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D-Lysergic acid diethylamide (LSD)—Effect on biogenic amines excretion in man

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SEVERAL LINES of experimental evidence have advanced the hypothesis that the central action of D-lysergic acid diethylamide (LSD) may involve interaction with serotonergic neurons in the brain.^{1,2} Further, it has been shown that LSD may decrease 5-hydroxytryptamine (5-HT) turnover rate,³⁻⁸ antagonize the action of neuronal 5-HT in the raphe nuclei,⁹⁻¹¹ and block 5-HT release from electrically stimulated brain slices.^{12,13} The potent pharmacologic effects evoked by microgram doses of LSD have stimulated interest in its application in experimental psychiatry, e.g. as an adjunct for psychoanalytical therapy or as an "experimental model" analogous to naturally occurring mental disorders. However, the relationship of the latter to schizophrenic psychosis is controversial.

Administration of LSD to man induces symptoms indicative of stimulation of the sympathetic nervous system.¹⁴⁻¹⁷ This prompted the quantitative determinations of urinary and plasma catecholamines by several investigators.¹⁸⁻²⁰ Further, it is likely that central and peripheral serotonergic and/or catecholineric mechanisms are associated with LSD-induced psychotic-like syndrome in man. Accordingly, the determination of certain biogenic amines which were not previously studied, i.e. 5-HT and dopamine (DA), and their respective major acid metabolites might reflect biochemical changes associated with behavioral manifestation.

A group of seven male psychoanalysts who were in a training program for the use of LSD in psychotherapy volunteered for this study. They provided excellent collaboration for diet control and urine collections. LSD was given by mouth in 200-300 µg at the beginning of psychoanalytical session. Twenty-four-hr urine collections were made for each subject on the day prior to as well as the day of LSD administration. Urine specimens were collected over acid, aliquoted and kept frozen at -20° until assayed. Urine samples were fractionated as previously described.²¹ The quantitative determinations of urinary DA, norepinephrine (NE), 5-HT, homovanillic acid (HVA), vanillylmandelic acid

(VMA), and 5-hydroxyindole-acetic acid (5-HIAA) followed established analytical procedures.²²⁻²⁷ Values for DA, NE and 5-HT are given for total (free + conjugated) amounts excreted in urine.

The effect of LSD administration on urinary excretion of DA, NE and 5-HT ($\mu\text{g}/24 \text{ hr}$) and their major acid metabolites, HVA, VMA and 5-HIAA ($\text{mg}/24 \text{ hr}$) is summarized in Table 1. LSD reduced significantly ($P < 0.02$) amounts of DA excreted in urine. Mean urinary DA was decreased from 617 ± 149 to $476 \pm 124 \mu\text{g}/24 \text{ hr}$ after LSD. Concomitantly, a 57 per cent decrease in urinary 5-HT excretion from pre-drug treatment value was measured. However, this decrease was not statistically significant ($P < 0.1$). Urinary excretion of NE, VMA, HVA and 5-HIAA was not altered by LSD administration.

TABLE 1. EFFECT OF D-LYSERGIC ACID DIETHYLAMIDE (LSD) ON THE URINARY EXCRETION OF DOPAMINE (DA), NOREPINEPHRINE (NE), SEROTONIN (5-HT), HOMOVANILLIC ACID (HVA), VANILLYLMANDELLIC ACID (VMA) AND 5-HYDROXYINDOLEACETIC ACID (5-HIAA)

Treat- ment (μg LSD)	Subject No.	24-hr urine volume (ml)	DA	NE	5-HT	HVA	VMA	5-HIAA
			($\mu\text{g}/24 \text{ hr}$)			(mg/24 hr)		
24 hr prior to LSD	1	875	652	88	135	7.3	2.3	6.7
	2	1370	470	99	94	1.9	2.6	5.1
	3	1280	539	91	174	8.0	1.1	4.3
	4	2435	865	150	182	7.3	3.8	5.9
	5	1930	719	55	124	7.3	3.8	5.9
	6	1595	440	38	109	4.7	5.8	2.9
	7	1500	635	98	35	8.2	2.3	3.7
Mean $\pm$ S.D.			617 ± 149	88 ± 36	122 ± 50	6.4 ± 2.3	3.2 ± 1.6	4.9 ± 1.4
250	1	1546	585	98	129	7.2	2.2	8.4
200	2	1985	279	81	59	1.8	2.7	2.2
300	3	1295	417	69	61	6.6	5.9	7.4
300	4	2364	433	90	29	10.1	3.1	5.0
200	6	1625	665	80	77	7.6	6.0	3.3
300	6	945	472	110	106	5.4	2.8	2.9
300	7	1215	483	62	27	4.9	3.8	2.3
Mean $\pm$ S.D.			$476 \pm 124^*$	84 ± 17	$70 \pm 38^\dagger$	6.2 ± 2.6	3.8 ± 1.6	4.5 ± 2.5

* Differ from baseline $P < 0.02$ by two-tailed t -test for correlated means.

$^\dagger P < 0.1$.

The heightened sympathetic activity produced by the administration of psychotomimetic drugs in man seems to exert little effect on the excretion of urinary epinephrine (E) and NE. This is indicated by unaltered amounts of urinary NE, E and VMA after LSD intake²⁰ and with moderate changes in E excretion after mescaline administration.²⁸ In the present study, LSD produced no changes in NE and VMA excretion and is compatible with the finding of Hollister and Moore.²⁰ However, LSD administration was associated with decreased urinary 5-HT formation without alteration of the major acid metabolite 5-HIAA. Similarly, administration of LSD decreased significantly urinary DA output but not of its major acid metabolite HVA. It should be noted, however, that LSD antagonizes the action of DA and NE in the brain,^{29,30} and increases³¹ and decreases 5-HIAA excretion of urine of experimental animals.³² The increase in 5-HT concentration concomitant with a decrease in its major acid metabolite 5-HIAA in rat brain has suggested a decrease in 5-HT turnover rate and possibly an increase in neuronal 5-HT binding or a decreased release from storage vesicles.⁵ In the present study, LSD administration was associated with a decrease in formation of urinary 5-HT and DA, and suggests that LSD may interfere in storage and/or release of the monoamines.

It is interesting to correlate the non-aggressive attitude frequently displayed by some subjects during LSD psychedelic experience with the observed decrease in DA excretion. This correlation contrasts both with manic states which are associated with a rise in DA excretion²² and with aberration in mood of psychiatric depressed patients during trials with L-3,4-dihydroxyphenylalanine (L-dopa) (DA precursor) coupled with an aromatic L-amino acids decarboxylase inhibitor (MK-486).³³ The latter compound markedly reduces the extracerebral decarboxylation of L-dopa in man^{34,35} and is thought to increase concentrations of DA derived from L-dopa in the brain.³⁶

The present results suggest that decreased urinary excretion of 5-HT and DA produced by LSD may reflect decreased turnover rate of these monoamines. It remains to be determined if this finding relates to the basic mode of action of LSD in man. However, a body of knowledge is developing which suggests that such biochemical alterations may be manifested by psychological changes.

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