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NOTES

Effect of Mescaline HCl on Resistance of Male Mice to Histamine Stress

A. STANLEY WELTMAN, ARTHUR M. SACKLER, and LEROY JOHNSON

Abstract □ Single intraperitoneal injections of mescaline HCl caused significant decreases in the ability of albino mice to tolerate histamine phosphate when administered intraperitoneally 40 min. after mescaline. The dose levels of mescaline HCl ranged from 5–100 mg./kg. of body weight. Eight subcutaneous injections of mescaline (100 mg./kg. of body weight) administered during a 2-week period showed no difference between the LD_{50} values of the test *versus* saline control groups when challenged with histamine 24 hr. after the eighth and last dose of mescaline. No effects were noted in the body weights and growth patterns of the test mice in the 2-week investigation.

Keyphrases □ Mescaline HCl—effect on histamine tolerance, mice □ Histamine tolerance, mice—effect of mescaline HCl □ Hallucinogens, mescaline—acute *versus* prolonged effects on growth, histamine stress resistance

Previous investigations have demonstrated that LSD-25 stimulates adrenocortical activity and inhibits growth, metabolism, and gonadal and thyroidal function in female (1–3) and male rats (4). LD_{50} analyses of male rats given eight sequential injections of LSD-25 spaced during a 2-week period presented suggestive evidence of increased ability of the treated animals to tolerate histamine stress (5). Parallel studies with male mice receiving mescaline HCl (6) revealed identical, but somewhat smaller alterations in adrenal and thyroidal function but no effects on body weight and food consumption. Adrenal weights and adrenocortical activity [*i.e.*, thymus involution and white blood cell count (WBC) decreases] were significantly increased (6). The lesser effects produced by mescaline *versus* LSD-25 may be attributed to the lower potency of mescaline. The equivalent hallucinogenic dose of mescaline in humans is 4000 times greater than that of LSD (7). As with LSD-25 (3, 4, 8), various physiological findings have demonstrated the development of tolerance or accommodation of the treated mice to mescaline (6). The present investigation sought to determine acute *versus* prolonged effects of mescaline administration on body growth and the resistance of male mice to histamine stress.

EXPERIMENTAL

Three series of young male experimental albino mice (Carworth Farms, CFW) averaging 22 g. in body weight were selected for histamine LD_{50} analyses. Series I and II test and control mice were challenged intraperitoneally with histamine phosphate 40 min. after receiving a single intraperitoneal injection of mescaline HCl dissolved in normal saline or equivalent doses of saline. Series III mice received histamine phosphate 24 hr. after the eighth and final subcutaneous injection of mescaline HCl or normal saline. The eight injections were administered over a 2-week period on alternate days with the exception that on the 13th and 14th days, the two doses were given consecutively.

Series I consisted of 225 mice divided equally into three groups (two test groups and one saline control). The two doses of mescaline administered were 5 and 20 mg./kg. body weight. Series II consisted of an equivalent number of mice also divided equally into two test and one control groups. The test mice received a single dose of either 50 or 100 mg./kg. body weight of mescaline HCl. Series III was represented by a single test (100 mg./kg.) and normal saline group. In general, the various test groups were challenged with 5–6 dose levels of histamine phosphate and utilized 15–19 mice per dose level. The appropriate challenging doses of histamine, depending on the susceptibility of the test and control groups, ranged from 350–1450 mg. histamine base/kg. body weight. Finney's (9) method of probit analysis was used to calculate the LD_{50} values and dose–response lines.

To determine further the effects of various doses of mescaline on survival periods, the time of death following histamine phosphate

Table I—Effects of Mescaline HCl[a] on the Resistance of Male Albino Mice to Histamine Stress (Single Intraperitoneal Injection)

Group	Dose	*n*	Body Wt., g.	LD_{50}, mg./kg.
	Series I			
Group 1	5 mg./kg.	75	24.5	830.5
±*SE*			±0.2	±25.4
Group 2	20 mg./kg.	75	24.2	753.3
±*SE*			±0.2	±28.2
Group 3	Saline	75	24.1	913.4
±*SE*	control		±0.2	±22.5
% Diff. 1 *vs.* 3			+1.7	−9.1
p value			0.17	0.05
% Diff. 2 *vs.* 3			+0.4	−17.5
p value			0.76	<0.01
% Diff. 1 *vs.* 2			−1.2	−9.3
p value			0.34	0.09
	Series II			
Group 4	50 mg./kg.	115	24.5	622.3
±*SE*			±0.1	±15.2
Group 5	100 mg./kg.	115	24.7	537.9
±*SE*			±0.2	±17.2
Group 6	Saline	95	24.6	921.6
±*SE*	control		±0.1	±39.2
% Diff. 4 *vs.* 6			−0.4	−32.5
p value			0.44	<.001
% Diff. 5 *vs.* 6			+0.4	−41.6
p value			0.67	<.001
% Diff. 4 *vs.* 5			+0.8	−13.6
p value			0.39	0.01

[a] Sigma Chemical Co., St. Louis, Mo., Lot No. 76B-1460.

injections was recorded for Series II animals. Proportionate numbers of mice receiving 50 or 100 mg./kg. of mescaline or normal saline were selected for analyses from groups given 850, 1050, and 1250-mg./kg. doses of histamine phosphate.

Prior to initiation of the investigation, all animals were housed for 1 week to acclimatize the mice to laboratory conditions. The animals were housed five per cage in stainless steel cages 40.64 × 45.72 × 27.94 cm. (16 × 18 × 11 in.) in an air-conditioned laboratory maintained at 22.7° (73° F). The mice used in the acute studies were weighed immediately prior to administration of the mescaline to permit calculation of the approximate doses of mescaline HCl and histamine phosphate. Animals used in the 2-week study were weighed initially and at the end of each week. Previous studies have indicated that prolonged isolation (10) or excessive crowding (11) and temperature changes (12) can produce metabolic and endocrinological alterations. Similarly, to minimize handling (13) and auditory stress (14, 15) influences, all animals were handled alike, and care was taken to prevent harsh and extraneous loud noises. The average level of the laboratory background noise during the period of experimentation was 68 decibels at daytime and 85 decibels at nighttime due to the increased nocturnal activity of the animals in the colony room.

RESULTS AND DISCUSSION

Standard *t*-test analyses (16), as indicated in Table I, revealed no significant differences between the various body weights of the randomly selected mice in the acute Series I and II tests *versus* control group studies. All *p* values had higher probabilities than the 0.05 level used for statistical significance. Table I also presents the LD_{50} data for the Series I and II groups administered single intraperitoneal doses of mescaline 40 min. before the histamine challenge. In both series, all doses of mescaline (5, 20, 50, and 100 mg./kg.), when compared with their respective controls, showed significant decreases in the resistance of the test mice to histamine stress (*i.e.*, 5 mg./kg. *versus* saline, $p = 0.05$). No significant difference was noted between the LD_{50} values of the two saline controls of Series I and II ($p = 0.86$). Comparisons further revealed significant differences between the various doses of mescaline when each level was compared with the other (*i.e.*, 20 *versus* 50 mg./kg., $p = <0.01$; 50 *versus* 100 mg./kg., $p = 0.01$; *etc.*). An exception was observed in the comparison of the LD_{50} values of the 5 *versus* 20-mg./kg. dose. The *p* value of 0.09, although low, was not statistically significant. Analyses of the slopes of the regression equations for the mescaline and saline groups, on the other hand, showed no significant differences ($p = >0.05$) between the various slope values when the test groups were compared with their respective controls and each other. In accord with LD_{50} findings, standard *t*-test analyses (16) of the time of death following histamine injections likewise revealed that prior administration of 50 or 100 mg./kg. of mescaline significantly hastened the onset of death. Compared to saline controls (control death time: 5.2 ± 0.2 min.), 50 mg./kg. of mescaline significantly reduced the time of death by 43.8% ($p = <0.01$) and 100 mg./kg. by 49.4% ($p = <0.001$). The difference in the time of death between the two mescaline doses was not statistically significant ($p = 0.36$).

At the time of histamine challenge, comparable studies with additional test and control groups revealed that at 40 min. the test mice had recovered from the depressive influences of mescaline and were displaying heightened locomotor activity when compared to the saline controls (17). The reduction in resistance to histamine may reflect the combined effects of two nonspecific stress agents (mescaline and histamine) administered within too short a time period of each other (40 min.). The decrease in resistance may also be related to hypoglycemic influences of mescaline. Speck (18) reported significantly lower blood glucose levels in male rats given single injections of mescaline at doses of 5 mg./100 g. body weight.

Table II presents the final body weights and the LD_{50} values of the test (100 mg./kg.) *versus* control group receiving eight repeated injections of mescaline (Series III). The findings indicated no differences between the initial body weights of the test and control groups (21.9 ± 0.3 g.) and no effects on the final body weights of the test *versus* control mice at the completion of the prolonged 2-week study ($p = 0.81$). Analyses further revealed no statistically significant differences between the LD_{50} values ($p = 0.82$) or the slopes of the regression equations ($p = 0.39$) of the test *versus* saline control group. The two LD_{50} control values of the acute Series I and II were significantly higher than the control of Series III (*p* values = <0.01). This difference in LD_{50}'s may possibly reflect the influences of eight repeated saline injections, a 2-week age factor, or biological and environmental variables resulting from a year's lapse in time between the previous series and Series III. Despite evidence of increased adrenocortical activity (6), as demonstrated in related test groups (*i.e.*, increased adrenal weights, thymic involution, and WBC decreases), no marked or significant increase was noted in the ability of the test mice to withstand histamine stress. Feasibly, other than the route of administration of mescaline, the difference in the increased mortality demonstrated by the mice receiving a single *versus* repeated doses might rest in the time lapse between the successive doses of mescaline and histamine challenge. In the acute study, the time period was 40 min. *versus* 24 hr. for the prolonged 2-week investigation. Further groups are required to duplicate the 40-min. time interval in mice receiving eight injections and the 24-hr. period in mice receiving a single injection. It should be noted that contrary to hypoglycemic effects produced by a single dose, Speck (18) reported hyperglycemia in rats injected daily for 1.5 months. In an additional 2-week study of mice receiving 50- or 100-mg./kg. doses of mescaline subcutaneously, significant increases were noted in blood glucose levels of both groups of test mice (19).

In conclusion, single intraperitoneal doses of mescaline (5–100 mg./kg.) were found to decrease significantly the resistance of male mice to histamine stress when challenged 40 min. later. Repeated injection of mescaline HCl administered subcutaneously

Table II—Effects of Mescaline HCl[a] on the Resistance of Male Albino Mice to Histamine Stress (8 Subcutaneous Injections in 2 Weeks)

Group	Dose	*n*	Final Body Wt. 2nd Wk., g.	LD_{50}, mg./kg.
	Series III			
Group 7	100 mg./kg.	81	26.7	678.4
±*SE*			±0.2	±44.5
Group 8	Saline	80	26.8	691.1
±*SE*	control		±0.4	±29.1
% Diff. 7 *vs.* 8			0.4	−1.8
p value			0.81	0.82

[a] Sigma Chemical Co., St. Louis, Mo., Lot No. 78B-1790.

during 2 weeks showed no significant effects on the histamine LD_{50} values of test *versus* control groups despite findings of increased adrenocortical activity (6). This may be related to the time interval factor between mescaline and histamine challenge. Histamine in this last instance was administered 24 hr. after the last mescaline injection. No significant effects were noted on body weights and growth patterns of mice in the 2-week investigation as demonstrated by the present and previous findings (6).

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Teratogenic Effects of Audiogenic Stress in Albino Mice

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Abstract □ The teratogenic effects of audiogenic stress were studied in 60-day-old pregnant Swiss-Webster mice by exposing the pregnant dams to the effects of a noise generator for varying periods during pregnancy. The most severe fetal effects were noted when the pregnant dams were stressed on Days 8–17 and Days 10–15 of pregnancy. In an attempt to discern the days of greatest susceptibility to stress, a second group of mice was studied, and it was determined that Days 7–8 was the period of maximal susceptibility. The teratogenic effects produced by audiogenic stress included a reduction in fetal weight, complete or partial resorption of fetuses, cranial hematoma, dwarfed hind limbs, and tail defects.

Keyphrases □ Teratogenicity—audiogenic stress effects, albino mice □ Audiogenic stress, effects—teratogenicity, albino mice

The maternal organism has been exposed to a wide variety of noxious chemicals and environmental changes in an effort to determine the effects of such exposure on fetal development (1–4). Procedures that only affect the maternal organism have, however, received little attention until recently. Environmental stresses to which virtually all maternal organisms are subjected during pregnancy have been proven to exert real and deleterious effects on fetal development (5–8). Geber (5) recently demonstrated that decreased fetal weight as well as resorption frequency can be produced in the offspring of rats subjected to audiovisual stress for varying periods during development. The stress of handling pregnant dams (6) and severe audiogenic stress (7) have been shown either to block pregnancy completely or to reduce the chance for successful fetal development. The purposes of this investigation were to study the effects of audiogenic stress on pregnant albino mice in an attempt to determine the effects of such stress on fetal development and also to determine the period of pregnancy in which the fetus is most susceptible to the deleterious effects of stress.

METHODS

Sexually mature Swiss-Webster mice, received at 60 days of age, were used throughout this study. They were kept in a separate room in the animal quarters for 1 week prior to breeding to allow for adjustment to their surroundings. When proestrus was determined by the technique of vaginal smearing (9), two females were placed with each male for an 11-hr. period. When the sexes were separated, the presence of a vaginal plug was taken as proof of pregnancy. This was then Day 0. Between 20–35% of the mated females became pregnant using this technique. Pregnant females were then isolated and kept in separate cages for the duration of pregnancy.

The stress chamber was rectangular [25.40 × 20.32 × 60.96 cm. (10 × 8 × 24 in.)] and constructed of stainless steel. Pregnant mice as well as controls were placed in this chamber in a separate room, and the stressed dams were subjected to the effects of a noise generator which consisted of a motorcycle horn connected to a microswitch timer and set to deliver an output of 82–85 decibels[1] at a

[1] Sound Level Meter, Type 1551-A, General Radio Co., Cambridge, Mass.