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LSD: EFFECT ON MONOAMINE METABOLITES IN RAT PREFRONTAL CORTEX

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Lysergic acid diethylamide (LSD) has been studied extensively with respect to its actions upon monoamine pathways. The central 5-hydroxytryptamine (5HT) system has been the object of the most extensive investigation (1-3), but catecholamine systems have also received substantial attention (4,5). Nearly two decades of research point to the conclusion that LSD impedes transmission in 5HT-containing neuronal systems. The concensus regarding the effects of LSD upon catecholamine systems is far less clear, and there may be regional brain differences (6). Recently, an area of rat forebrain has been identified which appears to possess some unusual properties. This region - prefrontal cortex - receives projections from a specific group of mesencephalic dopaminergic neurons which are selectively activated by stress (7,8), lack terminal and cell body autoreceptors (9), and respond uniquely to chronic neuroleptic administration (10). We became interested in the effect of hallucinogenic substances upon this region and report here some preliminary results of acute and intermittent LSD administration upon homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5HIAA) in rat prefrontal cortex and striatum.

MATERIALS AND METHODS

For the acute experiments male white rats (Sprague-Dawley obtained from Charles River and weighing approximately 200 g) were given an intraperitoneal injection of d-lysergic acid diethylamide tartrate (25 μg/kg, 0.05 μmole/kg actual LSD) or Brom-LSD (50 μg/kg, 0.12 μmole/kg actual BOL) between 9:00 and 10:00 a.m. and were decapitated 1.5 hr later. For chronic experiments rats received twice weekly intraperitoneal injections of LSD (25 μg/kg) and were killed 1.5 hr after the seventh injection at the beginning of week 4 of the intermittent LSD regimen. We chose this approach to chronic LSD administration since it is closer to the pattern of illicit hallucinogen abuse than daily exposure. Control animals received saline injections. LSD and BOL (NIDA) were provided by Michael Davis, Ph.D.

Both striata and prefrontal cortex were rapidly dissected and placed on dry ice. The prefrontal cortical section was obtained by use of a brain mold as previously described (11). For some experiments a larger sample of total cortex was obtained by removing the entire hemicortex above the bed of the caudate on both sides. Approximate frozen weights were 400 mg, 20 mg, and 70 mg for total cortex, prefrontal cortex, and striata respectively. Striata and cortex were assayed for HVA and 5HIAA by gas chromatography-mass spectrometry using deuterated internal standards (11,12). Experimental and control means for each region and drug condition were compared by an unpaired t test (two-tailed).

RESULTS AND DISCUSSION

Table 1 shows the results of the acute experiments with LSD. There was a highly significant increase in HVA in the prefrontal cortex compared to total cortex or saline control. A non-significant decrease in HVA after LSD was seen in total cortex compared to control.

There was a trend toward an increase in HVA in the striatum. No significant differences from control were seen for 5HIAA in either prefrontal cortex or striatum. Table 2 indicates that the increases in prefrontal cortical HVA seen with LSD were not seen following BOL administration. Table 3 shows that there was still a highly significant increase in prefrontal cortical HVA following chronic, intermittent LSD, although the absolute magnitude of the increase was less than that seen following acute LSD administration. Further, the HVA elevation in striatum reached significance on the chronic LSD regimen, and there was also a trend toward an increase in 5HIAA in prefrontal cortex.

Table 1. HVA and 5HIAA in rat prefrontal cortex, total cortex, and striatum after LSD*

	HVA		5HIAA	
	Control	LSD	Control	LSD
Prefrontal cortex	81 ± 5(12)	164 ± 24†(11)	324 ± 14(13)	338 ± 21(11)
Total cortex	52 ± 5(9)	42 ± 7 (10)		
Striatum	936 ± 51(15)	1070 ± 43‡(14)	567 ± 25(15)	583 ± 36(14)

* Values are ng/g (frozen weight) ± S.E.M. 1.5 hr after LSD (25 µg/kg i.p.). The number of animals is in parentheses.
† $P<0.002$, compared to control.
‡ $P<0.1$, compared to control.

Table 2. HVA and 5HIAA in rat prefrontal cortex and striatum after BOL*

	HVA		5HIAA	
	Control	BOL	Control	BOL
Prefrontal cortex	70 ± 5(6)	67 ± 5(9)	354 ± 26(8)	398 ± 25(10)
Striatum	1077 ± 40(10)	1090 ± 32(11)	599 ± 46(5)	656 ± 46(6)

* Values are ng/g (frozen weight) ± S.E.M. 1.5 hr after BOL (50 µg/kg i.p.). The number of animals is in parentheses.

Table 3. HVA and 5HIAA in rat prefrontal cortex and striatum after intermittent LSD*

	HVA		5HIAA	
	Control	LSD	Control	LSD
Prefrontal cortex	61 ± 3(12)	86 ± 5†(11)	312 ± 15(15)	355 ± 17‡(15)
Striatum	903 ± 31(16)	1161 ± 50†(16)	659 ± 22(16)	671 ± 20 (16)

* Values are ng/g (frozen weight) ± S.E.M. 1.5 hr after the seventh bi-weekly injection (25 µg/kg i.p.).
† $P<0.001$, compared to control.
‡ $P<0.1$, compared to control.

LSD, usually given in higher doses than those used here, has produced a variety of effects upon measures of central dopaminergic activity. Da Prada et al. (13) found biochemical evidence for decreased dopamine (DA) turnover in rat striatum and retina 6 hr

following 200 µg/kg LSD, given intraperitoneally, and they postulated that LSD could act as a central DA agonist. Christoph et al. (14) reported that LSD (25-50 µg/kg, i.v.), but not BOL, decreased the firing rate of 78% of dopamine-containing neurons in the substantia nigra of the rat, further evidence supporting a DA agonist-effect of LSD. Behavioral evidence of agonist activity was obtained by Kelly and Iversen (15) who found that LSD (1.0 mg/kg) produced a marked stimulation of locomotor activity in rats previously injected with 6-hydroxydopamine into the nucleus accumbens. Meltzer et al. (16) showed that LSD (50-200 µg/kg, i.p.) could act as a DA agonist by decreasing plasma prolactin in male rats. Persson (17) found increased DOPA accumulation in rat striatum following decarboxylase inhibition with both LSD and BOL (125-500 µg/kg). He also found evidence that these drugs have differing presynaptic effects in the nigrostriatal pathway. In a subsequent study, Persson (6) found some regional differences between LSD and BOL; LSD (500 µg/kg), in contrast to BOL, significantly increased DOPA accumulation after decarboxylase inhibition in cerebral cortex and brain stem. Persson concluded that this regional difference might be determined by a primary effect of LSD upon 5-hydroxytryptaminergic pathways and that both BOL and LSD probably block DA autoreceptors. Bürki et al. (18) observed a biphasic effect of LSD upon striatal dihydroxyphenylacetic acid (DOPAC), with decreases at lower doses (100-300 µg/kg) and increases at higher doses. Kehr and Speckenbach (19) also found that LSD increased tyrosine hydroxylation in the brain of intact rats and therefore questioned the postsynaptic agonist effects of this drug proposed by earlier reports. They also concluded that LSD possessed both agonist and antagonist properties at DA autoreceptors.

Most of the studies cited above employed much higher doses of LSD than those used in the present experiments. Persson's data are in partial agreement with our own despite a greater than tenfold difference in the dose of LSD administered (6). He found that LSD and BOL increased DOPA accumulation in striatum. We found that chronic but not acute LSD only increased striatal HVA. Persson also found increased DOPA accumulation in cortex after LSD but not BOL, a finding similar to our own results for prefrontal cortex. The findings of Kehr and Speckenbach with respect to LSD's effect on forebrain DOPA accumulation are also similar to our results for prefrontal cortex (19). However, the recent demonstration that prefrontal cortical DA projections lack autoreceptors suggests that our findings in prefrontal cortex cannot be explained on the basis of an effect upon DA autoreceptors (10). At the relatively low doses of LSD used here, we found evidence of increased DA metabolism in prefrontal cortex after acute and chronic, intermittent administration of LSD with little effect upon 5HT metabolism. However, actual determinations of 5HT turnover may be required to show effects of LSD upon 5HT metabolism (20).

These findings suggest that these doses of LSD may result in stimulation of DA neurons in the mesencephalon. In projections containing autoreceptors (striatum), this effect may become muted during acute exposure to LSD due to autoreceptor modulation of DA release and synthesis. In projections which do not possess autoreceptors (prefrontal cortex), increased DA release and synthesis may be unimpeded. It is tempting to speculate that a similar mechanism may be involved in the stress-induced activation of DA neurons projecting to prefrontal cortex (8). Perhaps chronic intermittent LSD administration produces an exhaustion of the autoreceptor regulation of DA release in striatum resulting in the significant increase in striatal HVA which we observed on the chronic LSD regimen. These results suggest that prefrontal cortex may be an area of brain uniquely vulnerable to the effects of LSD upon dopaminergic transmission. Recent studies indicate that certain cortical areas in rat brain possess autoreceptors (entorhinal cortex) while others do not (prefrontal and cingulate cortex) (21). If our hypothesis is correct, LSD should produce differential effects upon DA synthesis and release in these areas.

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