# Inhibition of Isolation-Induced Attack Behavior of Mice by Drugs

By EDWARD T. UYENO

**Three dose-response experiments indicated that psilocybin, mescaline, and 2-brom-lysergic acid diethylamide (BOL-148) inhibited isolation-induced attack behavior of 11-week-old Swiss-Webster mice, tested at the time of peak effect. The 3 dose-response curves show that the per cent inhibitory effects of these compounds are increasing monotonic functions of dose. The $ED_{50}$ and confidence limits for psilocybin, mescaline, and BOL-148 are 2.096 mg./Kg. (1.334–3.291), 5.413 mg./Kg. (2.904–10.090), and 1.183 mg./Kg. (0.676–2.069), respectively.**

In a previous study it was found that the per cent inhibitory effect of 0.1–1.6 mg./Kg. of *d*-lysergic acid diethylamide (LSD-25) on the attack behavior of mice, tested 5 min. after intraperitoneal injection (i.p.) was an increasing monotonic function of dose (1).

The present experiment was conducted in order to compare the results of the LSD-25 study with those obtained with 2 other hallucinogens: psilocybin (an indole derivative like LSD-25) and mescaline (belonging to the phenylethylamine group). Moreover, it was deemed important to compare the effects of 2-brom-lysergic acid diethylamide (BOL-148), a congener of LSD-25, reported to produce LSD-25-like psychic effects (2). More specifically, the effects of psilocybin, mescaline, and BOL-148 on isolation-induced attack behavior of Swiss-Webster male mice were investigated.

## METHOD

Six-week-old Swiss Webster male mice were socially isolated for 5 weeks in 18 × 10 × 12 cm. metal cages which had wire mesh fronts and floors. Another group was housed together (30/cage) in 44 × 26 × 16 cm. metal cages, constructed in the similar manner as the smaller cages. All animals were fed *ad libitum* some standardized dietetically optimum pellets.[1]

After 5 weeks, a 5-min. pretest was initiated by placing a "group-housed" mouse into the cage of an isolated mouse until attack behavior was observed. An attack was defined as an aggressive contact involving biting. When an attack occurred, the attack latency was recorded and the "group-housed" mouse was returned to its cage. (The group-housed animals did not attack, and hardly any of them retaliated when they were attacked.) On the basis of their attack latencies, the attackers were matched and assigned to control and 3 experimental groups (3 drugs). Each experimental group was divided into 4 subgroups (4 subgroups/drug).

**The Time of Peak Effect.**—Experimental animals ($n$ = 20 or 30/subgroup) were tested at 5, 15, 30, or 45 min. after i.p. injection of 4 mg./Kg. of psilocybin, 20 mg./Kg. of mescaline base, administered as the sulfate, or 2 mg./Kg. of BOL-148 in saline solution. The control animals were injected with 0.9% saline solution and were tested for attack behavior 30 min. later. A standard volume of 10 ml./Kg. of drug–saline and saline solution was administered to the experimental and control animals, respectively. Each attacker was paired with the same group-housed animal with which it had been paired in the pretest. The test was conducted in a manner similar to the pretest.

**Dose-Response.**—Dose-response experiments were conducted with 6-week-old Swiss-Webster male mice that were essentially similar to those used in the peak time study. At the end of a 5-week isolation period, the pretest was given. On the basis of attack latencies, they were assigned into a control and 3 experimental groups (3 drugs) with 4 graded dose groups per drug. ($N$ = 20 or 30/subgroups.) As before, the control animals were injected with 0.9% saline solution. After injection, the control and experimental animals were tested for attack behavior at the time of peak effect as determined from the earlier studies.

## RESULTS AND DISCUSSION

In the time of peak effect and dose-response experiments, all control animals attacked the group-housed animals, but many experimental animals did not attack. In the peak time study, the sum of nonattackers in each time group was expressed as a percentage of all the animals in that group (per cent effect). Per cent effect was plotted against post-injection time (Fig. 1). The time of peak inhibitory effects of 4 mg./Kg. of psilocybin and 2 mg./Kg. of BOL-148 was 30 min. after the i.p. injection. For 20 mg./Kg. of mescaline, the peak time was between 15 and 30 min. after the injection.

In the dose-response study the sum and percentage of nonattackers in each dose group were calculated for each compound (Table 1). Per cent effect was plotted against dose on logarithmic probability paper (Figs. 2 and 3). The data show that the per cent inhibitory effect of each compound is an increasing monotonic function of dose. Probit

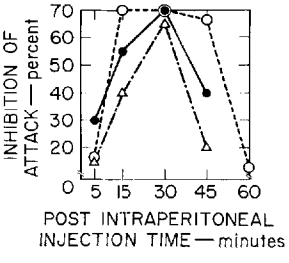


Fig. 1.—Time of peak inhibitory effect of 20 mg./Kg. of mescaline ($N$ = 30/plot), 4 mg./Kg. of psilocybin ($N$ = 20/plot), and 2 mg./Kg. of BOL-148 ($N$ = 20/plot) on attack behavior. Key: △, BOL-148; ●, psilocybin; ○, mescaline.

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[1] White Diet supplied by Simonsen Laboratories, Inc., Gilroy, Calif.

TABLE I.—PERCENTAGE OF NONATTACKERS IN EACH DOSE GROUP

| Compd. | Dose, mg./Kg. | N | Non-attackers | % Effect |
|---|---|---|---|---|
| Psilocybin | 8 | 20 | 16 | 80 |
| | 4 | 20 | 14 | 70 |
| | 2 | 20 | 11 | 55 |
| | 1 | 20 | 5 | 25 |
| Mescaline | 30 | 30 | 24 | 80 |
| | 20 | 30 | 21 | 70 |
| | 10 | 30 | 16 | 53 |
| | 1 | 30 | 8 | 27 |
| BOL-148 | 2.0 | 20 | 13 | 65 |
| | 1.5 | 20 | 10 | 50 |
| | 1.0 | 20 | 9 | 45 |
| | 0.5 | 20 | 7 | 35 |
| LSD-25[a] | 0.8 | 20 | 20 | 100 |
| | 0.5 | 20 | 17 | 85 |
| | 0.4 | 20 | 15 | 75 |
| | 0.3 | 20 | 10 | 50 |
| | 0.2 | 20 | 6 | 30 |
| | 0.1 | 20 | 4 | 20 |

[a] Data obtained from *Reference 1*.

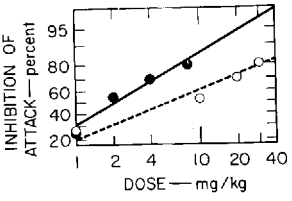


Fig. 2.—Dose response curves. Key: ●, 1.0–8.0 mg./Kg. of psilocybin ($N$ = 20/dose); ○, 1.0–30 mg./Kg. of mescaline ($N$ = 30/dose).

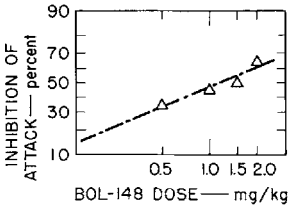


Fig. 3.—Dose response curve. Effect of 0.5–2.0 mg./Kg. of BOL-148 on attack behavior ($N$ = 20/dose).

analysis of the data was conducted by an electronic computer (3). The $ED_{50}$ and the confidence limits for psilocybin, mescaline, and BOL-148 are 2.096 mg./Kg. (1.334–3.291), 5.413 mg./Kg. (2.904–10.090), and 1.183 mg./Kg. (0.676–2.069), respectively. The equations of the 3 curves are: psilocybin, $Y_1 = 4.469 + 1.652\ (X_1)$; mescaline, $Y_2 = 4.314 + 0.935\ (X_2)$; BOL-148, $Y_3 = 4.916 + 1.160\ (X_3)$.

In general, experimental mice withdrew to the rear of the cage, remained inactive [as LSD-25 mice (1)], and did not attack. The latencies of a few that attacked were longer than their pretest latencies. In contrast, the latencies of the control animals were shorter than during the pretest. The inactive reaction of the psilocybin mice appeared to be consistent with that observed by Cerletti (4), who reported that this compound produced a distinct reduction of motor activity in mice, rabbits, and monkeys. Moreover, in humans, Hollister (5) and Delay *et al.* (6) found that an oral dose of 150 mcg./Kg. and 130 mcg./Kg., respectively, induced physical responses indicative of depressant behavior, such as drowsiness, fatigue, and weakness. The results of the mescaline experiment corroborate those of Saxena *et al.* (7), who found that in fish (*colisa lalia*) the fighting response to another male was completely blocked by intramuscular injection of 0.1–0.2 mcg. of mescaline sulfate. The lowered activity and withdrawal reaction of the mescaline mice in the present study are consistent with results reported for cats given 0.3–1.0 mg./Kg. of this compound (8). The depressant effect of mescaline was also observed in a pole climbing performance of rats that increased their latencies when they were injected 20 mg./Kg. i.p. of this compound 15 min. before test (9).

The results indicate that the times of peak effect of 4 mg./Kg. of psilocybin, of 20 mg./Kg. of mescaline, and of 2 mg./Kg. of BOL-148 were later than that (5 min. after the i.p. injection) of 0.4 mg./Kg. of LSD-25 (1), suggesting that the 3 former compounds may have slower rates of passage into the brain. Like LSD-25, the 3 compounds made most of the animals inactive and inhibited their isolation-induced attack behavior. Mescaline with the highest $ED_{50}$ (5.413 mg./Kg.) and LSD-25 (1) with the lowest $ED_{50}$ (0.265 mg./Kg.) seem to suggest the former is the least and the latter the most potent inhibitors of isolation-induced attack behavior.

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