Psychopharmacology 52, 291–297 (1977) No. 3

Psychopharmacology (Berl.) 52, 291-297 (1977). DES 1396

Psycho pharmacology

Possible Involvement of the Central Dopaminergic System in the Antireserpine Effect of LSD

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Abstract. Both LSD and apomorphine produced yperactivity in reserpine-treated mice, LSD being more potent and longer-acting than apomorphine. 2-Brom LSD and the serotonin (5-HT) receptor agonist quipazine were ineffective in reversing reserpine sedation. Treatments with phenoxybenzamine and methysergide failed to block the stimulant effects of either LSD or apomorphine, demonstrating the noninvolvement of 5-HT or norepinephrine (NE) receptors in their action. The ineffectiveness of α-methyl-p-tyrosine in modifying the stimulant effects of LSD and apomorphine indicated a probable direct stimulant effect of these two drugs on the dopamine (DA) receptors. Low doses of chlorpromazine, haloperidol, or pimozide blocked the effects of apomorphine in reserpinized mice. Although these neuroleptics significantly reduced the effects of LSD, they failed to block completely the LSD effects even at higher doses. Apomorphine reduced the α-methyl-p-tyrosine-induced depletion of DA in the whole brain of mice, but LSD failed to do so. From these findings it is postulated that apomorphine acts as a direct DA receptor agonist, and that LSD may act directly on a site structurally closely related to DA receptor, but not necessarily identical with it. Repeated treatments with LSD did not lead to development of tolerance to its locomotor effects in reserpinized mice. Moreover, mescaline and psilocybin, which are known to exhibit cross-tolerance to LSD, failed to produce LSD-like effects in reserpine-treated mice. The effects of LSD on the DA or a related site probably are not solely responsible for its psychotomimetic effects.

Key words: LSD – Reserpine – Dopamine – Apomorphine – Norepinephrine – Serotonin – Psilocybin – Mescaline – Hallucinogens – Brom-LSD – Neuroleptics – Clonidine – Quipazine.

Investigations of the mechanisms by which reserpine produces potent and persistent central nervous system (CNS) depression and by which *d*-lysergic acid diethylamide (LSD) exerts its psychotomimetic (hallucinogenic) effects were initiated over 20 years ago, and many studies were reported during this period on the interaction of these 2 agents (Shore et al., 1955; Winter and Flataker, 1956; Taeschler and Cerletti, 1957; Isbell and Logan, 1957; Himwich, 1959; Freedman, 1960). It was assumed in the earlier reports that the main effect of reserpine on the CNS was related to a depletion of brain 5-HT (for review of the earlier literature see Costa et al., 1962). It also was found that LSD had a potent anti-5-HT effect (Gaddum, 1953; Gaddum and Hameed, 1954; Woolley and Shaw, 1954). Hence, the results of the LSD-reserpine interaction studies were explained mainly on the basis of their effects on the 5-HT system. However, the subsequent finding that reserpine not only depleted brain 5-HT but also NE and DA (Holzbauer and Vogt, 1956; Brodie et al., 1957; Carlsson et al., 1958) and the report of Carlsson et al. (1957) that L-Dopa, the precursor of catecholamines (CA) but not 5-hydroxytryptophan (5-HTP), the precursor of 5-HT, reversed reserpine depression, led to the view that the reserpine-induced depression is due predominately to CA depletion and that drugs which reverse this depression are catecholaminergic. The later findings that drugs such as apomorphine which are direct DA receptor agonists but have little effect on the NE system (Ernst, 1967; Andén et al., 1967; Roos, 1969), can reverse reserpine depression (Janssen et al., 1965; Andén et al., 1967; McKenzie, 1971; Benešová and Beneš, 1972; Butterworth et al., 1975) led to the conclusion that antagonism of reserpine depression by an agent is mediated by its central DA effects. Therefore, the reserpine reversal test now is widely used to evaluate the dopaminergic potencies of new agents (for review see Klawans and Weiner, 1974).

From the above developments, it was felt that further studies are needed to explain the LSD-induced excitation in reserpinized animals (Taeschler and Cerletti, 1957; Elder and Dillie, 1962; Votava et al., 1967; Dixon, 1968). We thought that such an effect might be due to a dopaminergic action of LSD, hence we report here some studies we have made on the interaction between these two agents. For the purpose of comparison we have included apomorphine, 2-brom-LSD, psilocybin, mescaline, and quipazine. Apomorphine is well known to be a potent DA receptor agonist (Ernst, 1967 Andén et al., 1967; Roos, 1969). 2-Brom-LSD is a nonhallucinogenic analogue of LSD but retains its 5-HT antagonistic properties (Cerletti and Rothlin, 1955; Isbell et al., 1959). Psilocybin and mescaline are hallucinogens exhibiting cross-tolerance with LSD (Balestrieri and Fontanari, 1959; Isbell et al., 1961; Winter, 1971). Quipazine is a central 5-HT receptor agonist (Rodriguez and Pardo, 1971; Medon et al., 1973; Grabowska et al., 1974; Costall and Naylor, 1975).

METHODS

Drugs used in this study were: *d*-LSD tartrate (Sandoz Labs., Basel, Switzerland), apomorphine HCl (Eli Lilly & Co., Indianapolis, Indiana), reserpine, clonidine (both from Ciba-Geigy, Summit, New Jersey), psilocybin (National Institute on Drug Abuse), brom-LSD (BOL 148, Sandoz, Basel), mescaline HCl (Hoffman-La Roche, Basel), chlorpromazine HCl (CPZ), phenoxybenzamine (both from Smith, Kline and French Laboratories, Philadelphia), methysergide (Sandoz Pharmaceuticals, Hanover, New Jersey), pimozide (Janssen Pharmaceutica, Beerse, Belgium), haloperidol (McNeil Laboratories, Fort Washington, Pennsylvania), quipazine (Miles laboratories, Elkhart, Indiana), and *dl*-α-methyl-p-tyrosine methyl ester hydrochloride (αMT, Astra Pharmaceuticals, Södertälje, Sweden).

The LSD, brom-LSD, mescaline HCl, dibenzyline, CPZ, methysergide, clonidine, quipazine, and αMT were dissolved in distilled water. The apomorphine HCl was dissolved in distilled water containing 0.01% ascorbic acid. Solutions of reserpine, pimozide and haloperidol were prepared by dissolving them in glacial acetic acid and diluting with distilled water so that the final solution contained 0.01% acetic acid, (pH 4.0). Psilocybin was dissolved by warming in 0.1 N HCl and diluting with water. The drug solutions were administered i.p. in a volume of 0.01 ml/g body weight.

Male Swiss mice (Horton Laboratories, Oakland, California), average weight 23–28 g were used and the experiments were performed at a room temperature of 22 ± 1°C. All animals were pretreated with a 5 mg/kg dose of reserpine and were used 4 h later. Drugs were given to the reserpinized mice and their motor activity was recorded by placing them individually in opaque chambers (12.5 × 12.5 × 12.5 cm) placed on an activity meter (Model 2S, Columbis Instrument Co., Columbus, Ohio). Familiarization to the new environment before drug treatments was considered unnecessary because they were sedated by reserpine.

Reserpinized Mice. LSD, apomorphine, brom-LSD, mescaline, psilocybin, and quipazine were given to the reserpinized mice and their motor activity was measured by placing them immediately on the activity meter. LSD and apomorphine were tested in doses ranging from 0.1–6.0 mg/kg in order to obtain a dose-response relationship and duration of action. For each dose 9–12 animals were used. For the other drugs, namely mescaline (5, 50 and 200 mg/kg), psilocybin (5, 50 and 200 mg/kg), and brom-LSD (1 and 10 mg/kg), only three mice were used at each dose level. Since they had no effect, more animals were not tested.

LSD Pretreatment. These experiments were done in order to determine whether tolerance occurred for the antireserpine effect of LSD, and whether cross-tolerance existed between LSD and apomorphine. Novice mice received LSD according to the following schedule: On the first day they received two doses of LSD (3 mg/kg) at 9 A.M. and 4 P.M.; on the second day they received three doses of LSD (1 mg/kg each) at 9 A.M., 1 P.M., and 4 P.M. Control animals received 0.9% NaCl instead of LSD on the same schedule. On the third day at 9 A.M., both the experimental and control groups were treated with reserpine (5 mg/kg). Four hours later each group was divided into two groups and received either LSD (1 mg/kg) or apomorphine (1 mg/kg) and their motor activity recorded.

Effects of αMT and Receptor Blockers. Rerserpinized mice were given the drugs mentioned below. The time in parentheses indicates the times before the administration of either LSD (1 mg/kg) or apomorphine HCl, (1 mg/kg). The drugs used were αMT (250 mg/kg base, 3.5 h), phenoxybenzamine (10 mg/kg, 1 h), methysergide (3 mg/kg, 15 min), haloperidol (1 or 5 mg/kg, 15 min) and pimozide (0.5 or 3 mg/kg, 2 h). Immediately after LSD or apomorphine was given, motor activity was recorded.

Interactions with Clonidine. Four hours after reserpine treatment, the animals were treated with 1 mg/kg clonidine and 3 min later different groups received either LSD or apomorphine HCl (1 mg/kg), and their motor activity measured.

Brain Catecholamine Levels. Different groups of novice animals were treated with LSD (3 mg/kg), apomorphine HCl (3 mg/kg) or 0.9% NaCl. Ten minutes later, all 3 groups received αMT (250 mg/kg base). The mice were sacrificed 3 h later, the whole brains rapidly removed, the CA's extracted by our single extraction method (Fleming et al., 1965), and estimated by the method of Laverty and Taylor (1968). Simultaneous determinations also were made using untreated animals as well as those treated either with LSD or apomorphine alone.

RESULTS

Mice treated with reserpine (5 mg/kg) were completely inactive in 4 h, showing the typical reserpine syndrome, namely hunched back posture, loss of motor activity, and ptosis. The 1-h motor activity counts of 15 reserpinized mice was negligible (11 ± 4 counts), when compared with the 1-h activity of 12 novice mice receiving saline alone (2380 ± 342). Both LSD and apomorphine effectively antagonized this reserpine depression within 3 min, and in many respects their behavioral responses also were similar in this time. Animals treated with 0.3 mg/kg or more showed locomotor activity within 3–5 min. They constantly moved with a normal gait which occasionally became jerky. Additionally, in the case of LSD, occasional whole body jerks, tremor and continuous stereotyped sniffing behavior occurred in all animals as long as the

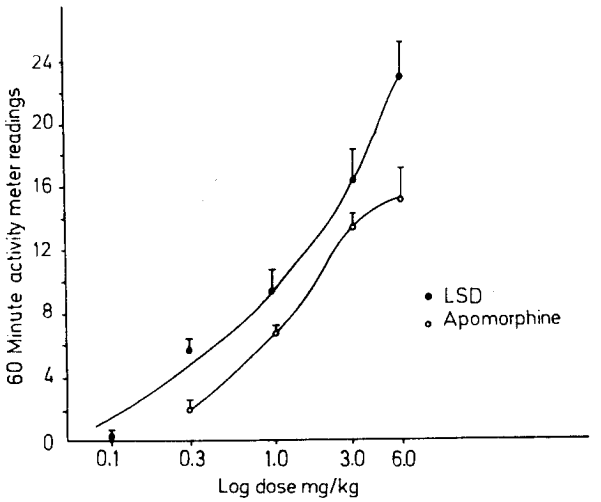

Fig. 1. Various doses of *d*-LSD tartrate (LSD) and apomorphine HCl were administered to mice pretreated with reserpine (5 mg/kg i.p., 4 h prior) and motor activity was recorded for 60 min. Each point represents the mean activity of 9–12 mice and the vertical bars indicate the standard error of the mean

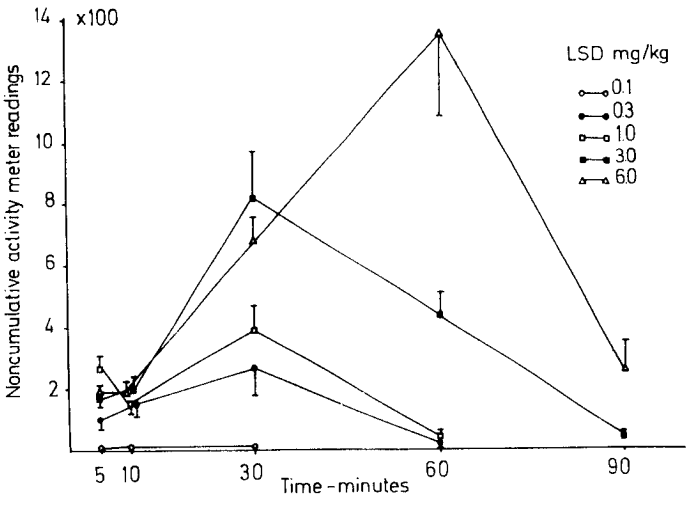

Fig. 2. Various doses of *d*-LSD tartrate (LSD) were administered to mice pretreated with reserpine (5 mg/kg i.p., 4 h prior) and their motor activity was recorded for 90 min. Each point represents the non-cumulative mean activity of 9–12 mice and the vertical bars indicate the standard error of the mean

motor activity lasted. Even at the highest dose, none of the animals showed stereotyped gnawing. In contrast, a considerable number of apomorphine-treated mice showed gnawing behavior and all of them also showed stereotyped sniffing. Thus, apomorphine in doses of 1, 3 and 6 mg/kg caused stereotyped gnawing in 40%, 66%, and 60% of the animals, respectively. The onset, intensity and duration of the stereotypy caused by both these agents chronometrically paralleled the motor excitation responses.

The dose-response curves of apomorphine and LSD show that at all doses, LSD was more active than apomorphine in causing motor activation in reserpinized mice (Fig. 1).

The effect of apomorphine reached a maximum at 3 mg/kg and the effect caused by 6 mg/kg was no different. On the other hand, larger doses of LSD caused proportionately greater effects, the curve failing to reach a plateau even at 6 mg/kg.

The duration of the antireserpine effects of various doses of LSD and apomorphine are shown in Figures 2 and 3. In order to get a clearer picture of the onset and duration of the antireserpine effects of LSD and apomorphine the noncumulative activity readings are given. For this purpose after each time interval, the meter was set back to zero. It may be seen that maximum motor excitatory effects of 0.3/kg LSD were seen at 30 min after which they declined rapidly thereafter (Fig. 2). At all these same doses, the peak effect of apomorphine occurred at 30 min, after which the effects declined to normal (Fig. 3).

Brom-LSD (1 mg/kg – 10 mg/kg) did not produce any observable effects in reserpinized mice. Mescaline

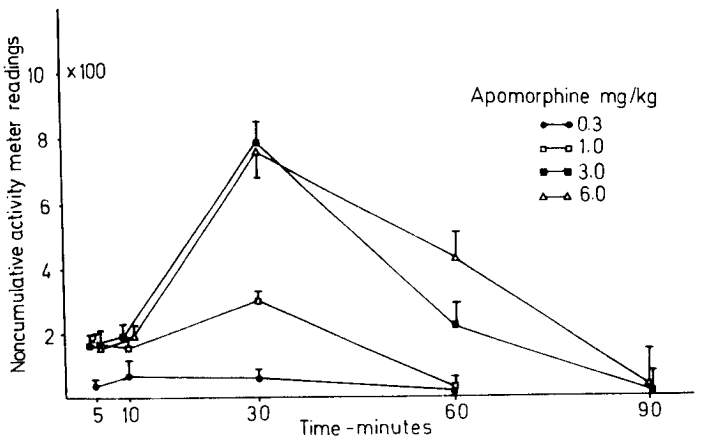

Fig. 3. Various doses of apomorphine HCl were administered to mice pretreated with reserpine (5 mg/kg i.p., 4 h prior) and their motor activity was recorded for 90 min. Each point represents the non-cumulative mean activity of 9–12 mice and the vertical bars indicate the standard error of the mean

HCl in doses of 5, 50, 100, and 200 mg/kg slightly modified the behavioral effects. At the higher dose, piloerection and repetitive movements of the forelimbs occurred. After psilocybin (5, 50, 100, and 200 mg/kg) the mice remained in the corners of the compartment, showing occasional whole body jerks and head twitches. Quipazine (25 mg/kg) initially seemed to have a slight antireserpine effect, but this consisted only of whole body jerks, head shakes and forelimb movements. Locomotor stimulation was not produced by any of these compounds in the doses used.

Table 1. Influence of drug treatments on the locomotor stimulation produced by LSD and apomorphine in reserpinized mice

Treatment	30 min motor activity readings ± S.E.	
	LSD 1 mg/kg	Apomorphine 1 mg/kg
Control (reserpine alone)	892 ± 128 (12)	622 ± 46 (12)
αMT 250 mg/kg	872 ± 143 (15)	459 ± 125 (21)
Phenoxybenzamine 10 mg/kg	736 ± 142 (12)	585 ± 172 (12)
Methysergide 3 mg/kg	750 ± 235 (12)	828 ± 74 $P < 0.025$ (9)
Chlorpromazine HCl 3 mg/kg	134 ± 17 $P < 0.01$ (9)	40 ± 6 $P < 0.001$ (9)
Haloperidol 1 mg/kg	326 ± 79 $P < 0.01$ (12)	54 ± 18 $P < 0.001$ (15)
5 mg/kg	168 ± 43 $P < 0.001$ (12)	
Pimozide 0.5 mg/kg	239 ± 38 $P < 0.005$ (9)	24 ± 13 $P < 0.001$ (12)
3 mg/kg	225 ± 29 $P < 0.005$ (12)	

Values given in parentheses indicate the number of mice used. Probability was calculated using the Student's t test by comparing with groups receiving drug-treatment against the control group. All these values were found to be significant to < 0.01 level when calculated using Dunnett's two tail comparison [Dunnett, C. W.: J. Amer. Statist. Ass. **50**, 1096 (1955)] except that of haloperidol 1 mg/kg + LSD ($P < 0.05$) and methysergide + apomorphine ($P > 0.05$)

Table 2. Influence of clonidine on the locomotor stimulation produced by LSD and apomorphine in reserpinized mice

Treatment		No. animals	30 min motor activity readings ± S.E.
LSD	1 mg/kg	9	794 ± 118
Apomorphine HCl	1 mg/kg	9	644 ± 56
Clonidine	1 mg/kg	9	76 ± 15
Clonidine 1.0 + LSD	1.0	12	1454 ± 170*
Clonidine 1.0 + Apomorph.	1.0	12	1472 ± 44*

Probability was calculated using Student's t test by comparing with the groups receiving either LSD or apomorphine. * $P < 0.001$ when compared with LSD or apomorphine alone

Table 3. Effect of apomorphine and LSD on the αMT-induced depletion and brain catecholamine in mice

Treatment	No animals	Brain catecholamine content (per cent of control ± S.E.)*	
		NE	DA
Control (no treatment)	20	99.98 ± 1.41	100.0 ± 1.73
Apomorphine HCl 3 mg/kg	5	98.10 ± 2.23	95.32 ± 5.00
LSD, 3 mg/kg	5	98.58 ± 2.64	99.1 ± 2.00
αMT, 250 mg/kg	20	57.45 ± 2.0	48.28 ± 1.41
Apomorphine 3 mg/kg + αMT	5	48.56 ± 3.3**	59.82 ± 6.0***
LSD 3.0 + αMT	15	56.89 ± 2.23	49.02 ± 1.7

* Catecholamine content expressed as mg/g fresh whole brain ± S.E. Control NE = 0.4075 ± 0.000; Control DA = 0.8613 ± 0.014 ($N = 15$)

** $P < 0.05$ } When compared with MT group using Student's t test

*** $P < 0.025$ }

In reserpinized mice receiving repeated doses of LSD, either LSD or apomorphine, 1 mg/kg, gave activity meter readings 94% and 95% respectively of the reserpinized saline-treated controls receiving the same doses of these 2 drugs. These activity changes were not statistically significant. Hence it was concluded that tolerance does not develop to the anti-reserpine effect of LSD nor between LSD and apomorphine.

The results of the drug interaction studies are given in Table 1.

αMT and phenoxybenzamine did not significantly modify the motor responses to either LSD or apomorphine in reserpinized mice. Methysergide potentiated the apomorphine effect but did not influence the effect of LSD. CPZ, haloperidol and pimozide almost completely abolished the apomorphine response. Although these compounds significantly reduced the effects of LSD, complete blockade comparable to the inhibition by these compounds on the effects of apomorphine was not seen even when the doses of these DA receptor antagonists were increased by 5–6 fold.

The effects produced by clonidine (1 mg/kg) in reserpinized animals consistered of marked piloerection and exophthalmos. Motor excitation did not occur. However, in the clonidine-treated mice both LSD and apomorphine caused motor excitation (Table 2).

In both these cases, the animals showed more well-coordinated locomotion than occurred after apomorphine or LSD alone. These mice, which also showed piloerection and exophthalmos, resembled mice treated with high doses of *d*-amphetamine.

Changes in brain catecholamine levels are given in Table 3.

Neither apomorphine nor LSD affected the levels of NE and DA in whole brain. LSD was ineffective in modifying the rate of αMT-induced depletion of brain CA's. On the other hand, apomorphine enhanced the depletion of NE and decreased that of DA.

DISCUSSION

The effect of reserpine on the central monoaminergic systems is purely presynaptic, depleting monoamines (for review see Costa et al., 1962) and leaving the postsynaptic sites unoccupied. Hence the effects of drugs acting on the NE, DA and 5-HT receptors can be conveniently studied in reserpinized animals. In the present studies the motor stimulant effects of apomorphine in reserpinized animals were not affected αMT, but were effectively blocked by the DA receptor antagonists. This, together with the inability of phenoxybenzamine to block the apomorphine effect, give evidence for a direct DA receptor stimulation by apomorphine. This is in accordance with many reports in the literature (see *Introduction* for references).

As mentioned in the *Introduction*, effective reversal of reserpine depression leading to locomotor stimulation can be produced only by drugs which activate the CNS dopaminergic system. In the present studies the 5-HT receptor antagonists brom-LSD and methysergide both failed to do so. Further evidence that the serotoninergic system is not involved in the LSD reversal of reserpine depression is the lack of activity of quipazine, a direct 5-HT receptor agonist (for references see *Introduction*), and the earlier report by Carlsson et al. (1957) that 5-HTP also had no such effect. Hence, the well-known effects of LSD on the central 5-HT system (for review see Aghajanian and Haigler, 1974), need not be considered in the present context. However, from the fact that methysergide potentiated the effect of apomorphine, but not that of LSD, it seems possible that the anti-5-HT effect inherent in the LSD molecule might have contributed to its comparatively greater effectiveness than apomorphine. Enhancement of apomorphine-induced stereotypy by methysergide has been reported by Weiner et al. (1975).

The phenylethylamine moiety of LSD and its behavioral effects in animals, namely hyperexcitability, hyperglycemia, exophthalmos, piloerection and rage reactions (for review see Rothlin, 1957) led earlier investigators to postulate that LSD causes CNS sympathetic stimulation and that NE is involved in its behavioral effects (Bogdanski et al., 1957; Brodie et al., 1959; Elder and Dille, 1962; Dixon, 1968). However, this does not seem to be the case in the reversal of reserpine depression since phenoxybenzamine, an α-adrenergic receptor blocking agent, and clonidine, a direct NE receptor agonist (Andén et al., 1970), both failed to cause motor excitation in reserpinized mice. Our finding with clonidine is in agreement with the reports of Andén et al. (1970) and Maj et al. (1972). They proposed that stimulation of both DA and NE systems are required for maximal locomotor activity. Apomorphine preferentially stimulates DA receptors and LSD seems to stimulate a functionally identical site. Clonidine, due to its NE-stimulating effects further enhances the locomotor effects of both apomorphine and LSD.

A direct DA receptor agonist effect would explain the antireserpine effects of LSD. In fact, LSD was more effective than apomorphine in this regard. Our drug interaction studies also give evidence for the DA effect of LSD, e.g. the stimulant effects of LSD, like apomorphine, were not blocked by αMT, but were reduced by the DA receptor antagonists.

While this work was nearing completion, a number of reports appeared also giving evidence for a DA receptor agonistic effect of LSD. Using the method of Ungerstedt et al. (1973), it was found that LSD, like apomorphine, caused rotational locomotion toward the intact side in unilateral 6-hydroxydopamine striatal lesioned rats (Fuxe et al., 1975; Pieri et al., 1975; Kelly, 1975). Brom-LSD was inactive in this model (Kelly, 1975). Also, low concentrations of LSD stimulate the DA-sensitive adenylate cyclase activity of rat corpus striatum (Von Hungen et al., 1975; Da Prada et al., 1975; Spano et al., 1975).

Effects of drugs on monoamine receptors also will be reflected in the turnover of the monoamines. DA receptor antagonists enhance the turnover of DA (Cheramy et al., 1970; Andén et al., 1972), and DA agonists have the opposite effect (Andén et al., 1967). Although unequivocal data indicating a decrease in the turnover of DA have been obtained in the case of apomorphine (Andén et al., 1967; Roos, 1969; Lal et al., 1972), the results obtained with LSD have been less convincing. Andén et al. (1968) observed that in a dose which significantly decreased the turnover of brain 5-HT in rats, LSD did not change that of DA. Fuxe et al. (1975) also failed to observe a change in the turnover of brain DA in rats. Da Prada et al. (1975) found only a minimally significant reduction in the turnover of DA. Although only microgram doses of LSD were required to produce turning behavior in rats (Fuxe et al., 1975; Pieri et al., 1975), 4–5 times higher doses were required to decrease the turnover of brain DA (Da Prada et al., 1975).

In the present studies, whereas apomorphine significantly reduced the αMT-induced depletion of brain DA, an equivalent dose of LSD, which exerted

more intense and durable antireserpine effects, failed to do so. This finding, together with the incomplete blockade by the neuroleptics of the motor stimulation caused by LSD, tempts one to postulate that there may be a new receptor site upon which LSD acts. It may be closely related structurally or contiguous with the main DA receptors, and the neuroleptics may act only as partial antagonists at this site. Much more experimental data will be required to support this hypothesis.

Whether or not LSD acting on this postulated site may be responsible for the psychotomimetic effects is of course open to question. It is well-known that both animals and humans develop tolerance to the behavioral effects of LSD (Cholden et al., 1955; Isbell et al., 1955; Gogerty and Dille, 1956; Freedman et al., 1958). In the present studies, repeated doses of LSD failed to produce tolerance to the effects studied. Moreover, drugs known to possess cross-tolerance with LSD, namely psilocybin and mescaline (see *Introduction* for references), failed to produce LSD-like effects in reserpinized mice even in doses 300 times higher than the minimal effective dose of LSD.

These facts, together with the report of Pieri et al. (1975) that the rotational behavior of LSD in striatal lesioned rats do not develop tolerance, indicate that this particular site upon which LSD acts is not solely responsible for its psychotomimetic effects. Whether or not it contributes to these effects is uncertain.

Acknowledgement. We are very grateful to the National Institute on Drug Abuse (NIDA), Rockville, Maryland for their efforts to make available to us as quickly as possible the LSD, brom-LSD, psilocybin and mescaline, and to the pharmaceutical firms mentioned under *Methods* for the other drugs. We also wish to express our gratitude to Dr. Edward Gocka, Chief, Predictive and Evaluative Models Research, V. A. Hospital, Sepulveda for the statistical evaluation of the data and to Mr. Alex Alcaraz, Neuropharmacology Research, ibid. for the excellent technical assistance in determining the CA's.

Supported by the Medical Research Service of the Veterans Administration.

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Received March 4, 1976; Final Version October 5, 1976