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Pimozide Does Not Shift Palatability: Separation of Anhedonia from Sensorimotor Suppression by Taste Reactivity

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PECIÑA, S., K. C. BERRIDGE AND L. A. PARKER. *Pimozide does not shift palatability: separation of anhedonia from sensorimotor suppression by taste reactivity*. PHARMACOL BIOCHEM BEHAV **58**(3) 801–811, 1997.—Several "taste reactivity" studies of dopamine and reward have concluded that pimozide suppresses the hedonic reaction patterns normally elicited by sucrose but enhances aversive reaction patterns elicited by quinine. However, other taste reactivity studies have failed to find hedonic/aversive shifts in reaction patterns after dopamine antagonists or dopamine lesions. The divergent conclusions have come from two different laboratories. To resolve the controversy regarding dopamine blockade and palatability, the present study joined the two laboratories to investigate the effect of pimozide on taste reactivity patterns elicited by sucrose and quinine. The results replicated many (but not all) of the earlier findings and identified procedural factors responsible for different outcomes. Overall, the results provide evidence for sensorimotor effects of pimozide on taste reactivity but not for a hedonic shift in palatability. Pimozide suppressed both hedonic and aversive reaction patterns in a gradual sensorimotor fashion when the eliciting taste stimulus was repeated or continued for several minutes. The general suppression typically did not alter the initial reaction to a taste but emerged only after an oral infusion of sucrose or quinine continued for several minutes or trials. Aversive reactions were never enhanced. The balance between hedonic and aversive reaction patterns was not shifted by pimozide. We conclude that pimozide produces a sensorimotor impairment of taste reactivity patterns but does not shift taste palatability toward anhedonia or aversion. © 1997 Elsevier Science Inc.

Pimozide Dopamine Dopamine antagonists Food reward Taste reactivity Palatability

BLOCKADE of dopamine receptors by neuroleptic drugs, such as pimozide, disrupts the motivational effectiveness of food and other rewards (18,20,22–24,34,47,56,58,61,69,70,73). Such effects have led many investigators to the conclusion that food reward is mediated in part by mesotelencephalic dopamine systems [e.g., (2,18,24,33,35,48,55,57,71,72,75)], although the relative roles of reward suppression vs. motor impairment on behavioral performance after dopamine antagonist administration has been the subject of much debate [e.g., (54,58,70)]. A review of the evidence in favor of a dopamine role for food reward in particular has been recently provided by Smith (58).

The most straightforward hypothesis for the role of dopamine in reward is that pimozide and other dopamine antagonists produce anhedonia, a specific reduction of the capacity for sensory pleasure [e.g., (68–70,73)]. Regarding food reward, this hypothesis implies that dopamine antagonists should shift food palatability, making preferred foods less palatable or unpreferred foods more aversive.

Perhaps the most direct method available for studying changes in hedonic or aversive palatability in human infants or adult animals is through affective reaction measures [e.g., (6,29,60)]. In rats, affective reaction patterns can be studied by using the taste reactivity technique developed by Grill and Norgren (31). *Hedonic* reaction patterns are emitted by rats to sweet tastes, whereas *aversive* reaction patterns are emitted to bitter tastes. Both categories of reaction are altered by physiological hunger and satiety, by conditioned aversions

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and appetites and by brain lesions and many other manipulations, as would be expected if they reflected palatability [for review of taste reactivity and palatability, see (6)]. Most directly relevant to this study, hedonic and aversive taste reactivity patterns also are shifted by several pharmacological manipulations that are believed to change palatability, such as systemic or intracranial administration of opioid or benzodiazepine agonists (5,10,16,27,40,41,44–46,49).

Several taste reactivity studies of pimozide effects on palatability conducted by Parker and colleagues at Wilfrid-Laurier University have appeared to support the anhedonia hypothesis. For example, Leeb et al. (37) found that repeated systemic administration of pimozide eventually suppressed hedonic reactions elicited by a 10-min infusion of sucrose into the mouth, especially during the second half of the test. Conversely, Parker and Lopez (43) reported that pimozide enhanced aversive reactions to a 2-min infusion of a concentrated quinine solution. In other words, pimozide appeared to make palatable tastes less pleasant and to make noxious tastes more unpleasant.

However, other taste reactivity studies of the role of dopamine in palatability, conducted primarily at the University of Michigan, have failed to find a palatability shift in hedonic or aversive reactions after manipulation of dopamine systems. For example, haloperidol pretreatment failed to reduce hedonic reactions or increase aversive reactions to a 1-min infusion of sucrose or quinine (64). More dramatically, 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal dopamine system, which made rats aphagic, also failed to reduce hedonic taste reactivity or to increase aversive taste reactivity to a 1-min infusion of sucrose or quinine (12). Even combined nigrostriatal and mesolimbic 6-OHDA lesions, which produced over 95% depletion of dopamine from neostriatum and accumbens, have failed to shift hedonic or aversive reaction patterns (9). These and related results have led Berridge (6) and Robinson and Berridge (50) to conclude that dopamine systems do not mediate hedonic or aversive palatability and that dopaminergic suppression does not produce anhedonia.

The present study was conducted to resolve this controversy. Because the studies that have reported differing conclusions have come from two different laboratories, in the present study the Wilfrid Laurier and Michigan laboratories joined together to combine procedures and reach agreement. Several experimental parameters have differed consistently between these two laboratories in previous studies: the duration of the test and of stimulus administration, the procedure used to score videorecords, whether the experiment used within-subject vs. between-subject comparisons of drug to vehicle, etc. In the present study, several parameters were changed systematically in cooperation with both laboratories, and the effects of pimozide administration on taste reactivity were assessed extensively.

EXPERIMENT 1: DOES PIMOZIDE MODIFY THE PALATABILITY OF A SUCROSE SOLUTION?

In experiment 1, the ability of pimozide to modify sucrose palatability in a 10-min test across 3 trials was assessed in both laboratories, once in a between-subjects design [a replication of a design by Leeb et al. (37)] and once in a within-subjects design (in which each rat serves as its own control, being tested both in drug and vehicle conditions). The tapes from the four experiments were shared and scored by both laboratories. Because the analyses performed by both laboratories were consistent for the two designs, only the results from one laboratory for each design are reported. We report the results of the between-subjects design collected at Wilfrid Laurier University (experiment 1A) and the results of the within-subject design collected at the University of Michigan (experiment 1B).

Method

Experiment 1A: Effect of pimozide on sucrose (Wilfrid-Laurier University: between-subjects design). Twenty male Sprague–Dawley rats (304–355 g) served as subjects. They were housed in individual wire-mesh cages and maintained in a room illuminated on a 12–12-h light–dark schedule. Throughout the experiment, all rats had ad libitum access to food and water. All experimental procedures occurred during the light phase of the cycle.

Procedure. One day after their arrival in the laboratory, the rats were maintained on unlimited access to a bottle containing 17% (0.5 M) sucrose solution and to a bottle containing water for a 3-week period. During the final week, they were surgically implanted with intraoral cannulae for presentation of flavors in the subsequent taste reactivity test, by using the surgical procedure described by Parker et al. (44).

One week after recovering from surgery, the adaptation trials began. For each trial, a rat was placed in the test chamber (22 cm $\times$ 26 cm $\times$ 20 cm) and was infused by intraoral cannula with water at the rate of 1 ml/min for 10 min. The rats received 2 adaptation trials, with each trial separated by 24 h.

Following the two adaptation trials, separate groups received 3 trials (48 h apart) during which one group was injected intraperitoneally (IP) with pimozide (0.5 mg/kg in 0.5 ml/kg, dissolved in 1.5% tartaric acid vehicle; $n = 10$) and the other group was injected with drug-free vehicle ($n = 10$), 4 h prior to an intraoral infusion of the familiar sucrose solution. During the 10-min intraoral infusion (1 ml/min), the rat's orofacial reactions were videotaped from a mirror located at an angle beneath the rat's cage.

Videoanalysis. The duration of rhythmic tongue protrusions (forward protrusions beyond the lip, with a cycle of roughly 6 Hz), paw licks (licking directed toward the paws or forelimbs) and rhythmic mouth movements (opening and closing of the jaw at roughly 6 Hz) were scored by using a keyboard event recorder in real time by an observer blind to the experimental conditions. Rhythmic tongue protrusions and paw licks are the most prominent among three taste reactivity components classified as strongly ingestive or hedonic [e.g., (31)]. Rhythmic mouth movements are a reaction that can be classified as either weakly ingestive or neutral. In addition, the occurrence of passive drips, a mildly aversive or neutral response, was counted as the number of drips observed. The frequency of rears (standing upward on the hindfeet) and bouts of forward locomotion (walking or running) were scored in terms of the number of bouts and summed to provide a measure of total activity. A bout was defined as a period of any length during which rearing or locomotion were continually emitted. Rearing and locomotion can be classified as either aversive or measures of general motor activity [for discussion of classification of taste reactivity components, see (7,42)].

Experiment 1B: Effect of pimozide on sucrose (University of Michigan: within-subjects design)

Subjects. This experiment aimed to establish the cross-laboratory reliability of the effect of pimozide on taste reactivity to a

prolonged 10-min oral infusion by using a within-subject design in which each rat served as its own control and a detailed slow-motion videoanalysis. Eight Sprague–Dawley rats (born at the University of Michigan) weighing 300–350 g at the beginning of the experiment were housed in pairs on a 14–10 cycle. Rats had free access to food and water. Experiments were conducted between 9:00 AM and 5:00 PM.

Procedure. A within-subjects design was used that essentially followed the procedure of experiment 1A, except that sucrose was novel to the rats when they were first tested. Rats were implanted with oral cannulae by using the surgical procedure of Grill and Norgren (31) 1 week prior to testing. The test chamber dimensions were 25 cm in round diameter × 28 cm high. Rats received 2 days of taste reactivity habituation with water. Testing began 48 h after the last habituation and continued every other day for 3 trials that compared pimozide with vehicle. On each day, rats were injected with pimozide or vehicle in alternating and counterbalanced order. Pimozide solutions were reheated to boiling each day and then allowed to cool to room temperature to redissolve any pimozide that had crystallized (chemical analysis was performed to ensure that the chemical potency of the pimozide solution was not diminished by this procedure). For each test, a rat was allowed to habituate to the chamber for 10 min prior to the infusion. A 10-min infusion of 17% sucrose solution (1 ml/min) was delivered by oral cannula with a syringe pump, and taste reactivity was videotaped from below for later analysis.

Videoanalysis of taste reactivity data. The behavior of each rat was scored by using a slow-motion videoanalysis procedure (frame by frame to 0.10 actual speed) (29). This slow-motion procedure is more laborious than a "real-time" analysis but provides a fine-grained record of behavior with great accuracy (7). Slow-motion analysis allowed inclusion of one extra type of hedonic reaction in addition to those counted in experiment 1A: lateral tongue protrusions (nonrhythmic, single protrusions past the side of the lip followed rapidly by forward extension and retraction). Neutral reactions included rhythmic mouth movements and plus passive dripping. General activity or aversive reactions included locomotion (walking or running) and rearing. Scoring criteria were as described in (46).

Statistics. A three-way repeated measures analysis of variance (ANOVA) was used to analyze the data, in which the separate factors were drug (pimozide vs. control), trial session (1, 2, or 3), and minute within trial (1–10). The role of the factors was subsequently analyzed in two ways: by post hoc tests with a Bonferroni adjustment for multiple comparisons and by separate two-factor ANOVA. These two methods of analysis produced the same conclusions in terms of statistical significance; thus, only the two-factor ANOVA results are described.

Results

Experiment 1A. Figure 1 presents the mean number of seconds that the rats pretreated with pimozide or vehicle spent displaying tongue protrusions, paw licking and mouth movements and the mean frequency of activity bouts during each minute of trials 1–3. The pimozide-pretreated group emitted progressively fewer tongue protrusions, paw licking and bouts of activity but progressively more mouth movements than the vehicle-pretreated group.

The data for each behavior depicted in Fig. 1 were analyzed in a 3-factor ANOVA. The between-groups factor was pretreatment drug (pimozide or vehicle) and the within-groups factors were trial (1–3) and minutes within each trial (1–10). Pimozide significantly suppressed emission of tongue protrusions [$F(1, 18) = 5.6$, $p < 0.05$]. Minutes within a trial [$F(9, 162) = 13.5$, $p < 0.01$] also was a significant factor for tongue protrusions, and there was an interaction between pretreatment drug and minutes [$F(9, 162) = 2.0$, $p < 0.05$]: pooled across test trials, pimozide suppressed tongue protrusions only during minutes 2, 3 and 5 (ps < 0.05). Trial number was also a significant factor [$F(2, 36) = 9.6$, $p < 0.01$], and there was a marginal 3-way interaction between trial, pretreatment drug and minute [$F(18, 324) = 1.6$, $p = 0.06$]. To identify the effect of trial, the data for each trial were analyzed in separate 2 × 10 mixed-factor ANOVAs, which revealed that pimozide suppressed tongue protrusions on trials 2 and 3 [Fs$(1, 18) > 4.4$, ps < 0.05) but not on trial 1.

For paw licking, there was only an overall suppression by pimozide [$F(1, 18) = 4.0$, $p = 0.06$]. For general activity, pimozide suppressed locomotion and rearing [$F(1, 18) = 18.3$, $p < 0.01$]. For rhythmic mouth movements, pimozide actually enhanced the amount of time spent in this mildly ingestive or neutral reaction [$F(1, 18) = 28.3$, $p < 0.01$].

Experiment 1B. As in experiment 1A, pimozide administration (0.5 mg/kg, IP) reduced total hedonic reaction patterns (combined tongue protrusions, lateral tongue protrusions and paw licking) emitted to 17% sucrose [3-way ANOVA for drug, minute and trial; main effect of pimozide, $F(1, 7) = 64.01$, $p < 0.01$; Fig. 2A]. When divided into individual reaction components, rats emitted fewer tongue protrusions [$F(1, 7) = 22.42$, $p < 0.01$] and fewer paw licks [$F(1, 7) = 84.36$, $p < 0.01$] but more mouth movements [$F(1, 7) = 25.4$, $p < 0.01$] after pimozide. Locomotion and rearing also decreased significantly under pimozide treatment [$F(1, 7) = 20.20$, $p < 0.05$]. Pimozide did not alter the emission of lateral tongue protrusions [$F(1, 7) = 1.32$, $p = 0.4$] or of passive dripping [$F(1, 7) = 0.42$, $p = 0.62$].

Minute was a significant factor for combined hedonic reactions [$F(9, 63) = 17.59$, $p < 0.001$] in the 3-way ANOVA. When the first minute of the 3 trials was analyzed with a 2-way ANOVA, pimozide had no detectable effect on hedonic reactions during the first minute of the three trials [$F(1, 7) = 2.71$, $p = 0.14$]. However, pimozide significantly depressed hedonic reactions during the 10th minute of the three trials [$F(1, 7) = 21.01$, $p < 0.01$], which is consistent with the conclusion of Leeb et al. (37) that the suppressive effect of pimozide becomes more marked over time. There was a significant trial × minute interaction for the suppression of hedonic reactions [$F(18, 126) = 3.13$, $p < 0.001$]. When each trial was analyzed separately by 2-way ANOVA (drug × minute), tongue protrusions were significantly reduced during trials 2 and 3 but not during trial 1 [trial 2: $F(1, 9) = 7.038$, $p < 0.05$; trial 3: $F(1, 9) = 7.975$, $p < 0.05$]. Similarly, paw licks were reduced during trials 2 and 3 [$F(1, 9) = 6.15$, $p < 0.05$] but not during trial 1 (Fig. 2B).

Discussion

The results of experiment 1 replicate the findings of Leeb et al. (37) that pimozide suppresses reactions elicited by sucrose infusions (tongue protrusions, paw licks, locomotion and rearing) and that the suppressive effects become larger over repeated trials. Suppression was typically not visible in the first minute of an oral infusion, which is consistent with the report of Treit and Berridge (64) that haloperidol fails to change hedonic reactions in a 1-min trial, but became significant in later minutes. Only the suppression of general activity (locomotion and rearing) did not require time to develop. The suppression of active reactions was not specific to a single affective category. Although pimozide suppressed tongue protrusions and paw licks, which belong to the hedonic category

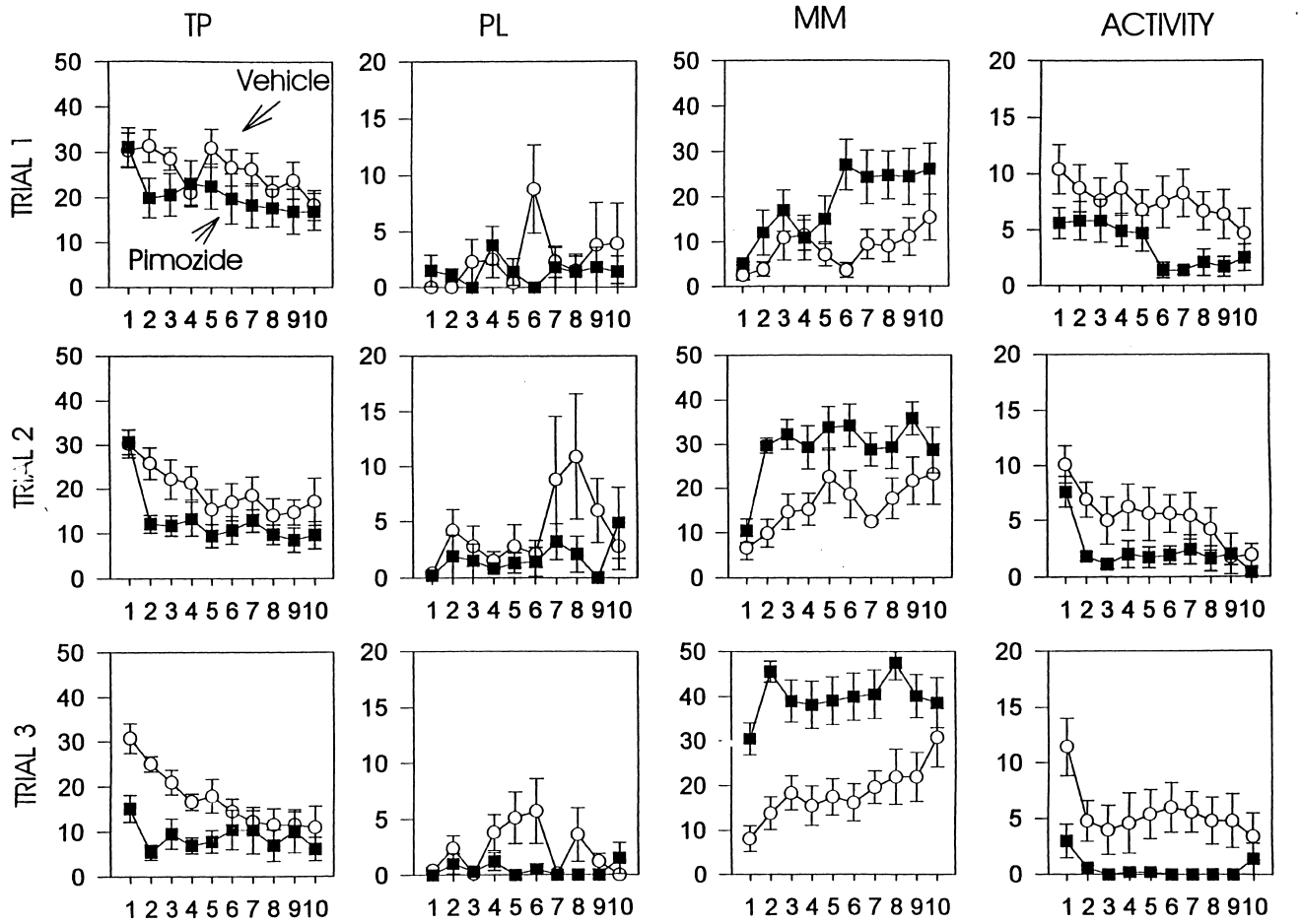

FIG. 1. Experiment 1A: Effects of pimozide (0.5 mg/kg) on hedonic taste reactivity patterns. Mean number of seconds (±SEM) per minute that rats spent displaying tongue protrusions (TP), mouth movements, paw licks (PL) and activity bouts in response to a 17% sucrose taste under pimozide or vehicle treatment on 3 consecutive trials (between-subjects design).

(i.e., they are elicited by preferred tastes), it also suppressed rearing and locomotion, which belong to the aversive or general activity categories (i.e., which are elicited by bitter quinine and which occur during exploration).

Mouth movements, which belong to a weakly hedonic or neutral category [i.e., they are correlated with taste preference but less linearly than are tongue protrusions, lateral tongue protrusions or paw licks (15,19,36,63)], were actually increased in frequency by pimozide. Passive dripping of the solution, which belongs to a weakly aversive or neutral category (i.e., they reflect the absence of any active reaction), was not changed by pimozide, indicating that actual ingestion of the sucrose was not suppressed. This result may be similar to that of Tryka and Smith (65,66) that dopamine antagonists are less effective at suppressing ingestion of intraorally delivered sucrose than at suppressing free intake of the same solution. In the present experiment, the reduction in tongue protrusions did not reduce the amount swallowed, which suggests that mouth movements merely replaced tongue protrusions as visible accompaniments to ingestion.

The reciprocal change in tongue protrusions and mouth movements could conceivably be due to sensorimotor effects of pimozide related to neuroleptic tardive dyskinesia. Although the literature on tardive dyskinesia suggests that neuroleptic-induced mouth movements are produced only after chronic treatment (17,25,26,67), Fowler et al. (21) reported that haloperidol produces a motor suppression of tongue extension even when administered acutely. In normal rats, electromyographic recordings have revealed that mouth movements are accompanied ordinarily by slight tongue protrusions that are too low in amplitude to be visible from outside (39). Suppression of the ability to protrude the tongue therefore may convert visible rhythmic tongue protrusions into mere mouth movements without visible protrusion of the tongue. Thus, the enhancement of mouth movements by pimozide may reflect an interaction with tongue control. If so, the change in mouth movements was a secondary consequence of a primary motor suppression of midline tongue protrusions through a conversion of attempted tongue protrusions into mouth movements.

Sensorimotor Suppression Alone or Anhedonia Too?

Interpretation of taste reactivity regarding palatability depends crucially on the pattern of change among reactions

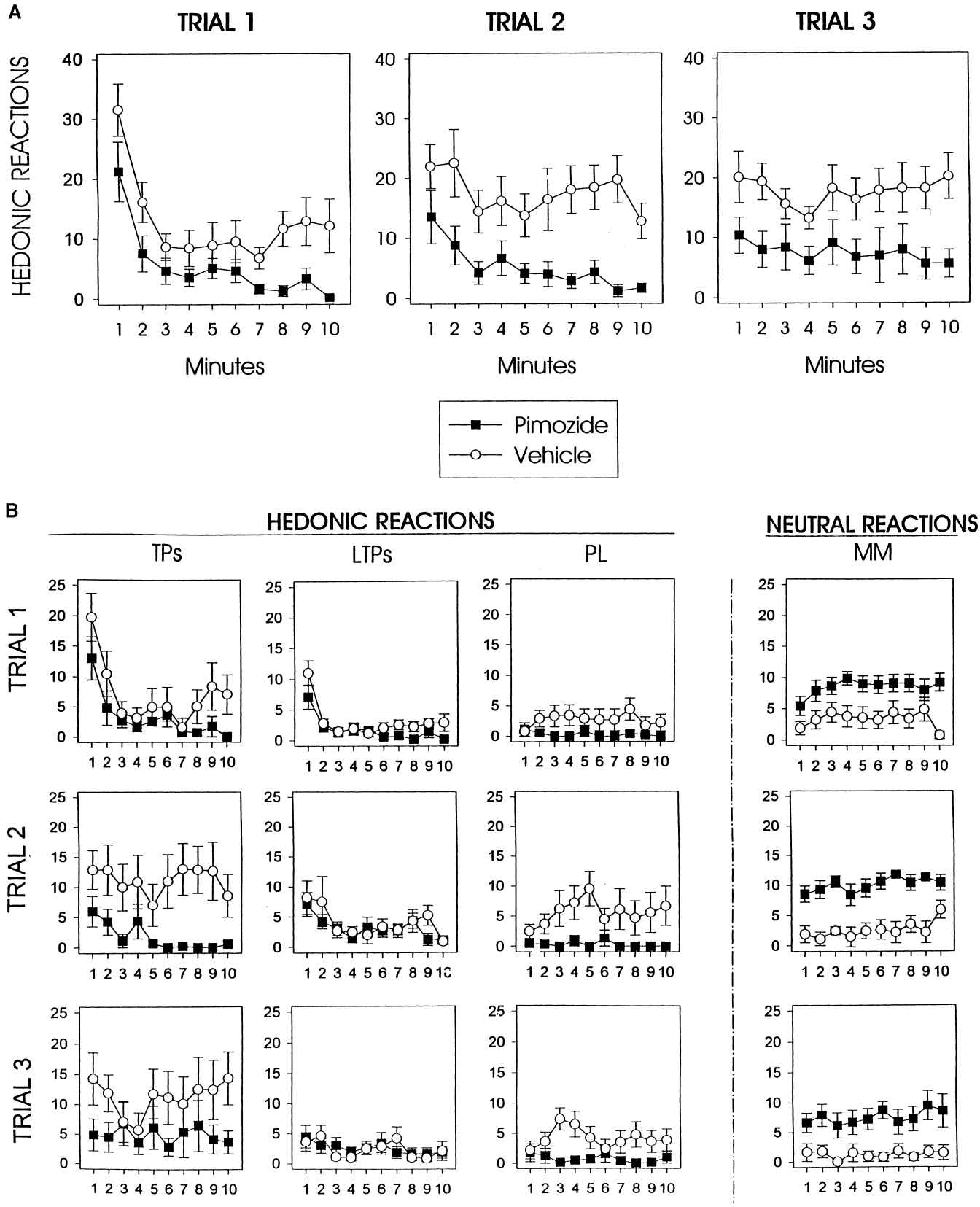

FIG. 2. Experiment 1B. A: Effects of pimozide (0.5 mg/kg) on hedonic taste reactivity patterns. Mean number of combined hedonic taste reactivity reactions per minute to a 17% sucrose solution under pimozide (0.5 mg/kg) (closed squares) or vehicle (open circles) treatment during 3 consecutive trials (within-subjects design). B: Effects of pimozide (0.5 mg/kg) on specific hedonic and neutral taste reactivity components. Mean number of hedonic (TPs, LTPs and PL) and neutral (MMs) taste reactivity reactions displayed per minute after pimozide (close squares) or vehicle (open circles) treatment in 3 consecutive trials (within-subjects design).

within and between hedonic/aversive categories. The question of whether pimozide produces anhedonia or merely a sensorimotor suppression depends on the pattern of suppression. Manipulations that change palatability typically alter all the members of a single affective category selectively (e.g., reduce all hedonic reactions without altering aversive reactions), or else they change the two categories in reciprocal directions (e.g., reducing hedonic reactions and enhancing aversive reactions). But manipulations that change different affective categories (hedonic and neutral in this case) in the same direction (suppression), as in experiment 1, imply a general sensorimotor effect rather than a specific shift in palatability [for discussion, see (7)].

In experiment 1, pimozide produced a general sensorimotor suppression of the capacity to emit most reactions to a sustained sucrose stimulus. What is not yet clear is whether it also produced a shift in palatability too. Both a "pure sensorimotor suppression" interpretation and a "sensorimotor suppression plus anhedonia" interpretation are consistent with the effects of pimozide on taste reactivity elicited by sucrose.

A choice between these alternative interpretations can come from an examination of the effect of pimozide on aversive reactions elicited by noxious tastes, such as quinine. If a primary effect of pimozide is to make tastes less palatable, then aversive reactions should be relatively immune to suppression. In fact, if it makes tastes more unpalatable, aversive reactions should be enhanced. By contrast, if pimozide simply produces a global sensorimotor suppression of the capacity to sustain high levels of motor responses in general and does not alter the balance between hedonic/aversive palatability, then aversive reactions to quinine should be suppressed by pimozide administration just as reactions to sucrose are suppressed.

EXPERIMENT 2: DOES PIMOZIDE MODIFY THE EMISSION OF AVERSIVE REACTIONS TO QUININE?

At first sight, this question would seem to have been answered by the finding of Parker and Lopez (43) that pimozide administration increases aversive gapes to oral infusions of highly concentrated quinine. However, Parker and Lopez reported the absolute number of gapes observable, which is complicated by the suppression of locomotion by pimozide demonstrated in experiment 1 (and found by Parker and Lopez). The complication is that suppression of locomotion could conceivably bias the videoanalysis of taste reactivity data by changing the proportion of a trial that a rat is "on screen" and able to be scored. Suppression of locomotion could increase time on screen, resulting in inflated reaction scores. Although sucrose elicits too little locomotion for this to distort hedonic scores, quinine normally elicits intense locomotion at the concentration used by Parker and Lopez (43). High locomotion makes it difficult during a quinine infusion for a videocamera to track the head and face of the moving rat. If locomotion is high enough, there may be substantial portions of the infusion trial when the rat is not "on screen." Because the absolute number of aversive gapes counted during a 2-min test, regardless of time on screen, were counted by Parker and Lopez (43), pimozide simply may have reduced locomotion and caused rats to spend more time in view of the camera compared with control rats, artificially inflating aversive reactivity scores. If so, the "higher" aversive score may simply have been an artifact due to greater visibility and not due to a real increase in the incidence of aversive reactions.

To resolve this issue, we took two steps. First, the original videotapes from the third experiment of Parker and Lopez (43) were rescored by both laboratories, and the calculation of gapes per minute was corrected for time the mouth was in view. Because the results of this rescoring showed that the original apparent enhancement of gapes was indeed illusory due to the scoring artifact described above, a second experiment was conducted at the University of Michigan to replicate the new conclusion. This experiment also extended the quinine stimulus duration to make it comparable to experiment 1 for the purpose of assessing sensorimotor suppression.

Method

Experiment 2A: Corrected effect of pimozide on gapes [reanalysis of the results by Parker and Lopez (43); Wilfrid Laurier University and University of Michigan] In Parker and Lopez (43), 19 rats had been injected with either 0.5 mg/kg pimozide or vehicle by using a between-subjects design. Four hours later, rats received 2 ml of 0.1% quinine solution at the rate of 1 ml/min during a 2-min trial. Both laboratories rescored the videotaped data for frequency of aversive reactions and for total amount of time on camera. To correct for time off screen in this reanalysis, the total score for each aversive reaction counted for each trial was divided by the total period that the face of the rat was in actual view, resulting in a final score of reactions per minute in view. Because both laboratories concurred in the results of the reanalysis of the videotapes, statistics from only one laboratory (Wilfrid-Laurier) are presented.

Experiment 2B: Corrected effect of pimozide on quinine aversion (University of Michigan). This experiment replicated the procedures of Parker and Lopez (43), except that it (a) increased the infusion duration to 10 min to make the trial duration comparable to experiment 1 so that the time course of pimozide effects could be compared, (b) incorporated the time-in-view calculation used in experiment 2A, (c) used a within-subject design so that each rat could serve as its own control (in counterbalanced order, 48 h apart) and (d) used a fine-grained slow-motion videoanalysis to assess the effects of pimozide on aversive reaction patterns as accurately as possible. Twenty-one male Sprague–Dawley rats served as the subjects. The rats were run in two different groups. Eight rats had previously participated in experiment 1B. The other 12 rats were naive to drug treatment. The taste stimulus used for infusion was 0.1% (2.6×10^{-3} M) quinine sulfate. Videoanalyses were conducted in slow motion as in experiment 1B.

Results

Experiment 2A. When time in view was controlled, the mean number of gapes, chin rubs, paw treads, head shakes or forelimb flails emitted per minute displayed by the pimozide-pretreated group did not significantly differ from that of the vehicle-pretreated group (Fig. 3). The apparent enhancement of gapes found by Parker and Lopez (43), in other words, appeared with reanalysis to be an artifact of the tendency of pimozide-treated animals to remain less active and thus in clear view of the camera when they received concentrated quinine rather than to an actual increase in the rate of gape emission.

Experiment 2B. A preliminary analysis showed that the source groups of rats did not differ from each other in taste reactivity, so the two groups were combined to form a single group for all subsequent within-subject analyses. As in experiment 2A, pimozide significantly reduced locomotion [$F(1, 19) = 10.12$, $p < 0.05$] and thus increased the proportion of time that the rats face presented a clear image on screen. When controlled for in terms of time on screen, pimozide administration (0.5 mg/kg, IP)

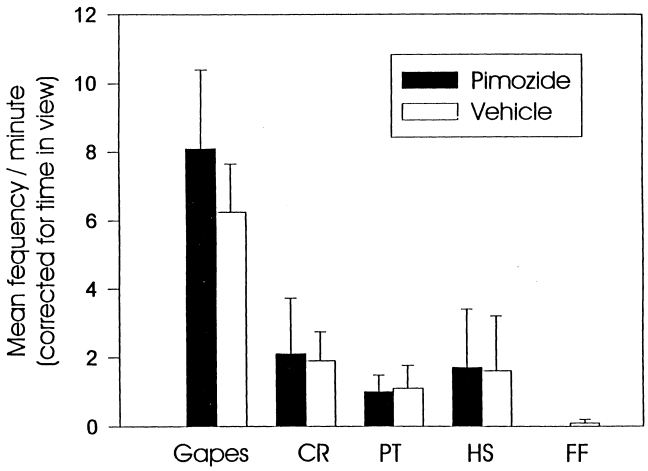

FIG. 3. Experiment 2A: Effects of pimozide (0.5 mg/kg) on aversive reactions corrected for time in view of camera [reanalysis of the results by Parker and Lopez (43)]. The mean number of gapes, chin rubs (CR), paw treads (PT), head shakes (HS) and forelimb flails (FF) per minute, corrected for time off screen, displayed in response to a 0.1% quinine taste after pimozide or vehicle treatment (between-subjects design).

again failed to enhance any aversive reaction. On the contrary, pimozide significantly reduced total aversive reactions (gapes, forelimb flails, head shakes, face washing, chin rubbing and paw treading combined) elicited by quinine per minute in view [$F(1, 19) = 14.31$, $p < 0.01$]. As was seen in experiment 1, the suppressive effect of pimozide was evident primarily in the later minutes of the 10-min oral infusion (Fig. 4). Aversive taste reactivity patterns remained unchanged after pimozide treatment during the first 2 min (which is consistent with the time course of suppression seen in experiment 2A). However, aversive reactions were reduced under pimozide treatment relative to controls after the 3rd minute ($p < 0.05$; Fig. 4).

When gapes and other reactivity components were analyzed separately, pimozide did not modify gapes during the first 2 min of the trial, again consistent with experiment 2A. However, pimozide administration reduced gapes emitted during minutes 3–10 [$F(1, 6) = 3.92$, $p < 0.05$]. Pimozide also reduced the emission of forelimb flails [$F(1, 6) = 18.60$, $p < 0.01$] and chin rubs [$F(1, 6) = 5.21$, $p < 0.05$] during these later minutes.

Discussion

Pimozide failed to enhance gapes or any other aversive reaction in either experiment once the suppression of locomotion (and increase of time on screen) was taken into account. On the contrary, pimozide suppressed the corrected rate of emission of most aversive reactions, including gapes, just as it suppressed hedonic reactions and activity in experiment 1. The suppression was not apparent in the first 2 min of the test but emerged after a delay as the oral infusion went on.

GENERAL DISCUSSION

These results directly contradict the hypothesis that dopamine blockade makes tastes seem more unpalatable. Rather, reactions from all categories (aversive, hedonic, and general activity) appear to be reduced similarly by pimozide administration. The most parsimonious interpretation of these results (and those of previous taste reactivity studies) is that pimozide produces a general sensorimotor impairment of the ability to sustain high rates of effortful taste reactivity components (active gapes, rhythmic tongue protrusions, etc.) in response to a protracted stimulus that lasts more than a few minutes. Some types of taste reactivity components, such as those which involve forward locomotion and limb use, may be more susceptible to this suppression than others (being suppressed even in the first minutes of a first trial). Reactions to short-term infusions of 1 min or less may not be suppressed at all because the suppression grows when the behavior has to be sustained (i.e., when the stimulus continues) or when trials are repeated. But virtually all taste reactivity responses succumbed eventually under pimozide when examined closely enough and long enough, which is the hallmark of a general sensorimotor suppression. Even the sole exception to general suppression, rhythmic mouth movements (without visible tongue protrusion), which were enhanced, may be interpreted as a secondary consequence of a sensorimotor suppression of midline tongue protrusions.

The reason overall suppression of lick emission by dopamine antagonists often has not been reported in free-intake tests (56,74,75) may be that free intake entails less strenuous response demands than the prolonged oral infusion used in our experiments. In a free-intake test, it is easier for a rat to pause between lick bouts because it controls the stimulus, but a sustained oral infusion may prompt the rat to respond actively to the taste for a longer period than it would otherwise do, thus exposing the pimozide-induced suppression more clearly as the infusion continues.

Separating Sensorimotor Suppression from Palatability Shifts

There are two features of our data that suggest pimozide-induced changes in taste reactivity are due solely to impairment of sensorimotor function rather than to shifts in palatability. The first feature is the timing of the drug-induced effect, and the second feature is the lack of selectivity of the effect.

Timing. Manipulations that alter hedonic or aversive taste palatability (such as hunger/satiety, aversion conditioning, brain lesions, opioid or benzodiazepine agents, etc.) typically produce taste reactivity changes that can be detected in the first seconds or minute of a taste infusion [e.g., (4,5,7,14,16,28, 30–32,44,59,62)]. Pimozide, by contrast, produced an effect in experiments 1 and 2 that emerged gradually over successive minutes as the oral infusion was continued and that sometimes grew in strength as trials were repeated (1), which is consistent with the report by Leeb et al. (37). The delayed effect argues against an immediate and direct change in taste palatability after pimozide administration but is more compatible with the interpretation that the rats cannot maintain high response rates after an initial burst of taste reactivity components. However, the effect of pimozide on general activity (locomotion and rearing) did not change across minutes or trials. Such general motor responses may be more susceptible to the sensorimotor suppressant effects of pimozide than are hedonic or aversive facial taste reactivity components.

Category specificity. Previous taste reactivity studies that reported pharmacological modulation of palatability (e.g., hedonic modulation by opioid or benzodiazepine agonists) have based their conclusions on the selectivity of drug-induced change across affective categories (hedonic vs. aversive) of reaction patterns. For example, drugs such as chlordiazepoxide, diazepam and similar benzodiazepine agonists, which appear to enhance palatability, selectively increase hedonic reaction

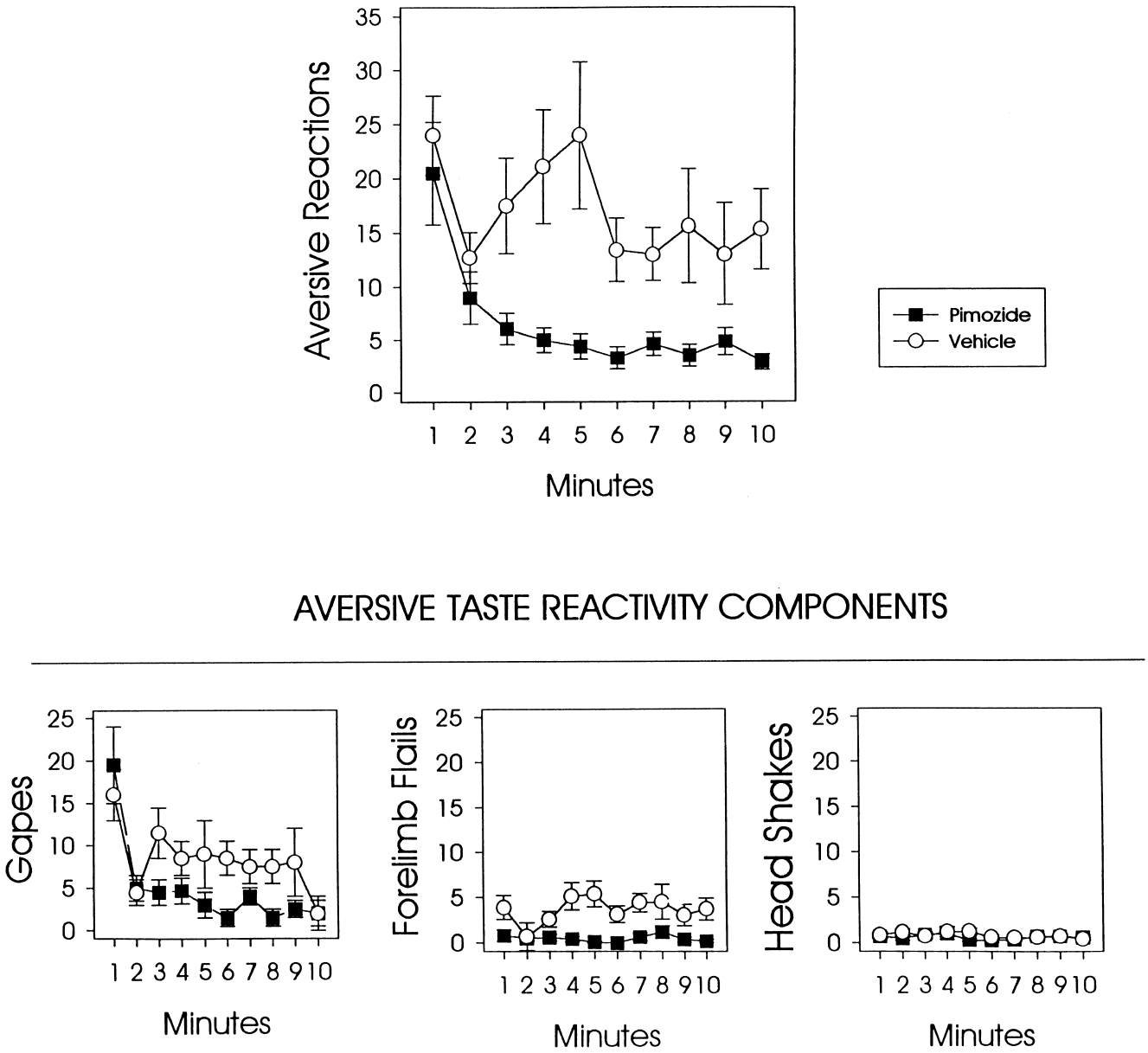

FIG. 4. Experiment 2B: Effects of pimozide (0.5 mg/kg) on aversive taste reactivity reactions. Mean number of combined aversive reactions and of separate aversive components, corrected for time off screen, displayed per minute in response to a 0.1% quinine sulfate taste after pimozide (closed squares) or vehicle (open circles) treatment (within-subjects design).

patterns in taste reactivity tests (7,10,27,40,41). Aversive reactions either are not altered or are suppressed by benzodiazepines (10,41,64), and locomotion is reliably suppressed (41). Similarly, opioid agonists such as morphine increase hedonic reactions but suppress aversive reactions, which is consistent with a positive shift in palatability (16,44,45,49). In all these cases, a palatability shift interpretation was made plausible by the directional selectivity of the effect on affective categories of taste reactivity.

The general pattern of overall response suppression produced by pimozide in the present experiments, however, was very different and is not conducive to a palatability shift interpretation. The pimozide suppression applied to hedonic, aversive and neutral categories of taste reactivity and to general activity. This general suppression is most parsimoniously interpreted as general impairment of the capacity to sustain high rates of motor reactions in response to a sustained eliciting stimulus. This sensorimotor interpretation is similar to the "anergia" hypothesis of dopamine function advanced by Salamone and his colleagues (38,51–54). They suggested, based on studies of instrumental behavior, that dopamine antagonists impair the sensorimotor capacity to sustain effort, especially in situations that have continuing high response demands. Our results suggest that this impairment also can apply to stimulus-elicited species-specific reactions, such as taste reactivity components.

Alternative Motivational Role of Dopamine Systems

Although our results indicate that pimozide fails to shift taste palatability, a motivational role for mesotelencephalic dopamine systems cannot be ruled out. There is considerable evidence that dopamine agents alter reward properties of food and other incentives, as described in the introduction, in addition to their sensorimotor effects [e.g., (58) for review]. How can the many demonstrations of reduced reward reported in the literature be reconciled with our conclusion that pimozide fails to shift hedonic/aversive palatability?

Reward Wanting vs. Liking: Incentive Salience Hypothesis

In an "incentive salience" hypothesis for the role of dopamine systems in reward, Berridge and others have suggested that food reward can be dissociated into two component processes, corresponding to liking and wanting (6,8,11,12,50). *Liking* is the colloquial word that best captures palatability: the actual hedonic impact of a reward, which is reflected by hedonic/aversive patterns of taste reactivity. Neuropharmacological agents that act on opioid or benzodiazepine/gamma-aminobutyric acid systems alter the liking component of food reward, as do many neural and psychological manipulations (6).

Our present results indicate that dopamine does not mediate taste liking, but hedonic liking is not the only component of food reward according to the incentive salience hypothesis. *Wanting* is a separate process needed to translate liking for a food incentive into free-intake or goal-oriented instrumental behavior. The hypothesis posits that motivation and reward require the attribution of incentive salience to the neural representation of the liked food reward, which makes the incentive event attractive and wanted. Incentive salience attribution is posited to be mediated in part by dopaminergic nigrostriatal and mesoaccumbens systems (6,8,11,12,50).

Ordinarily, liking and wanting change together when a manipulation alters reward value, but the incentive salience hypothesis suggests that pharmacological and neural manipulations which act primarily on mesotelencephalic dopamine systems can alter incentive salience or wanting specifically (6,50). For example, these manipulations include 6-OHDA lesions, which induce aphagia, or electrical simulation of the lateral hypothalamus, which elicits feeding, and the administration of dopamine antagonists. Although these manipulations produce dramatic changes in free intake, they fail to produce a shift in hedonic/aversive palatability as assessed by taste reactivity patterns (11,12,64). Our conclusion that the reward effects of neuroleptic drugs and other dopamine manipulations are not due to anhedonia seems consistent with a recent report that pimozide administration to humans failed to suppress the subjective ratings of "drug liking" given by subjects to amphetamine administration (13).

When these results are considered together, the previous reports of palatability shifts after pimozide administration may have been misled by the sensorimotor suppression effects of the drug (on overall taste reactivity patterns and on locomotion) and may not have been based on a true shift in hedonic/aversive palatability. An effect of dopamine antagonists specifically on food or drug reward is more likely to be due to a change in incentive salience (wanting) rather than to a shift in affect (liking). Interestingly, a recent study of human drug addicts has reported that the most powerful subjective effect of haloperidol administration is to suppress the conditioned craving for cocaine evoked by watching cocaine-related films (3). That report seems consistent with both the basic hypothesis that dopamine neural function is important to incentive salience attribution and to the related hypothesis that addiction is mediated in part by an amplification of the wanting component of reward, which is caused by neural sensitization of dopamine-related systems (8,50).

Conclusion

Pimozide does not shift the palatability of a sweet or bitter taste, although it does suppress taste reactivity components in a gradual sensorimotor fashion. Previous conclusions that pimozide shifted hedonic/aversive taste reactivity patterns appear to have been based on two sensorimotor consequences of the drug. The first effect was a general sensorimotor suppression of all taste reactivity components, regardless of hedonic/aversive/neutral category, which can produce an illusion of anhedonia. The second pimozide effect was a pronounced suppression of locomotion, which can artificially inflate reactivity scores, especially for quinine solutions that ordinarily elicit high locomotion. When these effects were identified and controlled for in the present study, no evidence remained for an anhedonic shift in palatability. Our conclusion that dopamine receptor blockade does not shift taste liking is not meant to rule out a role for brain dopamine systems in food reward. It simply indicates that neuroleptic reward effects must instead be mediated by suppression of some other psychological component of reward, such as incentive salience or wanting, which is separate from hedonics or liking.

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REFERENCES

1. Antelman, S. M.; Kocan, D.; Edwards, D. J.; Knopf, S.; Perel, J. M.; Stiller, R.: Behavioral effects of a single neuroleptic treatment grow with the passage of time. Brain Res. 385:58–67; 1986.
2. Bailey, C. S.; Hsiao, S.; King, J. E.: Hedonic reactivity to sucrose in rats: Modification by pimozide. Physiol. Behav. 38:447–452; 1986.
3. Berger, S. P.; Hall, S.; Mickalian, J. D.; Reid, M. S.; Crawford, C. A.; Delucchi, K.; Carr, K.; Hall, S.: Haloperidol antagonism of cue-elicited cocaine craving. Lancet 347:504–508; 1996.
4. Berridge, K.; Grill, H. J.; Norgren, R.: Relation of consummatory responses and preabsorptive insulin release to palatability and learned taste aversions. J. Comp. Physiol. Psychol. 95:363–382; 1981.
5. Berridge, K. C.: Brainstem systems mediate the enhancement of palatability by chlordiazepoxide. Brain Res. 447:262–268; 1988.
6. Berridge, K. C.: Food reward: Brain substrates of wanting and liking. Neurosci. Biobehav. Rev. 20:1–25; 1996.
7. Berridge, K. C.; Peciña, S.: Benzodiazepines, appetite, and taste palatability. Neurosci. Biobehav. Rev. 19:121–131; 1995.
8. Berridge, K. C.; Robinson, T. E.: The mind of an addicted brain: Neural sensitization of wanting versus liking. Curr. Direct. Psychol. Sci. 4:71–76; 1995.

9. Berridge, K. C.; Robinson, T. E.: The role of dopamine in reward: Hedonics, learning, and incentive salience after 6-hydroxydopamine lesions. Brain Research Rev. (in press).
10. Berridge, K. C.; Treit, D.: Chlordiazepoxide directly enhances positive ingestive reactions in rats. Pharmacol. Biochem. Behav. 24:217–221; 1986.
11. Berridge, K. C.; Valenstein, E. S.: What psychological process mediates feeding evoked by electrical stimulation of the lateral hypothalamus? Behav. Neurosci. 105:3–14; 1991.
12. Berridge, K. C.; Venier, I. L.; Robinson, T. E.: Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: Implications for arousal and anhedonia hypotheses of dopamine function. Behav. Neurosci. 103:36–45; 1989.
13. Brauer, L. H.; de Wit, H.: Subjective responses to d-amphetamine alone and after pimozide pretreatment in normal, healthy volunteers. Biol. Psychiatr. 39:26–32; 1996.
14. Breslin, P. A.; Davidson, T. L.; Grill, H. J.: Conditioned reversal of reactions to normally avoided tastes. Physiol. Behav. 47:535–538; 1990.
15. Breslin, P. A.; Spector, A. C.; Grill, H. J.: A quantitative comparison of taste reactivity behaviors to sucrose before and after lithium chloride pairings: A unidimensional account of palatability. Behav. Neurosci. 106:820–836; 1992.
16. Doyle, T. G.; Berridge, K. C.; Gosnell, B. A.: Morphine enhances hedonic taste palatability in rats. Pharmacol. Biochem. Behav. 46:745–749; 1993.
17. Egan, M. F.; Hyde, T. M.; Kleinman, J. E.; Wyatt, R. J.: Neuroleptic-induced vacuous chewing movements in rodents: Incidence and effects of long-term increases in haloperidol dose. Psychopharmacology 117:74–81; 1995.
18. Ettenberg, A.; Camp, C. H.: Haloperidol induces a partial reinforcement extinction effect in rats: Implications for a dopamine involvement in food reward. Pharmacol. Biochem. Behav. 15:813–821; 1986.
19. Flynn, F. W.; Grill, H. J.: Intraoral intake and taste reactivity responses elicited by sucrose and sodium chloride in chronic decerebrate rats. Behav. Neurosci. 102:934–941; 1988.
20. Fouriezos, G.; Wise, R. A.: Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. Brain Res. 103:377–380; 1976.
21. Fowler, S. C.; Ford, K. E.; Gramling, S. E.; Nail, G. L.: Acute and subchronic effects of neuroleptics on quantitative measures of discriminative motor control in rats. Psychopharmacology 84:368–373; 1984.
22. Franklin, K. B. J.; McCoy, S. N.: Pimozide-induced extinction in rats: Stimulus control of responding rules out motor deficits. Pharmacol. Biochem. Behav. 11:71–75; 1979.
23. Gallistel, C. R.; Boytim, M.; Gomita, Y.; Klebanoff, L.: Does pimozide block the reinforcing effect of brain stimulation? Pharmacol. Biochem. Behav. 17:769–781; 1982.
24. Geary, N.; Smith, G. P.: Pimozide decreases the positive reinforcing effect of sham fed sucrose in the rat. Pharmacol. Biochem. Behav. 22:787–790; 1985.
25. Glenthoj, B.: Persistent vacuous chewing in rats following neuroleptic treatment: Relationship to dopaminergic and cholinergic function. Psychopharmacology 1993:157–166; 1993.
26. Glenthoj, B.; Hemmingsen, R.; Allerup, P.; Bolwig, T. G.: Intermittent versus continuous neuroleptic treatment in a rat model. Eur. J. Pharmacol. 190:275–281; 1990.
27. Gray, R. W.; Cooper, S. J.: Benzodiazepines and palatability: Taste reactivity in normal ingestion. Physiol. Behav. 58:853–859; 1995.
28. Grill, H. J.: Production and regulation of ingestive consummatory behavior in the chronic decerebrate rat. Brain Res. Bull. 5:79–87; 1980.
29. Grill, H. J.; Berridge, K. C.: Taste reactivity as a measure of the neural control of palatability. In: Sprague, J. M.; Epstein, A. N., eds. Progress in psychobiology and physiological psychology. Orlando: Academic Press; 1985:1–61.
30. Grill, H. J.; Norgren, R.: Neurological tests and behavioral deficits in chronic thalamic and chronic decerebrate rats. Brain Res. 143:299–312; 1978.
31. Grill, H. J.; Norgren, R.: The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 143:263–279; 1978.
32. Grill, H. J.; Norgren, R.: The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. Brain Res. 143:281–297; 1978.
33. Hernandez, L.; Hoebel, B. G.: Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42:1705–1712; 1988.
34. Horvitz, J. C.; Ettenberg, A.: Haloperidol blocks the response-reinstating effects of food reward: A methodology for separating neuroleptic effects on reinforcement and motor processes. Pharmacol. Biochem. Behav. 31:861–865; 1988.
35. Hsiao, S. Smith, G. P.: Raclopride reduces sucrose preference in rats. Pharmacol. Biochem. Behav. 50:121–125; 1995.
36. Kiefer, S. W.; Dopp, J. M.: Taste reactivity to alcohol in rats. Behav. Neurosci. 103:1318–1326; 1989.
37. Leeb, K.; Parker, L.; Eikelboom, R.: Effects of pimozide on the hedonic properties of sucrose: Analysis by the taste reactivity test. Pharmacol. Biochem. Behav. 39:895–901; 1991.
38. McCullough, L. D.; Salamone, J. D.: Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: A microdialysis and behavioral study. Brain Res. 592:29–36; 1992.
39. Norgren, R.; Nishijo, H.; Travers, S. P.: Taste responses from the entire gustatory apparatus. Ann. N.Y. Acad. Sci. 575:246–263; 1989.
40. Parker, L. A.: Chlordiazepoxide nonspecifically enhances consumption of saccharin solution. Pharmacol. Biochem. Behav. 38: 375–377; 1991.
41. Parker, L. A.: Chlordiazepoxide enhances the palatability of lithium-, amphetamine-, and saline-paired saccharin solution. Pharmacol. Biochem. Behav. 50:345–349; 1995.
42. Parker, L. A.: Rewarding drugs produce taste avoidance, but not taste aversion. Neurosci. Biobehav. Rev. 19:143–151; 1995.
43. Parker, L. A.; Lopez, N., Jr.: Pimozide enhances the aversiveness of quinine solution. Pharmacol. Biochem. Behav. 36:653–659; 1990.
44. Parker, L. A.; Maier, S.; Rennie, M.; Crebolder, J.: Morphine- and naltrexone-induced modification of palatability: Analysis by the taste reactivity test. Behav. Neurosci. 106:999–1010; 1992.
45. Peciña, S.; Berridge, K. C.: Central enhancement of taste pleasure by intraventricular morphine. Neurobiology 3:269–280; 1995.
46. Peciña, S.; Berridge, K. C.: Brainstem mediates benzodiazepine enhancement of taste palatability: Comparison of diazepam microinjections into fourth versus lateral ventricles. Brain Res. 727:22–30; 1996.
47. Phillips, A. G.; Pfaus, J. G.; Blaha, C. D.: Dopamine and motivated behavior: Insights provided by in vivo analyses. In: Willner, P.; Scheel-Kruger, J. eds. The mesolimbic dopamine system: From motivation to action. Chichester: John Wiley & Sons; 1991: 199–224.
48. Phillips, A. G.; Blaha, C. D.; Pfaus, J. G.; Blackburn, J. R.: Neurobiologicaal correlates of postive emotional states: Dopamine, anticipation, and reward. In: Strongman, K. T., ed. International review of studies on emotion. New York: John Wiley & Sons; 1992:31–50.
49. Rideout, H. J.; Parker, L. A.: Morphine enhancement of sucrose palatability: Analysis by the taste reactivity test. Pharmacol. Biochem. Behav. 53:731–734; 1996.
50. Robinson, T. E.; Berridge, K. C.: The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Res. Rev. 18:247–291; 1993.
51. Salamone, J. D.: Complex motor and sensorimotor functions of striatal and accumbens dopamine: Involvement in instrumental behavior processes. Psychopharmacology 107:160–174; 1992.
52. Salamone, J. D.: The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav. Brain Res. 61: 117–133; 1994.
53. Salamone, J. D.; Cousins, M. S.; Bucher, S.: Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. Behav. Brain Res. 65:221–229; 1994.
54. Salamone, J. D.; Zigmond, M. J.; Stricker, E. M.: Characterization of the impaired feeding behavior in rats given haloperidol or dopamine-depleting brain lesions. Neuroscience 39:17–24; 1990.

55. Schneider, L. H.: Orosensory self-stimulation by sucrose involves brain dopaminergic mechanisms. Ann. N.Y. Acad. Sci. 575:307–319; 1989.
56. Schneider, L. H.; Davis, J. D.; Watson, C. A.; Smith, G. P.: Similar effect of raclopride and reduced sucrose concentration on the microstructure of sucrose sham feeding. Eur. J. Pharmacol. 186: 61–70; 1990.
57. Schneider, L. H.; Gibbs, J.; Smith, G. P.: D-2 selective receptor antagonists suppress sucrose sham feeding in the rat. Brain Res. Bull. 17:605–611; 1986.
58. Smith, G. P.: Dopamine and food reward. In: Morrison, A. M.; Fluharty, S. J., eds. Progress in psychobiology and physiological psychology. New York: Academic Press; 1995:83–144.
59. Spector, A. C.; Breslin, P.; Grill, H. J.: Taste reactivity as a dependent measure of the rapid formation of conditioned taste aversion: A tool for the neural analysis of taste-visceral associations. Behav. Neurosci. 102:942–952; 1988.
60. Steiner, J. E.: The gustofacial response: observation on normal and anencephalic newborn infants. Symp. Oral Sens. Percept. 4:254–278; 1973.
61. Stellar, J. R.; Stellar, E.: The neurobiology of motivation and reward. New York: Springer-Verlag; 1985.
62. Travers, J. B.; Grill, H. J.; Norgren, R.: The effects of glossopharyngeal and chorda tympani nerve cuts on the ingestion and rejection of sapid stimuli: An electromyographic analysis in the rat. Behav. Brain Res. 25:233–246; 1987.
63. Travers, J. B.; Norgren, R.: Electromyographic analysis of the ingestion and rejection of sapid stimuli in the rat. Behav. Neurosci. 100:544–555; 1986.
64. Treit, D.; Berridge, K. C.: A comparison of benzodiazepine, serotonin, and dopamine agents in the taste-reactivity paradigm. Pharmacol. Biochem. Behav. 37:451–456; 1990.
65. Tyrka, A.; Smith, G. P.: Potency of SCH 23390 for decreasing sucrose intake in rat pups depends on mode of ingestion. Pharmacol. Biochem. Behav. 39:955–961; 1991.
66. Tyrka, A.; Smith, G. P.: SCH23390, but not raclopride, decreases intake of intraorally infused 10% sucrose in adult rats. Pharmacol. Biochem. Behav. 45:243–246; 1993.
67. Waddington, J. L.; Cross, A. J.; Gamble, S. J.; Bourne, R. C.: Spontaneous orofacial dyskinesia and dopaminergic function in rats. Science 198–203:530–532; 1983.
68. Wise, R. A.: Common neural basis for brain stimulation reward, drug reward, and food reward. In: Hoebel, B. G.; Novin, D., eds. The neural basis of feeding and reward. Brunswick, Maine: Haer Institute for Electrophysiological Research; 1982:445–454.
69. Wise, R. A.: Neuroleptics and operant behavior: The anhedonia hypothesis. Behav. Brain Sci. 5:39–87; 1982.
70. Wise, R. A.: The anhedonia hypothesis: Mark III. Behav. Brain Sci. 8:178–186; 1985.
71. Wise, R. A.; Colle, L. M.: Pimozide attenuates free feeding: Best scores analysis reveals a motivational deficit. Psychopharmacology 84:446–451; 1984.
72. Wise, R. A.; Raptis, L.: Effects of naloxone and pimozide on initiation and maintenance measures of free feeding. Brain Res. 368: 62–68; 1986.
73. Wise, R. A.; Spindler, J.; deWit, H.; Gerberg, G. J.: Neuroleptic-induced “anhedonia” in rats: Pimozide blocks reward quality of food. Science 201:262–264; 1978.
74. Xenakis, S.; Sclafani, A.: The effects of pimozide on the consumption of a palatable saccharin-glucose solution in the rat. Pharmacol. Biochem. Behav. 15:435–442; 1981.
75. Xenakis, S.; Sclafani, A.: The dopaminergic mediation of a sweet reward in normal and VMH hyperphagic rats. Pharmacol. Biochem. Behav. 16:293–302; 1982.