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Pimozide Enhances the Aversiveness of Quinine Solution

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PARKER, L. A. AND N. LOPEZ, JR. *Pimozide enhances the aversiveness of quinine solution.* PHARMACOL BIOCHEM BEHAV **36**(3) 653–659, 1990.—The taste reactivity test was employed to assess the effect of pimozide pretreatment on rats' hedonic responsiveness to palatable and unpalatable tastants. Pimozide selectively enhanced the aversiveness of unconditionally unpalatable quinine solution (Experiment 1) and produced the greatest enhancement of aversion at the highest concentration of quinine (0.1%) solution tested (Experiment 3). Pimozide also enhanced the aversiveness of a conditionally unpalatable lithium-paired solution, but only when the dose of pimozide was relatively high and the strength of the baseline aversion was relatively low (Experiment 2). These results are discussed in light of the anhedonia and the sensorimotor deficit hypotheses of neuroleptic effects on reinforced responding.

Pimozide Neuroleptics Dopamine Palatability Taste Taste reactivity Quinine Sucrose Psychopharmacology Conditioned taste aversion Amphetamine Lithium

NEUROLEPTIC drugs which block dopamine receptors interfere with positively reinforced behaviors [e.g., (21)]. Two prominent hypotheses which account for these effects are the anhedonia hypothesis (20) and the motor deficit or sensorimotor deficit hypothesis [e.g., (4, 7, 13–16, 18, 19)]. The anhedonia hypothesis (21) proposes that since dopamine mediates the central reward system, neuroleptic-induced suppression of the dopamine system should result in interference of responding maintained by positive reinforcers. The sensorimotor deficit hypothesis, on the other hand, predicts that dopamine mediates responsiveness to sensory stimulation; therefore, neuroleptic pretreatment should interfere with performance by suppressing motor responding elicited by sensory stimulation.

Several studies designed to test the anhedonia hypothesis have found that neuroleptic drugs, such as pimozide, reduce the consumption of sucrose solution, presumably by reducing its positive hedonic assessment [e.g., (5, 22, 23)]. However, a more direct measure of a rat's hedonic assessment of a tastant is the taste reactivity (TR) test developed by Grill and Norgren (6). Rats display a characteristic set of orofacial and somatic responses when flavored solutions are infused directly into their mouths; for instance, sweet sucrose solution elicits an ingestive pattern of tongue protrusions and paw licking while bitter quinine solution elicits a rejection pattern of gaping, chin rubbing, paw treading, forelimb flailing, paw wiping and head shaking [e.g., (1, 2, 6, 12)]. This test may provide a more efficient assessment of shifts in the hedonic properties of flavored solutions produced by neuroleptic treatment than the standard consummatory tests. The experiments below investigated the influence of pimozide pretreatment on the orofacial and somatic responses elicited by unconditionally and conditionally palatable and unpalatable flavored solutions. The anhedonia hypothesis would predict that ingestive responding elicited by a palatable solution would be suppressed. Berridge, Venier and Robinson (3) recently suggested that the anhedonia hypothesis might be expanded to include the prediction that suppression of the dopamine system may not only suppress positive hedonic assessments, but also enhance aversive hedonic assessments by blunting the reward system; therefore, according to this interpretation of the anhedonia hypothesis, pimozide pretreatment should enhance aversive responses elicited by unpalatable solutions. On the other hand, the sensorimotor deficit hypothesis would predict that the taste reactivity responses elicited by any flavored solution should be suppressed in the pimozide-pretreated group.

EXPERIMENT 1

The first experiment assessed the ability of pimozide to modify

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taste reactivity elicited by sucrose solution or quinine solution. The rats were pretreated with 0.5 mg/kg pimozide or with the drug vehicle prior to receiving a five-minute intraoral infusion of 17% sucrose solution or 0.01% quinine solution and their taste reactivity responses were recorded on videotape.

METHOD

Subjects

Twenty-nine male Sprague-Dawley rats served as subjects. They were maintained on ad lib access to food and water except as indicated below.

Apparatus

The taste reactivity test was conducted in a glass chamber (22.5 × 26 × 20 cm). The room was illuminated by two 40-watt light bulbs placed on each side of the test chamber. Once the animals were placed in the chamber, their cannulae were connected to the infusion pump. A 35 cm long tube connected the infusion pump to the plastic adapter cap of the cannulae. A Hitachi HV-62 videocamera focussed on a mirror which was hung at an angle to facilitate viewing of the rat's ventral surface. The rat's image was transmitted to a Panasonic videorecorder. The tapes were later scored by a rater blind to experimental conditions via an event recorder attached to an Apple IIe microcomputer.

Procedure

One week after their arrival in the laboratory, the rats were surgically implanted with intraoral cannulae as described by Parker (8). The rats were given one week to recover. On the final recovery day, the cannulae were flushed with water to prevent stoppage by food.

All rats were initially adapted to the testing procedure. On each of the three days prior to the test day, each rat was placed in the taste reactivity test chamber with the plastic tube from the infusion pump attached to its cannula. One minute later, the rat received a 5 ml intraoral infusion of water at the rate of 1 ml/min for 5 minutes.

Twenty-four hr after the final adaptation trial, the rats received Test Trial 1. Four hours prior to testing, the rats were either injected intraperitoneally (IP) with 0.5 mg/kg of pimozide solution (n = 15) or were injected with the drug vehicle (n = 14). The pimozide was dissolved in a vehicle of 1.5% tartaric acid and distilled water in a volume of 1 mg/ml. During the TR test, half of the rats in each pretreatment condition received an infusion of 5 ml of 17% sucrose solution and half received an infusion of 5 ml of 0.01% quinine sulfate solution over a 5-minute period at the rate of 1 ml/min. The groups were as follows: Pimozide Sucrose (n = 8), Vehicle Sucrose (n = 7), Pimozide Quinine (n = 7), Vehicle Quinine (n = 7). The orofacial and somatic responses of the rats during the test session were recorded on videotape.

Data Analysis

The data for the rats infused with sucrose solution and the rats infused with quinine solution were analyzed separately, since different types of responses are unconditionally elicited by each of these solutions [e.g., (1, 2, 6, 12)]. The aversive TR responses included the frequency of occurrence in the 5-min session of chin rubbing (CR: forward projection of the head with the chin rubbing against a substrate), gaping (G: triangular, wide opening of the mouth), paw pushing (PP: rhythmic pushing of the forepaws against the floor of the cage), head shaking (HS: rapid shaking of the head from side to side) and limb flicking (LF: rapid flailing of the forepaws). The ingestive TR responses included the amount of time in the 5-min session spent showing tongue protrusions (TP: extensions of the tongue out of the mouth), mouth movements (MM: movement of the lower mandible without opening the mouth). Additionally, the neutral/mildly aversive TR response of frequency of passive dripping (number of drips which fall from the rat's mouth to the floor when the rat is not actively ejecting the solution by a rejection response) described by Berridge and Grill (2) was measured. Finally, as an assessment of general activity level, the frequency of bouts of vertical movement (rearing, with forelimbs off the floor of the cage) and horizontal movement (movement with the forepaws on the floor of the cage) were summated to produce a composite activity score (ACT).

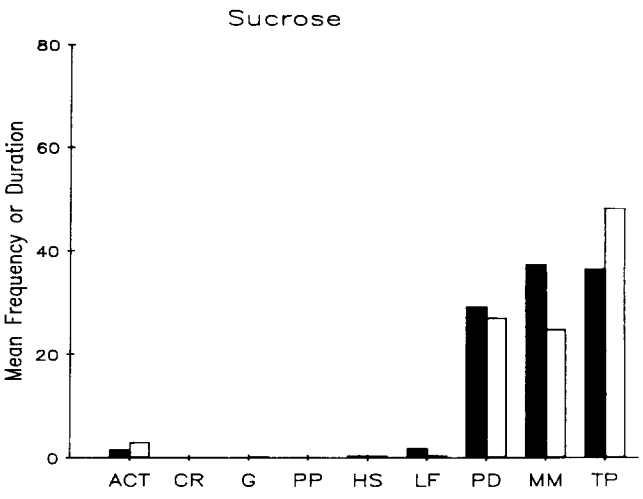

FIG. 1. Mean frequency or duration of various TR responses elicited by 17% sucrose solution in Experiment 1. The solid bars represent the pimozide pretreatment group and the open bars represent the vehicle pretreatment group.

RESULTS AND DISCUSSION

The mean frequency or duration of each TR response elicited by 17% sucrose solution is presented in Fig. 1. The pimozide-pretreated group is represented by solid bars and the vehicle-pretreated group is represented by open bars. The reactivity to sucrose solution was not modified by pretreatment condition when measured by any taste reactivity response category.

The mean frequency or duration of each TR response elicited by 0.01% quinine solution is presented in Fig. 2. Pimozide-pretreated rats demonstrated more frequent gaping, $t(12) = 1.8$, $p < 0.05$, than did the vehicle-pretreated rats during an intraoral infusion of unpalatable quinine solution. No other behaviors differed between the groups.

Pimozide pretreatment enhanced the aversiveness of the quinine solution as indicated by pimozide-induced potentiation of the aversive response of gaping. This finding is consistent with the broadened interpretation of the anhedonia hypothesis (20) suggested by Berridge, Venier and Robinson (3); that is, suppression of the dopamine system may enhance aversive hedonic assessments by blunting the reward system. However, the anhedonia hypothesis would also predict that pimozide should suppress the ingestive responding elicited by sucrose, but this prediction was not confirmed. Finally, pimozide did not modify the activity of the rats tested with sucrose or quinine solution, contrary to the

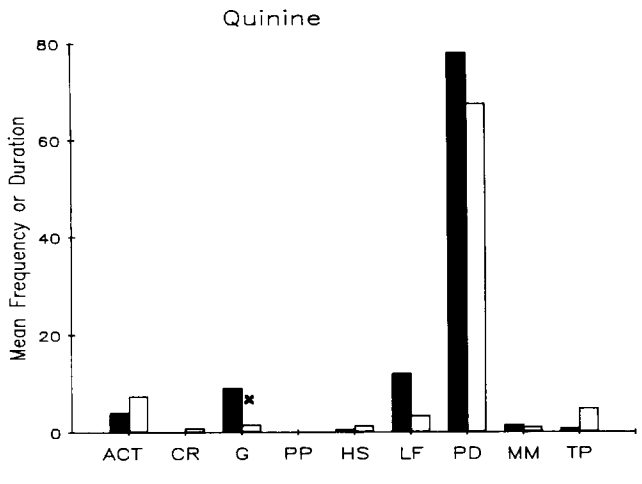

FIG. 2. Mean frequency or duration of TR responses elicited by 0.01% quinine solution in Experiment 1. The solid bars represent the pimozide pretreatment group and the open bars represent the vehicle pretreatment group.

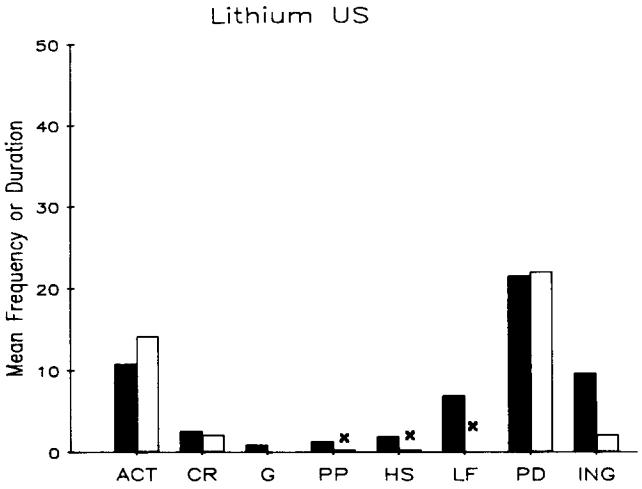

FIG. 3. Mean frequency or duration of TR responses elicited by lithium-paired saccharin solution in Experiment 2a. The solid bars represent the pimozide pretreatment group and the open bars represent the vehicle pretreatment group.

predictions of the sensorimotor deficit hypothesis [e.g., (4, 7, 13–16, 18, 19)]; however, it should be noted that the means in both the sucrose- and quinine-tested groups varied in a direction that would support a motoric deficit interpretation. It is conceivable that a more sensitive measure of motoric activity would reveal suppressed motor activity in the pimozide-pretreated groups.

EXPERIMENT 2

Pimozide pretreatment appeared to enhance the aversiveness of unconditionally unpalatable quinine solution. The next experiment assessed the ability of pimozide to enhance the aversiveness of conditionally unpalatable lithium-paired saccharin solution. Flavors paired with lithium are actively rejected in the TR test in a manner similar to that in which rats reject unconditionally aversive quinine solution [e.g., (6,12)]. On the other hand, equally avoided flavors in a conditioned taste avoidance test that have previously been paired with amphetamine solution are not actively rejected in the TR test (9–11, 22). The latter finding has led to the suggestion that lithium-paired flavors, but not amphetamine-paired flavors become conditionally unpalatable. If pimozide enhances the aversiveness of unpalatable solutions in the taste reactivity test, then pimozide pretreatment should enhance rejection responses elicited by lithium-paired flavored solutions, but not amphetamine-paired flavored solutions.

METHOD

Experiment 2 involved two experiments which were conducted two weeks apart and will be referred to as 2a and 2b. Experiment 2a employed 15 male Sprague-Dawley rats weighing between 292 and 388 g and Experiment 2b employed 15 male Sprague-Dawley rats weighing between 287–365 g. All rats were maintained on ad lib access to food and water except as indicated.

One week after their arrival in the laboratory, the rats were surgically implanted with intraoral cannulae in a similar manner as in the previous experiments. After a one-week recovery period from the surgery, the rats were placed on a daily drinking schedule during which each rat received 20 min of water per day for each of three days. The first conditioning trial occurred 24 hr after the final water adaptation trial. The rats each received three conditioning trials which were separated by 48 hr with a day of 20 min access to water intervening between trials. On each conditioning trial, the rats were presented with a graduated tube containing 0.1% saccharin solution for 20 min. Immediately after the tubes were removed, all rats were injected intraperitoneally (IP) with 50.2 mg/kg of 0.15 M lithium chloride solution in Experiment 2a or 3 mg/kg of d-amphetamine sulfate in Experiment 2b. If a rat drank less than 2 ml on any trial, the tip of a syringe was inserted into the rat's mouth and 1 ml of saccharin solution was washed across its tongue prior to administration of the injection.

In both Experiments 2a and 2b, three days after the final conditioning trial, the rats received the test trial. On the test trial, the rats were injected with either 1 mg/kg of pimozide in a 1.5% tartaric acid solution ($n=8$, Experiments 2a and 2b) or with the tartaric acid vehicle ($n=7$, Experiments 2a and 2b) 4 hr prior to the TR test trial. The TR test trial was conducted in a manner similar to the previous experiment except that the rats received 2 ml of 0.1% saccharin solution at the rate of 1 ml/min. The rats' orofacial and somatic responses were videotaped during the infusion. For purposes of data analysis, the ingestive responses of duration of Tongue Protrusions, Mouth Movements and Paw Licking were summated to produce a composite ingestion score (ING) in a manner similar to that described by Treit, Berridge and Schultz (17).

RESULTS AND DISCUSSION

Figure 3 presents the responses elicited by the lithium-paired saccharin solution in Experiment 2a. The solid bars represent the pimozide-pretreated groups and the open bars represent the vehicle-pretreated group. The lithium-paired saccharin solution elicited more frequent aversive responses of paw pushing, $t(13)=1.7$, $p<0.05$, head shaking, $t(13)=2.7$, $p<0.05$, and limb flicking, $t(13)=1.9$, $p<0.05$, in the pimozide-pretreated group than in the vehicle-pretreated group. None of the other behaviors measured differed between the pretreatment groups.

Figure 4 presents the responses elicited by the amphetamine-paired saccharin solution in Experiment 2b. The pretreatment groups did not significantly differ in any TR behavioral category.

Pimozide selectively enhanced the aversive responses of paw

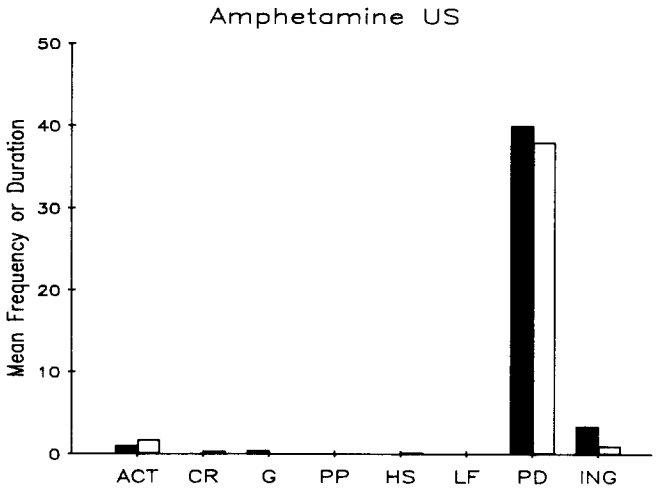

FIG. 4. Mean frequency or duration of TR responses elicited by amphetamine-paired saccharin solution in Experiment 2b. The solid bars represent the pimozide pretreatment group and the open bars represent the vehicle pretreatment group.

pushing, head shaking and limb flicking elicited by a lithium-paired flavored solution, but did not modify the hedonic responsiveness to an amphetamine-paired flavored solution. Since lithium-paired flavored solutions, but not amphetamine-paired flavored solutions, appear to become conditionally unpalatable in the taste reactivity test, as measured by their tendency to elicit rejection responding (9–11, 24), blockade of dopamine receptors may selectively enhance the aversiveness of unpalatable solutions. However, these results must be viewed with some caution since the aversive responses of chin rubbing and gaping were not modified by pretreatment with pimozide. The dose of lithium (50.2 mg/kg) used may have been too low to produce a palatability shift sufficient to elicit a strong tendency to display chin rubbing and gaping in either the vehicle- or pimozide-pretreated groups.

EXPERIMENT 3

Experiment 3 was conducted as an attempt to verify the ability of pimozide to enhance the aversiveness of a lithium-paired saccharin solution as well as various concentrations of unconditionally aversive quinine solution. The dose of lithium used was increased to 127.2 mg/kg to ensure a high baseline level of chin rubbing and gaping in the vehicle-pretreated groups. Furthermore, the design included noncontingently injected control groups for both the lithium- and amphetamine-conditioned groups. Finally, since a dose of 0.5 mg/kg of pimozide was sufficient to enhance the aversive response of gaping elicited by quinine, the dose of pimozide used was 0.5 mg/kg rather than 1 mg/kg.

The rats were pretreated with either pimozide or the vehicle prior to receiving one of two TR tests: The first assessed the TR responses to the drug-paired saccharin solution and the second assessed the TR responses elicited by one of three concentrations of quinine solution (0.001%, 0.01%, 0.1%). Both TR tests were two minutes in duration.

METHOD

Fifty-seven male Sprague-Dawley rats weighing between 225–270 g served as subjects. They were treated identically to those of Experiment 2 except as indicated. On each of three conditioning trials, the rats received 0.1% saccharin solution in a graduated tube for 20 min which was immediately followed by an IP injection of the appropriate agent. The agents were 127.2 mg/kg of 0.15 M LiCl, 3 mg/kg of d-amphetamine or physiological saline. Twenty-four hr after each conditioning trial, each rat was injected with its appropriate control agent; those rats in the Lithium or Amphetamine CS+ groups were injected with physiological saline and those rats in the Lithium or Amphetamine CSc groups were injected with 127.2 mg/kg of LiCl or 3 mg/kg of d-amphetamine respectively. All injections were in a volume of 20 ml/kg. The groups were as follows: Lithium CS+ (n = 15), Lithium CSc (n = 14), Amphetamine CS+ (n = 14), Amphetamine CSc (n = 14).

Four days after the final conditioning day, the rats received their first of five TR test adaptation trials in a manner similar to that of Experiment 2. On the following day, the rats received the test trial. Half of the rats in each group were injected IP with 0.5 mg/kg of pimozide in a 1.5% tartaric acid solution and half were injected with the tartaric acid vehicle 4 hr prior to the TR test trial. On the TR test trial, the rats received 2 ml of 0.1% saccharin solution at the rate of 1 ml/min. The rats orofacial and somatic responses were videotaped during the infusion.

Two days after the TR test with 0.1% saccharin solution, the rats were reassigned to groups balanced for previous experience and tested with one of three concentrations of unconditionally aversive quinine solution: 0.001% quinine, 0.01% quinine and 0.1% quinine solution. Four hr prior to the quinine TR test, the rats were injected with either 0.5 mg/kg of pimozide in solution with 1.5% tartaric acid or 1.5% tartaric acid vehicle. The rats received 2 ml of quinine solution at the rate of 2 ml/min during the TR test.

RESULTS AND DISCUSSION

Saccharin TR Test

Figures 5 and 6 present the mean frequency or duration of each behavior measured in Experiment 3 during the saccharin TR test for the groups conditioned with lithium or amphetamine. The solid bars represent the pimozide-pretreated groups and the open bars represent the vehicle-pretreated groups. The data for each behavior was analyzed by a $2 \times 2 \times 2$ completely randomized ANOVA with the factors of CS Condition (CS+, CSc), US Condition (Lithium, Amphetamine) and Pretreatment Condition (Pimozide, Vehicle). The analysis of the first behavior along the abscissae of Figs. 5 and 6, frequency of activity (rearing + active locomotion), revealed a significant main effect of pretreatment condition, $F(1,49) = 9.3$, $p<0.01$; the pimozide-pretreated groups were less active than the vehicle-pretreated group.

Analysis of the data for the aversive responses of chin rubbing and gaping revealed similar effects, but for neither behavior was there evidence of an effect due to pimozide pretreatment. For both behaviors, the CS effect [CR: $F(1,49) = 21.3$, $p<0.01$; G: $F(1,49) = 21.7$, $p<0.01$] and CS $\times$ US effect [CR: $F(1,49) = 12.2$, $p<0.01$; G: $F(1,49) = 7.01$, $p<0.01$] were significant. By subsequent t-tests using a pooled error term, Group CS+ Lithium showed more chin rubbing and gaping than any other group (p's<0.05); however, these aversive responses were not significantly enhanced by pimozide pretreatment. The analysis of the data for paw pushing, head shaking and limb flicking and passive dripping revealed no significant differences among conditions.

Finally, the analysis of the composite ingestive responses revealed a significant CS effect, $F(1,49) = 15.2$, $p<0.001$, and CS $\times$ US effect, $F(1,49) = 8.6$, $p<0.005$. By subsequent t-tests using a pooled error term, Group CSc Lithium spent more time showing ingestive responding than did all other groups (p's<0.05) and

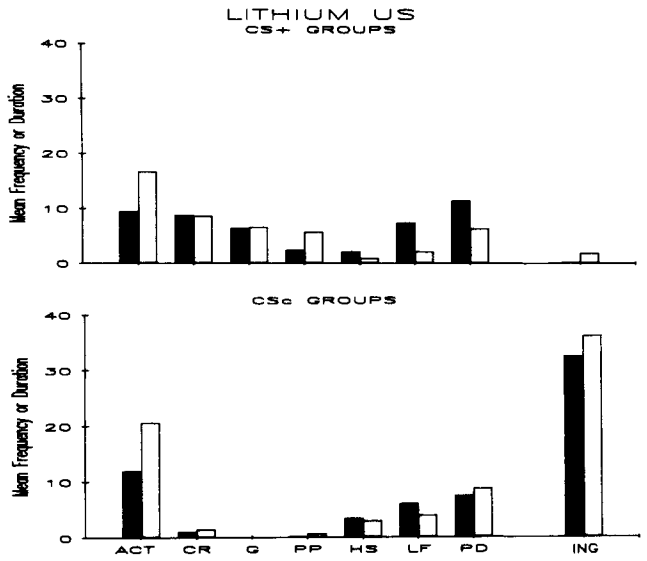

FIG. 5. Mean frequency or duration of TR responses for groups Lithium CS+ and Lithium CSc. The solid bars represent the pimozide pretreatment group and the open bars represent the vehicle pretreatment group.

Group CS+ Lithium spent less time showing ingestive responding than did all other groups (p's<0.05). Pretreatment Condition did not significantly interact with any factor.

Quinine TR Test

Figure 7 presents the mean frequency or duration of the TR responses elicited by various concentrations of quinine solution following pimozide or vehicle pretreatment in Experiment 3. Analysis of neither prior experience with pimozide nor prior conditioning experience differentially effected the results. Each TR behavior was analyzed as a 3×2 completely randomized ANOVA with the factors of quinine concentration and pretreatment condition. Analysis of the composite activity score revealed a significant pretreatment effect, $F(1,51)=8.4$, $p<0.01$; pimozide-pretreated rats were less active than vehicle-pretreated rats. The frequency of aversive responses of chin rubbing, gaping and paw pushing were effected in similar directions by the manipulations. The concentration effect [CR: $F(2,51)=14.7$, $p<0.01$; G: $F(2,51)=15.6$, $p<0.01$; PP: $F(2,51)=5.5$, $p<0.01$] and the concentration × pretreatment effect [CR: $F(2,51)=4.1$, $p<0.025$; G: $F(2,51)=4.95$, $p<0.01$; PP: $F(2,51)=3.3$, $p<0.05$] were significant for the chin rubbing, gaping and paw pushing behaviors. Furthermore, for gaping only, there was a significant pretreatment effect, $F(2,51)=7.2$, $p<0.01$; pimozide produced more gaping overall than did the vehicle pretreatment. Subsequent t-tests revealed that only at the 0.1% quinine concentration did pimozide significantly enhance the frequency of aversive responding of chin rubbing and paw pushing (p's<0.05). However, pimozide enhanced the frequency of gaping at both the 0.01% quinine concentration, as in Experiment 1, and the 0.1% quinine concentration (p's<0.05). Analysis of the TR responses of passive drip, head shakes and limb flicks did not reveal significant effects. The final response of duration of ingestive responding revealed a main effect of concentration that approached significance, $F(2,51)=2.8$, $p<0.07$. The rats tended to show less ingestive responding overall as the concentration increased.

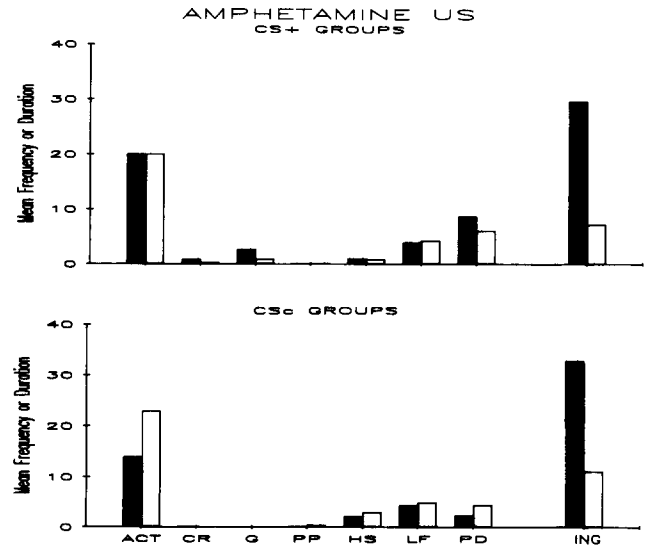

FIG. 6. Mean frequency or duration of TR responses for groups Amphetamine CS+ and Amphetamine CSc. The solid bars represent the pimozide pretreatment group and the open bars represent the vehicle pretreatment group.

GENERAL DISCUSSION

Pimozide appears to enhance the aversive responding elicited by unpalatable flavored solutions without modifying the ingestive responding elicited by palatable flavored solutions. Although the anhedonia hypothesis predicts that pimozide should produce suppressed ingestive responding elicited by palatable sucrose solution, the enhancement of aversive responding elicited by unpalatable flavored solutions supports a broad conception of the anhedonia hypothesis (20); that is, dopamine blockade increases the aversiveness of aversive stimuli by blunting the reward system (3). The sensorimotor deficit hypothesis would predict that pimozide-pretreated rats should be less responsive to sensory stimuli [e.g., (4, 7, 13–16, 18, 19)] contrary to our results with unconditionally unpalatable quinine solution. However, the sensorimotor deficit hypothesis also predicts that pimozide should decrease general activity level, which in fact occurred in Experiment 3 and, although not significant, was suggested by the consistent pattern of mean differences in Experiments 1 and 2.

Although pimozide pretreatment enhanced aversive responding elicited by quinine solution, it failed to suppress ingestive responding elicited by sucrose solution. The lack of pimozide-induced modification of hedonic reactivity to sucrose solution is surprising in light of reports by other investigators that pimozide suppresses the consumption of sucrose solution [e.g., (5, 22, 23)]. Berridge, Venier and Robinson (3) have recently reported that 6-hydroxydopamine lesions of the substantia nigra (SN) also failed to modify rats' reactivity to sucrose solution. However, in contrast to our findings, they also reported that these lesions failed to modify rats' reactivity to quinine solution. It is thus probable that the nonselective effect of peripheral IP pimozide injections in the present report produced a more widespread blockade of the dopamine system than did the SN lesions (3).

The effects of pimozide on rats' reactivity to lithium-paired saccharin solution is not conclusive. We had reasoned that if pimozide pretreatment enhances the aversiveness of unpalatable flavored solutions, it should selectively enhance the aversiveness of a lithium-paired saccharin solution, but should not enhance the aversiveness of an amphetamine-paired saccharin solution. This

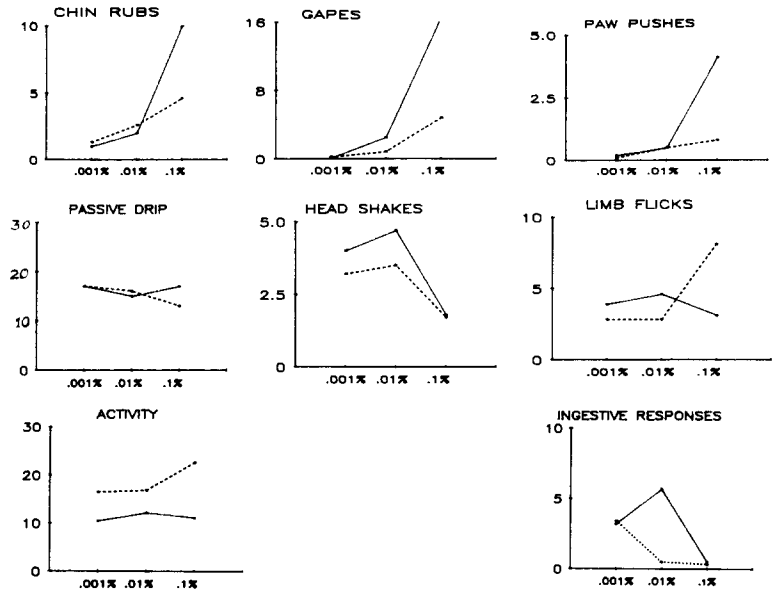

FIG. 7. Mean frequency or duration of TR responses elicited by 0.001%, 0.01% or 0.1% quinine solution in rats pretreated with pimozide (solid lines) or vehicle (dotted lines).

hypothesis was based on our previous findings that lithium-paired solutions elicit rejection responses in the taste reactivity test, but amphetamine-paired solutions do not elicit rejection responses in the taste reactivity test [e.g., (9–11, 24)]. In Experiment 1, when the dose of lithium was 50.2 mg/kg, a dose of 1 mg/kg of pimozide enhanced the frequency of the aversive TR responses of paw pushing, head shaking and limb flicking. However, in Experiment 3, when the dose of lithium was 127.2 mg/kg, the lower dose of 0.5 mg/kg of pimozide did not modify the rats' reactivity to the lithium-paired saccharin solution, although it did modify the reactivity to quinine solution. In neither experiment did pimozide modify the rats' reactivity to an amphetamine-paired solution. Future experiments will assess the effect of various doses of pimozide on the reactivity to saccharin paired with various doses of lithium in order to determine the threshold at which pimozide may enhance the aversiveness of a lithium-paired solution.

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