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# Effect of Serotonergic Drugs on Negative Contrast in Consummatory Behavior

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FLAHERTY, C. F., P. S. GRIGSON, M. K. DEMETRIKOPOULOS, M. S. WEAVER, K. L. KRAUSS AND G. A. ROWAN. *Effect of serotonergic drugs on negative contrast in consummatory behavior*. PHARMACOL BIOCHEM BEHAV **36**(4) 799–806, 1990.—The effect of acute and chronic administration of the 5-$HT_{1A}$ agonist buspirone on successive negative contrast was investigated in Experiments 1–6. Contrast in consummatory behavior was induced by shifting rats from a 32% to a 4% sucrose solution. Experiments 1–5 showed that buspirone (0.125, 0.25, 0.5, 1.0, 2.0, 15.0 mg/kg) was ineffective in alleviating contrast or in facilitating recovery from contrast. The 15 mg/kg dose substantially decreased consummatory responding. Experiment 6 showed that the chronic (24 days) administration of buspirone (0.5, 2.0 mg/kg) also did not alleviate contrast. The chronic, but not the acute administration of the 2.0 mg/kg dose decreased consummatory behavior. In Experiment 7 the 5-$HT_{1A}$ agonist gepirone (2.5, 5.0 and 10.0 mg/kg) was also found to be ineffective in reducing contrast but, at the higher doses, decreased overall sucrose intake. Experiments 8 and 9 found that the 5-$HT_2$ antagonists ketanserin (2.0 and 8.0 mg/kg) and ritanserin (0.63 and 2.5 mg/kg) also did not alleviate contrast. Midazolam (1.0 mg/kg), included as a positive control, eliminated contrast. These data suggest that serotonergic mechanisms are not involved in negative contrast.

Buspirone Gepirone Ketanserin Midazolam Ritanserin Sucrose Incentive Contrast

THE negative contrast effect that occurs in consummatory behavior when rats are shifted from a 32% to a 4% sucrose solution is affected by a number of drugs. The benzodiazepines chlordiazepoxide (CDP) and midazolam will substantially reduce or eliminate negative contrast (2, 25, 26); ethanol will also reduce contrast and it acts additively with CDP to alleviate contrast (3,4); finally, both morphine and sodium amobarbital have numerically small but reliable contrast-reducing effects (18, 20, 41). Other agents such as clonidine, pyrilamine, naloxone, and scopolamine are ineffective (2, 22, 27, 41). The results obtained with serotonergic agents have been mixed. Becker (2) found methysergide (3, 6, 12 mg/kg) to be ineffective, but both cyproheptadine (3, but not 6 or 12 mg/kg) and cinanserin (10 and 15, but not 5 and 20 mg/kg) to be effective. These three agents (cinanserin, cyproheptadine, and methysergide) are considered to be general serotonin antagonists. The experiments reported in the present paper are concerned with the effects of drugs more specific for serotonin receptor subtypes.

The novel anxiolytic buspirone, which has 5-$HT_{1A}$ agonist properties, has been found to have antipunishment effects in some operant conflict studies, particularly when pigeons are the subjects (1,46), but it may or may not be effective with rats and monkeys (29, 39, 42, 45). Similarly, buspirone has been found to have anticonflict effects in some studies using a punished drinking procedure (12, 28, 40, 45), but not in others (29,30). There is some indication that buspirone may be more effective in these procedures when a reversed light/dark cycle is used (12). Recently, buspirone and gepirone were reported (5) to have a taming effect in wild rats (*Rattus rattus*). Also, buspirone and gepirone reduce the magnitude of the potentiated startle response (36), but these effects are almost certainly not mediated by the serotonergic actions of buspirone (9,10). In the social interaction test, buspirone has been reported as both effective (7) and ineffective (14). Finally, buspirone is ineffective in the elevated plus maze (38) and in the defensive burying test (8). The pattern of results obtained with buspirone and other 5-$HT_{1A}$ agonists may suggest different subtypes of anxiety tapped by different animal models or it may suggest that some animal models are not predictive of anxiolytic activity in humans (11).

The effects of other manipulations of serotonergic function have also provided both support and the absence of support for a serotonergic mechanism of anxiety. Depletions of serotonin using either 5,7-dihydroxytryptamine lesions or synthesis inhibition by parachlorophenylalanine (PCPA) have produced anticonflict effects in a number of models (33,43), but such treatments have also failed to produce anticonflict effects (29, 34, 35, 44). Similarly, 5-$HT_2$ antagonists have been found to be effective in some

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situations but not others. For example, ritanserin has been reported to show anxiolytic effects in an emergence test (6) but not in a social interaction test, or in water-, or food-motivated conflict tests (6,29).

In the present paper we report the results of nine experiments in which the effects of buspirone, gepirone, ritanserin, ketanserin, and, as a positive control, midazolam were investigated. In Experiment 1, we investigated the effects of buspirone (0.5, 1.0 and 2.0 mg/kg) on the second postshift day, the point of maximal effectiveness of chlordiazepoxide and ethanol; in Experiment 2 the effects of subcutaneous (SC) and intraperitoneal (IP) administration of the 0.5 mg/kg dose of buspirone were compared [it has been reported that SC injections were ten times more potent then IP injections in affecting dopaminergic metabolism in the nucleus accumbens (37)]; in Experiment 3, the 0.5, 1.0 and 2.0 mg/kg doses of buspirone were administered on both the first and second postshift day; in Experiment 4, buspirone (0.125 and 0.250 mg/kg) was given on both the first and second postshift day; in Experiment 5, a dose of 15 mg/kg of buspirone was administered on the second postshift day; in Experiment 6, the effect of chronic (24 days) administration of buspirone (0.5 and 2.0 mg/kg) was investigated; in Experiment 7 and 7a the effects of the buspirone analog gepirone on postshift Day 2 were investigated; in Experiment 8 the effects of the 5-$HT_2$ antagonist ketanserin (2.0 and 8.0 mg/kg) on Day 2 were investigated along with the effects of the benzodiazepine midazolam [1.0 mg/kg, a dose previously shown to be highly effective in reducing contrast (2)]; and in Experiment 9 the effects of the 5-$HT_2$ antagonist ritanserin (0.63 and 2.5 mg/kg) were investigated on the first and second postshift day.

## METHOD

The subjects were 338 naive male Sprague-Dawley derived rats purchased from Blue Spruce or Harlan Sprague-Dawley. The rats were housed singly in standard metal cages with a 14-hour/10-hour light/dark cycle and with water always available. They were deprived to 82% of their free-feeding weight and maintained at that level by once per day feeding for the duration of each experiment. The rats were distributed across experiments as follows: forty rats were used in Experiment 1, 24 in Experiment 2, 24 in Experiment 3, 30 in Experiment 4, 24 in Experiment 5, and 36 in Experiment 6, 36 in Experiment 7, 24 in Experiment 7a, 40 in Experiment 8, and 60 in Experiment 9.

The subjects were tested in Plexiglas cages ($24.5 \times 17.5 \times 18$ cm) configured to receive a drinking spout through a 1 cm diameter hole on one wall of the cage, 7 cm above the hardware cloth floor. A contact relay circuit was used to record licks through a microprocessor. The current flow through the rat was approximately 1 μA as measured by a Simpson model 260 multimeter.

In each experiment one-half of the animals, the shifted groups, received access to 32% sucrose for ten days and then were shifted to 4% sucrose for four days (Group 32-4). The remaining animals, the unshifted groups, received 4% sucrose on all 14 days (Group 4-4). The access period was five minutes each day, timed from the rats' first lick. Each experiment included shifted and unshifted groups injected with the drug or vehicle.

Experiment 1 was designed as a $2 \times 4$ factorial in which shift condition (shifted versus unshifted) and drug condition (isotonic saline, or buspirone, 0.5, 1.0 or 2.0 mg/kg) were varied. The drugs were injected on the second postshift day (Day 12 of the experiment) only. The injections were administered IP 20 min prior to the start of the session.

In Experiment 2 the design and procedure were the same as Experiment 1 except that only the 0.5 mg/kg dose was used in the drug groups and separate groups of shifted and unshifted rats were injected either IP or SC, with drug or saline, on the second postshift day. The pretreatment time of 20 min was the same for both injection routes.

In Experiment 3 the drug doses used were the same as in Experiment 1 (saline, 0.5, 1.0 and 2.0 mg/kg buspirone) and the procedure was similar except that the animals were injected on both the first and second postshift days. Injections were IP 20 min prior to the session.

In Experiment 4 the design and procedure were the same as for Experiment 3, except lower drug doses were used. That is, separate groups were injected with saline or buspirone, either 0.125, or 0.250 mg/kg on both the first and second postshift days.

In Experiment 5 the design and procedure were the same as Experiment 1 except that the drug groups received a 15 mg/kg dose of buspirone. The drug was given IP on the second postshift day 20 min prior to the start of the session.

In Experiment 6 two buspirone doses, 0.5 and 2.0 mg/kg, and a saline control, were administered chronically. Drug treatment was initiated 10 days prior to the start of the preshift phase of the experiment and continued through the 10 preshift days and the four postshift days. Thus, there was a 20-day period of drug administration prior to the first shift day. The drugs were given IP, approximately at the same time each day, 20 minutes before the start of each sucrose session.

Experiment 7 was analogous to Experiment 1 except that gepirone (5.0 or 10.0 mg/kg) or saline was administered IP on the second postshift day. The drugs were administered 30 minutes prior to the start of the session. Experiment 7a was similar but only one dose of gepirone (2.5 mg/kg) was administered with saline as a control.

In Experiment 8 the animals were injected on the second postshift day with either ketanserin (2.0 or 8.0 mg/kg), midazolam (1.0 mg/kg), or saline. The ketanserin was administered IP 30 minutes prior to the session, the midazolam 20 minutes prior to the session. One-half of the saline controls were injected at each pretreatment time.

In Experiment 9 ritanserin (0.63 or 2.5 mg/kg) was administered on either the first or second postshift day. The low dose was dissolved in tartaric acid and the high dose in a mixture of lactic acid and tartaric acid. Half of the vehicle controls were injected with each vehicle. Injections were made one hour prior to the start of the session. This experiment was conducted in two replications.

The data in all experiments were analyzed (analysis of variance) in terms of lick frequencies. The postshift data were also analyzed in terms of proportion of preshift lick frequencies [licks on Day 11/(licks on Day 10 + licks on Day 11), etc.]. Post hoc comparisons following reliable analysis of variance effects were conducted using the least significant difference test ($p = 0.05$).

## RESULTS

### *Experiment 1*

One rat was dropped from the experiment for failing to lick the sucrose solution. On the last preshift day, the rats given access to 32% sucrose licked more than the rats given access to 4% sucrose [Sucrose × Day, $F(4,116) = 31.88$, $p < 0.001$, followed by least significant difference (lsd) test, $p < 0.05$].

The data for each postshift day are presented in Fig. 1 in terms of proportion of preshift lick frequency. The shifted animals licked relatively less than the unshifted animals, $F(1,31) = 110.01$, $p < 0.001$, and this contrast effect tended to recover across the postshift period [Sucrose × Day, $F(3,85) = 13.52$, $p < 0.001$]. Buspirone (0.5, 1.0, 2.0 mg/kg), which was injected on the second postshift day (Day 12), had no reliable effect on contrast

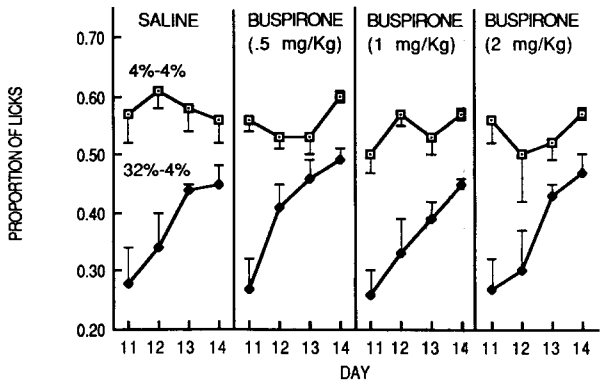


FIG. 1. Mean proportion of licks across the postshift period [Day 11/(Day 10 + Day 11)], etc., for the shifted (32-4) and unshifted (4-4) groups injected with either saline or buspirone (0.5, 1.0, 2.0 mg/kg). Injections were given only on the second postshift day (Day 12).

[Drug, $F(3,31)=1.73$, $p>0.15$; Drug × Day, $F(9,85)=1.13$, $p>0.35$; Drug × Sucrose and Drug × Sucrose × Day, $Fs<1.00$].

The 0.5 mg/kg dose of buspirone appeared to have more of an effect than the two higher doses, but this effect did not approach reliability in the above analyses, or when the data for the injection day were analyzed separately (Drug × Sucrose, $F<1.00$), or when the data for the shifted animals only were examined on the injection day only ($F<1.00$). Analyses of the lick frequency data (rather than proportions) yielded the same conclusions.

*Experiment 2*

There was an apparent tendency for the shifted animals injected IP with buspirone (0.5 mg/kg) to recover from contrast on the second postshift day (Fig. 2). However, although the overall contrast effect was reliable, $F(1,16)=10.90$, $p<0.01$, neither the effect of buspirone (all ANOVA terms, $F<1.00$) nor route of administration (all ANOVA terms, $Fs<1.00$) approached reliability.

*Experiment 3*

Buspirone (0.5, 1.0, 2.0 mg/kg) had no effect on contrast on either the first or second postshift day (Fig. 3). There was an overall negative contrast effect, $F(1,15)=51.77$, $p<0.001$, which tended to recover across the postshift period [Sucrose × Day, $F(3,45)=9.94$, $p<0.001$]. Neither the main effect of the drug treatment, nor any interaction of drug and shift and/or day approached reliability (all $Fs<1.00$). Analysis of the data in terms of proportions yielded the same pattern of results.

*Experiment 4*

The low doses of buspirone (0.125, 0.250 mg/kg) did not have an effect on contrast on either the first or second postshift day. There was an overall negative contrast effect, $F(1,24)=28.69$, which diminished across the postshift period [Sucrose × Day, $F(3,24)=10.57$, $p<0.001$]. The main effects of the drug and all interactions of the drug with the shift condition were unreliable [Drug, $F(2,24)=1.22$, $p>0.05$; Sucrose × Drug, $F(2,24)=1.20$, $p>0.05$; Sucrose × Drug × Day, $F<1.00$]. There was a numerical suggestion that the 0.250 mg/kg may have had a small contrast-reducing effect on the second postshift day, however analysis of this day (Day 12) alone revealed no indication of a reliable drug action [Drug, $F(2,24)=1.72$, $p>0.20$; Shift × Drug, $F<1.00$]. The data for this experiment are not illustrated.

*Experiment 5*

The 15 mg/kg dose of buspirone eliminated consummatory

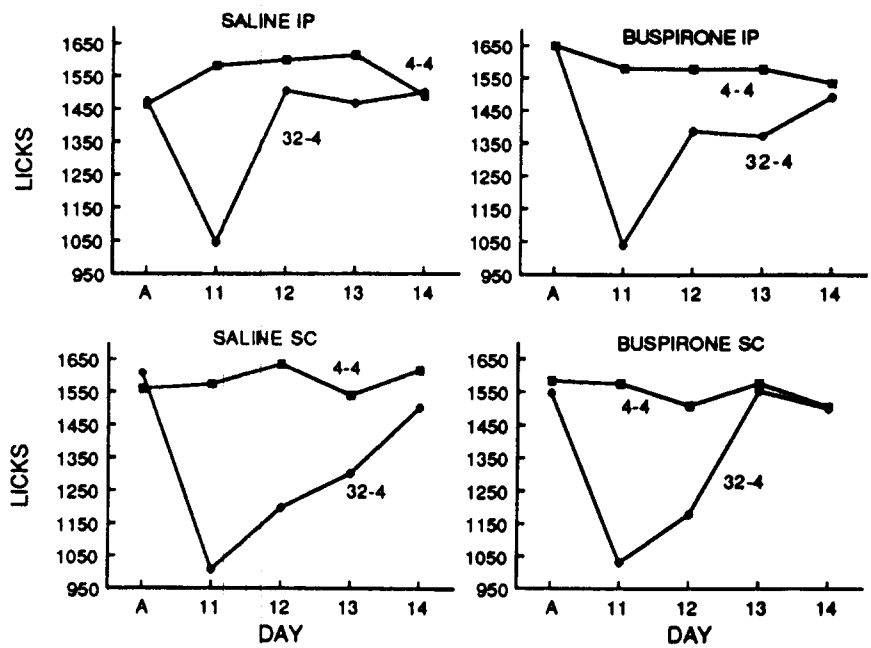


FIG. 2. Mean lick frequency on the terminal acquisition day (A) and the four postshift days for shifted (32-4) and unshifted (4-4) groups. The groups labelled "buspirone" were injected with 0.5 mg/kg of the drug either IP or SC on the second postshift day (Day 12).

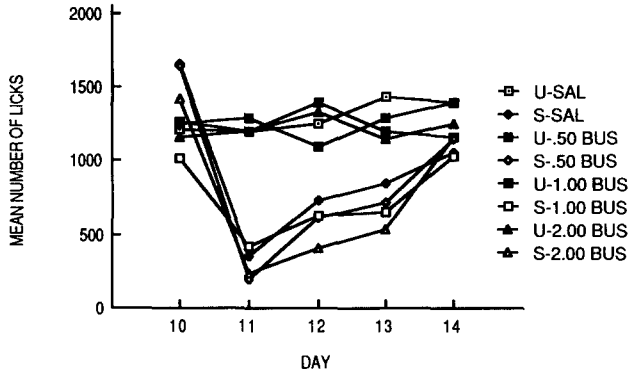


FIG. 3. Mean lick frequency at the end of acquisition (Day 10) and on each postshift day (11–14) as a function of shift condition (U = unshifted and S = shifted) and buspirone treatment. The drug treatments were given on *both* the first and second postshift days (Days 11 and 12).

behavior. As is evident in Fig. 4, contrast occurred in the saline group and recovered across the postshift period [Sucrose × Day, $F(3,30) = 19.02$, $p<0.001$]. Contrast also occurred in the drug group on the first postshift day, when no drug was administered [Sucrose × Day, $F(3,30) = 15.55$, $p<0.001$]. However, essentially no licking occurred in the drugged animals on the injection day [Day, $F(3,30) = 85.28$, $p<0.001$; followed by lsd tests which showed that lick frequency on Day 12 was less than on all other days] and no contrast was present in either group on the last two postshift days (lsd tests).

*Experiment 6*

The chronic administration of buspirone affected sucrose intake.

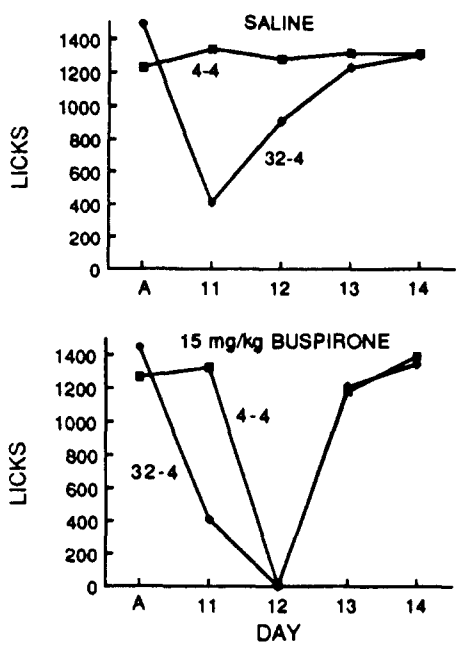


FIG. 4. Terminal acquisition (A) and daily postshift lick frequencies as a function of shift condition and drug treatment. The drug was administered on only the second postshift day (Day 12).

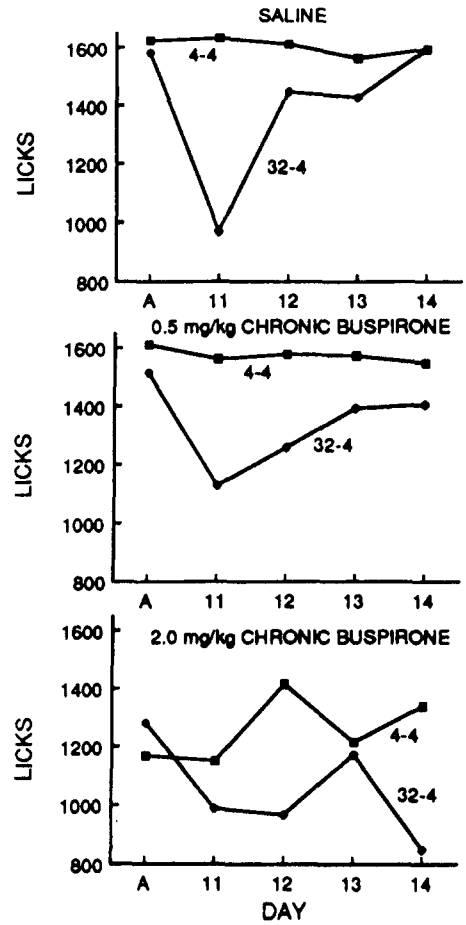


FIG. 5. Terminal acquisition and daily postshift lick frequencies as a function of shift condition and drug condition. The drug treatments were administered for twenty days before the shift in sucrose concentration and throughout the postshift period.

Over the ten-day preshift period there was a reliable drug effect, $F(2,29) = 11.42$, $p<0.001$, which indicated that the 2 mg/kg group licked less than the saline and 0.5 mg/kg groups (lsd tests). There was no terminal effect of sucrose concentration on licking ($F<1.00$) and the effect of the drug did not vary as a function of sucrose concentration [Sucrose × Drug, $F(2,29) = 1.41$, $p>0.25$; Sucrose × Drug × Day, $F<1.00$].

On the terminal preshift day (Day 10) there was no reliable difference in the intake of the two sucrose solutions, $F(1,30) = 2.09$, $p>0.15$. There was an overall effect of buspirone, $F(2,30) = 8.55$, $p<0.01$, which indicated that the 2 mg/kg dose reliably reduced intake compared to the saline controls and the 0.5 mg/kg drug group (lsd test, $p = 0.05$). The effects of the drug did not interact with the different sucrose concentrations ($F<1.00$).

The shift to 4% led to a reliable overall negative contrast effect, $F(1,30) = 16.50$, $p<0.001$, which tended to diminish across the postshift period, $F(3,90) = 4.11$, $p<0.01$. These data are presented in Fig. 5. There was also a reliable drug effect, $F(2,30) = 10.71$, $p<0.001$, which indicated that the group given the 2.0 mg/kg dose licked less than the other two groups. A reliable Sucrose × Drug × Day effect, $F(6,90) = 4.02$, $p<0.01$, indicated that the contrast was different across the postshift period for the three groups. Subsequent analyses (lsd test, $p = 0.05$) indicated

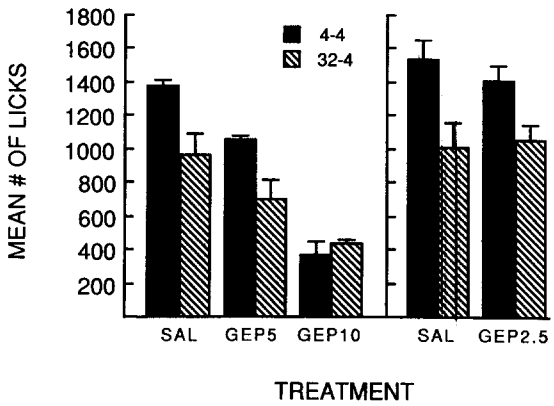


FIG. 6. Lick frequencies on the second postshift day (Day 12) in shifted (32-4) and unshifted (4-4) animals administered gepirone or saline.

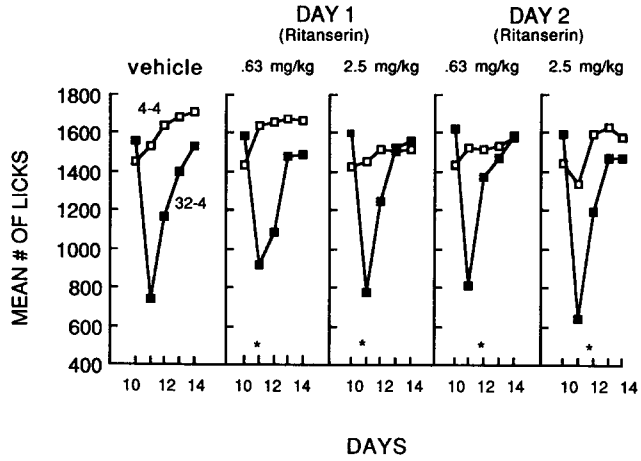


FIG. 8. Terminal acquisition (Day 10) and daily postshift (11–14) lick frequencies in animals injected with ritanserin or vehicle. The drugs were injected on *either* the first (Day 11) or the second (Day 12) postshift day.

that lick frequencies were lower and that contrast was more erratic and prolonged in the high-dose buspirone group. Specifically, contrast was reliable in the saline group on only the first postshift day; in the 0.5 mg/kg buspirone group on the first two postshift days; and in the 2.0 mg/kg group on the second and fourth postshift days. In addition, the unshifted animals given the 2.0 mg/kg dose of buspirone licked reliably less than the unshifted saline group and the unshifted 0.5 mg/kg buspirone group on the first and third postshift days. Also, the shifted 2.0 mg/kg group licked less than the shifted saline and 0.5 mg/kg groups on the second and fourth postshift days.

Analysis of the data in terms of proportion of preshift lick frequency presented a generally similar pattern of reliable findings; notable exceptions being that there was no overall drug effect, $F(2,30) = 1.92$, $p > 0.15$, indicating that the postshift drug effects continued the preshift pattern, and that the 0.5 mg/kg drug group, like the saline group, showed a reliable contrast effect on the first postshift day only.

*Experiments 7 and 7a*

Gepirone (5.0 and 10.0 mg/kg) did not reduce negative contrast, but the drug did affect sucrose intake. Analysis of the last preshift day and all four postshift days indicated a reliable Sucrose

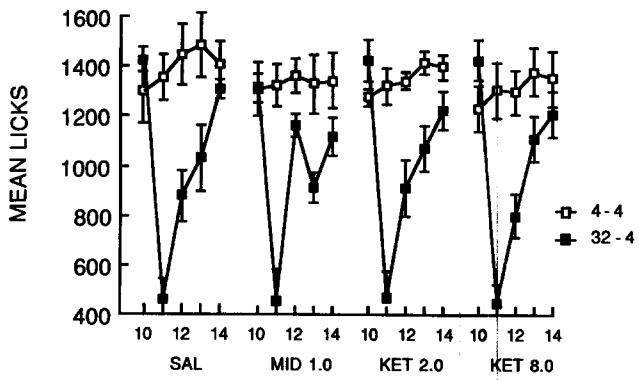


FIG. 7. Terminal acquisition (Day 10) and daily postshift (11-14) lick frequencies as a function of drug condition. The drugs (midazolam or ketanserin) were administered only on Day 12.

by Day interaction, $F(4,120) = 32.26$, $p < 0.001$. Subsequent analysis with the lsd test ($p = 0.05$) showed that the 32-4 group licked more than the 4-4 group on the last preshift day, but less than these unshifted controls on all four postshift days.

The data from the second postshift day, the day that the drug was administered, are presented in the left panel of Fig. 6. There was a reliable contrast effect, $F(1,30) = 11.59$, $p < 0.002$.

In addition, the drug reduced lick frequency in a dose-dependent fashion in both shifted and unshifted animals. Contrast remained reliable when the 5 mg/kg dose was administered, but not when the 10 mg/kg dose was administered. This loss of contrast was due to a substantial reduction in lick frequency in the 4% control group, not to any enhancement of lick frequency in the shifted group [Drug, $F(2,30) = 42.79$, $p < 0.001$; Drug × Sucrose interaction, $F(2,30) = 4.67$, $p < 0.02$; followed by lsd tests].

The low dose of gepirone administered in Experiment 7a (2.5 mg/kg) did not reduce sucrose intake and it had no effect on contrast. These data are presented in the right panel of Fig. 6. Analysis of these data revealed a reliable contrast effect, $F(1,20) = 15.88$, $p < 0.001$, but no effect of the drug (Drug and Sucrose × Drug, $Fs < 1.00$).

Thus, both 5-$HT_{1A}$ agonists, buspirone and gepirone, failed to influence contrast, but both decreased overall sucrose intake under certain dosages.

*Experiment 8*

Midazolam, but not ketanserin, eliminated negative contrast. The data presented in Fig. 7 show that a large negative contrast effect occurred in all groups on the first postshift day [Shift × Drug × Day, $F(12,128) = 2.00$, $p < 0.05$] followed by lsd tests ($p = 0.05$). On the second postshift day, the day the drug was administered, degree of contrast was equivalent in the saline control group and in the two groups administered ketanserin. However, the administration of midazolam statistically eliminated contrast, which returned again on the third postshift day (lsd, $p = 0.05$), when no drug was administered.

*Experiment 9*

Ritanserin had no effect on degree of contrast. These data are presented in Fig. 8. Analysis of Days 10–14 showed a reliable

Sucrose × Day term, $F(4,160)=70.94$, $p<0.001$, subsequent analysis of which showed that the 32-4 group licked more than the 4-4 group on the last preshift day, but less on the first three postshift days (lsd, $p=0.05$).

This negative contrast effect was uninfluenced by drug treatment (all Fs<1.00). Examination of the data in terms of proportion of preshift lick frequency produced a similar pattern of results. Similarly, analysis of the first postshift day alone revealed a reliable contrast effect, $F(1,24)=72.69$, $p<0.001$, which was uninfluenced by ritanserin (Sucrose × Drug, F<1.00). Analysis of the second postshift day alone, where there appeared to be a small effect of the 0.63 mg/kg dose of ritanserin (see Fig. 8) showed an overall contrast effect, $F(1,24)=18.70$, $p<0.001$, which was not altered by the drug [Sucrose × Drug, $F(2,24)=1.56$, $p>0.20$].

## DISCUSSION

The first seven experiments were concerned with the effects on contrast of the 5-$HT_{1A}$ agonists, and reputed anxiolytics, buspirone and gepirone. There was no indication in any experiment that the acute administration of buspirone (0.125, 0.250, 0.50, 1.0, 2.0, 15.0 mg/kg) would alleviate successive negative contrast in consummatory behavior. There was also no indication of differential effects with IP versus SC administration or with the administration of the drug on the first or second postshift day. The acute administration of the 15 mg/kg dose virtually eliminated consummatory behavior, but with no residual effect on the next day. The chronic administration of the 2 mg/kg dose of buspirone decreased consummatory behavior independently of the concentration of sucrose available. Chronic administration of the drug did not alleviate contrast. If anything, the higher dose may have prolonged contrast, but the postshift consummatory behavior of this group (2 mg/kg) was erratic and the apparent prolongation of contrast may be more related to the consummatory effects of the drug than to contrast-related mechanisms per se. Similarly, the buspirone analog, and more selective 5-$HT_{1A}$ agonist gepirone, did not reduce contrast but dose-dependently reduced overall lick-frequency for sucrose.

Experiments 8 and 9 showed that the 5-$HT_2$ antagonists ketanserin and ritanserin also did not reduce contrast and, with the doses administered, did not interfere with consummatory behavior. However, midazolam, included as a positive control, statistically eliminated contrast when administered on the second postshift day, replicating previous results reported from this laboratory (2).

The clear ineffectiveness of the serotonergic agents employed in these experiments in alleviating the depressive effects of reward reduction contrasts with the effectiveness of the benzodiazepines and ethanol (2–4, 17, 24, 26).

However, not all serotonergic agents have been ineffective in contrast. The results obtained with serotonin-relevant drugs investigated thus far in the contrast paradigm are summarized in Table 1. Only the general antagonists cinanserin and cyproheptadine have reduced contrast. Becker (2) found both drugs, but not the similarly classified methysergide, to be effective when administered on the second postshift day. Recently, we have obtained preliminary data suggesting that cyproheptadine (3 and 6 mg/kg) also potently, more potently than any other psychoactive agent that we have investigated, moderates the initial occurrence of contrast (23,32). Furthermore, Grigson found that the administration of PCPA (which produced an approximate 90% reduction in serotonin levels, as measured in the striatum) had no effect on negative contrast. More importantly, Grigson also found that this level of serotonin reduction did not interfere with the effectiveness of cyproheptadine in reducing contrast. Given the data obtained in the present experiment, Becker's finding with methysergide, and Grigson's findings with PCPA, it would seem the effects of cyproheptadine on contrast, and possibly those of cinanserin, are mediated through a nonserotonergic mechanism. The mode of action of these drugs, as they affect contrast, is currently under investigation.

TABLE 1

SEROTONIN-RELATED AGENTS USED IN CONSUMMATORY NEGATIVE CONTRAST

| Day 1 | Day 2 |
|---|---|
| Cyproheptadine (3,* 6* mg/kg) | Cyproheptadine (3,* 6, 12 mg/kg) |
| — | Cinanserin (5, 10,* 15*, 20 mg/kg) |
| — | Methysergide (3, 6, 12 mg/kg) |
| Buspirone (0.125, 0.25, 0.5, 1.0, 2.0 mg/kg) | Buspirone (0.125, 0.25, 0.5, 1.0, 2.0, 15 mg/kg) |
| Buspirone (chronic) (0.5, 2.0 mg/kg) | Buspirone (chronic) (0.5, 2.0 mg/kg) |
| — | Buspirone (IP vs. SC) (0.5 mg/kg) |
| — | Gepirone (2.5, 5, 10 mg/kg) |
| — | Ketanserin (2, 8 mg/kg) |
| Ritanserin (0.63, 2.5 mg/kg) | Ritanserin (0.63, 2.5 mg/kg) |
| PCPA (subchronic) (150, 300 mg/kg) | PCPA (subchronic) (150, 300 mg/kg) |

The asterisks indicate drug doses that had contrast-reducing effects.

The present data also suggest that the mechanisms involved in occurrence of, and recovery from, negative contrast must be different from those involved in other "anxiety" related models (15,31). For example, buspirone is unequivocally effective in reducing the magnitude of potentiated startle. Interestingly, both cinanserin and cyproheptadine are ineffective in altering potentiated startle (9). Thus, in spite of some similar pharmacological effects, such as in the case of benzodiazepines and barbiturates (10,16), a broader pharmacological profile suggests differences in mechanisms producing potentiated startle and negative contrast. One difference may be the involvement of a approach/withdrawal conflict in regard to consuming the postshift solution (26) in the negative contrast procedure, whereas the potentiated startle paradigm would probably not involve conflict.

Differences in the effectiveness of serotonergic agents in contrast and other animal models that would, a priori, seem to involve conflict remain difficult to explain, particularly since the drug is reported to be effective as an anxiolytic in humans (13). It is possible that the various procedures may differ in the sources or mechanisms of conflict. For example, Geller-Seifter-related procedures involve apparent conflict between an operant response for a needed substance and a concurrent punishment (usually shock). The punished drinking procedure involves apparent conflict be-

tween consummatory responding for a needed substance and concurrent shock. The contrast paradigm does not involve a physically aversive event.

Like contrast, the social interaction test and the elevated plus maze do not involve a physically aversive stimulus. However, these latter two tests may differ from contrast in the source of psychological conflict. That is, the conflict in the social interaction and elevated plus maze tests may be between the competing tendencies for investigation and caution elicited by novel conspecifics and/or environmental novelty, rather than the conflict between acceptance/rejection of a reduced reward elicited by the contrast procedure. The defensive aggression test used by Blanchard and colleagues (5) may be an extreme form of the social interaction test.

Soubrie (44) proposed a model in which diminished functioning of the serotonergic system acts not to reduce anxiety per se but to increase responding under conditions in which it would normally be inhibited ("impulsiveness"). Soubrie also states specifically that reward contrast might be one condition in which serotonergic antagonism might act to alleviate suppressed responding [(44), pp. 325 and 326], although the experiments he cited did not involve standard contrast manipulations. The general failure of manipulations of the serotonergic system to influence contrast in the present experiments casts doubt on the applicability of Soubrie's model to successive negative contrast involving consummatory behavior. Perhaps a more appropriate contrast procedure in which to examine Soubrie's model would be anticipatory contrast (19, 21, 28), a paradigm in which responding to one solution is suppressed when it is followed, after a time period, by the availability of a preferred solution. This is a procedure in which CDP is ineffective in altering contrast (28).

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