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Buspirone Antagonizes the Expression of Conditioned Taste Aversion in Rats

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ABSTRACT

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When the parameters of taste aversion conditioning and testing have been appropriately adjusted, benzodiazepines and barbiturates will markedly antagonize the expression of moderate taste aversions in rats. We call this the taste aversion conflict model of anxiety. In the present study, we investigate whether buspirone HCl (buspirone; p.o. and i.p.) is active in the taste aversion conflict model and whether buspirone will also increase unsuppressed saccharin (SACC) intake. We also investigated the effects of imipramine, desipramine, phenelzine sulfate, chlorpromazine, scopolamine and d-amphetamine sulfate in the taste aversion conflict model. To assess the possible effects of buspirone on the GABA-benzodiazepine supramolecular receptor complex, we compared buspirone with certain benzodiazepines, meprobamate and sodium phenobarbital on the antagonism of pentylenetetrazol-induced lethality in mice. Unlike benzodiazepines, meprobamate and phenobarbital, buspirone did not antagonize pentylenetetrazol-induced lethality. However, like those other anxiolytics, buspirone markedly antagonized the expression of conditioned taste aversion. All nonanxiolytic drugs tested had either no effect or very slight effects on the expression of conditioned taste aversion. These results suggest that the taste aversion conflict model is sensitive to novel anxiolytics and that it is selective for drugs clinically effective in the treatment of generalized anxiety disorders in man.

Key words: buspirone, anxiolytics, anxiety disorders, taste aversion conflict model

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INTRODUCTION

For several years, it has been known that anxiolytic drugs can be effective in antagonizing the expression of conditioned taste aversions measured with the one-bottle testing method [Cappell and LeBlanc, 1973; Jolicoeur et al., 1978, 1980; Rondeau et al., 1981]. Recently, we [Ervin and Cooper, unpublished observations] investigated both the parameters that were necessary to make the antagonism of conditioned taste aversion a sensitive screen for anxiolytic drugs and possible mechanisms by which anxiolytics may be affecting conditioned taste aversion and unsuppressed fluid consumption.

Pretreatment with known anxiolytic drugs markedly antagonized the expression of moderate saccharin (SACC) aversions which were conditioned with either 30 mg/kg lithium chloride (LICl; i.p.) or 25 mg/kg 1-5-hydroxytryptophan (1-5-HTP; i.p.). The rank-order of taste aversion antagonism was similar to the rank-order of clinical efficacy in the treatment of generalized anxiety disorder (lorazepam > chlordiazepoxide = diazepam > oxazepam > phenobarbital > meprobamate > chlormezanone) [Lippa et al., 1979]. Chlordiazepoxide had less or no effect in antagonizing stronger SACC aversions conditioned with higher doses of LICI or 1-5-HTP [Rondeau et al., 1981; Ervin and Cooper, unpublished observations], so taste aversion strength is a critical parameter of the taste aversion conflict model.

In the same study, we [Ervin and Cooper, unpublished observations] demonstrated that anxiolytic drugs antagonized the *expression* of conditioned aversions but that anxiolytics neither antagonized nor produced amnesia for the conditioned aversion. When water was conspicuously available in addition to SACC (i.e., two-bottle testing methods), anxiolytic-pretreated rats did not display any significant antagonism of taste aversion. Like ourselves, Riley and Lovely [1978] observed that chlordiazepoxide could antagonize the expression of a moderate conditioned taste aversion when it was measured with a one-bottle testing method but not with a two-bottle testing method. Because Riley and Lovely [1978] also observed that chlordiazepoxide could increase unsuppressed SACC intake, they concluded that the ability of chlordiazepoxide to antagonize the expression of conditioned taste aversion represented a dipsogenic effect but not necessarily an anxiolytic (or disinhibitory) effect. We concluded, however, that rats are not in conflict in the two-bottle taste aversion testing method and that this is why chlordiazepoxide exhibits no disinhibitory effect.

We attempted to understand why anxiolytics do appear dipsogenic under certain circumstances. Although we did observe that some anxiolytics could significantly increase unsuppressed SACC intake under our testing conditions, not all anxiolytics tested did significantly increase unsuppressed SACC intake [Ervin and Cooper, unpublished observations; Jolicoeur et al., 1980]. The antagonism of conditioned taste aversion, therefore, appears to be a more sensitive measure of anxiolytic drug action than increases in unsuppressed fluid intake. Next we compared anxiolytics with activators of homeostatic drinking mechanisms. We observed that 2M NaCl, isoproterenol HCl and histamine diphosphate [Fitzsimons, 1971; Kraly, 1984] significantly increased water consumption in rats maintained on ad libitum water but that chlordiazepoxide did not. In rats maintained on the fluid deprivation schedule (and hence highly motivated to drink), anxiolytics always antagonized the expression of conditioned SACC aversion and sometimes increased unsuppressed SACC intake, but activators of homeostatic drinking mechanisms did not. We also showed that 24 additional hr of fluid deprivation, another way to further activate homeostatic drinking mechanisms, did not antagonize the expression of conditioned SACC aversions like anxiolytics. Anxiolytics, therefore, do not appear to activate homoestatic drinking mechanisms, and anxiolytics appear to affect drinking most when an animal is highly motivated to drink yet moderately motivated to abstain from drinking.

It is easy to see how neophibia and conditioned aversions could produce a suppression of fluid intake, and an effect of anxiolytic drugs on those behaviors is consistent with an anxiolytic effect being expressed as a dipsogenic effect [Poschel, 1971; Cappell and LeBlanc, 1973]. The ability of anxiolytics to increase unsuppressed fluid consumption is a paradox.

This is obviously a dipsogenic effect, but can it be an anxiolytic effect? We see no reason why not. If the neurology of motivation contains both excitatory and inhibitory components, an antagonism of inhibitory components by anxiolytic drugs may produce effects even when a behavior is apparently unsuppressed. Apparently unsupressed behaviors may, in fact, actually be under some basal level of suppression, or increases in unsuppressed behaviors may by a side effect of anxiolytic drugs because of their anxiolytic effects. Besides drinking, other motivated behaviors, such as exploration [Crawley, 1985] and feeding [Cooper, 1980], are increased by anxiolytics, consistent with that idea.

In our previous study of the taste aversion conflict model [Ervin and Cooper, 1983], all drugs active in antagonizing the expression of conditioned taste aversion were those which act upon the GABA-benzodiazepine supramolecular receptor complex [Paul et al., 1981]. In the present study, we tested whether the taste aversion conflict model is sensitive to the novel anxiolytic buspirone. Buspirone is clinically active in the treatment of anxiety [Goldberg and Finnerty, 1979] but reportedly acts through unique neurochemical mechanisms [Riblet et al., 1982; Taylor et al., 1984; Eison and Eison, 1984]. In the present study, we assessed the neurochemical mechanisms of buspirone by comparing it with the effects of lorazepam, diazepam, chlordiazepoxide, oxazepam, phenobarbital, and meprobamate on the antagonism of pentylenetetrazol-induced lethality in mice. To further assess the selectivity of the taste aversion conflict model, we examined the effects of a monoamine oxidase inhibitor, phenelzine sulfate, and several tricyclic antidepressants, imipramine and desipramine, since such drugs can be effective in the treatment of certain anxiety conditions such as panic disorders and phobic disorders [Sheehan et al., 1980; Zitrin et al., 1983]. We also tested the effects of scopolamine, d-amphetamine, and chlorpromazine. Results are discussed in terms of the sensitivity and selectivity of the taste aversion conflict model.

MATERIALS AND METHODS

The Taste Aversion Conflict Model

Male Long-Evans rats (N=357), 8 weeks old, were purchased from Blue Spruce Farms (Altamont, NY) and were group-housed at 23°C on a 12-hr light-dark cycle (lights on from 0600–1800 hr) with free access to Rodent Blox pellets (Wayne Pet Food Division, Continental Grain Co., Chicago, IL) and tap water. After one week, rats were placed in single cages with ad libitum food and water several days before the taste aversion procedure. One day before the first day of taste aversion procedure, rats were deprived of water but not food.

The taste aversion conflict model takes ten test days. At about 1100–1300 hr every day, the racks of rats were individually rolled over to the sink. The water faucet was turned on while drinking tubes were filled with either 0.25% SACC or water, and then attached to cages. The racks were returned to their positions in the room and fluid consumption was measured to the nearest ml following the designated drinking period. On test day 1, tap water was available for 1 hour. On test day 2, tap water was available for 30 min. On test days 3, 4, 5, 6, 7, and 9, tap water was available for 15 min. After the drinking on test day 5, rats were allowed ad libitum water for 48 hours. Then rats were deprived of water for 24 hr before being offered water on test day 6. This interval between test days 5 and 6 allowed rats to rehydrate and allowed experimenters to take a weekend respite. On test day 8, rats were weighed at 0800 hr and SACC, instead of tap water, was made available for 15 min at the usual drinking time. Fifteen minutes after the SACC drinking period, rats received an i.p. injection of either 30 mg/kg LICl or 0.9% NaCl (2ml/kg). On test day 10, rats were weighed at 0800 hr and received an injection of a drug (i.p. or p.o.) or a control injection (2ml/kg 0.9% NaCl, p.o.; or 2 ml/kg 0.5% methyl cellulose, i.p.) 60 min before SACC was made available for 15 min at the usual drinking time.

Rats were tested in three separate groups (n = 117, 120, and 120, respectively). For each group, some rats (n = 12–17) received either LiCl or NaCl on test day 8 and a control

injection pretreatment on test day 10. These were called "aversion" and "control" rats, respectively. The difference between these NaCl- or LiCl-treated rats was used as a measure of the strength of the conditioned aversion, and the scores of a group of LiCl-treated rats which received a particular drug pretreatment on test day 10 (called "treated" rats) were expressed as the % antagonism of this score. (To obtain a % antagonism score for a "treated" rat, the difference of the intake of the "treated" rat and the mean intake of the "aversion" group was divided by the difference between mean intakes of "aversion" and "control" groups, then multiplied by 100.) The scores of "treated" rats were statistically compared with appropriate LiCl-treated, control-pretreated (or "aversion") rats with the two-tailed t test for independent samples.

One set of rats which had received NaCl treatment on test day 8 was administered 1 of 3 doses of buspirone before being offered SACC on test day 10. SACC intakes of these groups of rats were statistically compared with the appropriate NaCl-treated, control-pretreated (or "control") rats with the two-tailed t test for independent samples.

The Antagonism of Pentylenetetrazol-Induced Lethality in Mice

Male CD-1 mice, 16–20 g, were obtained from Charles River Co., and housed 6 per cage at 21°C with free access to food and water. On a test day, mice were housed in plexiglass cages, 6 per cage, and transferred to the testing room. Mice received a test drug (lorazepam, diazepam, chlordiazepoxide, oxazepam, phenobarbital, meprobamate, or buspirone) 30 min before s.c. injection of 125 mg/kg pentylenetetrazol. Alone, this dose of pentylenetetrazol was LD99, and deaths following drug pretreatment were recorded over the 30 min following pentylenetetrazol injection. Anxiolytic-pretreated mice were compared with untreated mice with the two-tailed t test for independent samples. There were at least 12 mice per dose, and the ED_{50} was calculated using 4 doses of a drug by the method of Miller and Tainter [1944].

Drugs

Buspirine HCl was a gift of Mead Johnson Pharaceutical Division (Evansville, IN) and was dissolved in 0.9% NaCl. Scopolamine HCl and d-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO) were also dissolved in 0.9% NaCl. LiCl (Mallinckrodt, St. Louis, MO) and chlordiazepoxide HCl (a gift of Hoffman-LaRoche, Nutley, NJ) were dissolved in double-distilled water. Imipramine, desipramine, phenelzine sulfate, chlorpromazine, sodium phenobarbital (Sigma Chemical Co.), diazepan, oxazepam (gifts of Hoffman-LaRoche) and meprobamate (a gift from Wallace Labs., Cranbury, NJ) were suspended in 0.5% methyl cellulose. Doses were expressed as the base or salt given.

RESULTS

The Effects of Drugs on the Expression of Conditioned Taste Aversion in Rats

In the three groups of rats tested, drinking on the fluid deprivation schedule and the expression of LiCl-induced taste aversion appeared consistent. Upon their second exposure to SACC on test day 10, groups of NaCl-treated "control" rats drank from 11.8(± 1.05) to 12.2(± .94) ml and groups of LiCl-treated "aversion" rats drank 2.4 (± .68) to 4.8 (± .54) ml (Tables 1–3).

The expression on the conditioned SACC aversion was antagonized 95% by pretreatment with chlordiazepoxide, and was strongly antagonized (36–65%) by i.p. or p.o. pretreatment with 1 and 5 mg/kg buspirone (Table 1).

One dose of imipramine and one dose of scopolamine had a very slight antagonism (35 and 22%, respectively) of the expression of conditioned aversion, but desipramine, d-amphetamine, phenelzine, and chlorpromazine had no statistically significant effects (Tables 2, 3). The antagonism of conditioned taste aversion by 16 mg/kg imipramine was not reproducible and was not seen after higher or lower doses (Table 3).

TABLE 1. Effects of Buspirone HCl on Saccharin Consumption of Rats With or Without Conditioned Saccharin Aversion

	Treatment after initial saccharin intake[1]		Treatment before second saccharin exposure[2]			Saccharin consumed during second exposure	% Antagonism of aversion
N	Drug	Dose (mg/kg; i.p.)	Drug	Dose (mg/kg)	Route	(ml; $\bar{x} \pm$ SEM)	($\bar{x} \pm$ SEM)
12	NaCl[3]	—	NaCl[3]	—	p.o.	12.2 ± 0.94	—
17	LiCl	30	NaCl	—	p.o.	4.8 ± 0.54	—
8	LiCl	30	Buspirone	0.5	p.o.	5.0 ± 1.13	2 ± 15.3
8	LiCl	30	Buspirone	1.0	p.o.	8.4 ± 1.31**	48 ± 17.8
8	LiCl	30	Buspirone	5.0	p.o.	9.6 ± 1.15***	65 ± 15.6
8	LiCl	30	Buspirone	10.0	p.o.	6.6 ± 1.46	25 ± 19.9
8	LiCl	30	Buspirone	15.0	p.o.	4.1 ± 0.64	−9 ± 8.7
6	LiCl	30	Buspirone	0.5	i.p.	5.8 ± 2.29	14 ± 31.1
6	LiCl	30	Buspirone	1.0	i.p.	8.2 ± 1.60*	46 ± 21.8
8	LiCl	30	Buspirone	5.0	i.p.	7.5 ± 0.71**	36 ± 9.6
6	LiCl	30	Chlordiazepoxide	7.5	p.o.	11.8 ± 1.45***	95 ± 19.7
8	NaCl	—	Buspirone	1.0	p.o.	11.1 ± 1.41	—
8	NaCl	—	Buspirone	5.0	p.o.	14.8 ± 1.26	—
8	NaCl	—	Buspirone	10.0	p.o.	13.4 ± 1.25	—

[1]On test day 8.
[2]On test day 10.
[3]0.95%; 2 ml/kg.
*$P < 0.02$.
**$P < 0.01$.
***$P < 0.001$.

In rats which did not have conditioned SACC aversion, pretreatment with buspirone (1, 5, and 10 mg/kg, p.o.) on test day 10 had no significant effect on SACC intake (Table 1).

The Effects of Drugs on Pentylenetetrazol-Induced Lethality in Mice

Lorezapam, diazepam, chlordiazepoxide HCl, oxazepam, sodium phenobarbital, and meprobamate anagonized pentylenetetrazol-induced lethality in mice, and the median effective doses for the antagonism of pentylenetetrazol-induced lethality in mice were similar in approximate size and order to the median effective doses for the antagonism of the expression of moderate conditioned taste aversions in rats (Tables 4,5). Unlike other anxiolytics tested, buspirone did not antagonize pentylenetetrazol-induced lethality in mice (Table 5).

DISCUSSION

Buspirone was unlike the benzodiazepines, meprobamate and phenobarbital, because it did not antagonize pentylenetetrazol-induced lethality in mice (Tables 4, 5). This result is consistent with the earlier report that buspirone did not antagonize pentylenetetrazol-induced seizures in rats [Riblet et al., 1982], and these data suggest that buspirone acts through unique neurochemical mechanisms. Other anxiolytics act through the GABA-benzodiazepine supramolecular receptor complex [Paul et al, 1981], but buspirone apparently does not [Skolnick et al., 1984]. Weissman et al. [1984] demonstrated an anticonflict effect of buspirone in squirrel monkeys, and this effect was not antagonized by the benzodiazepine receptor antagonist Ro 15-1788. Buspirone also increased punished responding in pigeons, and this effect was also not antagonized by Ro 15-1788 [Barrett et al., 1986]. Since buspirone is clinically efficacious in the treatment of generalized anxiety disorder [Goldberg and Finnerty, 1979] but acts through unique mechanisms, it represents a novel anxiolytic.

TABLE 2. Effects of Phenelzine, Chlorpromazine, and Imipramine on the Expression of Conditioned Taste Aversion

	Treatment after initial saccharin intake[1]		Treatment before second saccharin exposure[2]			Saccharin consumed during second exposure	% Antagonism of aversion
N	Drug	Dose (mg/kg; i.p.)	Drug	Dose (mg/kg)	Route	(ml; $\bar{x}$ ± SEM)	($\bar{x}$ ± SEM)
16	NaCl	—	Meth. cell.[3]	—	i.p.	11.8 ± 1.05	—
16	LiCl	30	Meth. cell.	—	i.p.	3.8 ± 0.33	—
8	LiCl	30	Phenelzine	12.5	i.p.	4.4 ± 0.80	7 ± 10.0
8	LiCl	30	Phenelzine	25.0	i.p.	3.8 ± 0.92	0 ± 11.5
8	LiCl	30	Phenelzine	50.0	i.p.	2.5 ± 0.82	−16 ± 10.3
8	LiCl	30	Chlorpromazine	0.5	p.o.	3.5 ± 1.44	−4 ± 18.0
8	LiCl	30	Chlorpromazine	1.0	p.o.	4.5 ± 1.24	9 ± 15.5
8	LiCl	30	Chlorpromazine	2.0	p.o.	4.9 ± 0.95	13 ± 11.9
8	LiCl	30	Chlorpromazine	4.0	p.o.	4.9 ± 1.03	13 ± 12.8
8	LiCl	30	Imipramine	2.0	i.p.	2.4 ± 0.50	−18 ± 6.2
8	LiCl	30	Imipramine	4.0	i.p.	2.9 ± 0.64	−12 ± 8.0
8	LiCl	30	Imipramine	8.0	i.p.	4.5 ± 0.98	9 ± 12.3
8	LiCl	30	Imipramine	16.0	i.p.	6.6 ± 1.19*	35 ± 14.9

[1]On test day 8.
[2]On test day 10.
[3]0.5% methyl cellulose; 2 ml/kg.
*$P < 0.001$.

TABLE 3. Effects of Imipramine, Desipramine, Scopolamine, and Amphetamine on the Expression of Conditioned Taste Aversion

	Treatment after initial saccharin intake[1]		Treatment before second saccharin exposure[2]			Saccharin consumed during second exposure	% Antagonism of aversion
N	Drug	Dose (mg/kg; i.p.)	Drug	Dose (mg/kg)	Route	(ml; $\bar{x}$ ± SEM)	($\bar{x}$ ± SEM)
12	NaCl	—	Meth. cell.[3]	—	i.p.	11.9 ± 0.85	—
12	LiCl	30	Meth. cell.	—	i.p.	2.4 ± 0.68	—
8	LiCl	30	Imipramine	8.0	i.p.	3.6 ± 0.80	13 ± 8.4
8	LiCl	30	Imipramine	16.0	i.p.	4.4 ± 0.98	20 ± 10.3
8	LiCl	30	Imipramine	24.0	i.p.	3.6 ± 0.98	13 ± 10.3
8	LiCl	30	Desipramine	1.0	i.p.	2.5 ± 0.50	1 ± 5.3
8	LiCl	30	Desipramine	5.0	i.p.	2.9 ± 0.48	11 ± 3.5
8	LiCl	30	Desipramine	10.0	i.p.	3.9 ± 0.91	15 ± 9.6
8	LiCl	30	Scopolamine	0.01	i.p.	4.5 ± 0.73*	22 ± 7.7
8	LiCl	30	Scopolamine	0.05	i.p.	2.1 ± 0.59	−2 ± 6.3
8	LiCl	30	Scopolamine	0.10	i.p.	2.3 ± 0.65	−2 ± 6.8
8	LiCl	30	Scopolamine	0.50	i.p.	0.5 ± 0.38	−20 ± 4.0
8	LiCl	30	d-Amphetamine	0.25	i.p.	4.1 ± 0.61	18 ± 6.4
8	LiCl	30	d-Amphetamine	0.50	i.p.	2.9 ± 0.55	5 ± 5.8

[1]On test day 8.
[2]On test day 10.
[3]0.5% methycellulose; 2 ml/kg.
*$P < 0.05$.

TABLE 4. Median Effective Doses of Anxiolytic Drugs for the Antagonism of LiCl- and 1-5-HTP-Induced Taste Aversions in Rats and the Antagonism of Pentylenetetrazol-Induced Lethality in Mice

	Median effective dose (mg/kg) for the antagonism of:			
	LiCl-induced aversion[1] ($\bar{x}$ and 95% c.l.)		1-5-HTP-induced aversion[1] ($\bar{x}$ and 95% c.l.)	Pentylenetetrazol-induced lethality[2] ($\bar{x}$ ± SEM)
Anxiolytic	p.o.	i.p.	i.p.	i.p.
Lorazepam	1.5(0.1–3.2)	0.7(0.4–1.2)	0.3(0.2–0.5)	0.2(± 0.1)
Diazepam	3.7(2.4–6.9)	3.0(1.9–5.5)	1.4(1.0–2.8)	0.9(± 0.2)
Chlordiazepoxide	2.5(1.6–3.8)	2.8(2.0–4.5)	2.7(.3–12.5)	2.8(± 0.5)
Oxazepam	7.1(1.6–35.5)	5.9(2.4–11.2)	8.9(5.0–25.0)	1.7(± 0.3)
Phenobarbital	10.8(7.1–14.1)	21.7(15.1–34.7)	14.1(11.5–17.0)	17.0(± 5.0)
Meprobamate	28.2(17.8–44.2)	50.1(39.8–66.1)	49.0(37.9–73.2)	42.3(± 5.2)

[1]These data are from Ervin and Cooper [1983]. Moderate taste aversions were induced with 30 mg/kg LiCl (i.p.) or 25 mg/kg 1-5-HTP (i.p.), and the expression of aversions was significantly antagonized by pretreatment with anxiolytics shown. MED and 95% confidence limits (c.l.) were calculated by the method of Snedecor and Cochran [1967].

[2]Pentylenetetrazol-induced lethality was induced with 125 mg/kg s.c. (LD99), and antagonized by anxiolytics shown. The MED (± SEM) was calculated by the method of Miller and Tainter [1944].

TABLE 5. Effects of Buspirone and Chlordiazepoxide on Pentylenetetrazol-Induced Lethality in Mice

Drug (i.p.)	Dose (mg/kg)	% Mice alive[1]
Buspirone HCl	3.125	0
	6.250	0
	12.5	0
	25.0	0
Chlordiazepoxide HCl	0.75	8
	1.5	17
	3.125	67*
	6.25	92*

[1]Based on 12 mice tested in each group.

*$P < 0.0001$ when compared with mice which received pentylenetetrazol alone ($n = 12$).

One and 5 mg/kg buspirone (i.p. and p.o.) significantly antagonized the expression of a moderate taste aversion by 36–65%, though a consistent dose-response relationship was not seen. Higher and lower doses of buspirone were not statistically significant in altering drinking suppressed by conditioned aversion (Table 1). Although 7.5 mg/kg chlordiazepoxide (p.o.) antagonized the expression of the conditioned taste aversion by 95% (Table 1), the effect of buspirone was still fairly robust. The taste aversion conflict model is very sensitive to buspirone, substantiating the utility of this conflict model.

Under the drinking parameters used here, 1, 5, or 10 mg/kg buspirone (p.o.) neither significantly increased nor decreased unsuppressed SACC consumption in rats which did not have conditioned aversion (Table 1). When parameters are appropriately adjusted, most anxiolytics can be shown to increase deprivation-induced drinking [e.g., Leander, 1983]. It would be interesting to see if buspirone is like other anxiolytics. Buspirone, however, unlike other anxiolytics, has been shown to disrupt the initiation of drinking [Weissman et al., 1984] and to disrupt operant responding for water [Geller and Hartmann, 1982] when tested at doses

which we tested here. Further work is needed to determine how buspirone will alter unsuppressed drinking.

Although 16 mg/kg imipramine (i.p.) did produce a slight but significant antagonism of the expression of conditioned taste aversion in one test (Table 2), that effect was not reproducible and was not seen after lower or higher doses (Table 3). Since phenelzine and desipramine also failed to significantly antagonize the expression of conditioned taste aversion (Tables 2, 3), the taste aversion conflict model is a selective screen for drugs active in the treatment of generalized anxiety disorder [American Psychiatric Association Task Force on Nomenclature and Statistics, 1980; American Medical Association, Council on Drugs, 1983] but not for drugs more selectively active in the treatment of panic or phobic anxiety disorders [Klein, 1964; Sheehan et al., 1980; Zitrin et al., 1983].

Chlorpromazine and d-amphetamine did not produce any significant alteration in the expression of a moderate conditioned taste aversion (Tables 2, 3). Although Rondeau et al. [1981] had previously observed that 0.75 mg/kg chlorpromazine could partially antagonize the expression of a strong LiCl-induced taste aversion, none of our data with 0.5–4 mg/kg chlorpromazine (p.o.) was consistent with that report. One dose of scopolamine, 0.01 mg/kg (i.p.), did produce a very small but statistically significant 22% antagonism of the expression of conditioned taste aversion (Table 3). We are not sure if this represents a small anxiolytic effect or not. If this only represents a false positive effect for the taste aversion conflict model, false positives are only small effects and are readily distinguishable from the more robust effects of anxiolytic drugs.

The taste aversion conflict model is easy to execute in large groups of rats and does not require costly or elaborate equipment. The taste aversion conflict model does require ten test days, but the daily testing is quick and assures consistent motivation and behavioral stability. Measuring the antagonism of pentylenetetrazol-induced seizures or lethality is much quicker than the taste aversion conflict model but it is not sensitive to novel anxiolytics such as buspirone (Table 4). The "thirsty rat conflict model" [e.g. Vogel et al., 1971] can be executed more quickly than the taste aversion conflict model, but the former model often uses 48 hr of fluid deprivation which is extreme and may influence responses to certain drugs. The taste aversion conflict model may be more sensitive to buspirone than the thirsty rat conflict model [e.g., Weissman et al., 1984; Goldberg et al., 1983] and may therefore offer a superior screen for novel anxiolytics. Our results clearly show that the taste aversion conflict model is both sensitive and selective for drugs active in the treatment of generalized anxiety disorder in man.

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