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Effects of Lysergic Acid Diethylamide on Attack Behavior of Male Albino Mice*

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With 2 Figures in the Text

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Since the discovery of hallucinogenic properties in lysergic acid diethylamide (LSD-25), considerable interest has been focused on the effects of this compound on aggressive behavior. That LSD-25 increases excitement and aggression has been demonstrated several times; for example, female Siamese fighting fish and newts treated with this compound showed a significant increase in aggressive responses (EVANS et al. 1958, EVANS and ABRAMSON 1958). Studies on cats (ELDER and DILLE 1962, GADDUM and VOGT 1956, RICE and MCCOLL 1960) and on rats (TAESCHLER 1960) showed that LSD-25 produced pronounced excitement and aggression. Moreover, HALEY (1957) reported that a total dose of 5 μgm (equivalent to 0.2 mg/kg) of this compound administered intracerebrally, induced hyperexcitability and aggression in CF-1 mice. The aggression consisted of a direct attack upon any object placed in front of the animals. These effects appeared for a brief time only and then were followed by a stuporous condition lasting about 12 hours.

On the contrary, other investigators have found that LSD-25 induces physical responses indicative of submissive behavior in higher animal species; for example, EVARTS (1956), and CHEN and WESTON (1960) found that monkeys given 0.1 mg/kg (i.p. or i.m., respectively) of LSD-25 lost their biting response and became docile. HOLLISTER (1962) noted that normal human subjects given LSD-25 experienced drowsiness, weakness, and dizziness. In another clinical study, GUEDES and LUIZ (1961) found that this compound produced numbness as well as drowsiness and lethargy. In an exploratory study on the isolation-induced attack behavior of mice, we found that a dose of 0.05 mg/kg (i.p.) of LSD-25 provoked no excitation and inhibited aggression in a small

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percentage of Swiss-Webster mice. The apparently contradictory findings may be due to differences in species, dose, and route of administration.

In an attempt to clarify some aspects of these apparent discrepancies, this dose-effect study was designed to investigate further the effects of LSD-25 on aggressive behavior of isolated mice toward non-isolated mice. The isolation-induced aggression test reported by YEN et al. (1958) and JANSSEN et al. (1960) was slightly modified. YEN et al. evaluated the effects of drugs on the immediate attack behavior of mice isolated for three weeks. JANSSEN et al., repeatedly tested mice isolated for approximately 9 days to select the 10% that consistently showed attack behavior. The animals selected were assessed for attack behavior 1, 4, or 25 hours after injection of various drugs. Our test of attack behavior differs from that of YEN et al. and JANSSEN et al. mainly in the duration of isolation, the number of preliminary tests of attack behavior, and the duration of test period.

A. Time of Maximum Effect

Methods

Fifty-five six-week-old Swiss Webster male albino mice were isolated in $18 \times 10 \times 12$ cm individual cages for 5 weeks; another 50 male mice of the same strain and age were housed together ("group-housed") in a $44 \times 26 \times 16$ cm cage. All "group-housed" mice were identified by staining of the fur with picric acid and by ear markings.

At the end of the fifth week, a five-minute pretest was initiated by placing a "group-housed" mouse in each individual cage of the isolated mice to determine which of these isolated mice would attack the "group-housed" mice (intruders). An attack was defined as an aggressive contact involving biting. When an attack occurred, the attack latency, i.e., the interval between the introduction of the intruder and the onset of the attack was recorded in seconds and the intruder was returned to the group cage.

On the following day, forty isolated mice that attacked within five minutes were used to determine the peak effect time of LSD-25. These attackers, matched according to their attack latencies, were divided into 4 equal groups. All groups were given 0.4 mg/kg (i.p.) of LSD-25 (0.1 ml aqueous solution per 10 gm body weight) and tested as described for the pretest. Each attacker was paired with the same matched intruder as in the pretest. The first group was tested 5 minutes after injection; and the second, third, and fourth groups were tested 15 minutes, 30 minutes, and 45 minutes post injection, respectively. Failure to attack within five minutes was scored as inhibition. In a separate control experiment, ten mice were isolated, pretested and assessed 5 minutes post injection in a similar manner using saline.

Results

In general, the mice given LSD-25 were relatively inactive, as demonstrated by their withdrawal to the rear of the cages. Piloerection and tachypnea were observed. As the intruders approached and "nosed" the backs of the LSD-25 mice, some of the latter animals exhibited sudden jumping movements, others often turned to one side, raised a hind leg, and kicked the advancing intruders. A few treated mice stood on their hind legs and vocalized. Some groomed their faces, especially their eyes, and started to "nose" and pursue the intruders. Finally, some experimental mice attacked the intruders. All control mice attacked the intruders.

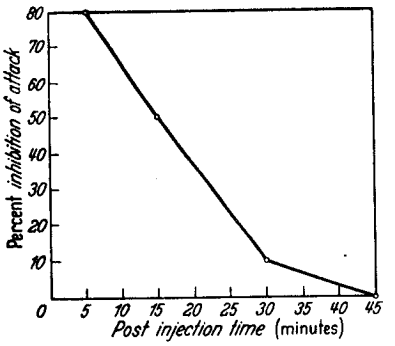

Fig. 1. Time of maximum effect of inhibition of 0.4 mg/kg (i.p.) of LSD-25 on isolation-induced attack behavior

In each group, the total number of non-attacking mice was obtained and expressed as percent non-attackers. These percentages were plotted against the time intervals (Fig. 1). The graph shows clearly that the five-minute post injection group had the highest percent of non-attackers. Therefore, the time of the greatest inhibitory effect of 0.4 mg/kg (i.p.) of LSD-25 under the conditions of this study was approximately five minutes after injection. Within 15 minutes, the inhibitory effects on attack behavior gradually dissipated. However, other effects, such as piloerection and tachypnea, persisted.

B. Dose-Effect Study

Methods

In this first dose-effect study, 170 male mice of the same strain and age as those used in part A were isolated in individual cages for five weeks. Another group of 170 males, similar in all respects, was housed together. At the end of the isolation period, the pretest was given in the same manner as described in Part A. On the following day, 140 attackers were matched on the basis of their attack latencies and divided equally into graded dose-related groups (20 mice/group), from 0.1 mg/kg to 0.8 mg/kg of LSD-25 plus controls. The control mice were injected with 0.9% saline solution; the experimental mice were given LSD-25 in aqueous solution. All animals were injected intraperitoneally with 0.1 ml of solution per 10 gm of body weight. Five minutes after injection, they were tested for attack inhibition in the same manner as described in Part A.

We were curious to determine whether or not a similar dose-effect test given at a time other than that of maximum effect would result in a curve parallel to the first one. Therefore, a second dose-effect study with 240 mice essentially similar to those used in the first study was performed. In addition, a higher dose, 1.6 mg/kg of LSD-25, was used. These mice were tested for attack inhibition fifteen minutes after injection.

Results

All the control mice attacked the intruders. Their attack latencies in the main test were shorter than those in the pretest. On the other hand, many "LSD-25 mice" did not attack, and in general those that attacked had latency scores longer than those of the controls. The study on the time of maximum effect and the two dose-effect experiments clearly indicate that LSD-25 injected intraperitoneally has inhibitory effects on the isolation-induced attack behavior of mice. Those mice given 0.8 or 1.6 mg/kg of LSD-25 also showed some side effects, including tremors, piloerection, and tachypnea.

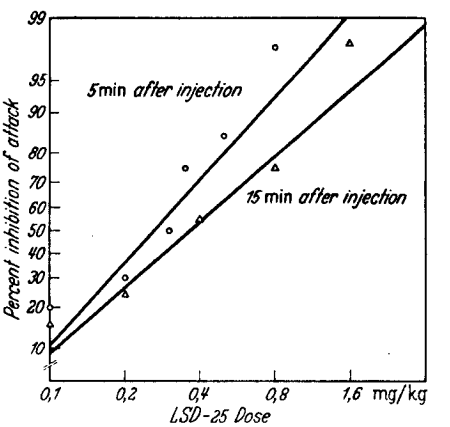

Fig. 2. Dose-effect curves of the inhibitory effects of LSD-25 on isolation-induced attack behavior

In each dose group of the first dose-effect study, the total number of mice that did not attack was expressed as a percent of all mice in each group. Percent effect is plotted against dose on logarithmic probability paper (Fig. 2). The curve shows that percent inhibition effect is an increasing monotonic function of dose. Some sigmoidal tendency in this regression line, evident at extremes of dose, makes the line appear nonlinear. This tendency is attributable to constraining a response to lie between certain limits (0—100%) and to a relatively limited number of subjects at each dose level. Nevertheless, the middle doses give points lying fairly close to a straight line, and an analysis of this portion of the data is considered to be reliable. According to the graphic log probit method of Litchfield and Wilcoxon (1949), the median ED_{50} of this curve is 0.265 mg/kg (0.212—0.331 mg/kg), and the slope function is 2.117 (1.616—2.773). Thus, under the conditions of this experiment, a dose of LSD-25 that inhibits the isolation-induced attack behavior of 50% of the

mice tested 5 min after intraperitoneal injection lies in the range whose limits are 0.212—0.331 mg/kg.

In a similar manner, percent effect in the second study is plotted against dose on the same graph (Fig. 2). The log probit analysis of the second curve shows that the ED_{50} is 0.365 mg/kg (0.261—0.511 mg/kg), and that the slope function is 2.619 (1.819—3.771). The two curves illustrate clearly that the five-minute group at all dose levels had more non-attackers than the fifteen-minute group. This finding corroborates the results obtained from the time phase of the investigation (Part A). Although the LITCHFIELD and WILCOXON (1949) test fails to show that the curves deviate significantly from parallelism, the curves suggest an interesting interaction between the dose and the post injection time of testing. The difference in the percent of inhibition between the five-minute group and the fifteen-minute group given the low doses seems distinctly smaller than the difference in the percent of inhibition between the two groups given the high doses.

Discussion

These experiments point out that LSD-25 injected intraperitoneally inhibits attack behavior of male Swiss-Webster, albino mice. The difference between our findings and those of investigators who used fish or cats may be ascribable to a species difference. The difference between our results and those of HALEY (1957) may be attributable to differences in the strain, age, dose, route of administration, and in the method of assessing aggression. In general, the results of this study seem to be consistent with those obtained from the study on monkeys by EVARTS (1956) and by CHEN and WESTON (1960), those obtained from clinical studies by HOLLISTER (1962), and those of GUEDES and LUIZ (1961).

Although from this study one cannot deduce the mechanisms of the inhibitory action of LSD-25 on isolation-induced attack behavior, one wonders whether this inhibitory action may not be related to (1) an inhibitory effect of LSD-25 on synaptic transmission in the brain (MARRAZZI and HART 1955), and/or (2) a hindrance of the transmission of impulses at the level of the lateral geniculate body (EVARTS and MARSHALL 1955). Other unidentified mechanisms may also occur.

Summary

These studies showed that the time of maximum inhibitory effect of LSD-25 on the isolation-induced attack behavior of 11 weeks old Swiss-Webster male mice is 5 min after its intraperitoneal injection. A dose-response study of the inhibitory effect of this compound on 120 mice tested at the time of maximum effect showed that the median ED_{50} is 0.265 mg/kg (0.212—0.331 mg/kg). A second dose-response study on

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similar mice, tested 15 min post-injection, indicated that the median ED_{50} is 0.365 mg/kg (0.261—0.511 mg/kg). All studies showed that LSD-25 given intraperitoneally to mice inhibits their attack behavior.

Résumé

Ces études, effectués sur souris males Swiss-Webster, agées de 11 semaines, ont montré que le temps d'effet inhibiteur maximum du LSD-25 sur le comportement d'attaque induit par l'isolement, est de 5 minutes après injection intrapéritonéale. Une étude dose-réponse de l'effet inhibiteur de ce produit, testé sur 120 souris au temps d'effet maximum, a montré que le médian ED_{50} est 0,265 mg/kg (0,212—0,331 mg/kg.). Une seconde étude dose-réponse sur des souris semblables, testées quinze minutes après injection, a indiqué que le médian ED_{50} est 0,365 mg/kg (0,261—0,511 mg/kg). Toutes études ont montré que le LSD-25, administré intrapéritonéalement aux souris, inhibe leur comportement d'attaque.

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