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Short communication

THE EFFECT OF LSD AND 2-BROMO LSD ON THE DOPA ACCUMULATION AFTER CENTRAL AND PERIPHERAL DECARBOXYLASE INHIBITION

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LSD and BOL were found to be equally potent in increasing the rat brain DOPA accumulation after decarboxylase inhibition. However, at the doses selected, the DOPA levels after haloperidol and apomorphine were increased by LSD but not by BOL. It is suggested that this difference is due to LSD's activating effect on central serotoninergic receptors.

Decarboxylase inhibition LSD BOL DOPA Haloperidol Apomorphine

1. Introduction

The potent psychotomimetic agent d-lysergic acid diethylamide (LSD) has been shown to have profound biochemical and electrophysiological effects on the serotonin containing cells and in higher doses on the serotoninergic synapses (Freedman, 1961; Aghajanian et al., 1968; Anden et al., 1968). However, evidence exists that LSD also interferes with the central catecholaminergic system (Rothlin, 1957; Sugrue, 1969).

We now report that LSD and BOL accelerate the brain DOPA accumulation after central decarboxylase inhibition. In order to get some insight into the nature of this increased DOPA generation, the effects of some drugs with established effects on monoaminergic mechanisms were also studied.

2. Materials and methods

2.1. Animals

Male Sprague—Dawley rats (Anticimex, Sollentuna, Sweden) weighing 200—299 g were used in all experiments. They were fed on Astra Ewos rat food and had access to water ad libitum. The experiments were performed at a room temperature of 22- 25°C. When haloperidol was administered the animals were kept at 30°C to avoid hypothermia.

2.2. Drugs

The following drugs were used: apomorphine · HCl, 2-bromo lysergic acid diethylamide bitartrate, BOL (Sandoz*, Basle), haloperidol (LEO*, Helsingborg), lysergic acid

diethylamide bitartrate, LSD (Sandoz*, Basle), phentolamine (CIBA, Basle), propranolol · HCl (ICI-Pharma*, Macclesfield, England), 3-hydroxybenzyl hydrazine · HCl, (NSD 1015) was kindly synthezised by Dr B. Magnusson, Department of Organic Chemistry, University of Umeå, Sweden. Doses of LSD and BOL refer to the base. Haloperidol was dissolved in 5.5% glucose after acidification with 200 µl glacial acetic acid. All other drugs were dissolved in 0.9% saline. The solutions were made up just before injection. All drugs were administered i.p.

2.3. *Experimental*

The animals were killed by decapitation. The brains were rapidly removed, chilled on ice and weighed, homogenized and extracted. DOPA in the extract was absorbed on alumina and separated from other catechols on a small column of a strong cation exchanger and quantitated essentially as in the method of Kehr et al. (1972a) with slight modifications (Persson, manuscript in preparation). For dosages and technical details see table 1.

TABLE 1

DOPA accumulation in the rat brain 20 min after administration of the central and peripheral decarboxylase inhibitor NSD 1015 (100 mg/kg). Most substances were administered 10 min before NSD 1015 i.e. 30 min before death. When apomorphine was combined with LSD or BOL it was injected 20 min before NSD 1015. Haloperidol was administered 60 min before NSD 1015.

Administered substance	mg/kg	DOPA, ng/g ± S.E.M. (*n*)
NaCl		163 ± 9 (6)
LSD	2	305 ± 12 (6)
BOL	2	340 ± 29 (3)
Phentolamine	10	145 ± 21 (3)
Propranolol	10	131 ± 12 (3)
Apomorphine	5	88 ± 13 (8)
Haloperidol	5	315 ± 15 (6)
Apomorphine (5 mg/kg) + LSD	2	212 ± 48 (5)
Apomorphine (5 mg/kg) + BOL	2	116 ± 19 (6)
Haloperidol (5 mg/kg) + LSD	2	510 ± 37 (6)
Haloperidol (5 mg/kg) + BOL	2	384 ± 32 (3)

2.4. *Statistical analysis*

The significance of the results was assessed using Student's *t*-test (Snedecor and Cochran, 1967).

3. Results

After administration of LSD to rats there was a dose-dependent increase of the DOPA accumulation in the brain (fig. 1). BOL was found to be as potent as LSD in this respect. In comparison with the controls the values were doubled by a dose of 2 mg/kg ($p < 0.001$). The slope of the dose–response curves for LSD and BOL indicates that the effect at the highest doses administered was not the maximal obtainable. In agreement with the finding of Kehr et al. (1972b) it was found that the rate of the DOPA accumulation was increased by the dopamine antagonist haloperidol and decreased by the dop-

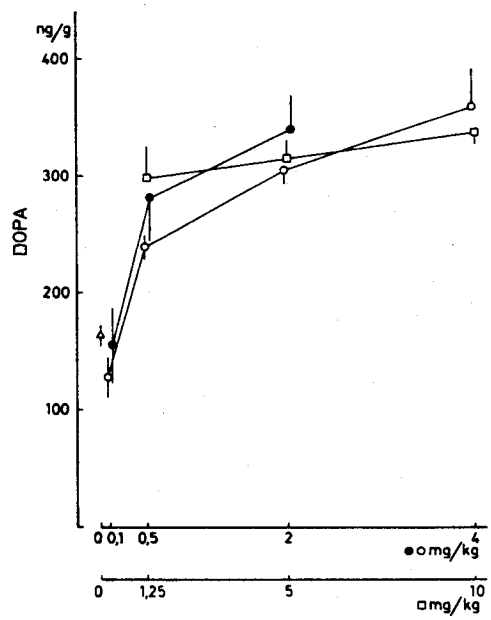

Fig. 1. Accumulation of DOPA in the brains of decarboxylase inhibited rats after i.p. administration of saline (△), LSD (○), BOL (●) and haloperidol (□). Each point represents the mean ± S.E.M. of 3–6 determinations.

amine agonist apomorphine. Administration of LSD to rats treated with a maximal dose of haloperidol further increased the accumulation by about 70% ($p < 0.001$). BOL on the other hand did not significantly change the haloperidol-induced increase. A further difference between LSD and BOL as regards the effect on catecholamine (CA) neurons was revealed after administration of the drugs to rats pretreated with apomorphine. LSD partly reversed the apomorphine effect, while BOL in the same dose did not significantly influence the apomorphine effect.

Neither the α-adrenergic blocking agent phentolamine nor the β-adrenergic blocking agent propranolol significantly changed the brain DOPA accumulation.

4. Discussion

The increased DOPA accumulation in the brain after LSD most probably reflects an increased activity in the CA neurons, which in turn might be related to the effect of LSD on serotoninergic mechanisms at the synaptic level (Andén et al., 1968). Our finding that BOL is as potent as LSD in increasing the brain DOPA accumulation is obviously not in accordance with such an interpretation since BOL is much less potent than LSD in activating 5-HT receptors (Andén et al., 1968; Aghajanian et al., 1970). A difference between the LSD and BOL effects was noted, however in experiments where the two drugs were given together with haloperidol or apomorphine. LSD, but not BOL, increased the haloperidol effect and reversed the apomorphine effect. The same potency of LSD and BOL as regards DOPA accumulation may thus be fortuitous. It might be that the LSD effect is due to its action on serotoninergic neurons while the BOL effect is a more direct one on the CA neurons. A more thorough explanation of these results is not now possible but our findings suggest a complex interaction between the serotoninergic and dopaminergic systems. Evidence of an increased activity in serotoninergic neurons after activation of DA receptors has been obtained on the biochemical (Grabowska et al., 1973) as well as on the electrophysiological level (Cools, 1974).

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