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cyclic adenosine 3′,5′-monophosphate in rat cerebrum after its i.p. administration[15]. BOL-148, an analogue of LSD believed to have very weak, if any, hallucinogenic properties[61], did not induce circling behaviour. In preliminary experiments, methysergide, another non-hallucinogenic lysergic acid derivative, and N,N-dimethyltryptamine, an idolealkylamine hallucinogen, were also inactive as dopamine receptor agonists. On the other hand, such an action has recently been described for some ergot alkaloids and derivates (ergocornine, 2-bromo-α-ergocryptine, ergometrine)[17,18].

The activation of striatal dopamine receptors is obviously not the only important central effect of LSD, since its overall behavioural effects differ considerably from those of agents believed to be fairly pure agonists of dopamine receptors. The possible importance of the dopaminergic component of the action of LSD for its hallucinogenic effect has yet to be demonstrated. It will be interesting to see whether LSD also activates dopamine receptors in brain regions other than the striatum, for example, in the limbic subsortical and cortical[18,19] structures, in the hypothalamus, in the medullary chemical trigger zone, and in the retina[22,23].

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LSD as an agonist and antagonist at central dopamine receptors

THE mechanisms involved in the psychotomimetic actions of D-lysergic acid diethylamide (D-LSD) and other hallucinogenic agents have not been defined. Neurophysiological and behavioural studies indicate that D-LSD may interact with serotonin and catecholamine receptors in the central nervous system. Thus, this drug seems to stimulate certain central serotonergic pathways[1,2], while inhibiting the activation of other pathways by serotonin[3,4].

D-LSD has also been reported to block the action of noradrenaline on central neurones[5] and to produce stereotypy in rats[6], a condition which is associated with dopaminergic hyperactivity[7]. Moreover, several recent reports have indicated that a number of ergot derivatives are capable of exerting dopamine-like actions on central neurones in the rat[8–10]. Recent investigations from this laboratory suggest that adenyl cyclase systems may be involved in the central actions of D-LSD (ref. 11 and K.v H., S.R., and D.F., unpublished). Thus, D-LSD is capable of stimulating adenyl cyclase activity, as well as antagonising the stimulation of this enzyme by serotonin, in cell-free preparations from the rat colliculus. Here we report evidence that D-LSD may act both as an agonist and an antagonist at dopamine receptors in the brain.

The methods employed for the preparation of brain subcellular fractions and measurement of adenyl cyclase activity have been described in detail elsewhere[12,13]. Brains were obtained from young, adult male rats of an inbred Sprague–Dawley strain. These rats were approximately 6 weeks old and weighed about 225 g. Particulate fractions were prepared from cerebral cortex or corpus striatum.

In relatively low concentration (10 μM), D-LSD, completely blocked the stimulation of cerebral adenyl cyclase activity by a combination of 10 μM noradrenaline and 10 μM dopamine (Table 1). At these concentrations, the catecholamines produced additive effects on enzyme activity[12]. Another serotonin antagonist, 2-bromo-D-lysergic acid diethylamide (BOL) also inhibited this response to the catecholamines. Comparable results were obtained when these serotonin antagonists at 100 μM concentrations were tested against equimolar amounts of either noradrenaline or dopamine. D-LSD also inhibited

Table 1 Influence of lysergic acid derivatives on activation of adenyl cyclase by catecholamines in particulate preparations from cerebral cortex of adult rats

Lysergic acid derivative	Cyclic AMP formed: Basal (nmol mg^{-1} protein h^{-1})	Increase with catecholamines (nmol mg^{-1} protein h^{-1})	(%)
None	8.46±0.18	6.39±0.22	76
D-LSD, 10 μM	9.46±0.26	0.31±0.29*	3
L-LSD, 80 μM	8.02±0.15	5.63±0.49	70
BOL, 10 μM	7.60±0.28	0.91±0.41*	12

The particulate preparations were crude mitochondrial fractions obtained by centrifuging the 1,000*g* supernatant fluids from cerebral homogenates at 10,000*g* for 20 min. Adenyl cyclase activity was determined from the conversion of ^{14}C-ATP to cyclic AMP by a procedure[12] which was based on the method of Krishna *et al.*[14]. The incubation medium (0.1 ml) contained the following components in the final concentrations indicated: 3.6 mM (0.5 μCi) 8-^{14}C-ATP, 5.0 mM $MgCl_2$, 1.0 mM cyclic AMP, 40 mM Tris-HCl (*p*H 7.3 at 37° C), 10 mM phosphoenolpyruvate, 4 μg pyruvate kinase, 15 mM $(NH_4)_2SO_4$ (added with pyruvate kinase), 20 mM caffeine, 0.1 mg bovine serum albumin, 0.2 mM EGTA, 5 μg phosphatidylserine and 50–100 μg brain protein. Protein was measured by the method of Lowry *et al.*[15]. L-Noradrenaline (10 μM) and dopamine (10 μM) were added together as the hydrochlorides, D-LSD and L-LSD as the free amines and BOL as the bitartrate. Incubation was conducted in air for 5 min. Values for cyclic AMP formed are averages ±s.e. for triplicate samples in a representative experiment. Where indicated, basal values shown were obtained in the presence of the lysergic acid derivative.

*$P < 0.001$ for the difference between this value and the value obtained with only the catecholamines added.

Table 2 Influence of blocking agents on activation of adenyl cyclase by dopamine and D-LSD in particulate preparations from corpus striatum of adult rats

Agent	Cyclic AMP formed			
	Basal (nmol mg^{-1} protein h^{-1})	Increase with dopamine (nmol mg^{-1} protein h^{-1})	(%)	Increase with D-LSD (nmol mg^{-1} protein h^{-1})	(%)
Experiment 1					
None	16.43±0.67	11 46±0.76	62	5.65±0.73	31
D-LSD (10 μM)	24.08±0.27	1.12±0.42*	5		
Chlorpromazine (10 μM)	17.34±0.31	0.49±0.76†	3	1.40±0.42†	8
Haloperidol (10 μM)	16.93±0.32	0.73±0.44*	4	1.40±0.33†	8
Experiment 2					
None	15.57±0.42	9.54±0.69	61	4.70±0.45	30
MLD (100 μM)	15.03±0.26	0.20±0.43*	1	−0.10±0.45†	−1
BOL (100 μM)	15.13±0.48	−1.70±0.52*	−11	−1.14±0.51†	−8
Propranolol (100 μM)	16.03±0.29	8.13±0.51	51	3.90±0.57	24
Cyproheptadine (100 μM)	13.56±0.12	0.58±0.37*	4	1.31±0.31†	10

The particulate preparations were obtained by centrifuging the homogenates at 10,000*g* for 20 min. See Table 1 for other explanations.
*$P<0.001$ for the difference between this value and the value obtained with only 10 μM dopamine or 10 μM D-LSD added.
†$P<0.01$.

the adenyl cyclase response to noradrenaline or dopamine in particulate preparations from the rat hippocampus, which resembles cerebral cortex in the responses of adenyl cyclase to the catecholamines[13]. Palmer and Burks[16] earlier reported that D-LSD and BOL block the noradrenaline-induced increase in cyclic AMP levels in slices of rat brain.

By itself, D-LSD tended to increase adenyl cyclase activity in the cerebral and hippocampal preparations. This effect was quite small however, (about 15%) and was not always significant. A survey of various brain regions of the rat revealed that cell-free fractions from the corpus striatum contained adenyl cyclase which was reproducibly activated by low concentrations of D-LSD. Significant stimulation could be obtained with concentrations of D-LSD as low as 0.1 μM. Adenyl cyclase activity in comparable fractions from other regions of rat brain (cerebellum, hypothalamus and brainstem) was completely refractory to the stimulatory action of this drug.

Adenyl cyclase activity in particulate preparations from striatal tissue of the adult rat was increased about 30% by 10 μM D-LSD (Table 2). This was about one-half the activation produced by an equimolar concentration of dopamine. The sensitivity of adenyl cyclase to dopamine in cell-free fractions from rat corpus striatum has been demonstrated earlier[13,17,18]. This region of rat brain is unusually rich in dopaminergic neurones[19]. The response to 10 μM dopamine in our investigations was completely blocked by the addition of 10 μM D-LSD. In addition, the responses of adenyl cyclase to either 10 μM dopamine or 10 μM D-LSD were almost completely blocked by equimolar concentrations of the antipsychotic dopamine-blocking agents, haloperidol and chlorpromazine. The serotonin antagonists, BOL, 1-methyl-D-lysergic acid diethylamide (MLD) and cyproheptadine were also capable, however, of inhibiting these responses (Table 2, experiment 2). The β-adrenergic blocking agent, propranolol, which markedly inhibits the response of adenyl cyclase to noradrenaline in rat brain cell-free preparations[12], did not block the stimulation of striatal adenyl cyclase by dopamine or D-LSD. None of these blocking agents by itself, with the exception of D-LSD, increased adenyl cyclase activity in the striatal preparations.

Our findings, combined with earlier observations from this laboratory[11], indicate that D-LSD is capable of blocking the interaction of noradrenaline, dopamine and serotonin with their respective receptors in various regions of rat brain. This drug also seems to activate central serotonin and dopamine receptors for adenyl cyclase. Interaction of D-LSD with dopamine receptors was blocked by dopamine-blocking agents (for example, haloperidol) or serotonin antagonists (for example, cyproheptadine), but not by the noradrenaline antagonist, propranolol. These investigations suggest that the hallucinogenic actions of D-LSD may be due to complex agonist and antagonist actions of this drug at central receptors for the several neurotransmitter monoamines.

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The activity of membrane bound enzymes in muscular dystrophic chicks

TISSUES from patients with Duchenne muscular dystrophy[1] (DMD) as well as animals with similar inherited[2] or experimentally produced[3] disorders have been shown to undergo