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# Effects of Single and Multiple Dose LSD on Endogenous Levels of Brain Tyrosine and Catecholamines

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*Abstract.* The effects on brain catecholamines of seven daily doses of *d*-LSD 520 µg/kg injected i.p. to Sprague-Dawley rats on a tolerance dosage schedule (L × 7) were compared with the effects of a single dose of LSD (L × 1) 520 µg/kg or 1040 µg/kg, over a 90 min time course. Compared to saline controls, after a single dose of 520 µg/kg LSD, there was a significant decrease in brain norepinephrine at 30 and 60 min, a rise in dopamine at 60 min, and a small rise in brain tyrosine at early time points followed by significant decline from control levels after 60 min. The effects of a single dose of 1040 µg/kg LSD were similar to the 520 µg/kg dose but were greater in both magnitude and duration of the brain catecholamine changes. After a tolerance dosage schedule there were significant changes in the response of brain catecholamines to 520 µg/kg LSD. The rise in brain dopamine at 60 min was abolished, brain tyrosine was uniformly below both saline and L × 1 animals, and brain norepinephrine returned to control levels slightly faster.

*Key words:* LSD – Catecholamines – Tolerance.

## *Introduction*

The effects of tolerance dosage schedules of *d*-lysergic acid diethylamide (LSD) on brain neurohumors can provide evidence for the role of specific biogenic amines in the mechanism of action of this drug. It has previously been demonstrated (Freedman *et al.*, 1958; Freedman and Aghajanian, 1959; Freedman *et al.*, 1964) that, after several daily injections of LSD to rats, tolerance develops to some of the acute behavioral effects seen after a single dose. Specifically, the cessation of responding for food on fixed ratio (FR) and effects on variable interval (VI) food reinforcement schedules are diminished in duration, magnitude or both after several injections; and so, too, are sympathomimetic effects in man and animals (such as mydriasis, piloerection, or pyrexia); EEG alerting and hind limb extension in the rat also show tolerance (Freedman and Giarman, 1963b). If the neurochemical changes which occur in brain biogenic amines after a single dose of LSD are also altered after a tolerance dosage schedule of multiple injections, this would provide additional support for the relation of mechanisms regulating biogenic amines as also mediating some of the behavioral effects of the drug.

Recent work in this laboratory (Boggan and Freedman, 1973; Freedman and Boggan, 1974) has shown such changes with respect to brain 5-hydroxyindole metabolism after multiple doses of LSD. The time course of brain neurochemical changes after a single dose of LSD (Freedman, 1961a; Freedman, 1961b; Rosecrans *et al.*, 1967; Freedman *et al.*, 1970; Halaris *et al.*, 1972; Anden *et al.*, 1968) is related to the course of acute behavioral effects of the drug in the rat. During this initial period of response, there is an increase of 12–20% in serotonin (5-HT) localized in the particulate fraction (Freedman, 1961a) and further localized in the nerveending fraction (Rosecrans *et al.*, 1967; Halaris *et al.*, 1972); a decrease in 5-hydroxyindoleacetic acid (5-HIAA) and a slowed turnover (Rosecrans *et al.*, 1967; Lovell *et al.*, 1967; Diaz *et al.*, 1968); decreased synthesis of serotonin from labelled tryptophan (Diaz *et al.*, 1968; Lin *et al.*, 1969; Shubert *et al.*, 1970; Shields and Eccleston, 1973) and an increase in levels of brain tryptophan reaching a maximum of 22% 60 min after drug injection (Boggan and Freedman, 1973; Freedman and Boggan, 1974). Firing of serotonergic neurons in the midbrain dorsal and median raphe nuclei is inhibited with roughly similar onset and duration as the amine changes (Aghajanian *et al.*, 1970). The increase in 5-HT (thought to be due to non-release and/or binding) and decrease in 5-HIAA begins close to the onset and appears to peak close to the termination of the acute behavioral effects seen in the rat after a single dose of LSD. For example, a period of no responding on either

rope climbing or bar pressing for food begins 5–10 min after intraperitoneal LSD, and persists for a 20–40 min period. An "LSD-crouch" and EEG alert period have roughly similar onset and duration (Freedman and Giarman, 1963). After several daily doses of LSD there are alterations in brain serotonergic response to LSD; these changes are seen both in the time course of neurochemical response (an earlier peak in brain 5-HT) and in the magnitude of response (diminished effects on brain tryptophan at 60 min and on 5-HIAA at 45 and 60 min).

Changes in catecholamines have also been implicated in the biochemical response to LSD, although the data here is less consistent. Significant indirect evidence for the participation of catecholamines in the behavioral response to LSD is the observation (Horita and Hamilton, 1969) that inhibition of catecholamine synthesis by α-methyl-p-tyrosine (αmpt) abolished or attenuated the signs of increased excitability produced by LSD in the rabbit; this effect is reversed by the administration of a combination of L-Dopa and a dopamine-*B*-hydroxylase inhibitor (DEDC) (Horita and Hamilton, 1973). More direct evidence comes from several groups of investigators who have reported decreases in rat brain NE after high doses of LSD, both in whole brain (Freedman, 1961b; Freedman *et al.*, 1963; Anden *et al.*, 1968; Barchas and Freedman, 1963) and in parts of brain (Sugrue, 1969). Leonard and Tonge (1969) and Tonge and Leonard (1970) have reported a significant decrease in concentrations of rat brain NE and also an increase in tyrosine and dopamine (DA) after relatively low, behaviorally active doses of LSD (100–200 μg/kg); however, they found no changes in NE, DA or tyrosine after 1 mg/kg LSD (Tonge and Leonard, 1971). Finally, there is some data suggesting a dopamine agonist and/or antagonist action of LSD (Pieri *et al.*, 1974; von Hungen *et al.*, 1974).

The purpose of the present experiments was to further examine the relationship between LSD and catecholamines, over a time course during which most of the acute behavioral effects occur in the rat, by comparing the neurochemical effects of single vs multiple injections of LSD on rat brain NE, DA, and tyrosine.

## *Methods*

The subjects were male Sprague-Dawley rats, 160–280 g in weight. They were housed under our standard laboratory conditions of a 7 a.m. to 7 p.m. light-dark cycle, *ad lib* access to Purina cat chow and water, and at a temperature of 73 ± 2 F. Rats were injected intraperitoneally with LSD (520 or 1040 μg/kg) or saline and were sacrificed by decapitation at the times indicated in the results below. Each experiment at a dose of 1040 μg/kg contained several time points. In the multiple dose experiments, using 520 μg/kg LSD, animals were injected once a day, between 5–8 pm, for 6 days and sacrificed in the mornings at various times (indicated in the results section) after injection of the 7th dose. Animals designated L × 7 received 7 injections of 520 μg/kg LSD; L × 1 animals were injected 6 days with saline and on the 7th day with 520 μg/kg LSD; and control animals received 7 days of injections with saline.

The brains were homogenized in 15 ml 0.4 N perchloric acid and the resulting homogenate was centrifuged at 15000 rpm for 15 min at 0 C (International B-20 refrigerated centrifuge). The supernatants were adjusted to equal volumes. A 4 ml aliquot of the adjusted supernatant was removed for tyrosine assay, following the method of Udenfriend (Udenfriend, 1962); the remaining supernatant was analyzed for NE and DA by the method of Anton and Sayre (1962).

Each time point was repeated in several experiments on different days. Each experiment consisted of three groups with 4–5 animals in each group, including a saline control group. Brains were individually assayed for NE, DA, and tyrosine (*i.e.*, they were *not* pooled). Differences between relevant groups were compared for each experiment, and statistical significance of the differences between 2 groups at the same time point, using data from several different experiments at this time point, was analyzed by a weighted *t*-test[1]; mean differences and variances on the different days were weighted for the number of animals in that experiment. Two-tailed probabilities were used. The computational formulas are given in the Appendix. The per cent difference of LSD from control values was calculated by a weighted mean per cent difference of several experiments, weighted for the number of animals. The per cent control values for S.E.M. were calculated from the S.E.M. in ng/g (for NE and DA) or μg/g (for tyrosine) and divided by saline control values for that time point.

## *Results*

*Single Dose of LSD (L × 1).* A *single dose* of 520 μg/kg LSD produced significant alterations in brain tyrosine, dopamine and norepinephrine, and there was an increase, in both the magnitude and duration, of the catecholamine response after the 1040 μg/kg dose as compared to the 520 μg/kg dose (Table 1).

*Dopamine.* Dopamine was significantly increased at 30 and 60 min after the 1040 μg/kg dose, and at 60 min after the 520 μg/kg dose.

*Norepinephrine.* NE was significantly decreased at 30 min at both doses and then began to return to baseline.

*Tyrosine.* Brain tyrosine showed a biphasic response; at the higher dose it was significantly increased at 30 min but fell below control values at 60 min after injection; at the 520 μk/kg dose there was also a significant decrease in brain tyrosine after 60 min. Data from a few experiments in which animals were sacrificed at time points longer than 90 min post injection show a prolonged response of brain tyrosine

[1] This statistical procedure was developed by Professor Paul Meier, Department of Statistics, University of Chicago.

Table 1. Brain norepinephrine, dopamine, and tyrosine after single injection of LSD at two doses

| | Mean (± S.E.M.) | | | | | |
|---|---|---|---|---|---|---|
| Time after injection (min) | 30 | | 60 | | 90 | |
| Dose (μg/kg) | 520 | 1040 | 520 | 1040 | 520 | 1040 |
| | Norepinephrine (ng/g) | | | | | |
| | ($N = 29^3$) | ($N = 22^3$) | ($N = 67^7$) | ($N = 55^7$) | ($N = 29^3$) | ($N = 23^3$) |
| LSD | 338.4 (11.7) | 326.0 (9.1) | 359.5 (14.9) | 309.9 (6.4) | 345.3 (13.0) | 321.6 (18.7) |
| Saline | 368.2 (11.9) | 386.3 (14.1) | 376.9 (14.2) | 333.5 (9.9) | 353.7 (14.3) | 335.6 (15.9) |
| *P* | < 0.01 | < 0.001 | < 0.05 | < 0.02 | N.S. | N.S. |
| | Dopamine (ng/g) | | | | | |
| | ($N = 29^3$) | ($N = 23^3$) | ($N = 63^7$) | ($N = 45^6$) | ($N = 18^2$) | ($N = 23^3$) |
| LSD | 884.9 (28.6) | 902.8 (36.0) | 929.2 (26.5) | 914.2 (30.0) | 857.8 (74.1) | 893.8 (41.6) |
| Saline | 921.1 (28.7) | 800.0 (31.3) | 870.8 (27.8) | 825.5 (42.2) | 874.5 (67.1) | 962.1 (45.4) |
| *P* | N.S. | < 0.02 | < 0.01 | < 0.001 | N.S. | N.S. |
| | Tyrosine (μg/g) | | | | | |
| | ($N = 57^6$) | ($N = 20^3$) | ($N = 66^7$) | ($N = 45^6$) | ($N = 20^2$) | ($N = 32^4$) |
| LSD | 27.2 (0.6) | 31.0 (1.5) | 24.2 (0.5) | 22.4 (1.5) | 19.4 (0.7) | 23.8 (0.9) |
| Saline | 27.0 (0.6) | 27.3 (1.8) | 25.9 (0.5) | 23.3 (1.7) | 21.8 (0.9) | 26.5 (1.6) |
| *P* | N.S. | < 0.001 | < 0.005 | < 0.03 | < 0.01 | < 0.001 |

Each value represents mean (± S.E.M.) from several experiments. ($N^e$) = number of animals in combined LSD and saline groups at this time point in "e" separate experiments. Since many of the experiments in which the 1040 μg/kg dose was used did not also contain a group at 520 μg/kg, separate saline control values are shown for the 1040 μg/kg and 520 μg/kg single dose experiments. *P* = 2-tailed probability value from weighted *t*-test performed by Meier's procedure (see text).

to the higher dose of LSD. Brain tyrosine had returned to control levels by *120* min after the lower dose (tyrosine after 520 μg/kg LSD − 22.7 μg/g; saline − 23.2 μg/g), but was still significantly decreased ($P < 0.05$) *150* min after the higher dose (tyrosine after 1040 μg/kg LSD 23.7 μg/g; saline − 26.5 μg/g).

The catecholamine response to LSD was not affected by several days of prior saline injection; there were no differences in the effects of 520 μg/kg LSD between animals who had been injected 6 days with saline and received LSD on the 7th day, and animals who received a single dose of 520 μg/kg LSD without prior saline injections.

*Seven Doses of LSD (L × 7).* Seven daily doses of 520 μg/kg LSD produced significant alterations in the catecholamine response found after a single dose of 520 μg/kg:

*Dopamine.* The brain dopamine response to LSD was abolished. In contrast to the rise in dopamine at 60 min seen in the L × 1 animals, there was no increase in DA in the L × 1 animals (L × 7 vs. L × 1 $P < 0.01$). Preliminary data on dopamine changes in the caudate showed a similar difference in brain dopamine in single vs. multiple dose animals (L × 1 5356.50 ng/g; L × 7 4845.80 ng/g).

*Norepinephrine.* The L × 7 animals also had a significant increase in endogenous NE levels at 90 min, compared to the L × 1 animals, and showed a slightly faster recovery of the decrease in NE.

*Tyrosine.* The neurochemical response of brain tyrosine to LSD was also significantly altered. The L × 7 animals had uniformly lower levels of brain tyrosine throughout the 90 min time course after the 7th LSD injection, and the tyrosine levels were significantly different from the L × 1 animals at 15, 30 and 60 min. Furthermore, the brain tyrosine level at time *0* on the graph indicates that there was a prolonged biochemical effect of several daily doses of LSD. Fourteen hours

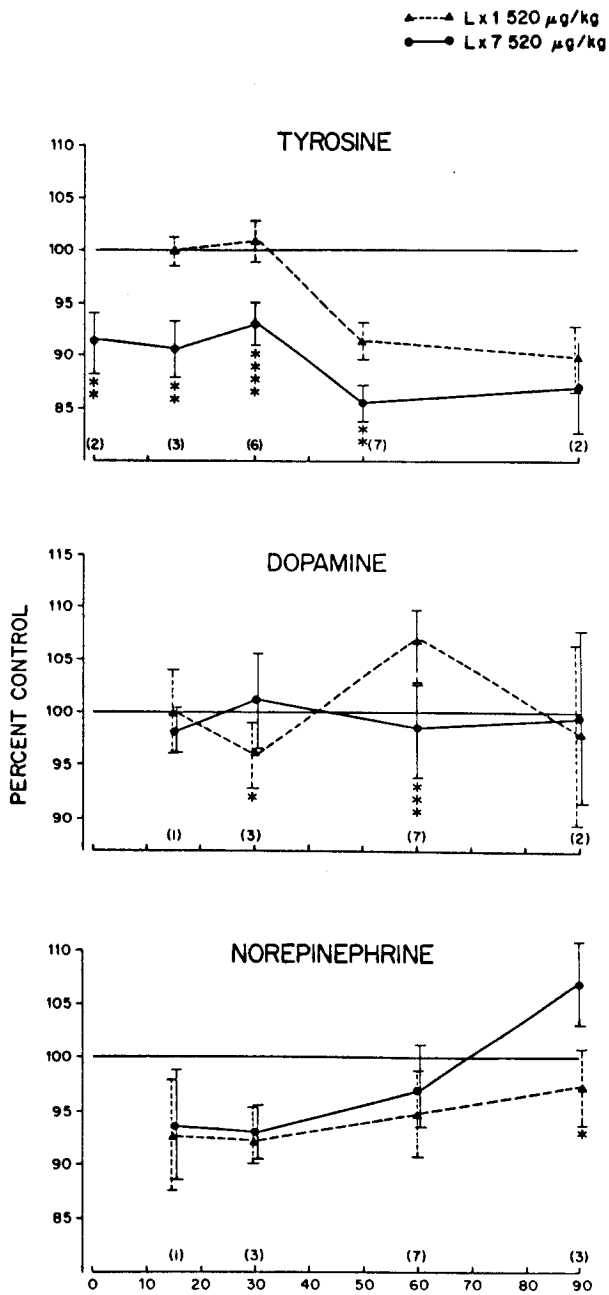


Fig. 1. Comparison of effects of a single dose vs. seven daily doses of LSD 520 µg/kg on endogenous levels of brain tyrosine, dopamine and norepinephrine. Each point represents mean percent saline control (± S.E.M.) determined from several experiments, each of which consisted of 3 groups (L × 7, L × 1, Saline) with 4–5 animals per group. (*N*) below each set of values is number of *experiments* at that time point. Actual control values at each time point are those shown for the saline animals for the 520 µg/kg LSD dose in Table 1. Additional saline control values for time points not shown in Table 1 are as follows: Tyrosine, time *0* = 28.9 ± 1.0; Tyrosine, 15 min = 27.8 ± 0.7; DA, 15 min = 832.1 ± 45.1; NE, 15 min = 283.4 ± 16.0. Statistical significance of the difference between L × 7 vs. L × 1, using 2-tailed values from weighted *t*-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.0001$

after the *6th dose* of LSD, at a time animals would have received their 7th dose, there was a significant ($P < 0.01$) decrease in brain tyrosine levels.

## *Discussion*

The effects of a single dose of LSD on brain catecholamines and the altered response of these biogenic amines to multiple injections of the drug provide additional support for the involvement of the brain catecholamine systems in the mechanisms of some of the effects of LSD.

The effects of a single dose of 520 µg/kg LSD on brain catecholamines were clearly significant, and the replication of these changes at the higher dose – with an increase in magnitude and duration of biochemical response – provides additional support for the consistency of the drug effect on brain catecholamines. The dose effect of LSD that we report here is consistent with the decrease in NE at higher doses previously found (Freedman, 1961b, c; Freedman *et al.*, 1962; Barchas and Freedman, 1963) but contrasts with the findings of Tonge and Leonard (Tonge and Leonard, 1970, 1971), who reported no changes in NE and DA at a high dose (1000 µg/kg) and no significant decrease in brain tyrosine at later time points at either low or high doses. These differences in catecholamine response to LSD may be due to some differences in experimental animals – *i.e.*, strain (Wistar vs. Sprague-Dawley), sex (both males and females vs. only males in our experiments), or size (90–100 g vs. 160–280 g); or they may be related to the greater number of experiments at each time point in our data compared to the single experiment, with 5 animals at each time point, on which Tonge and Leonard based their results.

Thus, as reported for the serotonergic system (Boggan and Freedman, 1973; Freedman and Boggan, 1974), there are also altered neurochemical responses in brain catecholamines to a tolerance dosage schedule of LSD, changes that occur during the period when increments or decrements of behavioral effects are reported. These changes manifest both in the decrease in magnitude of response (the lack of rise in DA at 60 min and decreased levels of brain tyrosine) and shifts in time (the earlier recovery of the decrease in NE).

The significant decrease in brain tyrosine at time *0*, 14 hrs after the 6th dose, also indicates that brain biochemical changes can be found many hours after all behavioural manifestations of the drug effect in the rat are no longer evident. Similar long term changes in indole metabolism were reported by Diaz and Huttunen (1971); over 18 hrs after the last injection of 20 µg/kg LSD, which had been given daily for a month, they found indications of increased serotonin

turnover. This occurred, at a time after the last injection, when no behavioral manifestations of the drug were evident. Peters (1974a, b) reports dose-dependent long term changes in indole and catechol measures of tyrosine hydroxylase activity, tyrosine, and NE, which he interprets as indicating increased turnover at 24 hrs after the last of multiple doses. The evidence thus suggests that prior to the 6th or 7th dose of LSD, the regulation of amines is different than prior to an initial dose, and our data indicate the amine response is different *during* the immediate post injection period with a tolerance dosage schedule. This immediate post injection period is one in which uptake and clearance of LSD in brain (Giarman and Freedman, 1965; Rosecrans *et al.*, 1967), as well as the 5HT and NE changes, have been observed.

The precise mechanisms underlying altered catecholamine responses during the first 90 min after the last of multiple doses of LSD have not been determined. After a *single dose* of the drug, reduction in NE has been interpreted as an increased rate of intraneuronal depletion of NE, on the basis both of histochemical studies (Sugrue, 1969) and the lack of increase in normetanephrine (Stolk *et al.*, 1974). Some support for the hypothesis that the increase in endogenous levels of brain dopamine after a single dose of LSD may reflect increased synthesis comes from two studies; Stolk *et al.* (1974) and Persson (1970) have found small increases in synthesis and turnover of both DA and NE after high doses of LSD. The mechanism of the rise in brain tyrosine after a single dose of LSD has received no direct experimental investigation.

Whether alterations in any of the specific mechanisms which govern the catecholamine response to a single dose of LSD would account for the post injection or longer term changes in endogenous levels after multiple doses remains to be determined. The neurochemical changes after multiple doses of LSD may result from a series of sequential, interrelated and feedback-contingent changes in catecholamine synthesis, release, uptake, and degradation. A comparison of the effects of single vs. multiple doses of LSD on indicators of norepinephrine and dopamine turnover (*e.g.*, HVA and MHPG after probenecid) at 30, 60, and 90 min after the final injection, and studies of labelled tyrosine uptake and disposition at the relevant time points after 1–7 doses of LSD, would help clarify the mechanism underlying the changes in endogenous levels that we report. With such sensitive measures, doses of LSD lower than 520 μg/kg, and thus more readily matched with doses used in parametric behavioral studies, can be used to further specify the nature of the relationship between biochemical changes and behavioral tolerance to LSD.

## *Appendix*

Formulas for calculation of weighted *t*-test.

$$t = \frac{A}{B} \qquad df = \sum_{i=1}^{p} (n_{di} + n_{ci}) - 2$$

$$A = \frac{\sum_{i=1}^{p} [n_i (\bar{x}_{di} - \bar{x}_{ci})]}{\sum_{i=1}^{p} n_i}$$

$$S.E._{\cdot i} = \sqrt{\frac{(S.D._{\cdot di})^2}{n_{di}} + \frac{(S.D._{\cdot ci})^2}{n_{ci}}}$$

$$B = \sqrt{\sum_{i=1}^{p} \left[ \left( \frac{n_i}{\sum n_i} \right)^2 (S.E._{\cdot i})^2 \right]}$$

$i$ = experimental day ($i = 1$ to $p$),
$n_{di}$ = number of animals (*i.e.* non-pooled brains) in drug treated group,
$n_{ci}$ = number of animals in control (saline) or other comparison group,
$n_i$ = smaller of the 2 numbers $n_{di}$ and $n_{ci}$,
S.D. = standard deviation,
$\bar{x}$ = mean.

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