

Bidirectional Modulation of Sweet and Bitter Taste by Chlordiazepoxide and Ro 15-4513: Lack of Effect with GABA Drugs

NANCY M. PETRY¹ AND GENE M. HEYMAN

Department of Psychology, William James Hall, Harvard University, 33 Kirkland Street, Cambridge, MA 02138 USA

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PETRY, N. M. AND HEYMAN, G. M. *Bidirectional modulation of sweet and bitter taste by chlordiazepoxide and Ro 15-4513: Lack of effect with GABA drugs.* *PHYSIOL BEHAV* 61(1) 119–126, 1997.—Five rats were trained to respond for 10% sucrose and 10% sucrose/0.006% quinine in an operant procedure. Both solutions were concurrently available on independent, variable-interval 5-s schedules of reinforcement. Rats reliably responded for both solutions throughout the sessions and made approximately 68% of their total daily responses for the sucrose solution. When injected prior to the sessions with 4 mg/kg of chlordiazepoxide, rats selectively increased quinine responding; injections of the benzodiazepine inverse agonist Ro 15-4513 (9 mg/kg) led to decreased quinine responding. The effects of both chlordiazepoxide and Ro 15-4513 were reversed by the benzodiazepine antagonist flumazenil. Pre-session injections of flumazenil, muscimol, baclofen, or picrotoxin all resulted in no changes in responding, or a decrease in responding for both solutions. These results are discussed in terms of a bidirectional modulation of sweet-bitter taste preference by drugs acting on the benzodiazepine receptor. Moreover, the data from these experiments suggest that any changes in the oral consumption of alcohol following administration of benzodiazepine drugs must be examined in light of their effects on taste palatability. *Copyright © 1996 Elsevier Science Inc.*

Taste	Sucrose	Quinine	Benzodiazepine	GABA	Ro 15-4513	Chlordiazepoxide	Lever press
Rat							

THE benzodiazepine (BZ)-GABA receptor complex is thought to mediate ethanol's effects (1,5,8,9,28,41,42,56,58,59). Ro 15-4513 (ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4, H,imidazo[1,5a][1,4] benzodiazepine-3-carboxylate) (5,6,42) is a BZ inverse agonist that reverses both behavioral (5,61) and in vitro (60) effects of ethanol. Several studies show that this drug, and others acting on this receptor site, reliably decrease ethanol consumption in rats (32,39,47,48,51,52). For example, in a study with concurrently available sucrose and ethanol/sucrose solutions, Ro 15-4513 selectively reduced ethanol responding and chlordiazepoxide increased ethanol responding (48).

Although ethanol may be ingested for its pharmacological effects, its consumption is also influenced by its taste (22,24,30,33). Few studies of pharmacological modulation of ethanol consumption have controlled for this possibility. The present study employed a procedure that provided concurrently available sucrose and sucrose/quinine solutions, and examined the effects of BZ drugs known to affect ethanol intake on consumption of sweet and bitter solutions. Although the taste of quinine may not be directly analogous to that of ethanol, these drugs' effects on responding for another aversive tasting solution may be related to their effects on ethanol consumption.

BZs affect consummatory processes through taste-related mechanisms. For example, numerous studies show an increase in consumption of palatable foods following BZ administration (2,12,15,20,21,66,68). Only a handful of reports, however, have examined the effects of these drugs on bitter-tasting substances. Some indicated that BZ agonists increase consumption of both sweet and bitter foods (19,31), and others found no change in consumption of quinine-adulterated foods (2). Few reports have examined the effects of Ro 15-4513 on taste-related consumption. Three studies showed a decrease in palatable food consumption following administration of BZ inverse agonists (14,17,34), but two others demonstrated that Ro 15-4513 produced no effect on consumption of food (9) or aversive salt solutions (15). Although the BZ antagonist flumazenil (Ro 15-1788) generally does not have intrinsic effects on consumption [(37,67); but see (13,18,62)], it reliably reverses the alterations in taste-related consumption produced by both chlordiazepoxide (66,67) and Ro 15-4513 (16).

Benzodiazepine receptor binding sites are associated with receptors for gamma-aminobutyric acid (GABA) (3,7,10,27,38,55,65), and evidence links GABA-ergic compounds to consummatory processes [(4,11,40,46); but see

¹ Requests for reprints should be addressed to Nancy M. Petry, Department of Psychiatry, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030-2103 USA. E-mail: petry@psychiatry.uche.edu

(53)]. For example, intercerebral injections of the GABA agonist muscimol (26,45) induced sated rats to eat, and BZ-induced consumption was antagonized by GABA antagonists picrotoxin and bicuculline (4,25,44). The effects of GABA-ergic compounds on sweet and bitter taste have not yet been systematically investigated.

Most research on taste preference has used drinking-bottle procedures, in which rats consume various fluids alone or with water as an alternative. The amount drunk is recorded daily, and consumption in baseline sessions is compared to that following drug injections. Any drug-induced changes specific to the test solution are inferred to result from the effect of the drug on taste mechanisms. Such procedures have certain limitations. For example, the animals tend to drink the palatable solution at a very high rate, but they do not consume, or consume at relatively low rates, the quinine or water solutions. Problems associated with floor and ceiling effects are introduced, and the animals may not even sample the less palatable reinforcer.

The present study employed a different paradigm to study taste preferences. Double-lever, double-dipper operant boxes had concurrently available isocaloric alternatives of differing tastes: 10% sucrose and 10% sucrose/0.006% quinine. Both solutions were available on variable-interval schedules of reinforcement. Using such a reinforcement schedule, maximal reinforcement is obtained by constantly switching between the 2 alternatives, and rats reliably approximate 50% responding on both sides when the 2 reinforcers and the 2 schedules are equivalent (29). However, when 2 different reinforcers are available, the animal will respond more, but not necessarily exclusively, for the preferred reinforcer. The animals occasionally press at the nonpreferred side, because the likelihood of availability of the less-preferred reinforcer increases while the rat is responding at the preferred side (36). Using this procedure, direct preference between a normally aversive and a normally preferred substance can be made.

In the present study, animals were trained to respond for 10% sucrose vs. 10% sucrose/0.006% quinine. Drugs that have been shown to affect ethanol consumption in analogous procedures (47,48) were tested for their effects on sweet and bitter taste consumption. Because of the purported interactions of BZ and GABA (8,47), we also examined the effects of GABA drugs using this procedure.

METHODS

Subjects

Five male Wistar rats obtained from Charles Rivers Breeding Company, Wilmington, MA, served as subjects. Rats were individually housed in standard perspex cages and were allowed at least 2 weeks acclimation to the laboratory with food and water freely available before the experiment commenced. Food was then rationed daily until each rat reached 85% of its free-feeding body weight, 330–400 g. These weights were maintained throughout the remainder of the experiment, with daily food rations given approximately 30 min following experimental sessions. Animals were housed in a room with a 12/12 light dark cycle, with lights on and off at 0600 h and 1800 h, respectively. Rats were run 7 days a week at the same time each day.

Apparatus

The experiments were conducted in 6 standard operant chambers (MED Associates: 28 cm, 20.5 cm, 26 cm, Georgia, UT). Two 5-cm wide levers were inserted into the front wall, 7 cm above the floor and 1 cm from each side. The levers were operated with a force of about 0.25 N. Two cm below each lever was

an opening into which a 0.1-ml dipper could be raised. Responses on the right lever resulted in presentations of the right dipper, and responses on the left lever resulted in presentations of the left dipper. All dipper presentations provided a 1.5-s access to a 0.1 ml dipper, followed by a 3-s time-out period, except during training when the access time was 3.0 s. The dippers, when not raised, rested in a trough that held approximately 170 ml of liquid. During the session, a 1 Watt lamp was illuminated above each lever. An exhaust fan provided air circulation for the operant chamber. Experimental events were arranged and recorded with an IBM-compatible personal computer that used MED-PC (Georgia, UT) software and interface (63).

Training

After reaching their 85% body weights, rats were initially shaped to lever press on a procedure that gave access to a 10% sucrose solution. A 3-s period access to both dippers was automatically provided at 30-s intervals; in addition, any lever presses were rewarded on an FR1 schedule. All rats learned to press within 3 30-min daily sessions. To obtain responding on both levers, rats were then trained on a schedule that required them to press consecutively on both levers to obtain a reinforcer. This schedule was in operation for 3 days.

The rats were then placed on concurrent, independent variable-interval 5-s schedules (variable-interval 5-s schedule on both levers), with 10% sucrose available at each lever. They were maintained on this schedule until responding approximated 50% on each side. Quinine then was introduced into one of the troughs. The concentration of quinine was adjusted until the group mean percent responding was about 60% sucrose/40% quinine, such that floor or ceiling effects would not be operative. All sessions were 30 min in duration, and 69 training sessions elapsed before drug testing commenced. The sides at which the 2 solutions were available alternated approximately every 3 weeks.

Drugs

All injected compounds were administered via the intraperitoneal route. Ro 15-4513 and flumazenil (donated by Hoffman LaRoche, Basel, Switzerland) were suspended in 2 drops of Tween 80 and diluted with 0.9% sodium chloride. They were injected, in a volume of 3 ml/kg, 15 min before the start of the session. When administered in combination, Ro 15-4513 (or vehicle) was administered first, immediately followed by flumazenil (or vehicle). Chlordiazepoxide, baclofen, muscimol, and picrotoxin were diluted with saline and injected in a volume of 1 ml/kg. Preadministration times for these drugs were 30, 30, 30, and 15 min, respectively.

Order of drug administration was chlordiazepoxide, flumazenil, picrotoxin, baclofen, muscimol, and Ro 15-4513. Chlordiazepoxide was administered in 4 doses: 1, 2, 4, and 10 mg/kg. The 4 mg/kg dose was administered alone and in combination with vehicle and 40 mg/kg flumazenil. Ro 15-4513 was injected in doses of 3 and 9 mg/kg, and the 9 mg/kg dose was also administered in conjunction with 40 mg/kg flumazenil or vehicle. Flumazenil was given in doses of 5, 10, and 20 mg/kg. This drug was also administered at a dose of 40 mg/kg in conjunction with another injection: 9 mg/kg Ro 15-4513, 4 mg/kg chlordiazepoxide, or vehicle. Muscimol was injected in 0.5, 1, and 2 mg/kg doses, and baclofen was administered in 0.5, 1.25, 2.5, and 5 mg/kg doses. Picrotoxin was given in doses of 1 and 2 mg/kg. One rat convulsed after receiving picrotoxin and was subsequently not administered this drug.

The doses were selected on the basis of pilot work and past, published research. Each dose was administered to each animal a minimum of 2 times, and doses were given in random order. A dose was administered 3 times to an animal only if the first 2 injections produced discrepant (greater than 15% differences) alterations in responding. At least 2 nondrug sessions were interspersed between injection days. Vehicle injections, in the same volume as the drug itself, were given for each compound studied.

Data analysis

For each dose of each drug tested, overall response rates are presented for both solutions in baseline, vehicle, and drug sessions. Because no differences were ever found in the order of injections, the response rates were averaged across the 2 to 3 repetitions of each dose of each drug. Within-session response rates are also presented. Response rates were calculated at 2-min intervals across the 2 or 3 repetitions of each dose of drug presented. Baseline response rates are from the sessions immediately preceding drug sessions. Percentage of sucrose responding of total responding was calculated as a measure of preference for sucrose.

Statistical analyses were carried out using repeated measures ANOVA for nonindependent groups, and contrasts were used to examine specific hypotheses (49). Repeated measures *t*-tests were used to examine differences between baseline and injection conditions. Because significant differences were never present between baseline and vehicle injection sessions, these were averaged together for purposes of statistical testing.

RESULTS

Figure 1a, b, c shows chlordiazepoxide data. In the top panel (a), overall session sucrose responding is shown by open bars, and sucrose/quinine responding by hatched bars. Sucrose responding was significantly affected by chlordiazepoxide administration, $F(4, 16) = 8.66, p < 0.001$. At both 4 and 10 mg/kg, sucrose responding was significantly altered or nearly so, $t(4) = 2.31, p < 0.10$ and $t(4) = 3.50, p < 0.05$, for the 2 respective doses. Although an omnibus ANOVA of changes in quinine responding did not reach statistical significance [$F(4, 16) = 2.21, p < 0.11$], a contrast was conducted to examine the specific hypothesis that quinine responding increased at low to moderate doses. Contrast weights were set at $-1, -1, 1, 2, \text{ and } -1$ for the baseline/vehicle, 1, 2, 4, and 10 mg conditions, respectively, and this contrast was significant, $F(1, 16) = 57.14, p < 0.001$. Quinine response rates at the 4 mg dose were significantly different from baseline rates, $t(4) = -2.88, p < 0.05$.

Chlordiazepoxide was also administered in conjunction with a flumazenil vehicle injection. Sucrose and quinine response rates following 4 mg of chlordiazepoxide plus flumazenil vehicle were significantly different from baseline rates, $t(4) = -3.939$ and $3.154, p < 0.05$, for sucrose and quinine, respectively. Flumazenil 40 mg/kg reversed the effects of 4 mg/kg of chlordiazepoxide, and no significant differences were found between baseline and blockade injections, $t(4) = 1.13, \text{ and } 0.28, p = \text{n.s.}$ for sucrose and quinine responding, respectively.

The middle panel of this figure (b) demonstrates sucrose and sucrose/quinine responding over the 30-min session. The data were collected in 2-min bins and averaged across the 5 subjects. In baseline sessions, response rates for the sucrose solution (open circles) gradually rose early in the session, and then remained at about 80 to 100 responses/min throughout the session. Quinine responding (filled circles) also rose in the first 6 min of the session, and then plateaued at about 50 responses/min. The time-course data following administration of 4 mg/kg dose of chlor-

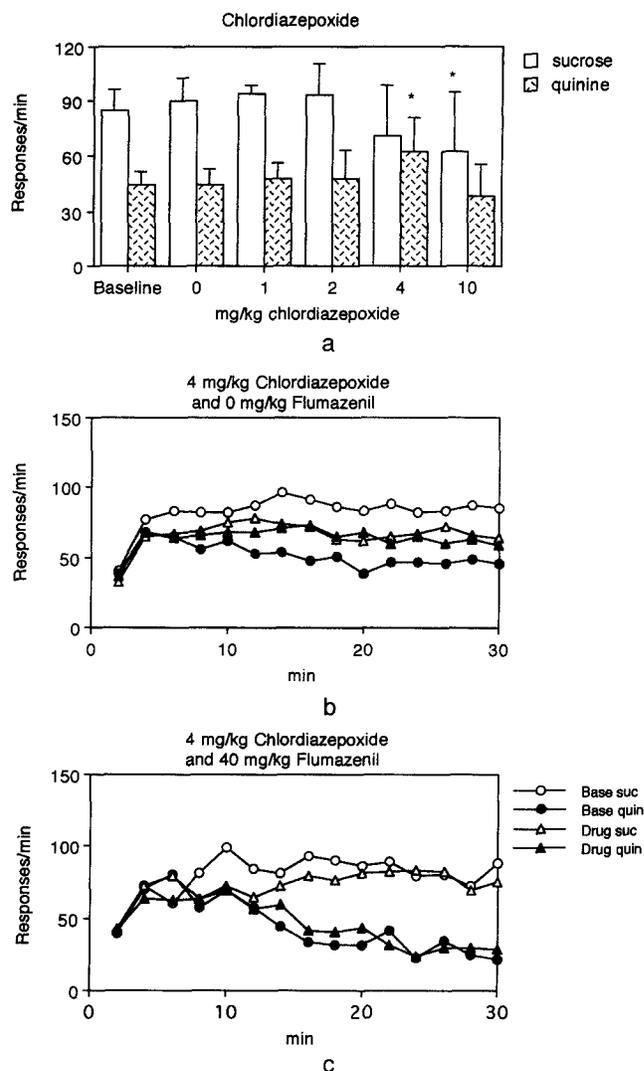


FIG. 1. (a) Mean session responding for sucrose and quinine/sucrose in baseline sessions and across doses of chlordiazepoxide. The error bars represent standard deviations. (b) Responding for sucrose (open circles) and quinine/sucrose (closed circles) in baseline sessions and following chlordiazepoxide plus 0 mg flumazenil (open and closed triangles for sucrose and sucrose/quinine, respectively). Data are averaged across 2-min bins. (c) Responding for sucrose and quinine/sucrose in baseline sessions and following chlordiazepoxide plus flumazenil. Data are averaged across 2-min bins.

diazepoxide plus flumazenil vehicle are also show in this figure. Mean quinine responding (filled triangles) increased from baseline and actually surpassed sucrose responding (open triangles) at some points. The bottom panel (c) demonstrates responding across the session following injections of 4 mg/kg chlordiazepoxide with 40 mg/kg flumazenil. The BZ antagonist blocked the effects of 4 mg of chlordiazepoxide, and responding for both solutions returned to baseline rates.

Table 1 shows preference for sucrose in baseline and drug conditions. The omnibus ANOVA for preference for sucrose was not significant following chlordiazepoxide, $F(4, 16) = 2.00, p < 0.10$. However, a contrast examining the hypothesis that preference for sucrose decreased at low to moderate doses of chlordiazepoxide (with weights set at 1, 1, $-1, -2, \text{ and } 1$) was sig-

TABLE 1
PERCENTAGE OF SUCROSE RESPONDING OF TOTAL RESPONDING

Drug	Dose (mg/kg)	% Sucrose Responding
Chlordiazepoxide	baseline	67 ± 10
	0	67 ± 10
	1	66 ± 10
	2	66 ± 9
	4	53 ± 10
	10	60 ± 13
	4/0	54 ± 10*
Ro 15-4513	baseline	70 ± 4
	0	68 ± 7
	3	71 ± 6
	9	80 ± 6
	9/0	87 ± 11*
	9/40	73 ± 5
	Flumazenil	baseline
	0	70 ± 12
	5	66 ± 10
	10	66 ± 10
	20	64 ± 11
	40/0	64 ± 10
Muscimol	baseline	62 ± 9
	0	60 ± 10
	0.5	65 ± 12
	1	72 ± 8
	2	64 ± 13
Baclofen	baseline	74 ± 7
	0	69 ± 8
	0.5	76 ± 8
	1.25	75 ± 8
	2.5	69 ± 10
Picrotoxin	baseline	68 ± 8
	0	72 ± 8
	1	58 ± 12
	2	80 ± 7

Standard deviations of means follow the ± signs.

* Significantly different from baseline sessions.

nificant, $F(1, 16) = 25.12, p < 0.01$. At the 4 mg/kg condition, sucrose preference decreased in all 5 of the rats. When 4 mg/kg of chlordiazepoxide was administered in conjunction with a vehicle flumazenil injection, preference for sucrose again dropped to 54%, similarly to when 4 mg/kg of chlordiazepoxide was given alone. This change was significantly different from baseline sessions, $t(4) = 4.01, p < 0.01$. The trend was reversed, and preference for sucrose was not different from baseline when 40 mg/kg of flumazenil was given with chlordiazepoxide, $t(4) = 0.70, p = n.s.$

The effects of Ro 15-4513 appear in Fig. 2a, b, c. The top panel (a) shows average sucrose and quinine responding across the baseline and injection sessions. Although the omnibus ANOVA was not significant, $F(2, 8) = 3.70, p < 0.10$, a contrast testing the hypothesis that quinine responding decreased linearly with increasing doses (weights set at 1, 0, -1 for baseline/vehicle, 3 mg, and 9 mg) was significant, $F(1, 8) = 14.38, p < 0.01$. The effects of flumazenil in conjunction with 9 mg/kg Ro

15-4513 were also studied, and response rates following 9 mg/kg Ro 15-4513 plus flumazenil vehicle were significantly different from baseline, $t(4) = 2.94, p < 0.05$. The effects of Ro 15-4513 were reversed by 40 mg/kg of flumazenil. Quinine responding rose from 22 to 31 responses/min, and this rate did not differ from the baseline rate of 34 responses/min, $t(4) = 0.27, p > n.s.$ An omnibus ANOVA of sucrose responding following Ro 15-4513 administration was not significant, $F(2, 8) = 2.61, p = n.s.$ Likewise, sucrose response rates were not significantly different from baseline rates when 9 mg/kg of Ro 15-4513 was administered in conjunction with a vehicle flumazenil injection, $t(4) = 1.29, p = n.s.$

The time-course data are shown in the middle (b) and lower (c) panels. Following 9 mg/kg of Ro 15-4513 plus a flumazenil vehicle injection, sucrose responding decreased slightly in the

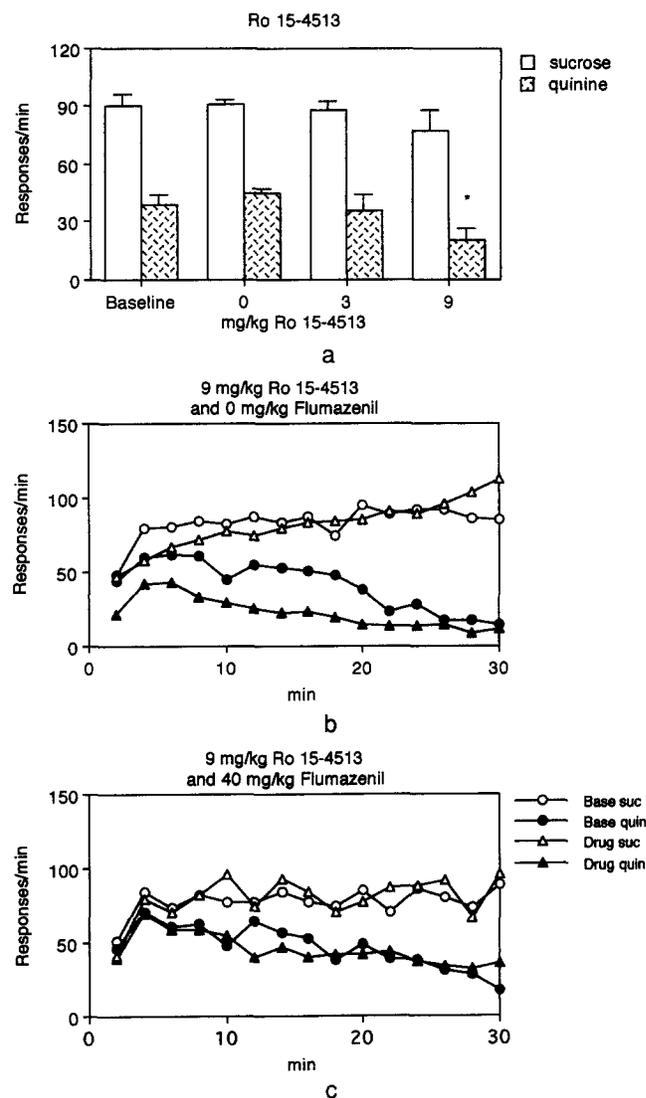


FIG. 2. (a) Mean session responding for sucrose and quinine/sucrose in baseline sessions and across doses of Ro 15-4513. (b) Responding for sucrose (open circles) and quinine/sucrose (closed circles) in baseline sessions and following Ro 15-4513 plus 0 mg flumazenil (open and closed triangles). Data are averaged across 2-min bins. (c) Responding for sucrose and quinine/sucrose in baseline sessions and following Ro 15-4513 plus flumazenil. Data are averaged across 2-min bins.

first half of the session and then returned to baseline rates. Quinine responding was severely disrupted by drug; it remained about 50% less than baseline until the end of the session. The bottom panel (c) demonstrates within-session responding in baseline and when 9 mg/kg Ro 15-4513 was given with 40 mg/kg flumazenil. Flumazenil reversed or partially reversed Ro 15-4513 effects.

Preference for sucrose following Ro 15-4513 administration is shown in Table 1. Although an omnibus ANOVA did not indicate a significant change in preference for sucrose with Ro 15-4513 injections, $F(2, 8) = 2.03$, $p = \text{n.s.}$, a contrast examining the hypothesis that preference for sucrose increased linearly with doses of Ro 15-4513 (weights set at -1, 0 and 1 for baseline/vehicle, 3 mg, and 9 mg) was significant, $F(1, 8) = 7.17$, $p < 0.05$. Preference for sucrose also increased to 87% when 9 mg/kg of Ro 15-4513 was administered in combination with flumazenil vehicle, and this change approached levels of statistical significance, $t(4) = 2.457$, $p = 0.07$. Flumazenil (40 mg/kg) reversed this trend, and preference was not significantly different from baseline, $t(4) = 0.13$, $p = \text{n.s.}$

The data for flumazenil appear in the top panel (a) in Fig. 3a, b, c, d. The left panel again shows overall session response rates for the 2 solutions across the doses tested. The * indicates that the highest dose (40 mg/kg) was tested with a Ro 15-4513 vehicle injection. No significant differences in responding for sucrose or quinine were noted across the doses, $F(4, 16) = 1.93$, and 0.77 , $p = \text{n.s.}$ The time-course data similarly show no change from baseline rates. Preference for sucrose, as shown in Table 1, was not affected by the drug, $F(4, 16) = 1.96$, $p = \text{n.s.}$

The data for muscimol injections appear in the second column from the top (b) in Fig. 3. Muscimol injections significantly affected quinine responding, $F(3, 12) = 9.98$, $p < 0.001$, with the 2.0 mg/kg dose producing a significant difference from baseline/vehicle sessions, $t(4) = 4.61$, $p < 0.01$. Sucrose responding was also significantly affected by the drug, $F(3, 12) = 7.70$, $p < 0.01$. The t -tests again indicated that only the highest dose significantly affected sucrose responding, $t(4) = 3.40$, $p < 0.05$. The time-course data in the right panel indicate that the 0.5 mg/kg dose did not affect responding for either alternative. Preference for the sucrose solution was not significantly affected by the drug, $F(3, 12) = 2.36$, $p = \text{n.s.}$

The data for baclofen injections appear in the third panel from the top (c) in Fig. 3. Both sucrose and quinine responding were significantly affected by baclofen injections, $F(4, 16) = 5.67$ and 8.27 , $p < 0.01$. The highest dose (5 mg/kg) significantly affected both quinine and sucrose responding, $t(5) = 3.94$ and 6.16 , $p < 0.05$, respectively, and lower doses did not significantly affect responding for either alternative. The time-course data for the 1.25 mg/kg dose appear in the right panel. No consistent changes in response rates for either alternative occurred with drug treatment. Preference for sucrose was not significantly affected by baclofen, $F(4, 16) = 1.72$, $p = \text{n.s.}$ (Table 1). At the highest dose, mean overall sucrose preference rates increased to 86%, but it occurred in only 4 of the rats.

The data for picrotoxin are shown in the bottom panel (d) of Fig. 3. One rat convulsed after the first injection of picrotoxin, and the data for this rat are not included in analyses. Sucrose responding was significantly affected by picrotoxin injections, $F(2, 6) = 21.86$, $p < 0.01$, but quinine responding was not, $F(2,$

$6) = 4.18$, $p = \text{n.s.}$ Paired t -tests indicated that sucrose responding was affected at both doses tested, $t(3) = 9.58$ and 5.62 , $p < 0.01$. The time-course data in the bottom (d) right panel show that, compared to baseline, responding for sucrose decreased and responding for quinine remained about the same. At the 2 mg/kg dose, all 4 animals reduced responding for both alternatives. Changes in preference for the sucrose solution approached a level of statistical significance, $F(2, 6) = 3.68$, $p < 0.10$, following picrotoxin administration, especially at the 1.0 mg/kg dose, $t(3) = 2.68$, $p < 0.10$.

DISCUSSION

The results of this study support the theory of a bidirectional modulation of sweet and bitter taste by drugs acting on the BZ receptor (4,17,31). The BZ agonist chlordiazepoxide and inverse agonist Ro 15-4513 had opposite effects on responding for a quinine solution. In all rats tested, 1 dose of chlordiazepoxide (4 mg/kg) increased responding for quinine and decreased responding and preference for sucrose. Conversely, 1 dose of Ro 15-4513 (9 mg/kg) decreased responding for quinine. Flumazenil reversed the effects of both chlordiazepoxide and Ro 15-4513, suggesting that the BZ receptor site is instrumental in these compounds' effects on palatability.

Although most past reports have shown an increase in consumption of palatable substances following BZ agonist treatment, the present study demonstrated an increase in responding for a bitter solution with a parallel decrease in responding for a sweet solution. These apparent discrepancies may be accounted for by a number of factors. First, the paradigm used in the present study is different from those used previously. In most studies, 1 group of rats consumes a sweet solution, and another a bitter one. Although large increases in consumption of the palatable food are usually noted following BZ agonist administration, changes in quinine consumption are usually minimal. This lack of effect on consumption of bitter solutions may be related to the low baseline rates of consumption of the quinine solution. In the present study, choice was direct between the 2 solutions, and floor and ceiling effects were minimized by employing concurrent variable-interval schedules of reinforcement. It is not known if increases in quinine responding following drug treatment would occur if the same solutions were available on other schedules of reinforcement. Differences in acceptance of solutions have been found among different schedules of reinforcement (54) and in operant vs. free-feed procedures (50,57). The changes in quinine-reinforced responding following drug administration in the present study also may have been dependent upon the concentration of quinine specific to this study and the palatable sucrose solution with which it was mixed. The taste of 10% sucrose/0.006% quinine is clearly not repugnant to the rats, as they did respond at high rates for it. The generalization of this effect to more aversive tasting solutions and other paradigms remains to be determined.

The increase in quinine responding following administration of BZ agonists can be interpreted in two ways. Chlordiazepoxide may have made the taste of quinine less aversive, thereby directly altering the palatability of the solution. Alternatively, it may have diminished the processes that normally inhibit responding for a less-preferred substance. Benzodiazepines reverse inhibitory effects of stress, fear, punishment, and anxiety (23,64). The in-

FIG. 3. Left panel: Mean session responding for sucrose (open bar) and quinine/sucrose (filled bar) in baseline sessions and across doses of flumazenil; b) muscimol; (c) baclofen; (d) picrotoxin. * this dose was given in combination with a second injection of vehicle. Right panel: Responding for sucrose (open circles) and quinine/sucrose (closed circles) in baseline sessions and following injections of (a) flumazenil plus vehicle injections (open and closed triangles); (b) muscimol plus vehicle; (c) baclofen plus vehicle; (d) picrotoxin plus vehicle. Data are averaged across 2-min bins.

crease in responding for a normally aversive quinine solution may be related to disinhibiting actions of BZs [see also (19)]. These same interpretations may apply to the decrease in quinine responding following Ro 15-4513. If Ro 15-4513 decreased quinine responding by augmenting inhibitory responding, further investigation of this drug's effects on stress, anxiety, and punishment are warranted (43). Any effects it may have on reversing ethanol's behavioral effects may be secondary to anxiogenic properties.

The results of this study may have important implications for examining the pharmacological basis of the oral administration of ethanol in the rat. The search for the pharmacological basis of ethanol has linked many of ethanol's effects to the BZ-GABA receptor complex. Numerous studies have demonstrated that Ro 15-4513 reduces ethanol intake (39) and ethanol-reinforced responding in both single lever (52) and choice operant procedures (47,48,51). In a study similar to the present one, with 10% sucrose and 10% sucrose/10% ethanol concurrently available, responding for the normally aversive-tasting ethanol solution decreased with Ro 15-4513 administration and increased with chlordiazepoxide injections. In the present study, Ro 15-4513 decreased and chlordiazepoxide increased responding for the normally less-preferred quinine solution. Because the taste of ethanol may be similar to that of quinine (35), drug-induced alterations in ethanol consumption may result from effects on taste-related motivational mechanisms and not necessarily ethanol's pharmacological effects. The extent to which these results from

rats can be extrapolated to human ethanol consumption, however, is unclear.

The results of this experiment indicate that the GABA agonists muscimol and baclofen have little effect on taste-related consumption. Neither of these drugs systematically altered responding for either a sucrose or a sucrose/quinine solution until the dose was quite high. At high doses, responding for both alternatives decreased, an effect most likely indicative of motor impairment. Picrotoxin, a drug that reverses the chloride ion flow at the BZ-GABA receptor complex and reverses some of the behavioral effects of ethanol, significantly decreased sucrose responding at doses that did not affect quinine responding. Because this drug is a convulsant, it is also plausible that picrotoxin decreased responding for the solution that engendered the highest response rates (23). Thus, picrotoxin's effects may be due to generalized behavioral disruption. Further research is required to clarify this issue.

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