Action of LSD on supersensitive mesolimbic dopamine receptors

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Since Ungerstedt & Arbuthnott (1970) described the amphetamine-induced rotation of rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra this *in vivo* preparation has been widely used to study the effects of drugs on dopaminergic mechanism in the brain. Recently it has been shown that LSD, like the dopamine agonist apomorphine, produces rotation towards the unlesioned side (Pieri, Pieri & Haefely, 1974) and it was suggested that LSD can act as a dopamine agonist. Since 6-OHDA lesions of the substantia nigra which destroy the nigrostriatal bundle also damage the mesolimbic dopaminergic innervation of the nucleus accumbens and olfactory tubercle we have examined whether this damage to the mesolimbic dopamine system is involved in the production of rotational behaviour.

Adult male Sprague Dawley albino rats were injected unilaterally with 8 μg of 6-OHDA into either the caudate nucleus or the nucleus accumbens septi. The 6-OHDA (hydrobromide) was dissolved in 2 μl of cooled saline containing 1 mg/ml ascorbic acid and injected at the rate of 1 μl/min. The caudate injection depleted striatal dopamine (DA) content by 76% without significantly affecting the concentration of DA in the nucleus accumbens or olfactory tubercle. The nucleus accumbens injection reduced the DA content of the nucleus accumbens by 91% and that of the olfactory tubercle by 78%, and caused a smaller (24%) reduction in striatal DA content. When injected with (+)-methamphetamine (5 mg/kg i.p.) or apomorphine (10 mg/kg i.p.) 10-14 days after the lesion, only the caudate-lesioned rats showed a large rotational response to these drugs. The rotation produced by LSD is therefore probably due to an action on striatal dopamine receptors.

To investigate whether LSD can act as an agonist at mesolimbic dopamine receptors we recorded its effect in rats with bilateral 6-OHDA lesions of the nucleus accumbens. These animals show a greatly enhanced stimulation of locomotor activity when injected with dopamine agonists such as apomorphine (Kelly, Seviour & Iversen, 1975) or N-*n*-propylnorapomorphine (Kelly, Miller & Neumeyer, 1975) compared to sham-operated animals, which may be due to supersensitivity of the denervated mesolimbic DA receptors. LSD (1.0 mg/kg i.p.), like apomorphine (1.0 mg/kg i.p.), produced a marked stimulation of locomotor activity in these animals although this dose did not increase the locomotor activity of control rats. The non-hallucinogen (+)-bromo-lysergic acid diethylamide (2.0 mg/kg i.p.) did not stimulate locomotor activity in 6-OHDA treated rats. The dopamine antagonist pimozide (0.5 mg/kg i.p.) blocked the locomotor stimulation produced by LSD. These results suggest that LSD can act as an agonist at mesolimbic dopamine receptors.

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References

KELLY, P.H., MILLER, R.J. & NEUMEYER, J.L. (1975). Effect of apomorphine alkaloids on central dopamine receptors. *Brit. J. Pharmac.*, in press.

KELLY, P.H., SEVIOUR, P.W. & IVERSEN, S.D. (1975). Amphetamine and apomorphine responses in the rat following 6-HDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Research*, in press.

PIERI, L., PIERI, M. & HAEFELY, W. (1974). LSD as an agonist of dopamine receptors in the striatum. *Nature*, **252**, 586-588.

UNGERSTEDT, U. & ARBUTHNOTT, G.W. (1970). Quantitative recording of rotational behaviour in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. *Brain Research*, **24**, 485-493.