on postsynaptic receptors would predominate and contralateral rotation would ensue. In intact animals LSD would both activate dopamine autoreceptors and disinhibit nigrostriatal activity indirectly by virtue of its serotonergic properties. The consequent perturbation of striatal dopaminergic function would be behaviorally manifested as rotation, albeit of relatively low magnitude.

The enhanced sensitivity of PCPA-pretreated animals suggests that in a state of partial serotonin depletion a lower concentration of LSD is required to reduce serotonin output to some critical level at which the disinhibition of nigrostriatal activity is manifested as rotation. On days 8 and 15, 0.125 mg/kg of LSD was maximally effective; in untreated rats this dose was submaximal. On day 8, there were no significant

increases in rotation following the 0.25 or 0.5 mg/kg doses. In fact, at 0.5 mg/kg rotation on day 8 was considerably lower than on day 1 (Fig. 4). Perhaps in PCPA-pretreated rats, 0.125 mg/kg of LSD produces maximal disinhibition of nigrostriatal activity without significantly interacting with nigrostriatal autoreceptors. Thus, robust rotation ensues. However, as the dose of LSD increases, the activation of autoreceptors also increases, resulting in rotation of a lower magnitude even though raphe activity may be completed turned off.

Bennett and Aghajanian (1976) estimated that the concentration of free LSD in the midbrain producing 50% inhibition of dorsal raphe firing was 4.6 nM, while the concentration producing complete inhibition was 9.7 nM. However, Von Hungen et al. (1974) found that LSD did not significantly stimulate striatal dopamine-sensitive adenylate cyclase at concentrations below 100 nM. If the interaction of LSD with nigrostriatal autoreceptors is comparable to the interaction with striatal adenylate cyclase, then the increased sensitivity of PCPA-pretreated rats could result from differential sensitivities of midbrain LSD receptors and nigrostriatal dopamine autoreceptors to LSD.

The direction of rotation induced by LSD, mescaline, or MDMT was the same and all three reversibly inhibit raphe firing. However, neither mescaline (Burt et al., 1976; Von Hungen et al., 1974) nor MDMT (Von Hungen et al., 1974) interact with striatal dopamine-sensitive adenylate cyclase or postsynaptic dopamine receptors. Thus, disinhibition of nigrostriatal activity may be the common mechanism by which they induce rotation in normal rats.

MDMT-induced rotation occurred almost entirely during the first 15 min of the 60-min testing period, whereas LSD-induced rotation was more or less constant. Although MDMT is a weak monoamine oxidase inhibitor (Brawley and Duffield, 1972), it is primarily a direct-acting serotonergic agonist (Fuxe et al., 1972; Graham-Smith, 1971). Since tachyphylaxis is a prominent feature of the central action of serotonin (Johnson et al., 1969; Roberts and Straughan, 1967), the transiency of rotation induced by MDMT may be due to tachyphylaxis of central serotonin receptor response. Furthermore, the dopaminergic properties of LSD may attenuate rotation concomitant with disinhibition of nigrostriatal activity. Recently, Christoph et al. (1977) found that 78% of dopaminergic nigral units exhibited decreased firing rates following intravenous LSD, whereas the remaining 22% were either excited or unaffected; non-dopaminergic units were excited. In contrast, MDMT had exclusively excitatory effects. Perhaps the inhibition exerted by LSD resulted from the interaction of its rate-increasing (via blockade of serotonergic inhibition) and rate-decreasing (via its dopaminergic actions) properties. MDMT, devoid of dopaminergic activity, would be exclusively rate increasing.

Methysergide-induced rotation was of low magnitude, but the direction was consistent from week to week, and the same as that induced by LSD. Methysergide partially antagonizes the inhibition of hippocampal pyramidal (Segal, 1975) or striatal neurons (Olpe and Koella, 1977) induced by iontophoretic serotonin or electrical stimulation of the midbrain raphe. Thus, methysergide could moderately disinhibit nigrostriatal activity via partial antagonism of serotonin.

2-Bromo-LSD is considered a central serotonergic antagonist (Vane et al., 1961), yet iontophoretic 2-bromo-LSD produced a slight decrease in dorsal raphe firing, and intensified the depressant effects of iontophoretic serotonin or LSD when administered concurrently (Aghajanian, 1976). Furthermore, the depressant effects of iontophoretic serotonin on identified, serotonergically innervated neurons were not attenuated by simultaneous iontophoretic administration of 2-bromo-LSD (Aghajanian, 1976). These data do not support 2-bromo-LSD as a serotonergic antagonist on dorsal raphe neurons or on neurons receiving serotonergic innervation.

The rotation induced by the highest dose of L-LSD was of very low magnitude (approximately six times less potent than D-LSD). Of all lysergic acid derivatives synthesized and assayed for psychotomimetic potency, only the D-isomers are active (Brawley and Duffield, 1972). Thus, L-LSD-induced rotation is probably not related to psychotomimetic potency, although high enough doses might have subjective effects.

The failure of LSD to alter the magnitude of apomorphine-induced rotation may be due to autoreceptor-mediated inhibition of nigrostriatal tyrosine hydroxylase activity. Apomorphine inhibits the conversion of ^{3}H-tyrosine to dopamine in rat striatal synaptosomal preparations (Iversen et al., 1976) and inhibits tyrosine hydroxylase activity in the absence of nigrostriatal impulse activity (Persson, 1977; Van Zwieten-Boot and Noach, 1975). Decreased dopamine synthesis could attenuate the effects of LSD-induced disinhibition of the nigrostriatal pathway. Furthermore, whereas amphetamine-induced rotation in normal rats has been correlated with a presynaptic asymmetry in striatal dopamine content (Glick et al., 1974; Jerussi and Glick, 1976b), apomorphine-induced rotation has been attributed to a postsynaptic asymmetry in dopamine receptor sensitivity (Glick et al., 1977b; Jerussi and Glick, 1975; Jerussi et al., 1977). Indeed, these two drugs usually induce rotation in opposite directions (Glick et al., 1977a). Since LSD usually induced rotation in the same direction as amphetamine, but not apomorphine, LSD plus amphe-

tamine would be expected to add to rotation whereas LSD plus apomorphine would not.

The increase in rotation induced by scopolamine plus LSD could reflect a dopaminergic–cholinergic reciprocity within the striatum. Amphetamine-induced rotation in unlesioned animals is decreased by pilocarpine, but increased by scopolamine (Jerussi and Glick, 1976b). Furthermore, the direction of scopolamine- and amphetamine-induced rotation is the same for individual animals (Jerussi and Glick, 1976b). Thus, amphetamine-induced increases in the release of nigrostriatal dopamine could inhibit the activity of intrinsic striatal cholinergic interneurons, while scopolamine would mimic this effect by blocking the output of these interneurons.

Which neural pathways subserve the serotonin-induced and LSD-antagonized inhibition of nigrostriatal activity? The behavioral literature indicates that in contrast to dorsal raphe lesions (Costall and Naylor, 1974; Jacobs and Cohen, 1976), median raphe lesions produce striking effects, such as potentiation of spontaneous locomotor activity or amphetamine-induced hyperactivity (Geyer et al., 1976; Jacobs and Cohen, 1976). Asymmetric lesions of the median raphe result in apomorphine-, amphetamine-, or methylphenidate-induced contralateral rotation, which can be decreased by haloperidol or methiothepin (Costall and Naylor, 1974). Following electrical stimulation of the median raphe, a decrease in neuronal firing in the substantia nigra (particularly in the pars compacta) which could be mimicked by iontophoretic serotonin has been observed (Dray et al., 1976). In this same study, lesions of the median raphe resulted in a decrease in nigral serotonin. Thus, it is plausible that LSD, by inhibiting the firing of median raphe neurons, would disinhibit the nigrostriatal pathway at the level of the substantia nigra.

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