Psychopharmacologia (Berl.) 11, 270—275 (1967)

Urinary Catecholamine Excretion Following Lysergic Acid Diethylamide in Man*

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Received November 15, 1966

Lysergic acid diethylamide (LSD) evokes symptoms and signs of sympathetic stimulation. Prominent clinical phenomena from the drug include feelings of anxiety and tension, blurred vision, dilated pupils, tremors, nausea and increased deep tendon reflexes. (HOLLISTER and SJOBERG, 1964). Some have considered LSD a phenylethylamine derivate capable of stimulating central adrenergic sites (BRODIE, 1958). Thus, LSD might be excepted to release catecholamines as part of its action. Previous data in humans on this point have been somewhat confusing. One study found no change in plasma concentration of epinephrine and norepinephrine following 50 mcg oral doses of LSD (LIDDELL and WEIL-MALHERBE, 1953). Such doses are rather small and technical advances in measurement have occurred over the past decade. Another study of mental patients given 40 to 60 mcg doses of LSD intravenously described an initial rise in plasma epinephrine followed by a fall below the starting level and then a late rise (MANGER *et al.*, 1956). Fragmentary data from psychiatric patients given 150 to 300 mcg orally indicated that those patients who developed a psychiatric reaction to the drugs tended to show a constant increase in epinephrine excretion with a variable effect on norepinephrine (ELMADJIAN *et al.*, 1958).

Two experiments were conducted in the present study, one comparing the effects of LSD and epinephrine in the same subjects following a control period, the other comparing a separate control period with a similar period during which LSD was given.

Methods

Four measurements of urinary catecholamine excretion were made. Epinephrine and norepinephrine were determined by the basic technique of ANTON and SAYRE, 1962. Adsorption of aliquots was done on Amberlite CG-50 at pH 6.5 rather than alumina at pH 8.6. The method of PISANO *et al.*, 1962, as modified by O'BRIEN and IBBOTT, 1962, was used

* This work was supported in part by grant MH-03030, National Institutes of Health.

for the extraction of 3-methoxy-4-hydroxymandelic acid (vanilmandelic acid, VMA) from the urine and its subsequent oxidation by periodate to yield vanillin. GOLDENBERG and WHITE's, 1962, method for the condensation of vanillin with thiosemicarbazone was then applied. The fluorescence was measured in an Aminco-Bowman Spectrophotofluorometer with an activation wave length of 360 mμ and a fluorescent wave length of 445 mμ. The procedure of PISANO, 1964, was used for isolation of the methoxy derivatives of epinephrine and norepinephrine and their subsequent conversion to vanillin. Fluorescence was measured as for VMA. Recovery of materials added to urine varied between 76 and 86 percent for those techniques.

The *first experiment* was performed in 13 normal volunteer subjects, the majority being men in the third or fourth decade of life without physical or emotional disorders. For each trial, subjects were instructed to fast from the time of the previous evening meal until the morning of the test, usually a period from 12 to 14 hours. Smokers were not permitted to smoke the morning of the test nor during it. After reporting to the hospital, subjects emptied their bladders prior to beginning collection of a control 2-hour urine specimen prior to drug administration. They were placed at rest, sitting or lying unrestrained in bed, and remained resting and fasting for the four hours following drug administration, separate urine specimens being collected during the first two-hour period and the second. Adequate hydration ensured a reasonable urine volume. Blood specimens were taken periodically during the study for determination of plasma free fatty acids (FFA), following the method of TROUT, ESTES and FRIEDBERG, 1960.

Drugs were given at weekly intervals, seven subjects receiving epinephrine (3 mcg/kg) first, the others receiving LSD (2 mcg/kg) first; the order was reversed for the second trial. All doses were administered subcutaneously and on any given trial, the order of administration was not known by the subjects.

The *second experiment* used 14 male volunteers, most of whom were in the third decade of life. Experiments were conducted on two consecutive days. On the first day, no drug was given, but subjects were kept under a load of 1000 ml of water as part of a study of antidiuretic effects. On the second day, the same procedure was carried out following administration of LSD, 1.5 to 2 mcg/kg orally. A pooled 8-hour specimen of urine was used for determination of the catecholamines over this period of time on the two consecutive trials.

Results

The comparative effects of epinephrine and LSD on catecholamine excretion are summarized in Table 1. Epinephrine evoked a brisk increase

Table 1. *Excretion of catecholamines following epinephrine (3 mcg/kg) or LSD (2 mcg/kg) in thirteen subjects*

	Epinephrine $N = 13$	Norepinephrine $N = 13$	VMA $N = 13$	Metanephrines $N = 9$
Epinephrine				
2 hrs. preceding	15.2 (7.6)	21.1 (9.6)	2.84 (.58)	.199 (.15)
0—2 hrs. trial	64.7 (23.2)[3]	13.4 (7.7)[1]	3.20 (.59)	.249 (.12)
2—4 hrs. trial	25.3 (9.4)[3]	16.1 (11.5)	2.89 (.73)	.328 (.23)[2]
LSD				
2 hrs. preceding	20.4 (11.6)	19.8 (8.1)	2.88 (.67)	.233 (.18)
0—2 hrs. trial	25.8 (12.0)	18.5 (11.8)	2.78 (.52)	.243 (.13)
2—4 hrs. trial	23.6 8.8)	22.0 (11.2)	2.72 (.51)	.240 (.17)

[1] $p < .05$; [2] $p < .01$; [3] $p < .001$, t-test correlated compared with baseline values for epinephrine and norepinephrine is nanograms/mg · creatinine; for VMA and total metanephrines in micrograms/mg · creatinine · Mean (standard deviation).

Table 2. *Plasma FFA levels following subcutaneous LSD (2 μg/kg) or Epinephrine (3 μg/kg)*

	N	Baseline mean (S.D.)	30 min mean (S.D.)	1 hour mean (S.D.)	2 hours mean (S.D.)	4 hours mean (S.D.)
LSD	13	596 (155)	759 (238)[1]	933 (331)[2]	913 (368)[1]	1216 (363)[3]
Epinephrine	13	554 (193)	1403 (510)[3]	884 (235)[2]	429 (127)	632 (174)

[1] $p < .05$; [2] $p > .01$; [3] $p > .001$; t-test correlated means, 2-tail. All values in micromoles/l.

in epinephrine excretion over the first two hours, with a reciprocal decrease in norepinephrine excretion. The rise in epinephrine excretion continued through the third and fourth hours. A slight but non-significant rise in VMA occurred during the first two hours. Total metanephrines increased during both time periods, significantly in the third and fourth hours. LSD produced no statistically significant changes in catecholamine excretion in either time period.

Both LSD and epinephrine evoked the usual clinical signs of sympathetic stimulation: feelings of anxiety, tremors, dilated pupils, and increased deep tendon reflexes, although differing considerably in the mental reaction evoked (Hollister, 1964). Sympathomimetic effects from epinephrine were quick in onset in duration and slightly more intense than those from LSD. The changes in plasma free fatty acid levels following the two drugs paralleled the clinical effects (Table 2). The increase in plasma FFA following epinephrine was early and lasted only a little

more than an hour; that from LSD was gradual in onset and still increasing after four hours. It should be noted that the peak increases were roughly the same from both drugs, despite the fact that they could not be given in equimolar doses. Thus, we have clear evidence that both drugs produced sympathetic stimulation at these doses.

Table 3. *Excretion of catecholamines over an eight-hour period following LSD (1.5—2.0 mcg/kg) or no treatment in fourteen subjects*

	Epinephrine	Norepinephrine	VMA	Metanephrines
Control	25.8 (8.7)	17.7 (11.1)	3.27 (.87)	.267 (.11)
LSD	25.6 (6.2)	18.5 (7.6)	3.23 (.66)	.247 (.07)

Values for epinephrine and norepinephrine in nanograms/mg · creatinine; for VMA and metanephrines in micrograms/mg · creatinine. Mean (standard deviation).

Table 3 summarized the excretion of catecholamines over an 8-hour period during which a water load was applied, both without and with administration of LSD. The water load apparently was stressful, as indicated by an increased excretion (as compared with the previous experiment) of epinephrine. On the other hand, no significant differences were noted between the two conditions in terms of catecholamine excretion.

Discussion

Data from both experiments was consistent in that administration of LSD in the range of doses commonly used for clinical studies did not significantly alter the excretion of catecholamines. These data suggest that the drug has little effect on the release of adrenal catecholamines and on the release of catecholamines at peripheral sympathetic synapses. Animal studies have shown that both total and particulate norepinephrine is decreased by LSD throughout the brain as well as the heart, but no measures of the excretion of norepinephrine or its metabolites has been made simultaneously (FREEDMAN, 1963). In the case of release of norepinephrine from brain, one should expect little to be reflected in the amounts excreted in the urine, as the total amounts would be small and the material is not able to pass the blood-brain barrier readily.

On the other hand, LSD and kindred drugs, such as mescaline and psilocybin, have been repeatedly described as producing clinical sympathomimetic effects. In one of the present studies, these effects were comparable to those produced by epinephrine. Further, the magnitude of sympathetic stimulation as measured by increased plasma FFA levels was also comparable. Yet, it is clear that while changes in the excretory pattern of catecholamines following exogenous epinephrine were easily measured, such were not evident following LSD. It is likely that in part

these differences are due to the time span of action; the much slower release of catecholamines following LSD might lead to their more complete catabolism than in the case of a relatively large dose of epinephrine exogenously administered.

Although adrenergic blocking agents are said to be effective in mitigating some of the effects of LSD, detailed study of the interactions of alpha- and beta-adrenergic blocking drugs on the clinical reactions from LSD has not yet been done. Chlorpromazine, which is usually used for treating adverse clinical reactions, is a powerful alpha blocker; however, it may very well be that its powerful sedative effects are of equal importance. Phenoxybenzamine, another alpha blocker, has also been said to raise the threshold for recognition of the clinical effects of threshold doses of LSD (MURPHREE, 1962). The present availability of alpha- and beta-blockers without sedative effects makes it possible to parcel out the relative effects of alpha- and beta-receptor stimulation as causes for the clinical symptoms of the LSD reaction.

The present studies indicate that a drug may produce a powerful sympathomimetic effects without any measurable change in the excretory pattern of catecholamines. While this lack of sensitivity may not hold for all drugs, such as amphetamine, which may act by releasing norepinephrine from peripheral synpapses, it indicates that such a measure is not a very good indicator of the gradual, modest and sustained degree of sympathetic stimultion produced by LSD or kindred drugs.

Summary

Two separate controlled experiments in man measured the excretion of epinephrine, norepinephrine, vanilmandelic acid (VMA) and total metanephrines following lysergic acid diethylamide (LSD), comparisons being made with an injection of a similar dose of epinephrine in the one instance and with a no-treament period in the other. LSD (2 mcg/kg) produced insignificant changes in urinary catecholamine excretion over a four-hour period while epinephrine (3 mcg/kg) evoked substantial increases in excretion of epinephrine, VMA and metanephrines with a concomitant decrease in norepinephrine excretion. Sympathomimetic effects of these doses of LSD were apparent clinically and as judged by the degree of elevation of plasma free fatty acids (FFA); the response to epinephrine was brief and intense, while that to LSD was sustained and more gradual in onset. In the second experiment, LSD (1.5 and 2 mcg/kg) produced no more changes in catecholamine excretion over an eight-hour period than a control no-treatment trial.

Although LSD has many sympathomimetic actions, these are not adequately reflected by measurement of urinary catecholamine excretion.

These experiments suggest that measurement of urinary catecholamines is a poor gauge of sustained sympathomimetic effects.

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