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The Effects of Pimozide on the Consumption of a Palatable Saccharin-Glucose Solution in the Rat[1]

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XENAKIS, S. AND A. SCLAFANI. *The effects of pimozide on the consumption of a palatable saccharin-glucose solution in the rat.* PHARMAC. BIOCHEM. BEHAV. 15(3) 435–442, 1981.—Two experiments investigated the role of dopamine in reward mechanisms by examining the effects of the specific dopamine receptor blocker pimozide on drinking behavior in the rat. In Experiment 1, the effects of pimozide on the consumption of a palatable saccharin-glucose solution were compared to the effects of quinine adulteration of the same solution. Pimozide and quinine both reduced 30 min/day consumption, decreased lick rate early in the drinking session and reduced lick efficiency in a dose related manner. In Experiment 2, the effects of pimozide on the consumption of a saccharin-glucose solution and water were compared in thirsty and nonthirsty rats. Pimozide suppressed the consumption of both water and the saccharin-glucose solution in a dose related manner. However, saccharin-glucose solution intake was suppressed more than water intake, and this effect was independent of thirst drive. The drug also decreased lick rate early in the drinking session and lick efficiency. The results are discussed in terms of the reward and sensory-motor deficits produced by dopamine receptor blocking agents.

Dopamine theory of reward Pimozide Quinine Saccharin-glucose consumption Licking behavior Dopamine receptor blocking agents

THERE is extensive evidence implicating the catecholamines in a central reward system ([6,16], for reviews see [13,38]). In the earlier studies, norepinephrine was implicated as the neurochemical substrate for reward [26,33]. More recent work, however, has placed considerable emphasis on the dopaminergic involvement in reward mechanisms [37]. The major pharmacological evidence for a specific role for dopamine in reward mechanisms includes the findings that dopamine receptor blockers attenuate operant responding for rewarding electrical brain stimulation [14, 15, 43], and that dopaminergic agonist drugs are readily self-administered by animals, including humans [1, 9, 27, 41, 42].

Recently, Wise *et al.* [39,40] have examined the effects of the dopamine receptor blocker pimozide on lever pressing and running for food rewards in rats. They reported that pimozide attenuated food rewarded responding without producing performance deficits. Moreover, pimozide treatment was found to mimic the effects produced by withholding the food reward (i.e., extinction) which is consistent with earlier results obtained with rewarding brain stimulation and intravenous amphetamine and cocaine injections [9, 14, 41]. Wise *et al.* [39,40] have interpreted the "extinction effect" of pimozide as evidence that dopamine receptor blockade reduces the rewarding impact of hedonic stimuli, including food. Other reports, however, question the similarity between the behavioral effects of dopamine receptor blocking drugs (i.e., neuroleptics) and extinction [25,34].

The present study further investigated the role of dopamine in mediating food reinforced behavior. In this case, the effects of dopamine receptor blockade with pimozide on consummatory, rather than operant behavior, was investigated. Experiment 1 compared the effects of pimozide treatment on the consumption of a saccharin-glucose (SG) solution to the effects of quinine adulteration of the solution. The SG solution is highly palatable to rats as evidenced by the large amounts of this sweet, low caloric solution consumed by nondeprived rats [31, 32, 35]. Adulteration with the bitter substance quinine, on the other hand, reduces the palatability of the SG solution in a concentration dependent fashion [7,8]. If pimozide treatment reduces the hedonic quality of food by interfering with a brain reward system then its effects on the intake of a SG solution should be similar to those produced by quinine adulteration of the solution. This prediction was tested in the first experiment.

In addition to measuring solution intake, Experiment 1 also analyzed the effects of pimozide treatment and quinine adulteration on licking behavior. Davis *et al.* [7,8] have demonstrated that the integrated licking rate (lick/min) of

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rats is influenced by the gustatory qualities of the solution. That is, increasing the sweetness of a solution results in an increase in lick rate whereas increasing the bitter taste of a solution results in a decrease in lick rate [7,8]. These changes in licking behavior are evident during the first minutes of ingestion and Davis has argued that they reflect alterations in the hedonic quality of the solution. In contrast, adulteration of the SG solution with compounds which alter the postingestive disposition of the solution, but not its taste, does not alter the initial lick rate [7,8]. Licking behavior, therefore, provides a sensitive measure to compare the effects of pimozide and quinine. Lick efficiency, as measured by fluid intake per lick was also analyzed in this experiment since previous reports indicate that treatment with dopamine receptor blocking agents produce deficits in oral-motor performance [18].

EXPERIMENT 1

METHOD

Animals

Eight naive female rats of the Sprague Dawley strain (Charles River Labs, Wilmington, MA) were used. All animals were housed singly in wire mesh cages in an air conditioned colony under a 12:12 light-dark cycle.

Apparatus

All testing was conducted in a separate room adjacent to the colony area. The rats were tested in eight wire mesh cages similar to those in which they were housed. Solutions were offered in graduated cylinders through a stainless steel drinking tube. The graduated cylinders were mounted on a retractable bottle holder which prior to testing kept the drinking tube out of reach of the rat. A spillage cup was placed below the drinking tube. At the start of the test session, the drinking tube was manually positioned 3 mm in front of the cage in reach of the animal. Access to the drinking tube was through a circular aperature (1.9 cm in diameter) located 3.2 cm above the cage floor. The drinking tubes were positioned such that licking behavior could be accurately monitored by a contact sensitive electronic drinkometer circuit. Licks were recorded on printout counters which printed cumulative licks every minute. At the end of the thirty minute session the drinking tubes wers retracted manually from the cages.

Drugs

Pimozide (0.5, 1.0, 2.0 mg/kg, McNeil Laboratories, Fort Washington, PA) was dissolved in hot 0.3% tartaric acid. Isotonic saline was used as the vehicle. Previous work in our laboratory has indicated 0.3% tartaric acid has no effect on fluid consumption under the conditions used in this experiment. All injections were administered intraperitoneally four hours prior to testing in a volume of 1 cc/kg BW.

Procedure

Animals were adapted to drink a solution containing 0.2% sodium saccharin (Sigma Chemical Co., St. Louis, MO) and 5% glucose (Fischer Scientific, Pittsburgh, PA) solution prepared w/v twenty hours prior to testing. Solutions were stored at room temperature. Food (Purina Chow) was removed four hours prior to testing. This mild deprivation was used to insure that the rats were not sated at the time of testing. Water remained freely available. Solution intake was recorded by weighing (to the nearest 0.01 gram) the graduated cylinder and spillage cup before and after testing. No effort was made to account for evaporation. At the termination of the drinking session the rats were returned to their home cage and given food. One animal was excluded from the study for failing to habituate to the adaptation procedures.

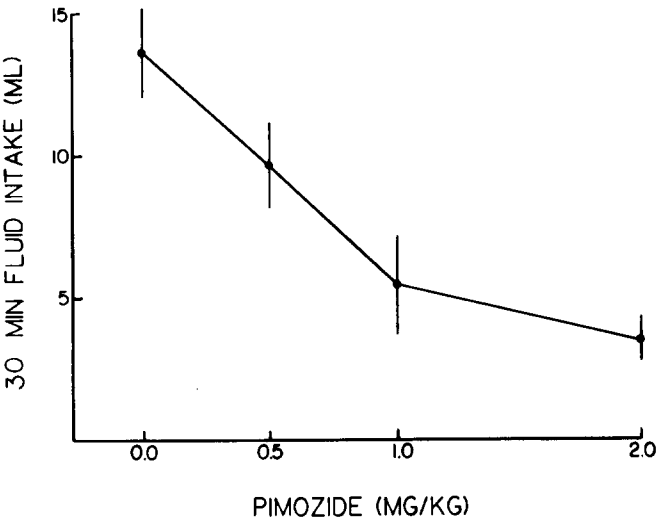

FIG. 1. Mean (±SEM) 30 minute intake of 0.2% saccharin+5% glucose solution after varying doses of pimozide or its vehicle (0 mg/kg).

Animals were tested with the SG solution 30 min/day, six days a week for the duration of the experiment. Pimozide or its vehicle was administered every 4–5 days and a vehicle test was given on the day preceding each pimozide test. Doses of pimozide were administered in an ascending order. Five days after the last pimozide injection, subjects were given access to the SG solution adulterated with 0.001% quinine hydrochloride (Sigma Chemical Co., St. Louis, MO). Thereafter the SG solution was adulterated with quinine every fourth day using the following concentrations: 0.002, 0.004, 0.008, and 0.016%.

RESULTS

During the saline tests the rats consumed 13.6 ml of the SG solution. As illustrated in Fig. 1, pimozide produced a dose dependent decrease in the consumption of the SG solution, $F(3,18)=14.16, p<0.001$. At the 0.5, 1.0, and 2.0 mg/kg doses the rats consumed 76%, 37%, 29%, respectively, of their saline baseline intake. The 30 minute cumulative lick rate functions are presented in Fig. 2. Pimozide produced a significant dose dependent decrease in cumulative licks as early as the third minute of testing, $F(3,18)=4.56, p<0.02$, as well as in the total 30 min licks, $F(3,18)=5.89, p<0.01$. Lick efficiency (LE) ratios were computed by dividing 30 min fluid intake by the total 30 min licks and Figure 3 presents these data. Pimozide produced a reliable dose dependent decrease in lick efficiency, $F(3,18)=7.62, p<0.01$.

The results of the quinine adulteration tests are summarized

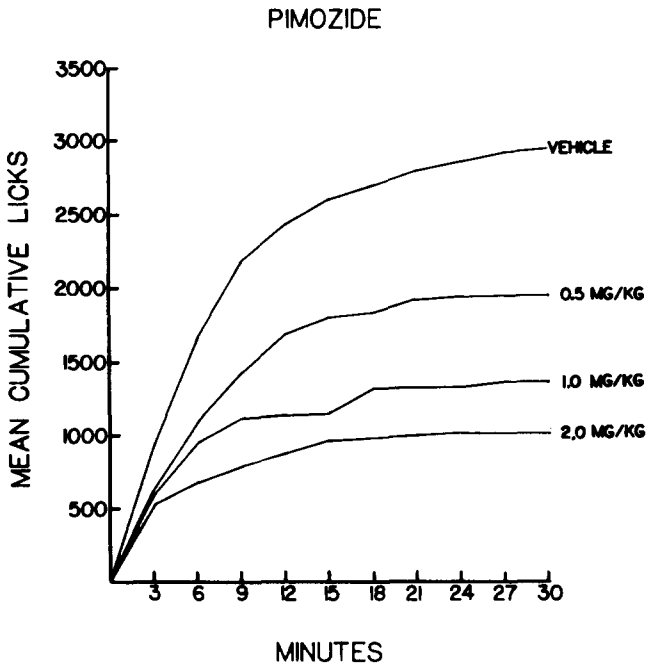

FIG. 2. Mean cumulative licks of 0.2% saccharin+5% glucose solution during 30 minute drinking sessions after varying doses of pimozide or its vehicle.

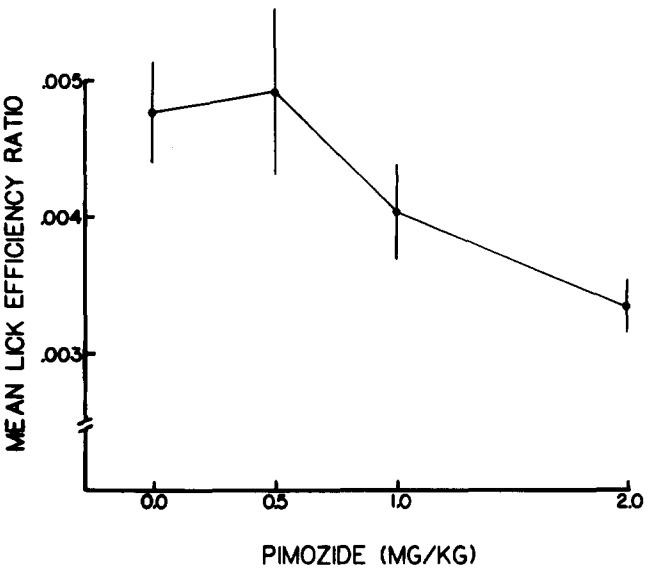

FIG. 3. Mean lick efficiency ratio (±SEM) as a function of pimozide dose during 30 minute drinking seesions.

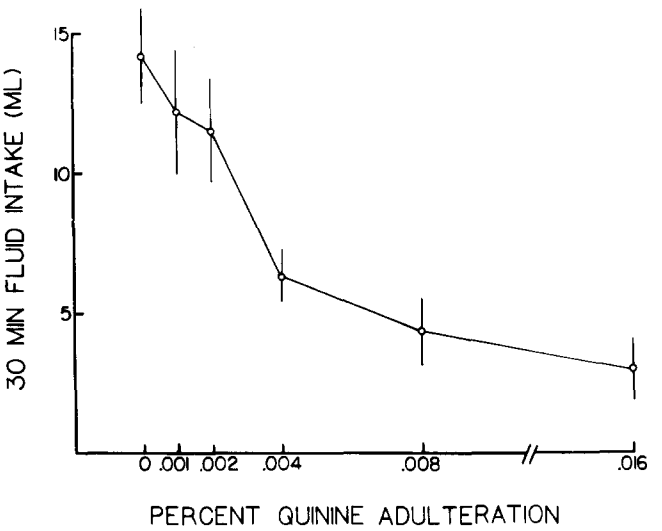

FIG. 4. Mean (±SEM) 30 minute intake of 0.2% saccharin+5% glucose solution as a function of percent quinine adulteration.

in Fig. 4. The fluid intake during the no quinine condition was 14.2 ml, which is comparable to the saline baseline intakes observed in the pimozide tests. Quinine adulteration of the SG solution produced a concentration dependent attenuation in consumption, $F(5,30)=27.59$, $p<.001$. At the four highest quinine concentrations fluid consumption was reduced 80%, 43%, 27%, 18%, respectively. As illustrated in Fig. 5, quinine adulteration also produced a concentration dependent decrease in lick rate as early as the third minute of testing, $F(5,30)=19.86$, $p<0.001$, and in total 30 minute licks, $F(5,30)=20.12$, $p<0.01$. Quinine adulteration also decreased lick efficiency in a dose related manner, $F(5,25)=8.78$, $p<0.001$, see Fig. 6. The data of one subject was excluded from the lick efficiency analysis because of it's aberrant ratio at the 0.016% concentration, which may have resulted from a measurement error. A Grubbs Outlier Test confirmed that the data from this rat was sufficiently aberrant to be rejected from the analysis, $T=1.98$, $p<0.05$.

DISCUSSION

The findings of Experiment 1 demonstrate that both pimozide treatment and quinine adulteration produce quantitatively similar effects on the intake, lick rate and lick efficiency of the palatable saccharin-glucose solution. These findings are consistent with a dopamine reward hypothesis. That is, after pimozide treatment, the rats responded to the SG solution as if the hedonic quality of the solution was reduced.

Alternative explanations for these findings are also possible. A number of studies have indicated that dopamine receptor blocking drugs, including pimozide, suppress water consumption induced by deprivation [3, 17, 22, 28, 30] and by specific thirst challenges [3,44]. These results suggest that dopaminergic neurons play a role in homeostatic thirst regulation, although they are not incompatible with a reward interpretation. The reduction in consumption of the SG solution after pimozide treatment in Experiment 1, therefore, may result from a disruption in thirst regulation. Note, however, that the rats were not water deprived in Experiment 1 and were presumably drinking the solution solely because of its palatability.

An alternative explanation for the suppressive effects of pimozide on the consumption of the SG solution involves

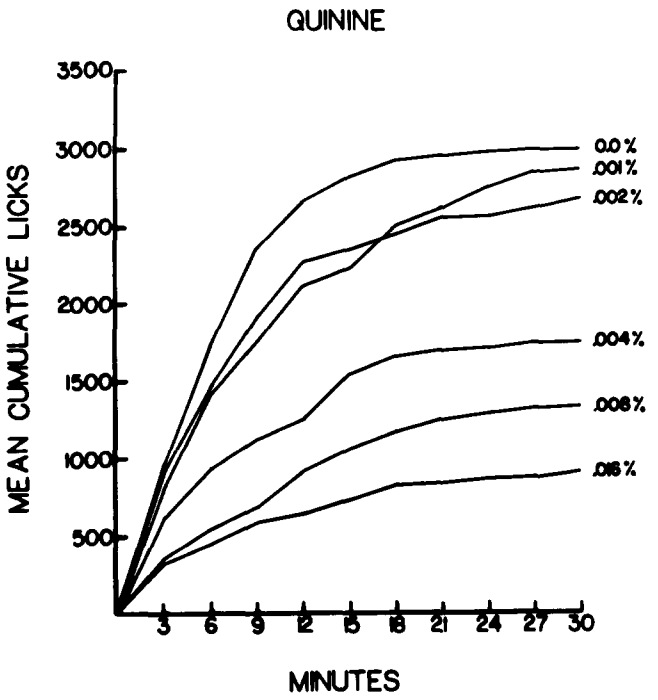

FIG. 5. Mean cumulative licks of 0.2% saccharin+5% glucose solution during 30 minute drinking sessions after varying concentrations of quinine adulteration.

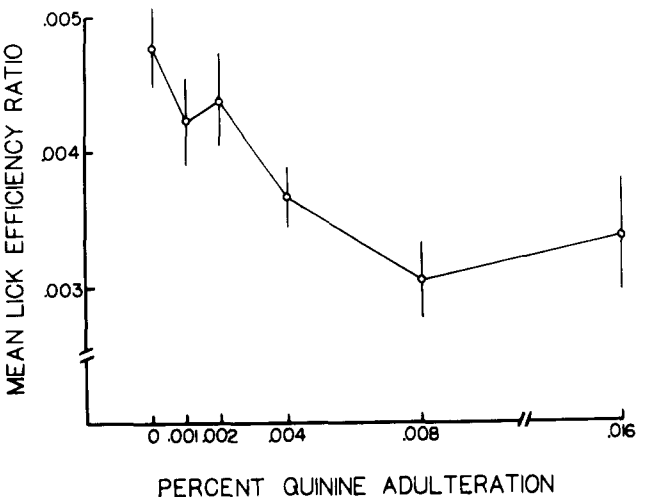

FIG. 6. Mean lick efficiency (±SEM) as a function of percent quinine adulteration of 0.2% saccharin+5% glucose solution.

nonspecific performance deficits, such as sedation and ataxia, which are associated with dysfunction of central dopaminergic systems. It is well known that dopamine depleting lesions of the lateral hypothalamus [11, 20, 21] and the nigrostriatal pathway [24] produce a behavioral syndrome characterized by sensory inattention and motor deficits, which appears to play an important role in the control of ingestive behavior [19]. Similarly, dopamine receptor blocking agents are known to produce catalepsy and sedation when administered systemically [5,23]. Moreover, recent reports indicate that chemical lesions of dopamine containing brain regions, as well as treatment with dopamine receptor blocking agents, cause a deficit in oral motor performance [4,18].

EXPERIMENT 2

The purpose of Experiment 2 was to further examine the role of dopamine in reward mechanisms by examining the effects of pimozide on the consumption of a saccharin-glucose solution or water in thirsty and nonthirsty rats. In the following experiment three groups of rats were tested with pimozide. One group (DEP-W) was water deprived and was tested with water. A second group (DEP-SG) was also water deprived but was tested with the SG solution. The third group (NDEP-SG) had water ad lib and was tested with the SG solution as in Experiment 1. According to a reward hypothesis, pimozide treatment should suppress the consumption of the SG solution more than water since the SG solution is more of a hedonic stimulus than is water. The thirst hypothesis predicts either that all groups should be equally affected by pimozide, or that the deprived groups should be depressed more than the nondeprived group, if the drug specifically interferes with homeostatic thirst. Finally, the nonspecific performance deficit hypothesis predicts that all groups should be equally affected by pimozide. Alternatively, it might be predicted that the intake of the SG solution would be less depressed than the intake of water since its more salient gustatory and olfactory cues would counteract the sensory-motor impairments produced by the drug.

METHOD

Animals

Twenty four naive adult female rats of the Sprague Dawley strain (Charles River Labs, Wilmington, MA) were used. The rats were housed in the same manner as described in Experiment 1. Twenty two animals completed all phases of the experiment and were included in the data analysis.

Apparatus

All testing was done in the same room as in Experiment 1. Ten test cages were used and the presentation of the graduated cylinders was now automated which insured that all rats were given access to the drinking tube at the same time. All other features of the apparatus were identical to that of Experiment 1.

Drugs

Pimozide (0.25, 0.5, 1.0, 2.0 mg/kg) was dissolved in hot 0.3% tartaric acid. Tartaric acid (0.3%) was dissolved in distilled water and was used as the vehicle. All injections were administered intraperitoneally four hours prior to testing in a volume of 1 cc/kg BW.

Procedure

The animals were split into three equal sized groups based on body weight and daily ad lib water intake. The DEP-W group was deprived of water for 23.5 hours/day and received distilled water (stored at room temperature) for 30

min/day in the test cages. The DEP-SG group was water deprived for the same time period but received 30 min/day access to the SG solution used in Experiment 1. The NDEP-SG group had water freely available and received 30 min/day access to the SG solution. For all groups food (Purina Chow) was removed four hours prior to testing, and fresh food was given after the daily drinking sessions.

Animals were adapted to the test schedule for twelve days. They were then treated with pimozide every 4–5 days and a vehicle injection was administered on the day prior to each pimozide treatment. A counterbalanced drug sequence was employed; each group was divided into two subgroups, one of which received the pimozide doses in an ascending then a descending order, while the other subgroup received the drug in the reverse sequence. Therefore, the subject received each dose of pimozide twice, except that four rats of the DEP-SG group inadvertantly received only one injection of the 0.25 mg/kg dose. The four missing scores were estimated using multiple regression. All other aspects of the testing procedure were identical to Experiment 1.

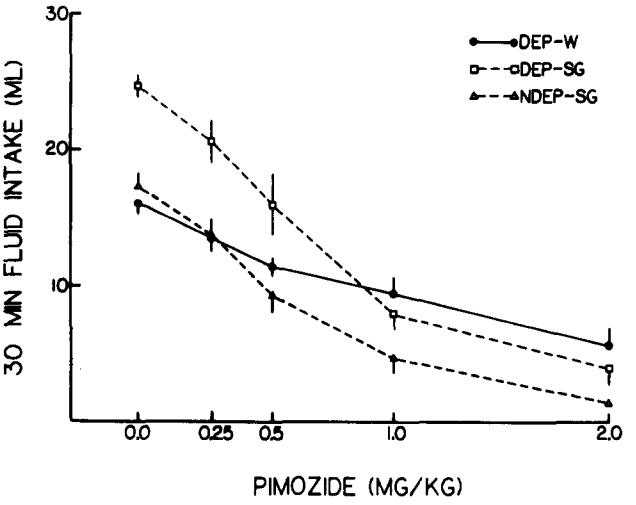

FIG. 7. Mean (±SEM) 30 minute intake of 0.2% saccharin+5% glucose solution or water as a function of varying doses of pimozide.

RESULTS

An initial analysis of the data indicated that the order of drug treatment did not significantly affect the drinking response, and therefore the data from the subgroups were combined.

As illustrated in Fig. 7, the DEP-W group and the NDEP-SG group consumed comparable amounts of fluid after vehicle treatment (16.1 ml vs 17.3 ml, respectively), and both groups consumed significantly less fluid than did the DEP-SG group (24.6 ml; $F(2,19)=24.70, p<0.001$). Pimozide produced a highly significant dose dependent reduction in fluid consumption for all groups tested, $F(4,76)=105.62$, $p<0.001$. Individual group comparisons were made using a two way analysis of variance with repeated measures. Since the main effect of the drug was significant ($p<0.01$) in all cases this will not be described further.

A comparison of the DEP-SG and DEP-W groups revealed both a significant group, $F(1,13)=6.21, p<0.05$, and a group by drug interaction, $F(4,52)=9.57, p<0.001$. That is, without pimozide the DEP-SG group drank more of the SG solution than the DEP-W drank of water. With increasing doses of pimozide, however, the DEP-SG group suppressed its intake more than did the DEP-W group, so that by the two highest doses its fluid intake was less than that of the DEP-W group. Analysis of percent change in fluid consumption also indicated that pimozide differentially affected the intake of the two groups. For example, at the 1.0 mg/kg dose the DEP-SG group suppressed its intake by 67.5% whereas the DEP-W groups suppressed its intake by 41.6%, $t(13)=2.80$, $p<0.05$.

Analysis of the intake data from the NDEP-SG and DEP-W groups indicated that the group effect was not significant but that the group by drug interaction was, $F(4,48)=4.26, p<0.01$. Without pimozide the NDEP-SG rats drank as much of the SG solution as the DEP-W rats drank water. As indicated in Fig. 7, however, pimozide suppressed the fluid intake of the NDEP-SG rats more than that of the DEP-W rats. At the 1.0 mg/kg dose, for example, the NDEP-SG rats reduced their intake by 73.1% compared to the 41.6% reduction displayed by the DEP-W rats, $t(12)=2.94, p<0.01$.

A comparison of the DEP-SG and NDEP-SG groups revealed a significant group difference, $F(1,13)=16.81$, $p<0.01$, but not a reliable group by drug interaction. The deprived rats consumed more of the SG solution then the nondeprived group under all drug treatments and both groups were equally affected by pimozide.

The effects of pimozide on the mean cumulative lick rates are plotted in Fig. 8. Pimozide produced a significant dose related reduction in lick rate as early as the third minute of testing ($p<0.001$). An examination of the cumulative lick rate functions indicated that pimozide reduced the licking of the saccharin-glucose solution more than the licking of water. The effects of pimozide on the total 30 minute cumulative licks for the three goups is shown in Fig. 9. Pimozide produced a dose dependent decrease in total licks for all three groups and results of the individual group comparisons paralled the results of the absolute intake data. That is, a comparison of the DEP-W and the DEP-SG groups revealed a significant group, $F(1,13)=5.06, p<0.05$, and group by drug interaction, $F(4,52)=9.35, p<0.001$. The analysis of the total lick rate data of the NDEP-SG and the DEP-W group revealed a significant group by drug interaction, $F(4,48)=5.78$, $p<0.001$, but the group effect was not reliable. A comparison of the DEP-SG and the NDEP-SG revealed a significant group effect, $F(1,13)=13.95, p<0.001$, but the group by drug interaction was not significant.

The effects of pimozide on the lick efficiency are shown in Fig. 10. Pimozide produced a reliable dose dependent decrease in the lick efficiency of the DEP-W, $F(4,24)=3.37$, $p<0.05$, and the DEP-SG, $F(4,28)=10.48, p<0.001$, groups but not of the NDEP-SG group. Although the NDEP-SG rats reduced their lick efficiency as the pimozide dose increased there was considerable variability in the individual LE scores. There was no significant group or group by drug interaction effects on the LE measure.

GENERAL DISCUSSION

The results of Experiment 1 indicated that, at the dose and concentration ranges used, pimozide and quinine produced similar suppressions in the consumption of a highly palatable

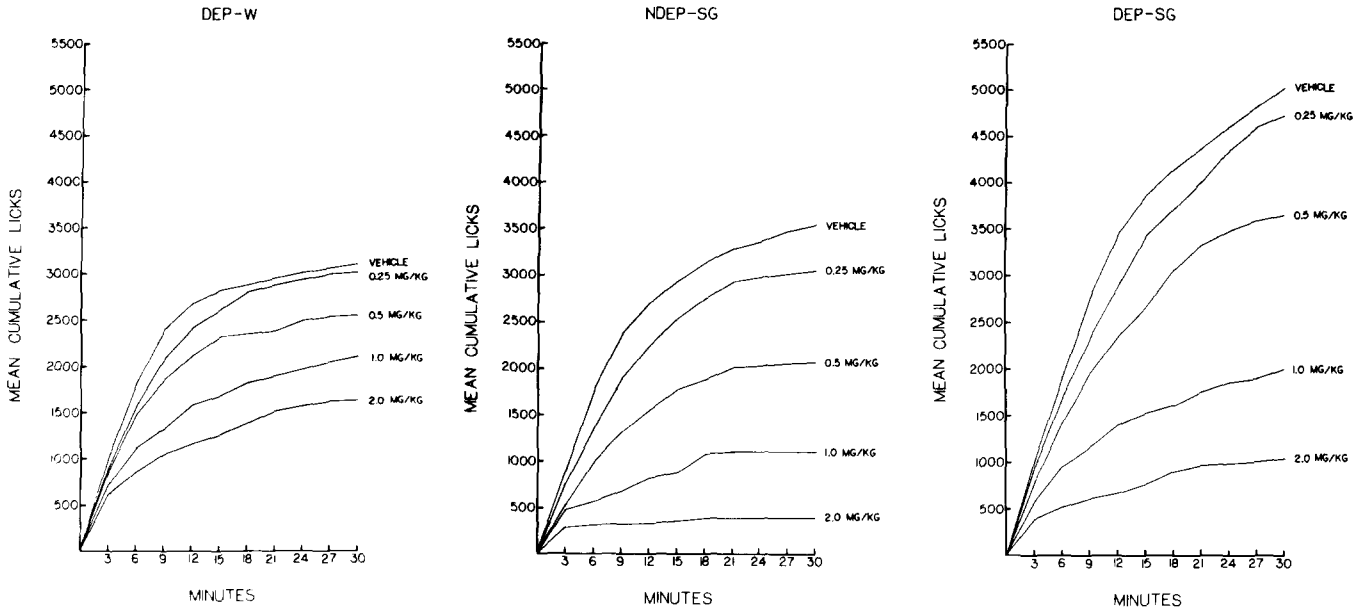

FIG. 8. Mean cumulative licks after varying doses of pimozide.

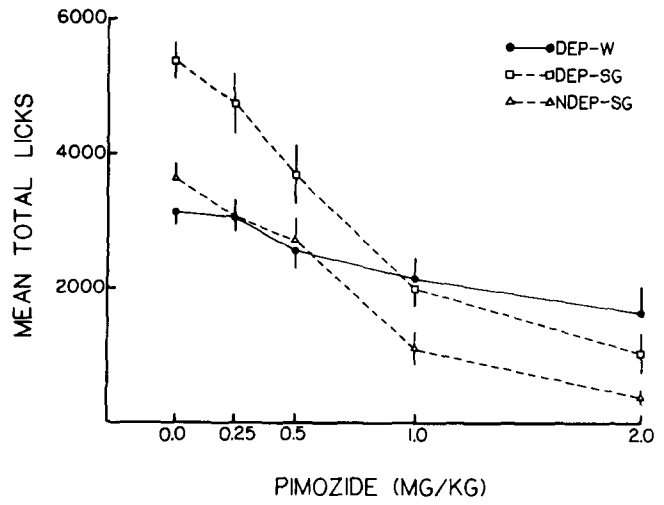

FIG. 9. Mean total licks (±SEM) as a function of varying doses of pimozide.

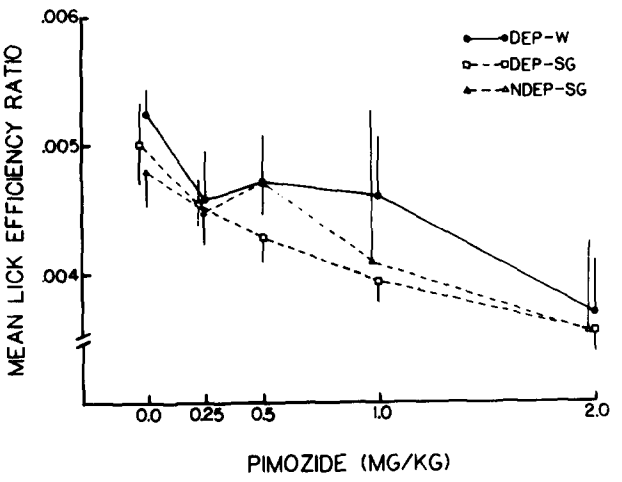

FIG. 10. Mean lick efficiency ratio (±SEM) as a function of varying doses of pimozide.

saccharin-glucose solution. The results of the quinine adulteration test confirm previous findings showing that reducing the palatability of sweet solutions by adding a bitter taste produces a concentration related decrease in ingestion [7,8]. Moreover, our results further replicated the finding that quinine produces a concentration dependent decrease in lick rate as early as the third minute of testing [7,8]. Davis *et al.* [7,8] have attributed this effect to a reduction in the hedonic quality of the solution. Similarly, pimozide produced a dose dependent decrease in the consumption of the SG solution and lick rate early in the test session. This decrease in the initial rate of ingestion suggests that, like quinine, pimozide reduced the hedonic aspects of the taste stimulus. These findings are consonant with the hypothesis [39,40] that pimozide blunts the rewarding properties of food and other hedonic stimuli. On the other hand, the results of Experiment 1 do not necessarily indicate that the mechanisms of action of pimozide and quinine are the same. Quinine presumably reduced the reward quality of the SG solution by adding an aversive component (i.e., bitter taste). In contrast, pimozide may have simply reduced the positive quality of the SG solution without adding an aversive component.

Experiment 2 was conducted to examine alternative explanations for the results obtained in the first experiment. Previous work suggests that central dopamine receptors are involved in homeostatic thirst regulation [3, 17, 22, 30, 44] which raises the possibility that pimozide suppresses the intake of the SG solution because it reduces thirst. The results of Experiment 2 confirm previous reports that pimozide reduces water intake in deprived rats and further demonstrate that pimozide depresses the consumption of a SG solution in deprived and nondeprived rats. However, the fact that pimozide suppressed SG solution intake more than water intake, and that its effects on SG solution intake were independent of deprivation level do not support the hypothesis that a reduction in homeostatic thirst was responsible for the pimozide-induced reduction in SG solution intake. Moreover, the finding that pimozide suppresses the water intake of deprived rats can be interpreted within a reward hypothesis framework. Water, although less palatable than a saccharin-glucose solution, is rewarding to thirsty rats. On the other hand, the present results do not rule out the possibility that dopamine blockade with pimozide affects homeostatic thirst regulation.

Another explanation for the present findings involves the nonspecific performance deficits produced by pimozide. Dopamine receptor blocking agents are known to reduce responding for many types of rewards and this effect has often been attributed to sensory-motor and or arousal deficits [12, 28, 36]. In the present experiments somnolence was observed after the administration of the 2.0 mg/kg pimozide dose, but the lower doses did not produce any observable arousal or sensory-motor impairments. In particular, at these doses, the rats all displayed short latency licking responses to the presentation of the drinking tube. These observations do not preclude the possibility that the lower pimozide doses produced subtle performance deficits [4,18] or increased fatigueability [10,15]. In agreement with previous findings [18] pimozide was observed to produce a dose-dependent reduction in lick efficiency (but see below).

The results of Experiment 2 do not, however, support a performance deficit hypothesis. If pimozide produced a general sensory-motor deficit then it should have suppressed the fluid intakes of all three groups to the same degree. Alternatively, it might be hypothesized that the intake of the two groups drinking the SG solution should have been suppressed less than the intake of the group drinking water because the salient olfactory and gustatory cues of the SG solution would have counteracted the sensory and arousal deficits produced by pimozide. The findings that the intake of the SG solution was suppressed more, not less, than the intake of water clearly does not support these predictions. Furthermore, the results of Experiment 1 indicate that the decreased lick efficiency produced by pimozide treatment cannot, by itself, be taken as evidence for a oral motor performance deficit. That is, quinine adulteration of the SG solution produced a similar reduction in lick efficiency. Thus, the effect of pimozide on this measure may, in fact, result from its reward inhibitory action rather than its effect on motor performance.

The results of Experiment 2 are most consistent with the reward interpretation. Irrespective of deprivation condition, baseline intake, or baseline licking rate, pimozide suppressed the intake of the highly palatable SG solution more than of the bland tasting distilled water. The findings of both experiments, therefore, provide additional support for the role of dopamine in central reward mechanisms and, in particular, in the mediation of the hedonic quality of palatable fluids. This is not to say, however, that all behavioral effects of pimozide are a result solely of blockade of positive reinforcement systems since, as suggested by others [2, 25, 29, 34], it is clear that neuroleptics exert multiple effects on behavior.

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