Effect of Lysergic Acid Diethylamide (LSD-25) on Growth Metabolism and the Resistance of Male Rats to Histamine Stress

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Depending on dosage and time-pattern relationships, the s.c. administration of LSD-25 at dosage levels of 500 or 750 mcg./Kg. of body weight in eight sequential injections to male Wistar rats during a 2-week experimental period was found to cause significant decreases in body weight, body weight gain, food consumption, and a loss of efficiency in food utilization processes. LD_{50} analyses indicated an increased ability of treated rats to tolerate histamine stress. The data agree with previous evidence of hypothyroidism and adrenocortical hyperactivity in rats injected with LSD-25.

THE PSYCHIC aberrations of mentation elicited by minute doses of lysergic acid diethylamide (LSD-25) resemble in many aspects those peculiar to schizophrenia (1, 2). Previous investigations have demonstrated that LSD-25 stimulates adrenal activity and inhibits growth, metabolism and thyroidal, and gonadal function in female (3, 4) and male Wistar rats (5). These findings in rodents agree with the observation that LSD-25 caused reduced food intake, anorexia, and accentuated body weight losses in man (6). This study presents further data on body growth and food metabolism changes produced by LSD-25 in males and reports alterations in the resistance of rats to histamine stress conferred by prolonged administration of LSD-25.

EXPERIMENTAL

Two hundred and ten male Wistar rats averaging 110 Gm. in body weight were matched by weight and divided equally into three groups. Group *A* and *B* rats received a series of s.c. injections containing 500 or 750 mcg./Kg. body weight of LSD-25 dissolved in 1 ml. of normal saline. Group *C*, control, received an equivalent volume of saline. All animals were housed five per cage in metal cages of the following dimensions: 16 × 18 × 11 in.; in a laboratory maintained at 73°F. Previous studies have indicated that prolonged isolation (7) *per se* as well as excessive crowding (8) can produce metabolic and endocrinological alterations. Similarly, to minimize handling (9) and auditory stress (10, 11) influences, all animals were handled alike and care was taken to prevent undue harsh and extraneous loud noises. The average level of the laboratory daytime background noise during the period of experimentation was 68 decibels.

In order to observe changes in time-patterning relationships caused by LSD-25 and to reduce the development of tolerance and resistance to the hallucinogenic agent (12, 13), eight injections of the respective test doses were administered over a 2-week period on alternate days with the exception that on the thirteenth and fourteenth days, the test rats received daily injections. Body weight and food consumption measurements were determined weekly during the 2-week experimental period.

Twenty-four hours after the eighth and final injection of LSD-25, 60 group *A* and *B* experimental rats and 60 control animals were selected from each group, and equal aliquots were tested for the degree of resistance to histamine stress. The animals were challenged intraperitoneally with four dose levels of histamine phosphate (450, 600, 750, and 900 mg. histamine base/Kg. body weight). Finney's (14) method of probit analysis was used to calculate the LD_{50} values and dose-response lines.

RESULTS AND DISCUSSION

Table I presents the average body weight and body weight gain data per test and control rat and Table II the food consumption and food utilization ratios[1] computed on the basis of five animals per cage.

Analyses of the data for the 2-week period indicated that administration of LSD-25 at both dose levels caused either marked or statistically significant reductions in the final body weights, total body weight gains, total food consumption, and food utilization processes of the test rats when compared with control values. In general, the 750 mcg./Kg. dose produced somewhat more pronounced decreases than those shown by the 500 mcg./Kg. dose, although the differences between the two test groups were not statistically significant (*i.e.*, final body weights: group *A*, 5.0%, group *B*, 5.4%; body weight gains: group *A*, 13.2%, group *B*, 14.3%, etc.).

Analyses and comparisons of the alterations on a weekly basis revealed, however, that the per cent decreases induced by the group *B* dose during the first week were approximately double those shown by group *A* rats (*i.e.*, body weight gains: group *A*, 11.6%, group *B*, 21.6%; food consumption: group *A*, 5.1%, group *B*, 10.1%, etc.). The differences between the weight gains, food intake, and food utilization ratios of group *A* and *B* test rats during the first week either approached significance (p values ranging from 0.07–0.08) or were statistically significant (body weight gain: p value <0.01).

Analyses of the body weight gain, food consumption, and food utilization findings during the second week indicated differences between the response patterns of group *A* and *B* animals to the drug. Whereas group *A versus* control group per cent differences at the first and second weeks revealed tendencies toward progressively greater decreases in those parameters (*i.e.*, body weight gain, group *A*: first week, 11.6%, second week, 15.1%), in group *B* the response patterns were reversed, indicating diminishing effects of the drug on body weight gains, food consumption, and food utilization processes as LSD-25 treatment continued. Although no statistically significant differences were noted between the group *A versus* group *B* body weight gains, food consumption and food utilization data for the second week period, comparisons of the pattern-shifts, and

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[1] Food utilization ratio = weight gain, Gm./food consumption, Gm.

TABLE I.—EFFECT OF LSD-25 ON BODY WEIGHTS AND BODY WEIGHT GAINS OF MALE WISTAR RATS DURING A 2-WEEK PERIOD

Dose	n	Body Wt. Initial, Gm.	Body Wt. 1st Wk., Gm.	Body Wt. 2nd Wk. Final, Gm.	Body Wt. Gains 1st Wk., Gm.	Body Wt. Gains 2nd Wk., Gm.	Body Wt. Gains Total, Gm.	Body Wt. Gains Diff. Between 1st and 2nd Wk.
Group *A*, 500 mcg./Kg.	68	109.4	137.6	166.3	28.3	28.7	57.0	+0.4
± S.E.		±0.9	±1.3	±1.8	±0.9	±1.1	±1.6	±1.1
Group *B*, 750 mcg./Kg.	67	109.3	134.4	165.6	25.1	31.2	56.3	+6.1
±S.E.		±0.9	±1.2	±1.7	±0.7	±1.1	±1.4	±1.1
Group *C*, saline	67	109.3	141.2	175.0	32.0	33.8	65.7	+1.8
±S.E.		±0.8	±1.5	±1.8	±0.9	±0.9	±1.5	±1.1
% Diff. between groups *A* and *C*		+0.1	−2.5	−5.0	−11.6	−15.1	−13.2	...
p value[a]		>0.90	0.08	<0.001	<0.01	<0.001	<0.001	0.39
% Diff. between groups *B* and *C*		...	−4.8	−5.4	−21.6	− 7.7	−14.3	...
p value		>0.90	<0.001	<0.001	<0.001	0.07	<0.001	<0.01
% Diff. between groups *A* and *B*		−0.1	−2.3	−0.4	−11.3	+ 8.7	−1.2	...
p value		>0.90	0.08	0.78	<0.01	0.11	0.75	<0.001

[a] Snedecor, G. W., "Statistical Methods," Iowa State College Press, Ames, Iowa, 1949.

TABLE II.—EFFECT OF LSD-25 ON FOOD CONSUMPTION AND FOOD UTILIZATION PROCESSES OF MALE WISTAR RATS DURING A 2-WEEK PERIOD

Dose	n[a]	Food Consumed[b] 1st Wk., Gm.	Food Consumed[b] 2nd Wk., Gm.	Food Consumed[b] Total, Gm.	Food Utilization[b] 1st Wk.	Food Utilization[b] 2nd Wk.	Food Utilization[b] Total	Food Utilization[b] Diff. Between 1st and 2nd Wk.
Group *A*, 500 mcg./Kg.	12	504.8	561.8	1066.7	0.2832	0.2611	0.2717	−0.0221
± S.E.		± 8.5	±10.9	±17.5	±0.0107	±0.0101	±0.0086	±0.0108
Group *B*, 750 mcg./Kg.	13	478.2	550.2	1028.3	0.2615	0.2821	0.2731	+0.0206
± S.E.		±10.6	±11.3	±19.6	±0.0052	±0.0127	±0.0084	±0.0103
Group *C*, saline	12	531.7	594.3	1125.9	0.3044	0.2823	0.2929	−0.0221
± S.E.		± 9.9	±11.5	±21.0	±0.0064	±0.0068	±0.0051	±0.0086
% Diff. between groups *A* and *C*		−5.1	−5.5	−5.3	−7.0	−7.5	−7.2	...
p value		0.05	0.05	0.04	0.10	0.10	0.05	>0.90
% Diff. between groups *B* and *C*		−10.1	−7.4	−8.7	−14.1	−0.07	−6.8	...
p value		<0.01	0.01	<0.01	<0.001	>0.90	0.06	<0.01
% Diff. between groups *A* and *B*		−5.3	−2.1	−3.6	−7.7	+8.0	+0.5	...
p value		0.07	0.47	0.17	0.08	0.21	>0.90	<0.01

[a] *n*, number of cages, each containing five rats. [b] Averages based on five rats.

changes noted between the first and second weeks of the group *B* rats were of interest. To illustrate, analyses demonstrated that the +6.1 Gm. body weight gain difference between the first and second weeks of group *B* rats was statistically significant when compared to the differences computed for group *A* (+0.4 Gm.) and the control group (+1.8 Gm.). Analyses of group *A versus* group *C* differences were not significant. Similarly, comparisons of the pattern changes and differences noted between the food utilization ratios of group *B* animals (+0.0206) during the first and second weeks of treatment were likewise statistically significant when compared to group *A* (−0.0221) and group *C* ratio changes (−0.0221). Again, no statistical significance was found in the comparison of the differences between the group *A* and *C* values.

It should be noted that similar observations of diminishing effects being produced by the higher dose during the second week period were likewise found in the previous lysergic acid male rat study (5). Thus, in both investigations, the 750 mcg./Kg. dose induced comparably smaller decreases in the body weight gains and food utilization ratios of the test rats during the second week than the 500 mcg./Kg. dose. These alterations occurred despite the persistent and significant decreases in the food consumption activities of the group *B* animals. These changing-shifts may either be attributed to alterations in time-pattern relationships produced by LSD-25 on the metabolic and endocrine processes of the test rats or may be due to the possible development of tolerance to the drug. Further studies with the 500 mcg./Kg. dose level will demonstrate whether the pattern of changes noted in group *B* can be duplicated by continued administration of the drug to group *A* animals.

Table III presents the LD_{50} data and the regression equations for the LSD-25 treated and control groups. Analyses of the LD_{50} values indicated that the 500 and 750 mcg./Kg. dose levels caused respective 5.9 and 6.5% increases in the tolerance capacities of the test rats to histamine stress. Although none of these differences was statistically significant, the relative consistency in the LD_{50}'s shown by the two test groups and the respective low *p* values strongly suggest that administration of LSD-25 increased tolerance to histamine stress. No significant differences were observed between the slopes of the test and control group regression equations.

It is apparent that depending on dosage, the body

TABLE III.—EFFECTS OF LSD-25 ON THE RESISTANCE OF MALE WISTAR RATS TO HISTAMINE STRESS

Dose	LD_{50}, mg./Kg.	Regression Equations and p Values of Slope
Group *A*, 500 mcg./Kg. ± S.E.	850.6 ±35.8	$Y = -24.65 + 10.12\ X$
Group *B*, 750 mcg./Kg. ± S.E.	856.1 ±36.0	$Y = -24.59 + 10.09\ X$
Group *C*, saline ± S.E.	803.5 ±28.5	$Y = -32.30 + 12.84\ X$
% Diff. between groups *A* and *C*	+5.9	...
p value	0.18	0.27
% Diff. between groups *B* and *C*	+6.5	...
p value	0.14	0.31
% Diff. between groups *A* and *B*	+0.6	....
p value	0.88	>0.90

weight, food intake, food utilization, and resistance data indicate that LSD-25 can induce significant alterations in the metabolic processes of the test animals which may be related to altered endocrine activity—namely, reduced thyroid and increased adrenal function. Previous investigations (5) have revealed that similar injection periods with identical doses of LSD-25 caused either corresponding marked or significant decreases in the absolute thyroid weights of the male rats as well as marked or significant decreases in the oxygen consumption rates. Kar *et al.* (15) and Lingjaerde *et al.* (2) have also reported decreased uptake of ^{131}I and ^{32}P by the thyroids of LSD-25 treated rats. Evidence that LSD-25 stimulated adrenal output and function is derived from alterations in adrenal weights (5), total leukocyte counts (16), and elevations in urinary 17-ketosteroid (4, 17) and 17-OH corticosteroid levels (4, 18).

Thus, the growth, food metabolism, and resistance data, while indicative of hypothyroidal and increased adrenal function, also offer supporting evidence for the physiodynamic scheme of hormonal equilibration advanced by Sackler *et al.* (19, 20). These investigators postulated a synergistic and antidyne relationship between the adrenal glucocorticoid hormones on the one hand and the thyroid, gonad, and a possible thymic hormone on the other. Evidence for this concept has been derived in part from thyroparathyroidectomy (20, 21), thymectomy (22, 23), and gonadectomy (24) procedures which have all produced increases in rat tolerance to histamine stress. In contrast, adrenalectomy (25) caused significant reductions in the ability of rats to tolerate histamine.

In conclusion, depending on time and dosage, administration of LSD-25 has been found to induce significant effects on growth, metabolism, and food consumption and cause a loss of efficiency in the conversion of food energy to body mass. Suggestions of changing time-pattern relationships or the earlier development of tolerance were noted in animals treated with the heavier dose during the second week of the study. Suggestive evidence of increased capacities to resist histamine stress was likewise indicated.

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