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LYSERGIC ACID DIETHYLAMIDE: EVIDENCE FOR STIMULATION OF CEREBRAL DOPAMINE RECEPTORS

M. DA PRADA, A. SANER, W. P. BURKARD, G. BARTHOLINI AND A. PLETSCHER

Research Division, F. Hoffmann–La Roche, Basel (Switzerland)

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SUMMARY

In the rat, lysergic acid diethylamide (LSD) decreased the striatal and retinal content of homovanillic acid. LSD did not change the level of dopamine (DA), but delayed the α-methyl-*p*-tyrosine-induced disappearance of this amine in the telencephalon. In the cat, LSD diminished the DA output into the perfusate of the caudate nucleus. Furthermore, LSD increased the activity of adenylate cyclase in striatal homogenates of rat. These and other findings indicate that in the central nervous system LSD stimulates DA receptors which may be involved in LSD-induced psychosis.

INTRODUCTION

D-Lysergic acid diethylamide (LSD), a psychotomimetic substance, decreases the 5-hydroxytryptamine (5-HT) turnover in the brain[1,20], possibly as a consequence of stimulation of pre- and/or postsynaptic 5-HT receptors[15,18,23]. The interaction of LSD and catecholamine neurons has been less extensively investigated[36]. In rats high doses of LSD cause a slight decrease in the cerebral content of dopamine (DA) and noradrenaline (NA)[3,10] as well as stereotyped behavior[11,13]. The possibility has to be considered that LSD acts on DA receptors since structurally related ergot alkaloids and derivatives, *e.g.*, ergocornine, ergometrine and 2-Br-α-ergocryptine, were demonstrated to be DA receptor agonists[8,22,29,38]. However, in brain slices LSD did not stimulate the DA-activated adenylate cyclase, although it increased the cerebral cyclic adenosine-5′-monophosphate *in vivo*[37].

The present paper provides evidence that LSD decreases the DA turnover in the central nervous system of rats probably as a consequence of DA receptor stimulation.

MATERIAL AND METHODS

Male albino rats (100–150 g, stock Füllinsdorf, SPF), fasted for 16 h, were kept normothermic in a heated box (30 °C) during the period between drug administration and decapitation. LSD was injected intraperitoneally at various times before sacrifice. Homovanillic acid (HVA) was extracted into *n*-butylacetate[25] and measured fluorimetrically[2] in the striatum or in the eye. For each determination a pool of corpora striata from 2 rats or of 24 whole eyes of light-adapted rats was used. Other rats received i.p. either LSD or L-α-methyl-*p*-tyrosine (α-MT) or both compounds. DA and NA were determined in the tel-diencephalon at various time intervals (see Table I) according to the method of Shellenberger and Gordon[30]. Saline-injected rats served as controls.

In a further series of experiments the effect of LSD on the adenylate cyclase of striatal homogenates of untreated rats was measured in the absence or presence of DA according to Kebabian *et al.*[19].

Moreover, cats of either sex (2.5–3 kg) were anesthetized with ether, tracheotomized, artificially ventilated and kept normothermic. All wound and pressure points were repeatedly infiltrated with a local anesthetic. After injection of gallamine through a catheter inserted into the femoral vein, ether was withdrawn, and the caudate nucleus was perfused (100 μl/min) by means of a push–pull cannula (2 concentric cannulae; internal diameter of the outer and inner cannula = 0.9 and 0.2 mm, respectively) implanted stereotaxically according to the atlas of Snider and Niemer[31] (coordinates: A = 16, L = 3.8, H = +4.5), as previously described[34,35]. The perfusate of the first 30 min was discarded; thereafter, samples were collected into chilled centrifuge tubes containing 100 μl 0.01 *N* perchloric acid. LSD was injected intravenously 1 h after beginning of the sample collection (control period). DA was measured in the perfusate by the radioenzymatic method of Coyle and Henry[9]. Statistical analysis of the results was performed by the Student's *t*-test (two-tailed).

Chemicals

LSD was a gift from Sandoz, Basel. The doses refer to the tartrate. L-α-Methyl-*p*-tyrosine, an inhibitor of tyrosine hydroxylase, was synthetized by Dr. A. Kaiser, Chemical Dept., Hoffmann–La Roche, Basel.

RESULTS

Fig. 1 shows that in rats 0.2 mg/kg LSD i.p. diminished the concentration of HVA in the striatum to about 70% of control values in 6 h. The level of the acid returned to normal values between 8 and 16 h. The content of HVA in the eye was also significantly diminished 4 h after i.p. administration of 0.5 mg/kg LSD. In contrast (Table I) LSD did not alter the concentration of tel-diencephalic DA and NA. However, the hallucinogen significantly delayed the α-MT-induced disappearance of DA, but not that of NA.

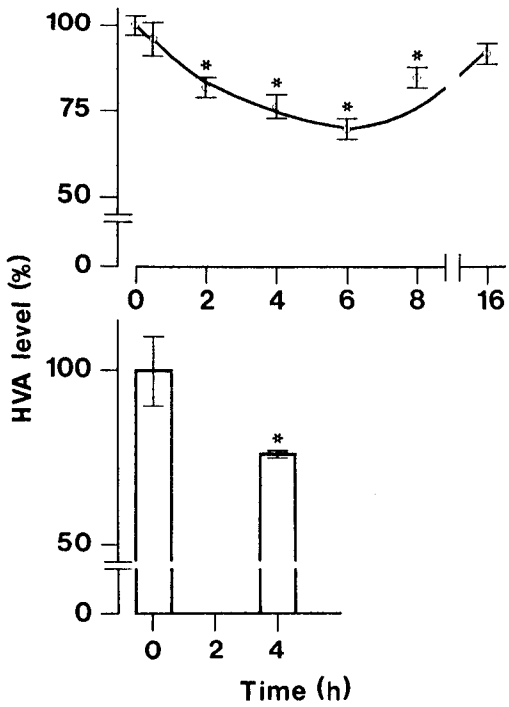

Fig. 1. Effect of LSD injected intraperitoneally to rats, on the homovanillic acid (HVA) content of the striatum (upper part, LSD 0.2 mg/kg) and of the eye (lower part, LSD 0.5 mg/kg). The values are averages with S.E.M. of results from 3 to 8 experiments and are expressed in per cent of saline-treated controls (= 100). Absolute control values: striatum, 856 ± 24; eye, 43 ± 4 ng/g. * $P < 0.01$ *versus* corresponding control value (= 100%).

TABLE I

EFFECT OF LSD ON THE L-α-METHYL-*p*-TYROSINE (α-MT)-INDUCED DOPAMINE (DA) AND NORADRENALINE (NA) DEPLETION IN THE RAT TEL-DIENCEPHALON

α-MT was administered i.p. either in a single dose (200 mg/kg) 2 h before decapitation or in 2 doses of 200 and 100 mg/kg, 4 and 1 h, respectively, before sacrifice. LSD (1 mg/kg) was injected i.p. 15 min before the first dose of α-MT. The values are expressed in % of saline-treated controls (DA = 891 ± 12; NA = 327 ± 18 ng/g).

Treatment	*n*	*DA*	*NA*
Saline	12	100.0 ± 1.3	100.0 ± 5.5
LSD, 15 min	12	101.7 ± 2.4	90.2 ± 3.7
LSD, 4 h 15 min	8	96.2 ± 3.0	86.5 ± 5.0
α-MT, 2 h	6	43.0 ± 1.1	56.3 ± 2.4
LSD + α-MT, 2 h	4	50.6 ± 3.0*	55.0 ± 5.8***
α-MT, 4 h	9	21.7 ± 0.9	37.6 ± 1.2
LSD + α-MT, 4 h	9	27.2 ± 1.2**	35.2 ± 1.2***

n = number of experiments. Statistical significance: * $P < 0.05$; ** $P > 0.01$; $P > 0.05$ *versus* α-MT alone. α-MT *versus* controls and LSD alone, $P < 0.01$; LSD *versus* controls, $P > 0.05$.

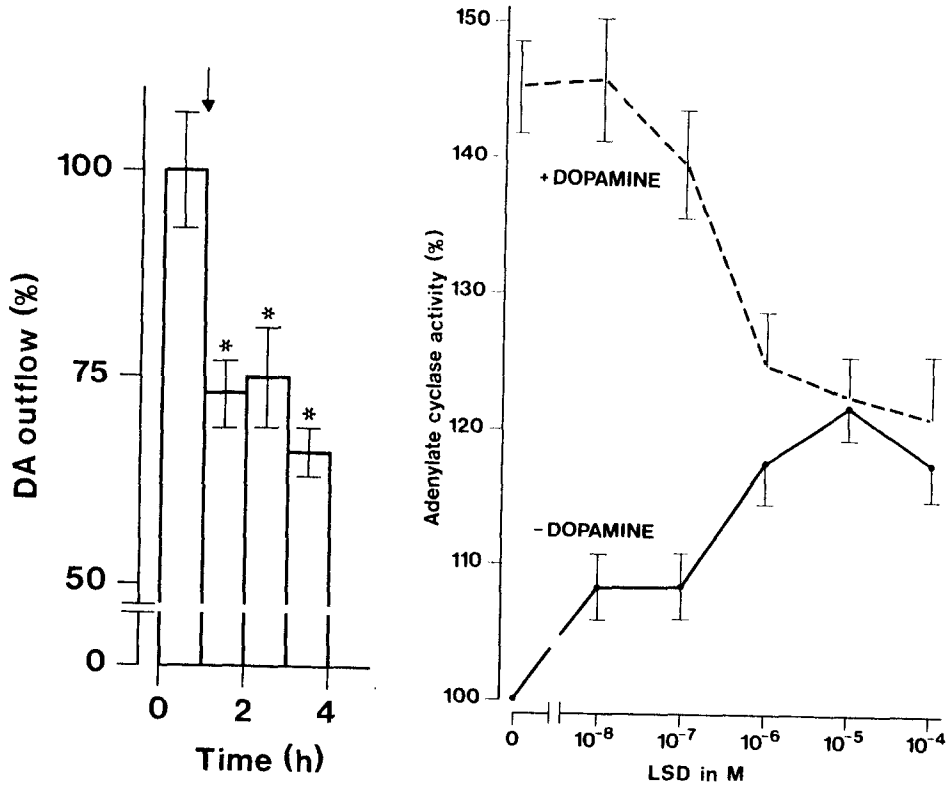

Fig. 2. Output of DA into the perfusate of the head of the cat caudate nucleus. LSD (1 mg/kg) was injected intravenously (arrow) 1 h after beginning of the perfusate collection. The values are averages with S.E.M. from 4 to 6 experiments and indicate the DA released/h expressed in per cent of the 1 h preinjection (control) period (= 100). Absolute control value: 1194 ± 92 pg/h. * $P < 0.01$ *versus* control value.

Fig. 3. Effect of LSD on the adenylate cyclase activity in homogenates of rat striatum in the absence (−) or presence (+) of DA (1×10^{-5} *M*). Each point indicates a mean value with S.E.M. from 7 experiments. The enzyme activity without DA or LSD was 107.4 ± 4.9 p*M* adenosine-3′,5′-monophosphate formed during 10 min at 30 °C/2 mg tissue. The values at 10^{-6}–10^{-4} *M* are significantly different ($P < 0.01$) from those of the corresponding controls without LSD (0 values).

In the cat (Fig. 2), injection of LSD (1 mg/kg i.v.) caused for at least 3 h a marked reduction of the DA output into the perfusate of the caudate nucleus as compared to the preinjection (control) period.

In striatal homogenates (Fig. 3), in the absence of DA, LSD significantly activated the adenylate cyclase in a concentration-dependent manner, maximal values being reached with 10^{-5} *M* LSD. This was about half the maximal activation of the enzyme induced by 10^{-5} *M* DA. LSD (10^{-7}–10^{-4} *M*) also progressively antagonized the DA-induced activation of the adenylate cyclase.

DISCUSSION

The actions of LSD in rats, *i.e.* (a) the decrease of the concentration of HVA in

the striatum as well as in the eye (where the acid is formed from retinal DA[12,26]), and (b) the delay of the α-MT-induced DA disappearance in the tel-diencephalon suggest a diminution of the amine release due to the hallucinogen. The reduced output of DA from the perfused caudate nucleus of the cat treated with LSD confirms this view. These results, together with the unaltered concentration of DA in the rat brain after LSD, indicate that the hallucinogen decreases the turnover of the amine. In contrast, the NA turnover is not affected by LSD.

The reduced turnover of DA — which probably results from a feedback inhibition of dopaminergic neurons — is likely to be due to stimulation of the synaptic[7] and/or postsynaptic DA receptors by LSD. This view is supported by the finding with striatal homogenates, which are in agreement with recent results[16]. Accordingly, LSD activated the adenylate cyclase — which is probably related to the DA receptors[6,19] — and antagonized the DA-induced activation of the enzyme. These findings indicate that LSD and DA compete for the same active site of the enzyme. In contrast, 2-Br-D-lysergic acid diethylamide (BOL), a non-hallucinogenic derivative of LSD, did not stimulate the adenylate cyclase (enzyme activity after 10^{-5} *M* BOL = 95.1 ± 4.4%, controls = 100%; n = 4, $P > 0.05$).

Stimulation of postsynaptic DA receptors by LSD is also evident from behavioral studies in rats with unilateral degeneration of the dopaminergic nigrostriatal pathway induced by application into the medial forebrain bundle of 6-hydroxydopamine or 5,6-dihydroxytryptamine. In these animals LSD (0.1–1.5 mg/kg i.p.) caused marked turning towards the unoperated side indicating a stimulation of the hypersensitive striatal DA receptors of the lesioned side[27,28].

Since cerebral DA is thought to be involved in psychotic states[33], the present findings are of interest with regard to the LSD-induced psychosis. In particular, the visual hallucinations[32,33] might be connected with the stimulation of DA receptors by LSD. Thus, dopaminergic neurons[12,14,26] as well as a DA-sensitive adenylate cyclase[5,21] occur in the retina, and in the present experiments LSD decreased the level of retinal HVA. An action of LSD on retinal DA receptors might be connected with the increase in unitary firing rate caused by LSD in the cat visual system (retina, optic tract, lateral geniculate nucleus)[4]. Finally, involvement of DA receptors in the psychotomimetic action of LSD is supported by the fact that, in man, neuroleptic drugs — which block DA receptors — counteract the LSD-induced psychosis, including visual hallucinations[17,24]. However, the confused and psychotic states, which dopaminergic agents such as L-DOPA and amphetamine occasionally cause in man, are not identical with those produced by LSD[33]. Therefore, stimulation of DA receptors probably does not explain the full psychotomimetic action of LSD, but is likely to be one of several mechanisms determining the psychopathological profile of the compound.

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