Taste aversions induced by d-amphetamine: Dose-response relationship

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Learned taste aversions, as measured by increased time to complete 100 licks of a milk solution 3 days after training, were induced in rats by a single pairing of sweetened condensed milk solution with doses of 1.0 to 4.0 mg/kg d-amphetamine sulfate. This result supports previous findings of aversions induced by 2.0 mg/kg d-amphetamine in several other paradigms and suggests that a dose of 1.0 mg/kg also induces reliable aversions.

Learned taste aversions, dramatic shifts in flavor preferences, result from the pairing of novel flavors with treatments inducing obvious sickness in rats. Berger (1969, 1972) reported that single administration of several drugs which do not produce obvious sickness also induced taste aversions. Testing single dose levels of various psychoactive drugs, he found that aversions were induced by the phenothiazine major tranquilizer chlorpromazine, the benzodiazepine anxiolytic lorazepam, and the stimulant, d-amphetamine sulfate. Berger tested d-amphetamine at a dose of 2 mg/kg. This report describes dose-related taste aversions induced by d-amphetamine using a procedure similar to that developed by Berger (1969).

METHOD

Subjects

Thirty naive male Holtzman strain rats, weighing 173-256 g at the time of training, served as subjects. The rats had been housed in groups for 2 weeks and were moved to individual cages 3 days before training. Lab chow and water were available ad lib except during the 24-h period prior to training and test sessions.

Apparatus

Training and test sessions were carried out in a small cubicle (23.5 x 20.5 x 19.3 cm, Scientific Prototype Model A-100). A bottle containing a solution of sweetened condensed milk (one part Borden's Eagle Brand sweetened condensed milk to two parts distilled water at room temperature) was attached to the outside of the cubicle. A metal drinking tube extended up to and was flush with a 19-mm opening (65 mm above the grid floor) in an end wall of the cubicle. Each rat could easily lick the tube while standing on the grid floor. Individual licks were monitored by a drinkometer connected to programming equipment located in an adjacent room.

Procedure

On the training day, each rat was removed from its cage, weighed, and carried to the room which contained the apparatus. The drinking tube was previously adjusted so that a drop of milk solution hung from the end of the tube. Each rat was allowed to complete 100 licks and then was removed from the apparatus and injected intraperitoneally according to its group designation with .5, 1.0, 2.0, or 4.0 mg/kg d-amphetamine sulfate dissolved in isotonic saline, or with saline alone. Volume of injection was

constant at 2 ml/kg. Rats were then returned to their home cages; food and water access was resumed 2 h after training.

The test session was conducted 3 days after training and was identical to the training session except that no drug was administered. The time to complete 100 licks was measured to the nearest .1 sec. If a rat failed to complete 100 licks in 600 sec, it was removed from the apparatus and assigned a score of 600.0.

RESULTS

The individual times to complete 100 licks on the test session are shown in Figure 1. Rats in the groups which had been trained without drug or with .5 mg/kg d-amphetamine sulfate drank milk rapidly on the test session and did not differ from each other. Groups

Figure 1. Individual times to complete 100 licks of a sweetened condensed milk solution 3 days after that solution was paired with injection of d-amphetamine sulfate. The arrow on the ordinate indicates the mean time to complete 100 licks on the training session (prior to injection) for all animals shown.

trained with 1.0, 2.0, or 4.0 mg/kg d-amphetamine sulfate exhibited significantly prolonged drinking times as compared with the control group, indicating aversions to the taste of sweetened condensed milk (Mann-Whitney U tests, two-tailed, $p < .005$, $p < .002$, $p < .002$, respectively). These groups did not differ significantly among themselves. Many of these rats did not complete 100 licks during the test session. It is unlikely that these results reflect an inhibition of drinking by direct action of d-amphetamine since the test was conducted 3 days after drug administration.

DISCUSSION

Berger (1972) found a statistically significant aversion to milk solution induced by a single dose of 2.0 mg/kg d-amphetamine sulfate. The present experiment demonstrates strong aversions induced by that dose and a lower dose (1 mg/kg).

Other authors have reported dose-related decrements in absolute volume of saccharin consumption (taste aversions) following a single pairing of saccharin solution with d-amphetamine. Cappell and LeBlanc (1971) showed an overall statistically significant decrease in saccharin consumption 3 days after training with 2.0, 4.0, or 8.0 mg/kg d-amphetamine sulfate. They did not test for statistical significance at individual dose levels. Carey and Goodall (1974) found a dose-related reduction in consumption 1 day after a single pairing of saccharin and d-amphetamine. Their data suggest a slight reduction at .5 mg/kg and marked reductions at 2.0 and 4.0 mg/kg; however, no statistical evaluation of individual dose levels was reported. Braveman (1975) reported significant taste aversions using a one-bottle consumption test 3 days after 2 mg/kg d-amphetamine was paired with saccharin.

In a paradigm in which drug served both as CS and US, Carey (1974) reported the development of aversions to the taste of .001%-.05% solutions of d-amphetamine. The degree of aversion was positively related to the concentration of the solution.

Further, taste aversions induced by d-amphetamine have been demonstrated by Gamzu (Note 1) using a preference procedure. In this experiment, saccharin ingestion was paired with 2.0 mg/kg d-amphetamine or control (no drug) injection. On a test session 3 days later, animals were offered both saccharin and water. Significantly lower saccharin preferences (saccharin consumption relative to total fluid consumption) were demonstrated by animals for whom saccharin and amphetamine had been paired.

Thus, experiments which represent a variety of techniques for inducing and measuring learned taste aversions consistently report that taste aversions are induced by a single administration of d-amphetamine. Our results confirm these findings and suggest that reliable taste aversions can be induced with a single pairing of a novel taste with 1.0 mg/kg d-amphetamine.

Positively reinforcing properties of similar dose levels of d-amphetamine have also been reported (e.g., Schuster & Thompson, 1969). Amphetamine is not unique in having both positively reinforcing and aversive properties at similar doses.

Other drugs that can serve as positive reinforcers have been shown to induce learned taste aversions as well (see review by Vogel, 1975). Learned taste aversions are induced by ethanol (Cappell, LeBlanc, & Endrenyi, 1973), morphine (Jacquet, 1973), barbiturates and methaqualone (Vogel & Nathan, 1975) and THC (Elsmore & Fletcher, 1972). The exact mechanism or mechanisms by which these drugs can induce taste aversions is not understood.

REFERENCE NOTE

1. Gamzu, E. *Pre-exposure to unconditioned stimulus alone may eliminate taste aversions*. Paper presented at the 15th Annual Meeting of the Psychonomic Society, Boston, 1974.

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