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BRIEF COMMUNICATION

Acquired Aversion to Amphetamine Solutions[1]

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CAREY, R. J. *Acquired aversion to amphetamine solutions.* PHARMAC. BIOCHEM. BEHAV. 1(2) 227–229, 1973. –Aversion to *d*-amphetamine solutions in a two-bottle amphetamine vs. water test increased as the concentration of *d*-amphetamine was increased. Initial exposure to a high concentration (0.5 mg/cc) of *d*-amphetamine resulted in a subsequent aversion to a low concentration (0.001 mg/cc). An aversion to a 0.1 mg/cc *d*-amphetamine solution was rapidly acquired even when the alternative solution was a nonpreferred bitter quinine solution. Significantly, the quinine solution continued to be consumed even when the amphetamine solution was replaced with water. The results were discussed in terms of a learned aversion to amphetamine.

d-Amphetamine Oral self-administration Learned aversion

RAT'S self-administer amphetamine by intravenous injection [2] but reject amphetamine when given the opportunity for oral self-administration [1,4]. One purpose of this investigation was to study the significance of amphetamine concentration in the rejection of amphetamine solutions in an oral self-selection situation. Evaluation of a wide range of amphetamine concentrations seemed useful since the only study in which concentration was varied employed but a two-fold range in concentration. In a second experiment, a nonpreferred quinine solution was offered as the alternative choice to an amphetamine solution. Rejection of the amphetamine solution in this situation would require the rat to ingest the unpalatable quinine solution. This arrangement provided an opportunity to gauge the strength of the rejection of amphetamine solutions.

EXPERIMENT 1

Animals

Forty naive, male, Sprague-Dawley rats, approximately 110 days old at the start of testing, were used throughout the experiment. The rats were maintained in individual cages in a temperature- (72° ± 4°F), humidity- (60% ± 5%), and illumination- (12-hr light, 12-hr dark) controlled room. Purina lab pellets were always available in wire feeders attached to the outside of the cage.

Procedure

The rats were randomly divided into four groups of 10 each. A standard two-bottle choice procedure was used in which bottle positions were changed daily. Intakes were recorded to the nearest 1/10 g uncorrected for spillage. Estimates of spillage from bottles placed on empty cages averaged less than 0.5 g. *d*-Amphetamine HCL (K and K Laboratories, Jamaica, N.Y.) was used in the preparation of the amphetamine solutions. The amphetamine solutions were prepared by the addition of amphetamine to tap water and the alternative solution available was tap water. Over the first 10 days (1–10) of preference testing each of the groups was offered one of the four amphetamine solutions vs. water. The four amphetamine concentrations were: 0.5 mg/cc, 0.1 mg/cc, 0.01 mg/cc and 0.001 mg/cc. For Days 11–18 the 0.5 mg/cc, 0.1 mg/cc and the 0.01 mg/cc groups were all offered the 0.01 mg/cc amphetamine vs. water choice. Finally, for four days (19–22) the two groups originally offered the 0.5 mg/cc and 0.1 mg/cc amphetamine solutions were preference tested with the 0.001 mg/cc amphetamine solution vs. water.

Results

The preference testing results are shown in Fig. 1. Not surprisingly, the intake of the amphetamine solutions

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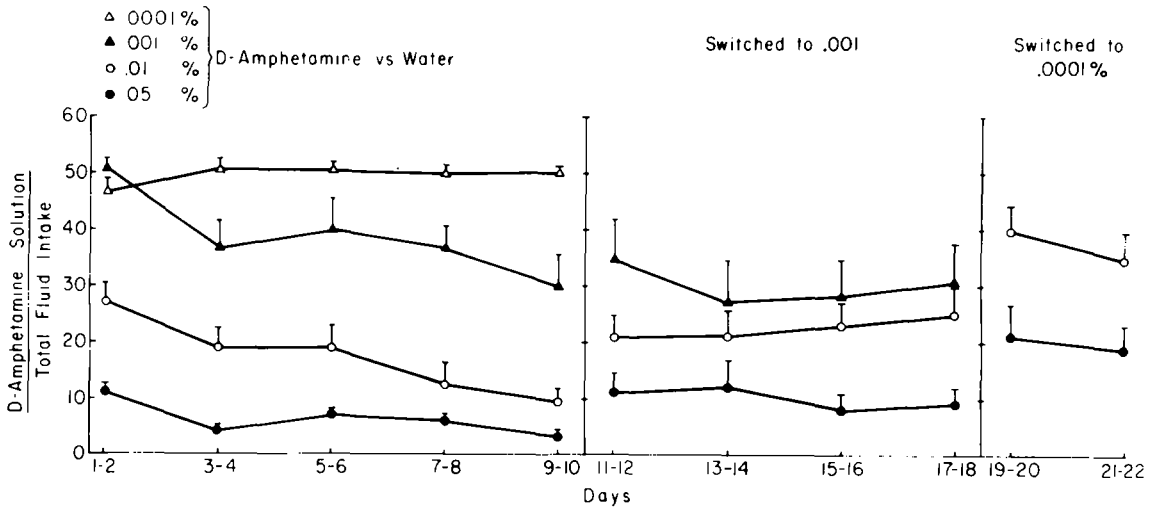

FIG. 1. Means and standard errors of amphetamine to water ratios in two-day blocks. On Days 11–18 the original 0.001%, 0.01%, and 0.05% groups were switched to 0.001% amphetamine vs. water. On Days 19–22 the original 0.01% and 0.05% groups were switched to 0.0001% amphetamine vs. water.

decreased as the concentration of the amphetamine solution increased ($F = 40.1, df = 3, 36, p < 0.01$). Furthermore, over days the intake of the three highest concentrations of amphetamine decreased and at approximately the same rate.

This result is consistent with a previous report [4] which showed that intake of amphetamine solutions decreased with repeated imbibition. Although a forced-drinking procedure was combined with a self-selection procedure in the previous report, this study showed that the self-selection alone was sufficient to demonstrate an acquired aversion to amphetamine solutions. Also, Fig. 1 shows that exposure to higher amphetamine concentrations markedly enhanced rejection of lower amphetamine concentrations. This result was most dramatic for the 0.5 mg/cc group which displayed a clear-cut aversion to even the 0.001 mg/cc amphetamine solution.

EXPERIMENT 2

Animals

Twenty naive, male, 120–140 day old Sprague-Dawley rats were used. The housing arrangements were the same as in Experiment 1.

Procedure

The rats were divided into two groups of 10 each. Again, *d*-amphetamine HCL was used for preparation of the amphetamine solutions and quinine dihydrochloride (Gotham Pharmaceuticals, Brooklyn, N.Y.) was used for preparation of the quinine solutions. The same two-bottle choice preocedure was used. First, one group (Q–D) was offered a choice between 0.1 mg/cc *d*-amphetamine vs. 0.05 mg/cc quinine dihydrochloride for 12 days. The quinine solution was selected on the basis of a pilot investigation which indicated that this concentration was initially non-preferred relative to the 0.1 mg/cc amphetamine solution. From Days 13–30 this group as well as a previously untested group (Q–W) were offered a choice between the 0.5 mg/cc quinine solution vs. water.

Results

The preference testing results for Experiment 2 are presented in Fig. 2. The acquired aversion to the 0.1 mg/cc amphetamine solution is clearly evident in Fig. 2. Initially, the rats showed a clear-cut preference for the amphetamine solution but rapidly acquired an aversion relative to the quinine solution. More importantly, when subsequently offered a choice between water and the 0.05 mg/cc quinine solution over Days 13–30, the preference for the quinine solution remained. The group which was not exposed to the amphetamine solution, however, displayed an almost complete rejection of the quinine solution. The difference in quinine intake between the two groups was highly significant statistically ($F = 46.6, df = 1, 18, p < 0.01$).

DISCUSSION

The first study showed that amphetamine solutions over a 500-fold range in concentrations were either aversive or were neutral. Significantly, the aversiveness of the amphetamine solutions increased with repeated exposure. Furthermore, repeated exposure to the higher amphetamine concentrations appeared to sensitize the rats to the taste of amphetamine since exposure to the 0.5 mg/cc solution resulted in the subsequent rejection of the 0.001 mg/cc solution. Thus, rather than acclimation with amphetamine one observes sensitization. This type of effect is not unique to amphetamine since other investigators [5] have observed a similar effect with other aversive solutions. In previous studies, however, a forced-drinking procedure was used which resulted in fluid and food deprivation being associated with the taste of the aversive solution.

The results of the second experiment can be readily interpreted in a learned aversion framework [3]. Briefly, the postingestional consequences of imbibition of the amphetamine solution resulted in the aquisition of an aversion to the taste of the amphetamine solution. In contrast, imbibition of the distinctly different quinine solution is not associated with the aversive consequences of the amphetamine solution and therefore, the rat learns that

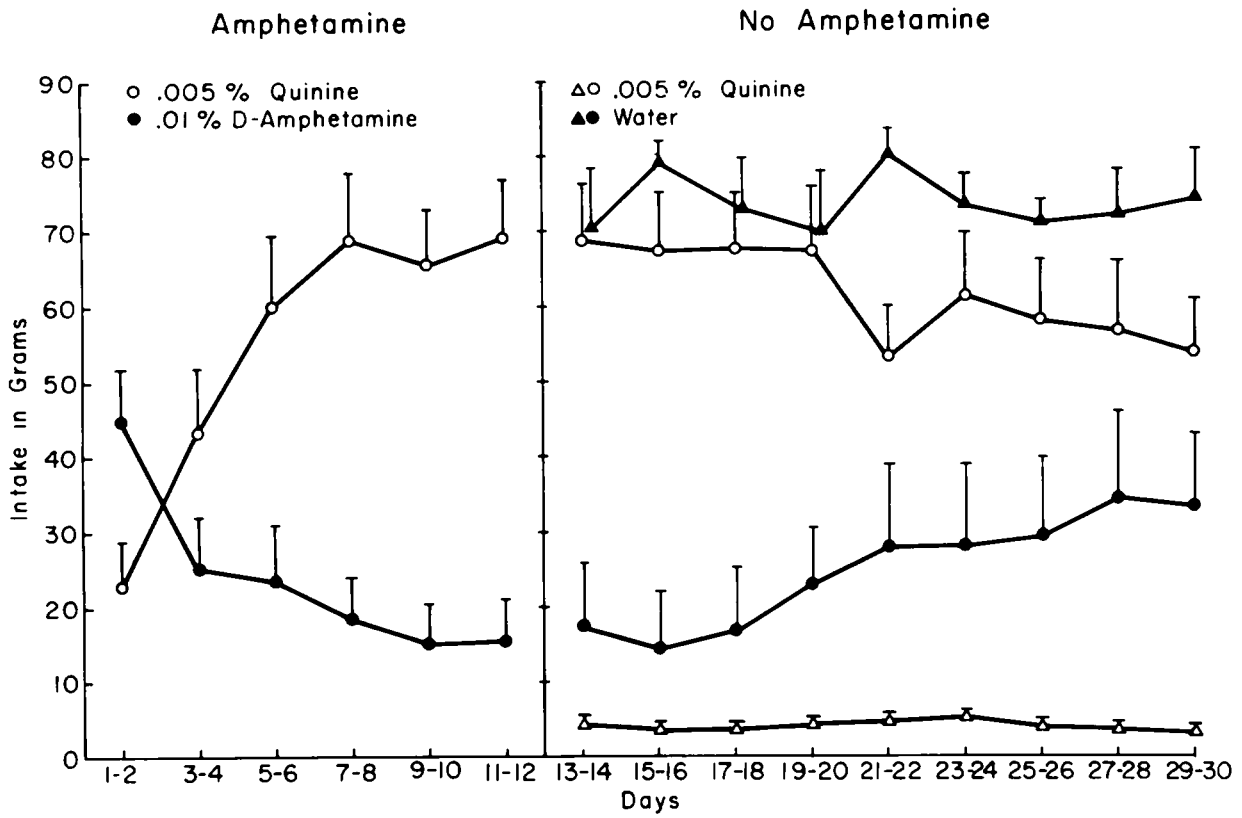

FIG. 2. Means and standard errors of intakes of test solutions in two-day blocks. The triangles designate the group only offered the quinine vs. water choice.

the quinine is the safe solution. The persistent ingestion of the quinine solution when water is substituted for the amphetamine solution shows that taste factors alone do not determine choice in this situation. Rather, it appears that it is simpler for the rat to detect the presence of the safe quinine solution that the absence of amphetamine from the amphetamine tap-water solution.

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