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MAO Inhibition and the Effects of Centrally Administered LSD, Serotonin, and 5-Methoxytryptamine on the Conditioned Avoidance Response in Rats

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Abstract. Pretreatment with the MAO-inhibitors iproniazid, clorgyline, or deprenyl abolishes the effects of LSD on the conditioned avoidance response (CAR) in rats. The effects of serotonin (5-HT) and 5-methoxytryptamine (5-MT) are greatly potentiated by these substances. Brain levels of LSD are not affected by MAO inhibition whereas levels of 5-HT and 5-MT are significantly elevated. It is postulated that the decreased behavioral response to LSD is the result of 'MAO inhibitor-induced' changes whereas the increased response of 5-HT and 5-MT results from increased brain levels of these compounds.

Key words: LSD – Serotonin – 5-Methoxytryptamine – MAO inhibitors – Conditioned avoidance response

Evidence suggests that LSD and related agents exert their behavioral effects by actions on one or more of the monoaminergic systems within the CNS (Aghajanian and Freedman, 1968; Dixon, 1968). Since these systems can be selectively influenced by the use of specific inhibitors of type A or type B monoamine oxidase (MAO) (Yang and Neff, 1974). we studied the effects of centrally administered LSD, serotonin (5-HT), and 5-methoxytryptamine (5-MT) on the conditioned avoidance response (CAR) in rats that were pretreted with iproniazid (MAO-A and B inhibitor), clorgyline (MAO-A inhibitor), and deprenyl (MAO-B inhibitor).

Material and Methods

Male Wistar rats weighing 250 – 300 g received chronic cannulae into the right lateral ventricle as described (Prozialeck and Vogel, 1978). Intraventricular injections (5 – 10 µl) were performed over a 1 min period by using a hand-operated micrometer injecting system.

The CAR was studied in a Lehigh Valley Model 113-04 shuttlebox as described (Cohen et al., 1974). Parameters measured were avoidances, shocks, premature responses (PR), reaction time (latency of avoidance response = RT), and escape time (latency of escape = ET). Experimental sessions consisted of a 15-trial warm-up period followed by a 100-trial 'baseline' session. Ten minutes following this session, each animal received an intraventricular injection of artificial CSF. Three minutes later, the animal was subjected to a 100-trial 'control' session. Ten minutes after this session, the animal received an intraventricular injection of LSD, 5-MT, or 5-HT dissolved in artificial CSF. After 3 min, the animal was subjected to a 100-trial 'test' session. Repeated injections of artificial CSF were without effect on the animal in the shuttle box, indicating that 2 injections and the length of the experiment did not interfere with the performance of the animal. Animals were used repeatedly but no animal received drugs on consecutive days. In addition, no animal received more than two different drugs or more than two administrations of the same drug. No differences were found if the animal had received a drug first or after treatment with the same or another drug.

To determine levels of these compounds, different rats received LSD (15 nmoles), 5-HT (25 nmoles), and 5-MT (25 nmoles) intraventricularly and were sacrificed after 10 min. LSD was assayed fluorometrically by the method of Axelrod et al. (1957). Values for 5-MT and 5-HT are from Prozialeck and Vogel (1978).

Results

Table 1 shows that intraventricular injections of artificial CSF and 5-HT had no effect. LSD produced a marked disruption of the CAR whereas ET, RT, and the number of PR were not affected. 5-MT caused a less pronounced but still statistically significant disruption of the CAR lasting for about 15 min.

Pretreatment with the MAO inhibitors, which by themselves did not affect the CAR, greatly modified the behavioral response to LSD, 5-HT, and 5-MT. Following pretreatment with iproniazid, clorgyline, or deprenyl, 5-HT and 5-MT produced a marked disruption of the CAR with 5-MT also significantly decreasing the number of PRs. Pretreatment with each of the MAO inhibitors completely abolished the behavioral

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Table 1. MAO inhibition and the effects of centrally administered LSD, 5-HT, and 5-MT on the CAR in the rat

Pretreatment	Drug	Shocks	Premature
Baseline[a]	–	16 ± 10	11 ± 7
No	Vehicle[b]	10 ± 6	11 ± 7
	LSD[c]	50 ± 7*	12 ± 10
	5-MT[c]	20 ± 9*	10 ± 8
	5-HT[c]	18 ± 9	18 ± 13
Iproniazid 50 mg/kg i.p.	Vehicle[b]	12 ± 7	11 ± 6
	LSD[c]	14 ± 10	9 ± 11
	5-MT[c]	38 ± 11*	3 ± 2*
	5-HT[c]	29 ± 7*	7 ± 7
Clorgyline 1 mg/kg i.p.	Vehicle[b]	10 ± 6	13 ± 8
	LSD[c]	12 ± 11	10 ± 7
	5-MT[c]	53 ± 27*	4 ± 3*
	5-HT[c]	42 ± 5*	9 ± 4
Deprenyl 1 mg/kg i.p.	Vehicle[b]	12 ± 8	12 ± 8
	LSD[c]	13 ± 6	10 ± 6
	5-MT[c]	56 ± 15*	8 ± 6*
	5-HT[c]	28 ± 5*	10 ± 4

Animals were pretreated with the MAO inhibitors 15 h prior to behavior testing. LSD (15 nmole), 5-HT (25 nmole), and 5-MT (25 nmole) were administered in 10 µl artificial CSF solution (vehicle).

* $P < 0.01$ as determined by a paired t-test.

[a] First 100 trials; [b] second 100 trials; [c] third 100 trials

effects of LSD. Identical results were obtained when LSD was given i.p.

MAO-inhibition did not affect LSD concentrations in the brain; 0.4 ± 0.1 µmoles/brain were found without MAO inhibition and about 0.4 ± 0.1 µmoles/brain after pretreatment with each of the 3 MAO inhibitors. In contrast, MAO inhibition greatly increased brain levels of 5-HT and 5-MT (Prozialeck and Vogel, 1978). For instance, clorgyline and deprenyl increased brain levels of 5-HT 8.5-fold and 4.4-fold and of 5-MT 20-fold and 5-fold, respectively.

Discussion

To the best of our knowledge this is the first report that MAO inhibition blocks the effects of LSD on the CAR in rats. In man, it has been reported that MAO-inhibitors decrease the psychic effects of LSD and N,N-dimethyltryptamine (Resnick et al., 1964; Sai-Halasz, 1962). Since brain levels of LSD remained unchanged in our animals, the effect is probably due to a specific 'MAO inhibitor-induced' change in the CNS which interferes with the action of LSD.

In contrast, MAO inhibition increased markedly the effects of 5-HT and 5-MT on the CAR. Since levels of 5-HT and 5-MT in the CNS were significantly elevated in these animals, the potentiation of the behavioral effects are most likely the result of these increased brain levels. However, no quantitative correlation exists between brain levels and behavioral performance which could suggest a different mechanism of action.

The behavioral effects of 5-MT, 5-HT and LSD differed in our studies which could indicate that these compounds exert their effects on the CAR via different mechanisms within the brain.

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References

Aghajanian, G. K., Freedman, D. X.: Biochemical and morphological aspects of LSD pharmacology. In: Psychopharmacology: A Review of Progress 1957–1967, (D. H. Efron, ed.), pp. 1185–1193. Washington: Public Health Service Publication No. 1836, 1968

Axelrod, J., Brady, R. O., Witkop, B., Evarts, E. V.: The distribution and metabolism of lysergic acid diethylamide. Ann. N.Y. Acad. Sci. **66**, 434–444 (1957)

Cohen, I., Fischer, J. F., Vogel, W. H.: Physiological disposition of β-phenylethylamine, 2,4,5-trimethoxyphenylethylamine, 2,3,4,5,6-pentamethoxyphenylethylamine and β-hydroxymescaline in rat brain, liver and plasma. Psychopharmacologia **36**, 77–84 (1974)

Dixon, A. K.: Evidence of catecholamine mediation in the aberrant behavior induced by lysergic acid diethylamide in the rat. Experientia **24**, 743–747 (1968)

Prozialeck, W. C., Vogel, W. H.: Deamination of 5-methoxytryptamine, serotonin and phenylethylamine by rat MAO in vitro and in vivo. Life Sci. **22**, 561–570 (1978)

Resnick, O., Krus, D. M., Ruskin, M.: LSD-25 action in normal subjects treated with a monoamine oxidase inhibitor, Life Sci. **3**, 1207–1214 (1964)

Sai-Halasz, A.: The effect of MAO inhibition on the experimental psychosis induced by dimethyltryptamine. Psychopharmacologia **4**, 385–388 (1963)

Yang, H.-Y. T., Neff, N. H.: The monoamine oxidases of the brain: Selective inhibition with drugs, and the consequences for the metabolism of the biogenic amines. J. Pharmac. Exp. Therap. **189**, 733–740 (1974)

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