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The Effects of *dl*-Cathinone in a Gustatory Avoidance Paradigm[1]

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FOLTIN, R. W. AND C. R. SCHUSTER. *The effects of* dl-*cathinone in a gustatory avoidance paradigm.* PHARMAC. BIOCHEM. BEHAV. 14(6) 907–909, 1981.—When the presentation of a novel food to a rat is followed by the injection of certain compounds, including many psychomotor stimulants, the animal consumes less of that food on subsequent presentations compared to an animal injected with saline. This phenomenon has been termed gustatory avoidance conditioning. The effect of *dl*-cathinone, a psychomotor stimulant drug structurally similar to amphetamine, was determined in this paradigm. Fluid intake was limited to a single 15 min presentation, seven days a week. Following the determination of baseline water intake, sweetened milk was presented for five consecutive sessions. There were six groups of rats with each group receiving a different dose of cathinone (0–16.0 mg/kg) five min after the session each day. Following these five days of milk-cathinone pairings, milk intake was significantly decreased only in the rats receiving 16 mg/kg. These results indicate that cathinone which is nearly as potent as amphetamine in many other behavioral measures, is less potent in inducing gustatory avoidance responses.

Cathinone Khat Gustatory avoidance conditioning CTA Rats

THE LEAVES of the plant *Catha edulis* (Khat) are extensively chewed by the natives of certain areas of East Africa. Consumption of fresh leaves produces behavioral effects similar to those produced by amphetamines [6]. The active alkaloids isolated from the plant are structurally related to amphetamine [6,10]. Cathine, *d*-norpseudoephedrine, was initially believed to be responsible for the central effects of *Catha edulis*. However, in fresh or well preserved material cathine is only a minor component and the major component is cathinone, which has an asymmetric carbon atom with a configuration corresponding to the nucleus of *d*-norpseudoephedrine and *d*-amphetamine [10]. In the presence of oxygen, cathinone rapidly decomposes which impeded its isolation and purification. The effects of *dl*-cathinone on general activity and DRL performance are amphetamine-like, while many of its other pharmacological properties are ephedrine-like [8,12].

In a previous study, 2.25 mg/kg (IP) *dl*-cathinone suppressed milk intake in rats by fifty percent while the dose of *d*-amphetamine that produced the same decrease in intake was 1.48 mg/kg (IP) [9]. In addition, cathinone has been shown to maintain intravenous self-administration in rhesus monkeys [7,12].

Many psychomotor stimulants have been shown to decrease milk intake in a gustatory avoidance paradigm [2]. In this procedure an organism is presented with a novel flavored sweet fluid for consumption followed by the presentation of certain stimuli (e.g., lithium chloride-induced illness). On subsequent exposures to the fluid the organism characteristically drinks less and when given a choice test drinks more of the alternate fluid. In the present study this procedure was used to assess the ability of *dl*-cathinone to induce an avoidance response. Although cathinone was found to function in this capacity it was clearly demonstrated only at a dose of 16 mg/kg.

METHOD

Animals and Apparatus

Thirty-six adult male Sprague-Dawley albino rats (Holtzman, Madison, WI) weighing between 250 and 300 g at the start of the experiment were housed individually in stainless steel ceiling suspended cages with food (4% Mouse and Rat Chow, Tekland, Winfield, IA) available ad lib. Room lights were on 8:00 a.m. to 8:00 p.m. daily. All fluids were

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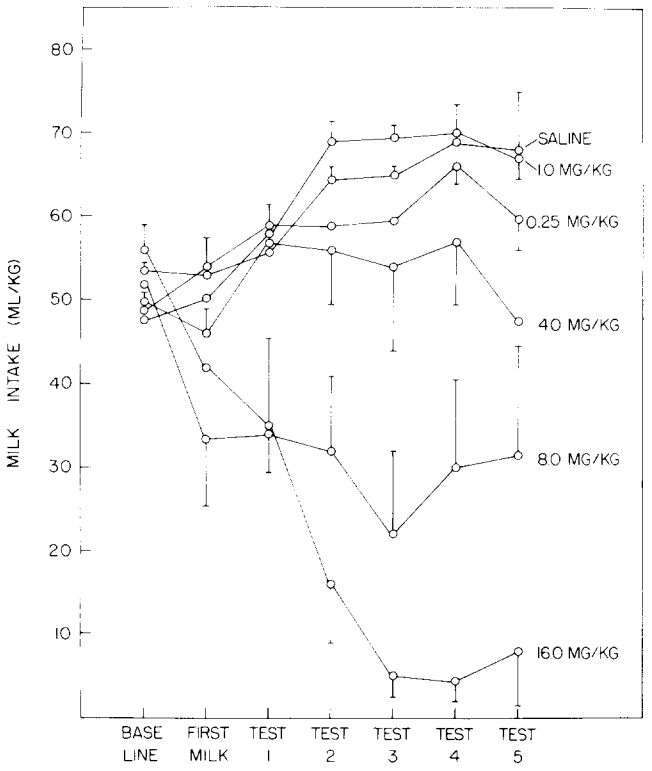

FIG. 1. Mean milk intake (ml/kg) and SEMs for each group as a function of test day (some SEMs omitted for clarity).

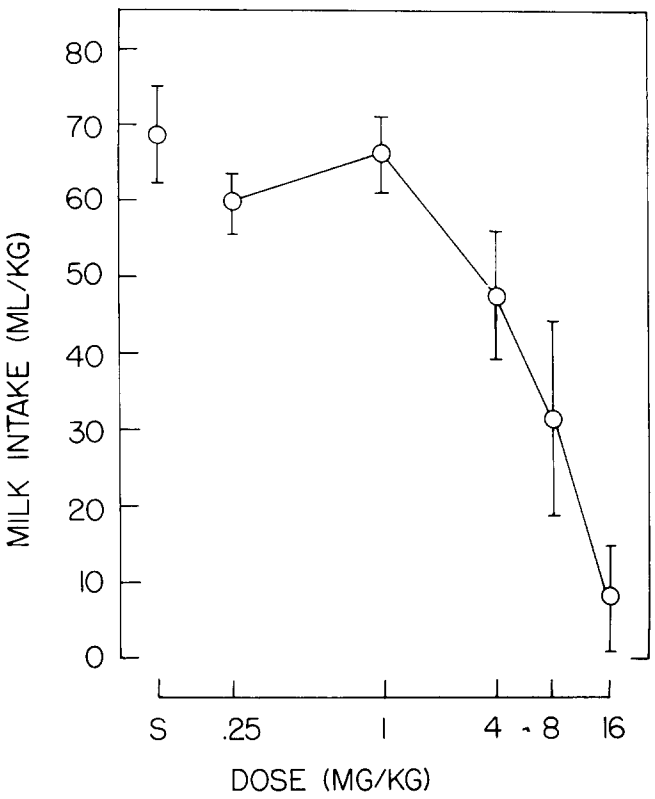

FIG. 2. Dose-response function for intake as a function of dose of *dl*-cathinone on the last test session following five days of milk-drug pairings.

presented in Wahmann (Baltimore, MD) 100 ml calibrated bottles.

Procedure

Experimental sessions consisted of a single 20 min fluid presentation occurring from 4:00 to 4:20 p.m., seven days a week. Following five days of water baseline intake, the animals were randomly assigned to six groups with all groups containing six animals. On the following day all animals were given access to a novel sweetened condensed milk solution (Borden's, Columbus, OH, 1:2 with tap water) as their only fluid during the session. Five min after the session, all rats received injections of either *dl*-cathinone (0.25, 1.00, 4.00, 8.00, 16.00 mg/kg, IP, one dose per group) or physiological saline (IP) in a volume of 1 ml/kg. This procedure was repeated for four additional consecutive sessions. Twenty four hrs after the fifth day, a final test session occurred with intake again measured, but without any subsequent injections.

RESULTS AND DISCUSSION

The mean baseline intake, intake on the first day of milk availability and intake on each of the five test sessions can be seen for each dose in Fig. 1. There were no significant differences between groups for baseline or first day milk intake, $p>0.10$, $F(5,35)=1.72$, and $F(5,35)=1.53$ respectively. However, there were significant differences between groups in milk intake for all five test sessions ($p<0.01$). The saline, 0.25, 1.00 and 4.00 mg/kg groups increased their intake on test days one to four and show a slight decrease on test day 5 compared to day 4. Compared to baseline, the saline and 1.00 mg/kg groups showed significantly greater intakes during the test session, $F(6,35)=2.69$, $p<0.05$, and $F(6,35)=4.44$, $p<0.01$, respectively. Although both the 8.00 and 16.00 mg/kg groups showed decreased intake over test sessions, only the 16 mg/kg group decrease was significant, $F(6,35)=13.93$, $p<0.001$. Intake on test session 5 is presented in Fig. 2 as a function of dose. The two lowest doses had no effect on intake, but further increases in dose decreased intake in a dose-dependent manner, $F(5,30)=11.11$, $p<0.001$.

This data suggests that cathinone, the principal active alkaloid of the Khat leaf, which is chewed by natives of eastern African countries, is capable of inducing a gustatory avoidance response at the highest dose tested. It is possible, however, since the drug was given daily that the decreased milk intake was produced by cumulative drug effects which lasted from the post-session injections until the next day. This explanation does not receive support from a previous study in which it was reported that a dose of 4.0 mg/kg of cathinone suppressed food intake for only 2 hrs [13]. In addition, in studies conducted in our laboratory if food intake is

limited to a single 15 min session each day, which is more comparable to the procedure used here, *dl*-cathinone suppresses intake for two hours and in addition a residual drug effect is never seen 24 hours following acute administration (Foltin and Schuster, unpublished observations). For these reasons it appears that the decreased milk intake is not a function of direct cumulative drug effects but rather indicates that *dl*-cathinone can induce a gustatory avoidance response.

The dose range of amphetamine which has been reported to induce significant gustatory avoidance responses is similar to the dose range that decreases milk intake when given prior to access to milk [1, 3, 4, 5, 11]. A similar relationship does not appear to be true for cathinone as doses significantly larger than those required to suppress milk intake when given presession are required to induce a gustatory avoidance response. The reason for this difference in potency between cathinone and amphetamine, which are similar in many other behavioral tests [8,12], requires further investigation.

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