Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 3, pp. 413-420, 1994

0091-3057/94 $6.00 + .00

Amphetamine-Induced Modification of Quinine Palatability: Analysis by the Taste Reactivity Test

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Received 8 February 1993

PARKER, L. AND K. LEEB. *Amphetamine-induced modification of quinine palatability: Analysis by the taste reactivity test.* PHARMACOL BIOCHEM BEHAV 47(3) 413-420, 1994. —The effects of low doses of *d*-amphetamine (0.25-0.5 mg/kg, IP) on taste reactions elicited by quinine solutions in a 5-10-min taste reactivity test were assessed in a series of three experiments. Amphetamine consistently suppressed aversive reactions elicited by quinine solutions. The results suggest that amphetamine, like morphine, attenuates the aversiveness of the taste of quinine solution.

Amphetamine Taste reactivity Taste Flavor Quinine Palatability Reinforcement Dopamine Drinking behavior Ingestive behaviors

AMPHETAMINE modifies ingestive behavior. At moderate to high doses (above 1 mg/kg), *d*-amphetamine has been consistently shown to suppress feeding and sham feeding of solid and liquid foods [e.g., (3,5,15,18,20-22,28,29,31,34)]. At low doses, the reported effects are less consistent; doses of amphetamine below 1 mg/kg have been reported to enhance feeding [e.g., (7-10,12,30,35)], produce no effect on feeding [e.g., (5,34)], or suppress feeding [e.g., (31,39)] of solid and liquid foods. The reported enhancement of food intake produced by low doses of amphetamine is evidenced as a preferential enhancement of intake of sugar, sugar and chow mixture, but not saccharin and chow mixture (10), and this effect appears to be mediated by increased activity at dopamine postsynaptic receptors (7-10,12,14,15,27,30,34). Furthermore, dopamine antagonists, such as pimozide, have been shown to suppress feeding and sham feeding [e.g., (11,38,36,40)].

The effects of dopamine agonists and antagonists on feeding have generally been assessed by consumption tests. Consumption tests require that a rat actively approaches the source of the food or fluid to gain exposure to the tastant. Since dopamine is involved in motor responding, such measures are potentially confounded by the motor activation produced by dopaminergic agonists and the motor impairment produced by dopaminergic antagonists. In fact, Wolgin and his colleagues (29,39) have reported that amphetamine (0.5-4 mg/kg) produces greater suppression of milk intake in rats that are presented milk by a bottle, requiring approach responding, than in rats that are presented milk by intraoral infusion, requiring no approach responding. The authors suggest that the suppression of feeding by amphetamine may be, in part, a function of competing motor responses interfering with appetitive responding.

An alternative measure of a rat's responsiveness to a tastant is the taste reactivity (TR) test, devised by Grill and Norgren (13) as a direct measure of palatability. Since the experimenter controls the delivery of the tastant, the TR test eliminates the appetitive motor response requirement of approach that is a necessary component of a consumption test. Another advantage of the TR test is that the effects of pharmacological pretreatment on responding elicited by naturally aversive tastants can be assessed. In standard intake tests, floor effects in the baseline intake of aversive tastants, such as quinine solution, prohibitively mask detection of pharmacologically induced changes in consumption. When intraorally infused, quinine solution elicits the aversive reactions of chin rubbing, gaping, and paw treading [e.g., (13)]. In the experiments reported

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here, the effects of amphetamine pretreatment on quinine palatability will be assessed using the taste reactivity test.

Other agents that modify dopaminergic activity have been reported to modify the palatability of tastants. The neuroleptic agent, pimozide, has been shown to enhance aversive reactions elicited by quinine solution (25) and to attenuate ingestive reactions elicited by sucrose solution when assessed in a 10-min test (19). Since pimozide blocks dopamine receptors, the modification of palatability is presumably the result of a decrease in the activity of the dopaminergic system. Furthermore, we have recently reported that morphine pretreatment suppresses the aversive reactions elicited by quinine solutions (26). Like amphetamine, the rewarding properties of morphine have been reported to be mediated by enhanced extracellular dopamine release at the nucleus accumbens (4,6,37).

The following experiments employed the TR test to determine the effects of low doses of the indirect dopaminergic agonist, *d*-amphetamine, on responding elicited by quinine solutions over a 5-10-min TR test. Treit and Berridge (32) have previously reported that amphetamine (0.25 and 1.5 mg/kg) did not modify the taste reactions elicited by sucrose or quinine solutions in a 1-min TR test. However, it is conceivable that a longer period of exposure to the tastant under the influence of amphetamine is necessary to detect modifications in responding. Morphine and naltrexone (26) and pimozide (19,25) are ineffective in modifying the palatability of sucrose and quinine solutions in brief TR tests, but are effective when a 5-10-min TR test is used.

EXPERIMENT 1

In the experiments reported below, the ability of low doses of amphetamine to modify taste reactions elicited by quinine solutions were assessed. As reported above, pimozide enhances the aversive reactions elicited by quinine solution (25). If dopamine mediates the palatability of tastants, then one might expect that the indirect dopamine agonist, *d*-amphetamine, would suppress aversive reactions elicited by quinine solution.

METHOD

Subjects

Twenty-three male Sprague-Dawley rats weighing 280–350 g served as subjects. They were housed in individual stainless steel cages and were maintained on ad lib Purina rat chow and water. The illumination of the room was maintained on a 12 L : 12 D schedule.

Procedure

Surgery. One week after arriving in the laboratory, the rats were implanted with intraoral cannulae as previously described by Parker (23). After being deprived of water for 24 h, each rat was anesthetized with sodium pentobarbital (50 mg/kg, IP). A 15-ga, thin-walled, stainless steel SC needle was inserted through the rat's skin in the mid-neck region and exited through the inside of its cheek behind the first molar. The skin around each of the punctured sites was swabbed with iodine. With the needle in place, a 10.2-cm length of polyethylene (PE 90) tubing was inserted through the barrel. The needle was then removed and the tubing was secured at the neck by a 20-ga intramedic adapter and in the mouth by a 5-mm plastic washer.

TR testing. One week after the surgery, the rats received the first of three TR test trials. On each trial, a rat was injected intraperitoneally (IP) with 0.5 mg/kg of amphetamine solution (n = 12) or with physiological saline solution (n = 11) in a volume of 1 ml/kg. Thirty minutes later, the rat was placed in the glass TR test chamber (22.5 by 26 by 20 cm). The room was illuminated by two 100-W light bulbs with one placed on the side of the chamber and one aimed at the mirror below the chamber. Once the animal was placed in the chamber, its cannula was connected to the infusion pump (Razal Syringe Pump) by a 35-cm long tube. One minute later, the rat received a 10-ml intraoral infusion of 0.05% (6.7×10^{-3} M) quinine solution at the rate of 1 ml/min for 10 min. The rat's orofacial and somatic responses during the infusion were recorded on videotape. A Panasonic videocamera, focused on the mirror that hung at an angle below the chamber to facilitate viewing of the rat's ventral surface, recorded the rat's reactions during the test session. The rats received two additional TR test trials, with each trial separated by 2 to 3 days.

Behavioral categories. The videotapes of the TR test were scored by an observer blind to the experimental conditions in real time by means of an event recorder package for the IBM computer ("The Observer," Noldus, Inc, NL). The tapes were scored in real time to facilitate the identification of response patterns that are most clearly detectable as a series of movements that require the mobility of the animals (e.g., chin rubs, paw pushes, active locomotion), as previously described (24).

The behavioral categories (2) included the frequency of the aversive reactions of chin rubbing (CR: forward projection of the head with the chin rubbing against a substrate), gaping (G: trianglular, wide opening of the mouth), and paw pushing (PP: rhythmic pushing of the forepaws against the floor of the cage). These aversive reactions were combined to produce a composite aversive reaction score. The neutral/mildly aversive reaction (1) of passive drips (PD: number of drips of the test solution that drip from the rat's mouth to the floor when the rat is not actively ejecting the solution by an aversive response) was also measured.

The frequency of the activity measures of bouts of active locomotion (AL: occurrences of horizontal movements along the floor of the cage with both forepaws on the floor) and rearing (R: occurrences of vertical movements with both forepaws off of the floor of the cage) was measured. Additionally, the total amount of time during the test period that the rats displayed ingestive reactions to the nearest 0.1 s was measured. The composite ingestive reactions included the following: tongue protrusions (TP: extensions of the tongue either to the side or the front of the mouth), paw licking (PL: licking the solution by catching it with the paws as it enters the mouth), and mouth movements (MM: movement of the lower mandible without opening the mouth).

RESULTS AND DISCUSSION

Figure 1 presents the mean frequency or duration of taste reactions elicited by quinine during each test trial of Experiment 1. The data for each class of TR response depicted were analyzed as a 2 by 3 mixed-factor ANOVA with the factors of pretreatment (amphetamine or saline) and trials. The pretreatment effect was significant for the aversive reactions, $F(1, 21) = 5.3, p < 0.05$, and for the frequency of bouts of activity, $F(1, 21) = 10.3, p < 0.025$. No other effects were significant. The amphetamine-pretreated rats displayed fewer aversive reactions and more bouts of activity than did the saline-pretreated rats during the quinine infusion. An examination of the individual components of the aversive response category

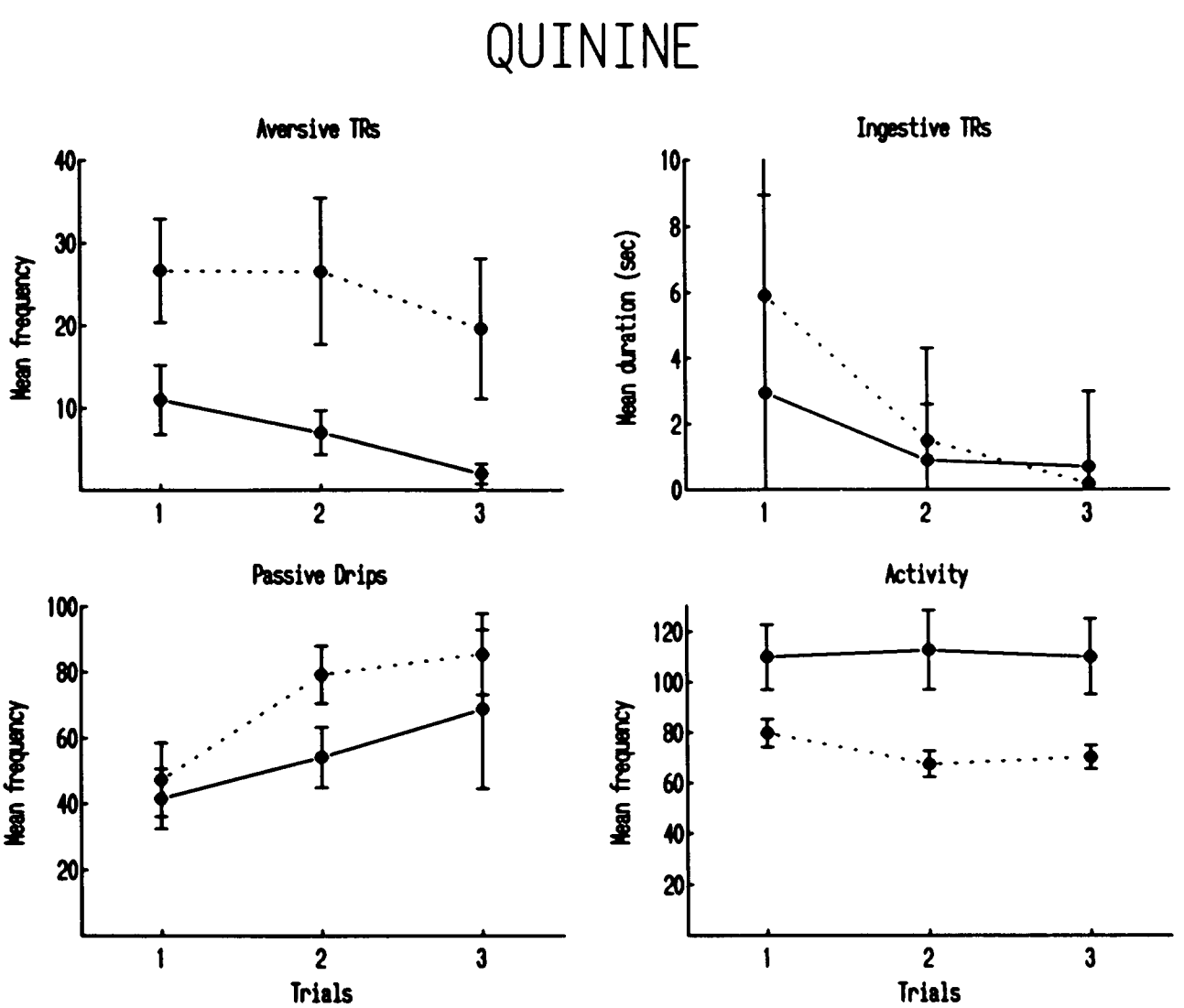

FIG. 1. Mean frequency or duration (s) of TR responses elicited by 0.05% quinine solution in the amphetamine (0.5 mg/kg)- or saline-pretreated groups on each test trial of Experiment 1.

revealed a significant effect of amphetamine pretreatment on the response of gaping only, $F(1, 21) = 5.1, p < 0.05$.

Additionally, to detect pretreatment-induced modifications of palatability of quinine solution across minutes of testing, the composite aversive, ingestive, and activity TR scores on trial 1 were analyzed as 2 by 10 mixed-factor ANOVAs with the factors of pretreatment and minutes of testing. The response categories elicited by quinine that were effected by pretreatment conditions on trial 1 are presented in Fig. 2.

Figure 2 presents the mean frequency of aversive reactions and activity reactions elicited by quinine solution on test day 1. The 2 by 10 mixed-factor ANOVAs of the aversive reactions, ingestive reactions, and activity reactions elicited by 0.05% quinine solution revealed a significant effect of pretreatment, $F(1, 21) = 5.0, p < 0.05$, and minutes, $F(9, 189) = 44.1, p < 0.001$, for the activity responding (presented in the lower half of Fig. 2). The pretreatment effect also approached significance, $F(1, 21) = 3.3, p < 0.08$, for aversive reactions on day 1 (presented in the upper half of Fig. 2). The amphetamine-pretreated group was more active than the saline-pretreated group, and the activity level of both groups declined across the minutes of testing; however, the effect of amphetamine pretreatment did not vary across minutes of testing.

EXPERIMENT 2

In Experiment 1, 0.5 mg/kg of *d*-amphetamine produced enhancement of motor activity. One might argue that the increased activity level interfered with other behavioral responding during the TR tests and, therefore, suppressed aversive reactions elicited by quinine solution. However, the likelihood that this suggestion is accurate is weakened by consideration of the pattern of responding across the 10 min of testing during test day 1. Across the 10 min of testing, general activity was suppressed in both groups to a greater extent during the later period of testing than during the earlier period of testing, but the frequency of aversive responding did not vary across minutes of testing.

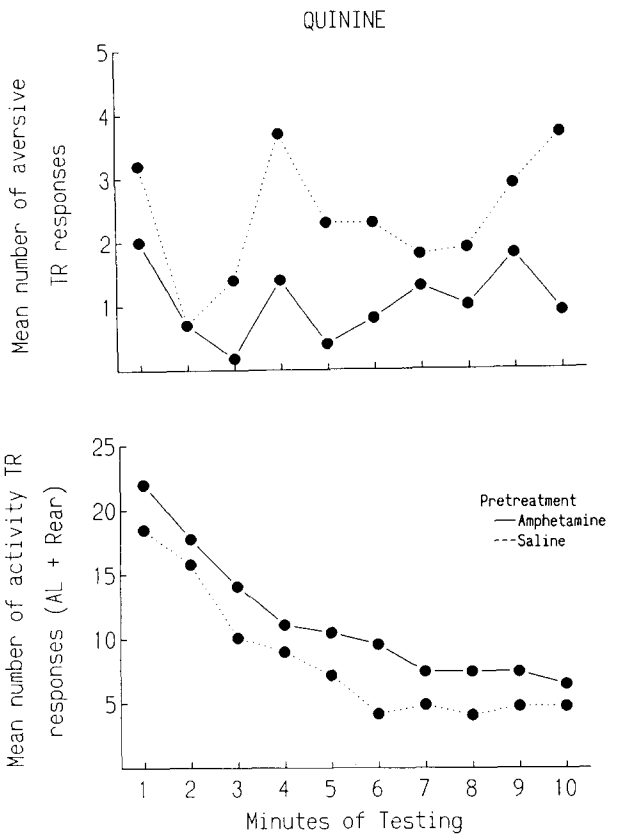

FIG. 2. Mean frequency of aversive TR responses and activity responses elicited by 0.05% quinine solution in the amphetamine (0.5 mg/kg)- or saline-pretreated groups during each minute of test trial 1 of Experiment 1.

In an attempt to reduce the potential effect of enhanced activity on taste reactivity, Experiment 2 was designed to determine the effect of a lower dose of amphetamine (0.25 mg/kg) on taste reactivity elicited by each of two concentrations of quinine solution (0.005%, 0.05%).

METHOD

Twenty-one male Sprague–Dawley rats weighing 286–326 g on the first test day served as subjects in Experiment 2. They were treated identically as in Experiment 1 except as indicated. The pretreatment conditions were: 0.25 mg/kg amphetamine (n = 11) and saline (n = 10). The rats received two TR test trials, separated by 1 week, during which they were intraorally infused with one of two concentrations of quinine solution, 0.005% and 0.05%, in a counterbalanced order during each of the TR trials.

RESULTS AND DISCUSSION

Figure 3 presents reactions elicited by the two concentrations of quinine solution for the rats pretreated with 0.25 mg/kg of amphetamine or saline solution. Amphetamine pretreatment suppressed aversive reactions elicited by 0.005%, $F(1, 19) = 11.4$, $p < 0.025$, and by 0.05%, $F(1, 19) = 4.8$, $p < 0.05$, quinine solutions, passive drip responding elicited by 0.05% quinine solution, $F(1, 19) = 13.5$, $p < 0.01$, and ingestive responding elicited by 0.005% quinine solution, $F(1, 19) = 45.0$, $p < 0.01$. Amphetamine pretreatment also enhanced activity elicited by both concentrations of quinine solution, $F(1, 19) > 7.7$, all $p < 0.025$.

A low systemic dose of amphetamine (0.25 mg/kg) suppressed aversive responding elicited by both concentrations of quinine solution and suppressed passive drip responding elicited by 0.05% quinine solution. The pattern of responding suggests that amphetamine pretreatment reduced the aversive properties of quinine solution. However, even at the low dose of 0.25 mg/kg, amphetamine enhanced general activity level and suppressed ingestive responding elicited by a weakly concentrated quinine solution.

EXPERIMENT 3

Although amphetamine consistently suppressed aversive reactions elicited by quinine solutions, it also suppressed ingestive reactions elicited by the weaker concentration of quinine and enhanced activity elicited by both concentrations of quinine in Experiment 2. Furthermore, unpublished data collected in the laboratory also indicated that amphetamine pretreatment suppressed ingestive reactions elicited by 20% sucrose solution, when the rats were tested in a novel environment as in Experiments 1 and 2. Therefore, an alternative explanation to palatability modification for the differences in taste reactions displayed by the amphetamine- and saline-pretreated rats is conceivable. In each of the above experiments, the effect of amphetamine pretreatment on reactivity to quinine was assessed in a novel test chamber. Since amphetamine has been reported to interfere with habituation to environmental stimuli (33), it is possible that during the TR tests, environmental stimuli competed with taste stimuli for attention to a greater extent in the amphetamine-pretreated rats than in the saline-pretreated rats. The purported direct attenuation of aversive properties of the taste of quinine may instead reflect the failure of the amphetamine-pretreated rats to attend to the properties of the tastant.

In Experiments 3a and 3b, all rats were habituated to the TR test chamber on four occasions prior to receiving the test trial. Therefore, on the test trial, the familiar chamber cues would be less likely to compete for attention with the novel taste cue. Furthermore, the effect of amphetamine pretreatment on both quinine (Experiment 3a) and sucrose (Experiment 3b) palatability was assessed. If the effect of amphetamine on taste reactions merely reflects interference with attention to the tastes, then amphetamine pretreatment should suppress sucrose-elicited ingestive reactions as well as quinine-elicited aversive reactions.

METHOD

In Experiment 3a, 24 male Sprague–Dawley rats weighing 319–391 g on the test trial, and in Experiment 3b, 24 male Sprague–Dawley rats weighing 330–387 g served as subjects. The rats were treated identically as in Experiment 2 except as indicated.

In each experiment, 1 week after recovering from surgery, the rats were given four 10-min TR adaptation trials on successive days. On each adaptation trial, the rat was placed in the glass TR test chamber with its cannula connected to the infusion pump by a 35-cm long tube. One minute later, the rat received a 10-ml intraoral infusion of water at the rate of 1 ml/min for 10 min.

On the day following the final adaptation trial, the rats received the TR test trial. In Experiment 3a, the rats were

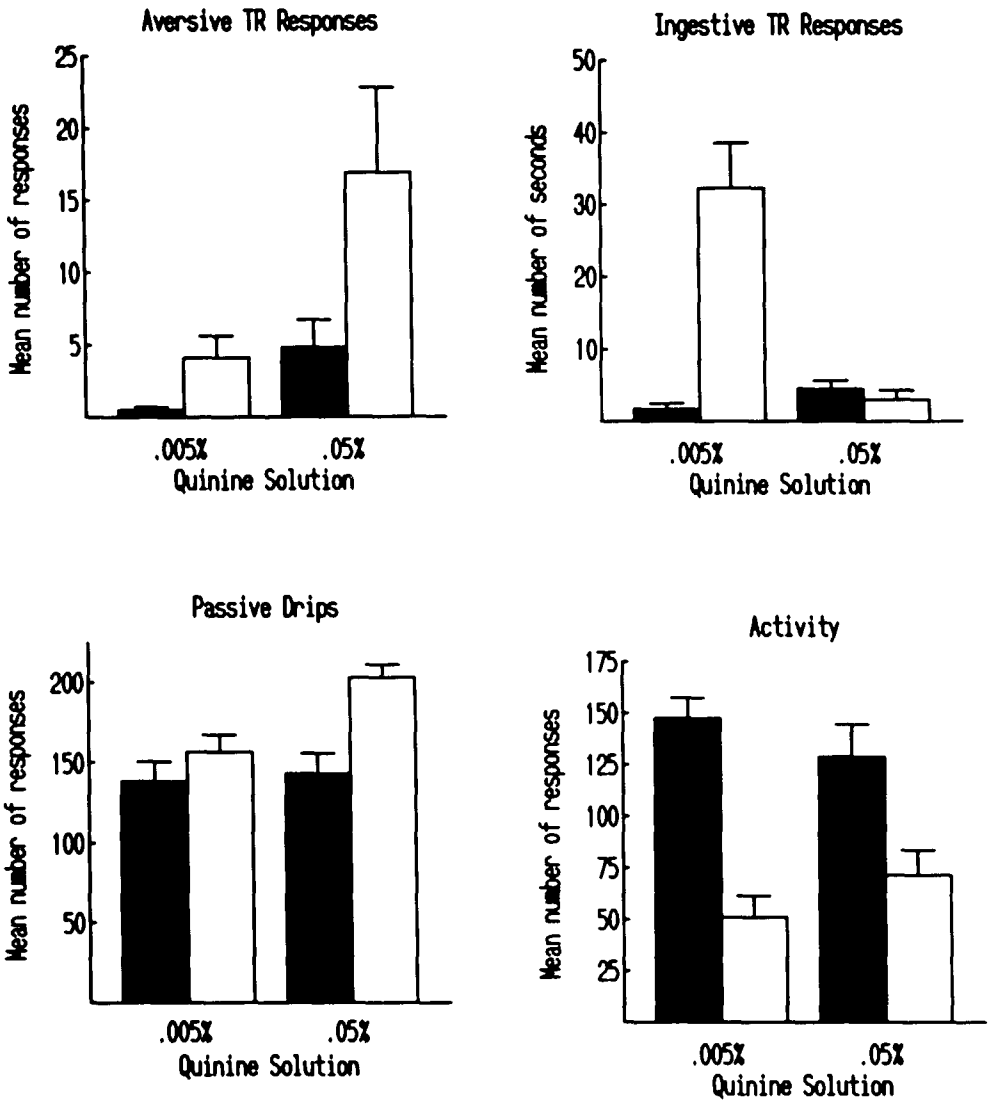

FIG. 3. Mean frequency or duration (s) of TR responses elicited by 0.005% or 0.05% quinine solution in amphetamine (0.25 mg/kg)- and saline-pretreated groups in Experiment 2.

injected IP with 0.25 mg/kg of *d*-amphetamine (n = 12) or with physiological saline solution (n = 12) 30 min prior to receiving a 5-min intraoral infusion of 0.05% quinine solution. In Experiment 3b, the rats were injected IP with 0.25 mg/kg of *d*-amphetamine (n = 12) or with physiological saline solution (n = 12) 30 min prior to receiving a 5-min intraoral infusion of 20% sucrose solution.

RESULTS AND DISCUSSION

Figure 4 presents the mean frequency or duration of taste reactions elicited by 0.05% quinine solution (Experiment 3a) or 20% sucrose solution (Experiment 3b). The left half of the figure presents the TR categories displayed by the rats infused with 0.05% quinine solution. The category of ingestive responding is not displayed because few rats displayed any ingestive reactions when infused with this high concentration of quinine solution, as was also evident in Experiments 1 and 2. The top section presents the mean frequency of aversive reactions. The data for each category of reaction were analyzed as a 2 by 5 mixed-factor ANOVA with the factors of pretreatment condition and minutes of testing. The analysis of the aversive reactions revealed a significant pretreatment effect, $F(1, 22) = 4.4$, $p < 0.05$; the amphetamine-pretreated rats displayed fewer aversive reactions than the saline-pretreated rats. This effect was most pronounced during min 1, $F(1, 22) = 7.5$, $p < 0.01$. Neither the passive drip data nor the activity data revealed significant effects of pretreatment or pretreatment by minute interaction during the 5 min of testing.

The right section of Fig. 4 presents the mean duration of ingestive responding and the mean frequency of passive drip and activity responding during each minute of testing for the rats infused with 20% sucrose solution in Experiment 3b. The

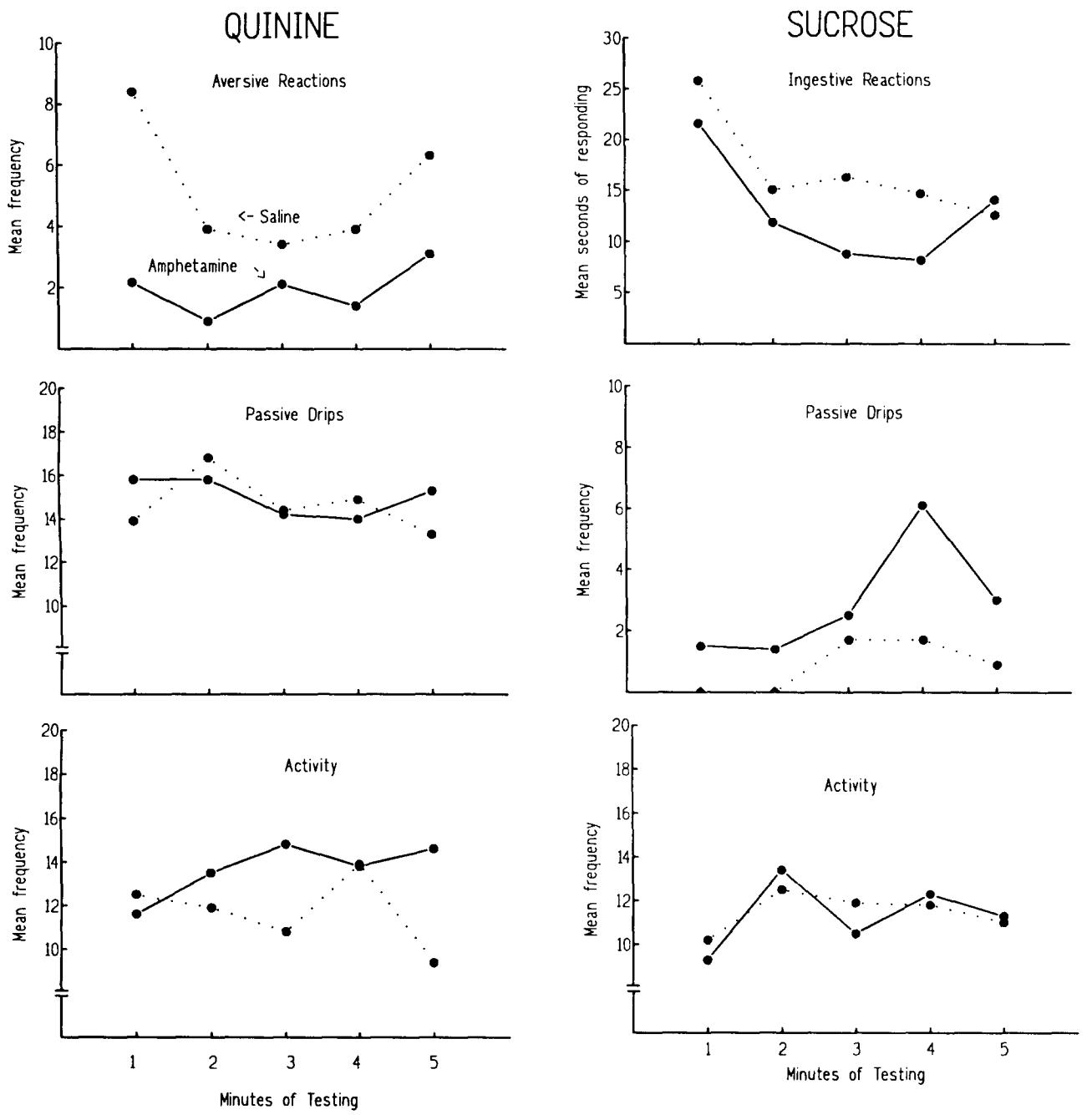

FIG. 4. Mean frequency or duration (s) of TR responses elicited by 0.05% quinine solution or 20% sucrose solution in amphetamine (0.25 mg/kg)- and saline-pretreated groups in Experiments 3a and 3b, respectively, when the test chamber was familiar.

mean frequency of aversive reactions is not displayed because few rats demonstrated any evidence of aversive reactions when infused with 20% sucrose solution. The 2 by 5 mixed-factor ANOVAs for each category revealed no significant effects for any of the reactions.

When the rats were tested in a familiar test chamber, the amphetamine-pretreated group displayed fewer aversive reactions to an intraoral infusion of quinine solution than did the saline-pretreated group. This effect replicated the findings of Experiments 1 and 2 in which rats demonstrated suppressed aversive responding to quinine solution when tested in a novel chamber. Furthermore, when tested in a familiar chamber, pretreatment with 0.25 mg/kg of amphetamine did not modify taste reactions elicited by 20% sucrose solution. Finally, when tested in the familiar chamber, rats pretreated with 0.25 mg/kg of amphetamine did not demonstrate enhanced

activity level during an infusion of either quinine or sucrose solution.

GENERAL DISCUSSION

The pattern of results in Experiments 1 to 3 suggests that amphetamine pretreatment attenuated the aversiveness of quinine solution. This pattern of results is similar to that produced by another reinforcing drug, morphine, which has also been shown to enhance food intake at low doses [e.g., (10)] and activate dopamine release in the nucleus accumbens (6,37). Like amphetamine, morphine suppresses the aversive TR responding elicited by quinine solutions.

It is unlikely that the modification of TR responding produced by amphetamine pretreatment is merely an indirect effect of the general activity enhancement produced by the drug. Although amphetamine (0.25–0.50) increased the frequency of bouts of active locomotion and rearing in rats during an intraoral infusion of quinine solutions when rats were tested in a novel chamber during Experiments 1 and 2, a dose of 0.25 mg/kg of amphetamine did not modify activity level during an intraoral infusion of quinine solution when rats were tested in a familiar chamber during Experiment 3. Since, in each experiment, amphetamine suppressed aversive reactions to quinine, this effect does not appear to be the result of response competition.

Furthermore, the amphetamine-induced suppression of aversive reactions elicited by quinine solution does not appear to be the result of the failure of the amphetamine-pretreated rats to attend to the properties of the tastant. In Experiment 3, when the rats were tested in a familiar environment, they displayed suppressed aversive reactions when infused with quinine solution, but did not display suppressed ingestive reactions when infused with sucrose solution. On the other hand, unpublished observations in our laboratory revealed that when tested in a novel environment, 0.25 mg/kg of amphetamine does, indeed, produce suppression of ingestive reactions during a sucrose infusion. Furthermore, in Experiment 2, amphetamine-pretreated rats displayed suppressed ingestive reactions during an infusion of a weak concentration of quinine solution when tested in a novel environment. Therefore, it is conceivable that the novel environment in Experiments 1 and 2 competed with the tastant for attention, resulting in suppressed taste reactivity. In Experiment 3, however, when the test chamber was familiar, amphetamine pretreatment continued to suppress quinine-elicited aversive reactions without modifying sucrose-elicited ingestive reactions. The consistency across experiments in the amphetamine-induced suppression of aversive reactions suggests that the effect on palatability is direct.

Treit and Berridge (32) reported that pretreatment with 0.25 or 1.5 mg/kg of amphetamine did not modify the palatability of quinine solution in a 1-min TR test. However, in Experiment 3, we report that the suppressive effect of quinine aversive reactions produced by amphetamine pretreatment is greatest during minute 1. It is possible that the difference in findings is the result of differences in quinine concentrations. The concentration employed by Treit and Berridge (32) was 3×10^{-4} M of quinine solution and the concentration employed in the above experiments was 6.7×10^{-3}. The concentration of quinine has been previously demonstrated to be an important factor in evaluating the ability of agents to modify palatability. Pimozide pretreatment has only minimal effectiveness in enhancing the aversive reactions elicited by quinine concentrations within the range employed by Treit and Berridge (32), but is extremely effective in enhancing the aversive reactions elicited by quinine concentrations within the range (and higher) employed in the present experiment (25).

The doses employed in the present study have been reported to enhance intake of sweetened food (7–10). Our results are consistent with these reports, since amphetamine appeared to modify the palatability of quinine solution in a manner that reduced its aversive properties. Furthermore, consistent with our findings, the direct dopaminergic antagonist, pimozide, has been reported to enhance aversive reactions elicited by quinine solution (25). Finally, morphine, which has been reported to produce its rewarding properties by enhancing extracellular dopamine at the nucleus accumbens (4,6,37), has also been reported to suppress aversive reactions elicited by quinine solution (25). It is thus conceivable that agents that enhance the activity of the dopaminergic system are also effective in suppressing the aversive properties of quinine solution.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Susan Maier, Ms. Morven Rennie, and Ms. Karen McLeod for assistance in data collection of Experiments 2 and 3. We would also like to thank Dr. Roy Wise for insightful comments on an earlier version of this manuscript. Experiment 3 was included to address issues raised in these comments. The *d*-amphetamine was generously supplied by NIDA. The research was supported by an NSERC Undergraduate Research Award to Kira Leeb and by an NSERC grant (#0092057) held by Linda Parker.

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