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LSD as an Agonist at Mesolimbic Dopamine Receptors

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Abstract. The dopamine agonist apomorphine (1.0 mg/kg i.p.) produced an enhanced stimulation of locomotor activity compared to control animals in rats injected bilaterally 14 days previously with 6-hydroxydopamine (6OHDA) into the nucleus accumbens. (+)-Lysergic acid diethylamide (LSD) also produced a marked stimulation of locomotor activity in the 6OHDA treated animals at a dose (1.0 mg/kg i.p.) which was ineffective in control rats. (+)-Bromo-lysergic acid diethylamide (2.0 mg/kg i.p.) did not stimulate locomotor activity in 6OHDA treated rats. The locomotor stimulation produced by LSD was blocked by pretreatment with the dopamine antagonist pimozide (0.5 mg/kg i.p.). It is suggested that LSD acts as an agonist at mesolimbic dopamine receptors.

Key words: LSD – Dopamine – Mesolimbic system – Nucleus accumbens – Neuroleptics – Locomotor activity.

Introduction

Recent data from both *in vitro* and *in vivo* studies supports the view that one of the actions of (+)-lysergic acid diethylamide (LSD) is to act as a dopamine agonist in the mammalian CNS. Activation of adenylate cyclase is implicated in dopaminergic neurotransmission (Greengard *et al.*, 1972; Miller and Kelly, 1975) and a dopamine-sensitive adenylate cyclase present in cell free preparations of the rat striatum has proved a useful *in vitro* model of the dopamine receptor (Kebabian *et al.*, 1972; Miller *et al.*, 1974). In this *in vitro* system LSD like dopamine stimulates the production of cyclic AMP and this effect is reduced by the antipsychotic dopamine antagonists chlorpromazine and haloperidol (von Hungen *et al.*, 1974). In the *in vivo* rotational model of Ungerstedt and Arbuthnott (1970) LSD produces rotation away from the side of the lesioned nigrostriatal pathway (Pieri *et al.*, 1974). Rotation in this direction produced by the dopamine agonist apomorphine has been attributed to direct stimulation of supersensitive denervated striatal dopamine receptors (Ungerstedt, 1971).

The purpose of the present experiment was to investigate whether LSD acts as a dopamine agonist in an *in vivo* model for assessing drug effects on mesolimbic dopamine receptors. This model has been described in detail previously (Kelly *et al.*, 1975a, b) and will be outlined only briefly here. Injection of 6-hydroxydopamine (6OHDA) bilaterally into the nucleus accumbens septi (NAS) of rats destroys the mesolimbic dopamine innervation of the nucleus accumbens and olfactory tubercle without significantly affecting the striatal dopamine content (Kelly *et al.*, 1975b). When injected with dopamine agonists such as apomorphine (Kelly *et al.*, 1975b) or N-n-propylnorapomorphine (Kelly *et al.*, 1975a) these animals show a much greater stimulation of locomotor activity than control animals. This motor stimulation can be blocked by the dopamine antagonist pimozide (Iversen *et al.*, 1975). In the present experiments the ability of LSD to stimulate locomotor activity in rats with 6OHDA lesions of the nucleus accumbens has been investigated. The results are consistent with the view that LSD can act as a dopamine agonist.

Materials and Methods

Subjects and Surgery. Experiments were performed on adult male Sprague-Dawley albino rats. Subjects were unoperated control rats or rats with bilateral 6OHDA-induced lesions of the nucleus accumbens, used 14–30 days after 6OHDA treatment. Lesions were made by bilateral stereotaxic injection of 8 µg (expressed as base) of 6OHDA hydrobromide (Sigma) dissolved in 2 µl of 0.9% saline containing *l*-ascorbic acid (1 mg/ml). Rats were anaesthetized with Equithesin (3 ml/kg) and the 6OHDA solution was injected at the rate of 1 µl/min through a 30 gauge stainless steel cannula aimed at the nucleus accumbens. Stereotaxic co-ordinates were + 3.4; 1.7; 7.2 according to the atlas of Pellegrino and Cushman (1967).

Drugs. The following drugs were injected i.p.: apomorphine hydrochloride (McFarlan Smith), (+)-lysergic acid diethylamide tartrate (LSD-25) (Sandoz), (+)-bromo-lysergic acid diethylamide bitartrate (BOL 148) (Sandoz) and pimozide (Janssen). Apomorphine, LSD and BOL 148 were dissolved

in 0.9% saline. Pimozide was dissolved in a drop of glacial acetic acid and diluted with distilled water. Control rats for pimozide experiments were injected with acetic acid of the same pH (3.2). Doses of drugs are expressed as the forms above.

Apparatus. For measurement of locomotor activity rats were placed in individual wire cages (25 × 40 × 20 cm) each with two horizontal photocell beams along the long axis. The cages were contained in a room which was masked with white noise and maintained at 22°C. Interruption of the photocell beams activated electromechanical counters housed in a separate room. Noncumulative recordings of photocell beam interruptions were taken every 10 min after drug injection.

Procedure. Lesioned animals were tested with apomorphine (1.0 mg/kg) 14 days post-lesion and divided into three matched groups of five animals on the basis of their response. Responses to other drugs were tested between 20 and 30 days post-lesion. Rats were habituated to the activity cages for 1 hr before injection of apomorphine, LSD-25, BOL 148 or 0.9% saline. Pimozide was injected 2 hrs before LSD-25. Drug tests were separated by at least 48 hrs.

Statistics. The significance of statistical differences were calculated using Student's *t*-test.

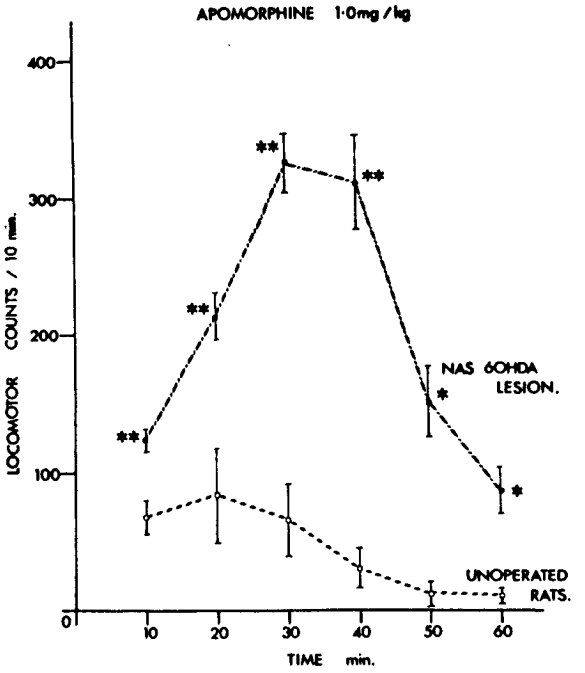

Fig. 1. Locomotor activity after apomorphine (1.0 mg/kg) injected into 6-hydroxydopamine nucleus accumbens lesioned rats ($n = 15$) or unoperated controls ($n = 6$). Mean ± S.E.M. * $P < 0.025$; ** $P < 0.005$, compared to unoperated rats

Results

Apomorphine (1.0 mg/kg) produced a greater stimulation of locomotor activity in animals with the bilateral 6OHDA nucleus accumbens lesion than un unoperated control animals (Fig. 1). There were no differences between the matched groups of lesioned animals.

LSD (1.0 mg/kg) also produced a marked stimulation of locomotor activity in lesioned animals (Fig. 2A) although this dose did not significantly affect the locomotor activity of unoperated rats (Fig. 2B). In a lower dose (0.2 mg/kg) LSD did not significantly increase the activity of the 6OHDA-treated animals. There were qualitative differences between the effects of apomorphine and LSD in nucleus accumbens lesioned animals. After apomorphine the rats showed continuous locomotor activity with the back arched and the nose close to the cage floor whereas after LSD the rat's whole body tended to be flattened close to the floor. BOL 148 (2.0 mg/kg) did not stimulate locomotor activity in nucleus accumbens 6OHDA lesioned rats (Fig. 2A) and actually inhibited activity during the first 10-min period after injection.

The stimulation of locomotor activity by LSD (1.0 mg/kg) injected into lesioned rats was blocked by pretreatment with the dopamine antagonist pimozide (0.5 mg/kg) (Fig. 3).

Discussion

In the present study LSD has been shown to have properties in common with those previously reported for the dopamine agonists apomorphine and N-n-propylnorapomorphine (Kelly *et al.*, 1975a, b; Iversen *et al.*, 1975). When injected into animals whose mesolimbic dopamine system has been largely destroyed by stereotaxic injection of 6-hydroxydopamine into the nucleus accumbens these compounds markedly stimulate locomotor activity. However, they are ineffective when injected into control animals. This enhanced effect in the lesioned animals may be due to supersensitivity of the denervated mesolimbic dopamine receptors. The locomotor stimulant effects of both LSD and apomorphine are blocked by pretreatment with the dopamine antagonist pimozide. These findings are consistent with the view that LSD can act as an agonist at mesolimbic dopamine receptors.

Further evidence is consistent with an interaction of LSD with dopaminergic systems. In high doses it produces stereotyped behaviour in rats (Fog, 1969). Stereotyped behaviour probably reflects an action on striatal rather than mesolimbic dopamine receptors since injection of a small volume of dopamine solution into the caudate nucleus produces stereotypy (Fog *et al.*, 1967) and drug-induced stereotyped behaviour is affected by 6OHDA lesions of the caudate which do not destroy the mesolimbic dopamine system (Kelly *et al.*, 1975b). In animals with unilateral destruction of the nigrostriatal dopamine-containing pathway LSD produces turning away from the lesion (Pieri *et al.*, 1974) like the dopamine agonist apomorphine

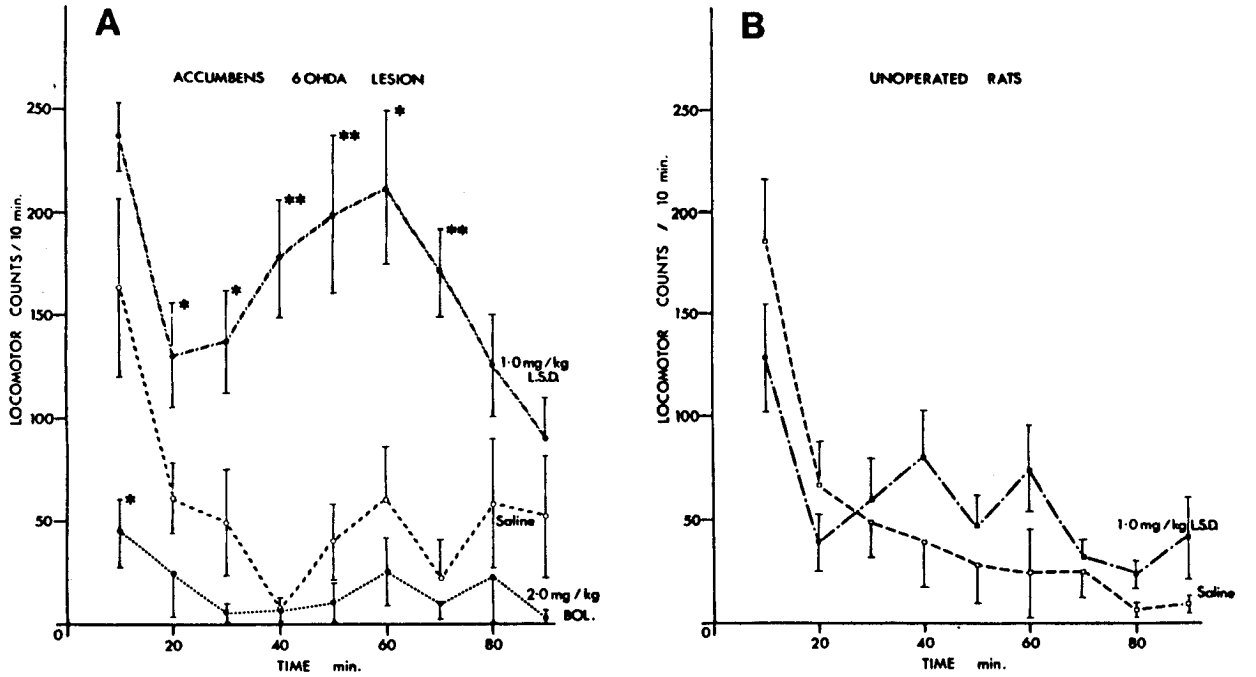

Fig. 2. (A) Effect of LSD (1.0 mg/kg) or BOL 148 (2.0 mg/kg) on locomotor activity in rats injected bilaterally with 6-hydroxydopamine into the nucleus accumbens septi. (B) Effect of LSD (1.0 mg/kg) on locomotor activity of unoperated rats. Mean ± S.E.M. for groups of five rats. * $P < 0.05$; ** $P < 0.005$, compared to saline

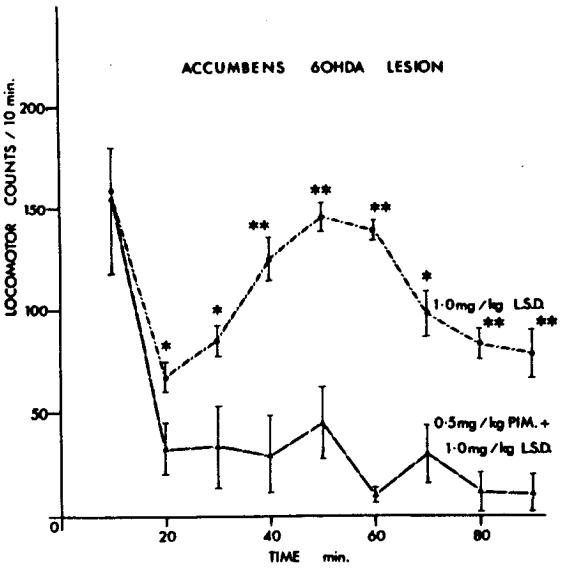

Fig. 3. Effect of pimozide (0.5 mg/kg, 2 hrs before LSD) on the locomotor activity elicited by LSD (1.0 mg/kg) in rats with 6-hydroxydopamine lesions of the nucleus accumbens. Pimozide was dissolved in acetic acid, pH 3.2, and control rats were pretreated with acetic acid of the same pH as the pimozide solution. Mean ± S.E.M. for groups of five rats. * $P < 0.025$; ** $P < 0.005$, compared to pimozide/LSD

(Ungerstedt, 1971). LSD and dopamine both stimulate adenylate cyclase activity in homogenates of rat striatum, and these effects are blocked by neuroleptic dopamine antagonist drugs (von Hungen *et al.*, 1975).

There is, therefore, evidence that LSD can act as an agonist at both striatal and mesolimbic dopamine receptors. These actions may contribute to the hallucinogenic action of LSD since BOL 148 which is only very weakly hallucinogenic (Isbell *et al.*, 1959) does not share these properties. Other actions of LSD are obviously of importance, however, since the effects of pure dopamine agonists only partly resemble those of LSD. The probable serotonin agonist action of LSD which is seen after very low doses (Aghajanian *et al.*, 1970) is another important central effect which is not shared by BOL 148.

Dopaminergic mechanisms are implicated in psychosis (Matthysse, 1974; Snyder *et al.*, 1974). The dopamine agonist actions of LSD may contribute to LSD-induced psychotic symptoms since these are at least partially blocked by chlorpromazine and other dopamine antagonist drugs (Isbell and Logan, 1957). An effect on dopaminergic mechanisms which have been shown to be present in the retina (Brown and Makman, 1973) may also contribute to the visual hallucinations which are a prominent feature of the LSD psychosis.

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