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Effect of Chlorpromazine and Haloperidol on Negative Contrast

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FLAHERTY, C. F., H. C. BECKER, S. CHECKE, G. A. ROWAN AND P. S. GRIGSON. *Effect of chlorpromazine and haloperidol on negative contrast.* PHARMACOL BIOCHEM BEHAV **42**(1) 111-117, 1992.—Rats shifted from 32 to 4% sucrose consume substantially less of the 4% solution than animals that have not had prior experience with the 32% sucrose. This negative contrast effect was not substantially influenced by chlorpromazine (1, 3, and 5 mg/kg) or haloperidol (0.1, 0.5, and 1.0 mg/kg). Haloperidol decreased overall lick frequency, but this decrease occurred proportionately in shifted and unshifted rats, leaving contrast intact. The benzodiazepine flurazepam (5, 10, and 20 mg/kg), included as a positive control, reduced contrast at the two highest doses. The results suggest that neuroleptics do not disrupt consummatory contrast and that dopaminergic antagonists may not influence reward relativity.

Chlorpromazine Haloperidol Flurazepam Neuroleptic Sucrose Contrast

THE negative contrast effect that occurs in consummatory behavior when rats are shifted from a 32 to a 4% sucrose solution is alleviated by a number of drugs with anxiolytic action, including chlordiazepoxide (CDP), midazolam, ethanol, morphine, and sodium amobarbital (1,2,16,17,34). Of these anxiolytics, the benzodiazepines are the most effective in promoting recovery from contrast.

Nonanxiolytics such as clonidine, pyrilamine, naloxone, and scopolamine have been found to have no effect on contrast (17,23). Recent experiments with serotonergic agents have led to mixed results. Whereas the nonspecific 5-hydroxytryptamine (5-HT) antagonist cyproheptadine has potent effects both in promoting recovery from contrast and in preventing its occurrence 1,23), other compounds, such as the 5-HT_2 antagonists ketanserin and ritanserin, the 5-HT_{1A} agonists buspirone and gepirone, and the general antagonist methysergide, have been ineffective (18).

To date, there are relatively little data concerning the effects of neuroleptics on contrast. Such data are of interest because neuroleptics disrupt operant behavior supported by a variety of positive reinforcers—an outcome often interpreted in terms of an "anhedonic" effect of the drugs (48). While there is no doubt that neuroleptics disrupt reinforced operant and consummatory behavior, there is doubt that the effects directly parallel the withdrawal of reinforcement [e.g., (3,21, 44,46)].

The above-cited studies have been concerned with the *absolute* effects of a reinforcer and, to our knowledge, there have been no studies of the influence of neuroleptics on *relative* reinforcement other than two runway contrast studies and one operant study described below.

EXPERIMENT 1

Early animal tests showed that the neuroleptic chlorpromazine (CPZ) had a general disruptive effect on both schedule control and stimulus control [e.g., (7,26,37,38,45)]. An exception to this pattern was reported by Terrace (41), who found that CPZ disrupted multiple schedule performance when pigeons were trained in a standard fashion but not when they were trained using a "fading" or errorless procedure.

The general pattern of disrupted performance apparently does not apply to negative contrast effects. The only two experiments that seem to have addressed this problem were conducted in runways and they found that CPZ did not influence negative contrast, even though it did have an overall deleterious effect on runway performance (32,33). However, positive behavioral contrast was found to be eliminated in three experiments by CPZ (4).

There have been no studies of the effects of CPZ on contrast in consummatory behavior—the procedure used in the majority of psychopharmacological studies of negative contrast. Data on the effects of neuroleptics on contrast in consummatory behavior would also be of interest because there is not a one-to-one correspondence between contrast in consummatory behavior and contrast in runway behavior (5,15).

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The effects of CPZ (1, 3, and 5 mg/kg) were examined separately on the first and second day following a shift from 32 to 4% sucrose. The drug was administered to separate groups on either the first or second postshift day because earlier studies have indicated that different processes may be involved in the initial occurrence of contrast and subsequent recovery from contrast and that some compounds may be differentially effective in these circumstances (17,19). The doses were selected to parallel those used in the runway contrast studies (32,33).

METHOD

Animals

Eighty-four male Sprague-Dawley-derived rats purchased from Blue Spruce were used as subjects. Animals were approximately 90 days old at the start of the experiment. They were deprived to 82% of their free-feeding weight and maintained at that level by once-per-day feeding, but water was continuously available. A 14L:10D cycle was in effect throughout the experiment and animals were run approximately 2 h into the light phase of the cycle.

Apparatus

The experiment was conducted in six identical metal grid cages (24.5 × 17.5 × 18 cm). A centrally located hole, 1 cm in diameter and 7 cm above the cage floor, was present in one wall. Sucrose solutions were presented in a graduated cylinder with a metal spout. Licks were recorded through a contact relay circuit.

Procedure

Rats were randomly assigned to 14 groups, 7 of which received 4% sucrose throughout the experiment and 7 of which received 32% sucrose for the first 8 days of the experiment and then were shifted to 4% for the remaining 4 days. The seven subgroups of each shift condition differed in drug treatment. One subgroup was injected with isotonic saline on each of the first 2 postshift days. The remaining six groups received CPZ injections either 1, 3, or 5 mg/kg on either the first or the second postshift day. On the day these subjects were not injected with the drug, they were injected with saline. No injections were administered on the third postshift day.

Access was given to the sucrose solutions for 5 min each day, beginning with each rat's first lick. The drugs were administered IP 2 h prior to the test session. The sucrose solutions were mixed daily by weight [sucrose/(sucrose plus water)] from commercial cane sugar and tapwater. All unshifted groups were run first each day.

To equate for individual differences on the last preshift day, the postshift data were analyzed in terms of proportion of preshift lick frequency [i.e., lick frequency on first postshift day/(lick frequency on first postshift day + lick frequency on last postshift day), etc.]. The proportion data were converted to arcsine proportion for purposes of analysis. This same procedure was used in all three experiments.

RESULTS

One animal was dropped from the experiment for failing to lick the sucrose solution during the preshift period.

On the last preshift day, animals receiving the 32% solution licked at a higher frequency (M = 1448) than animals receiving the 4% solution (M = 796), $F(1, 69) = 118.20$, $p < 0.001$. The drug treatment, which was a pseudovariable at this point, did not have a reliable effect ($F < 1.00$).

On each of the first 2 postshift days, the data for the groups that received the drug injection on that day were compared to that of the saline control group. The groups that received the drug injection on the alternative day were analyzed separately. In the case of animals injected on the first postshift day, the shifted animals licked less than the unshifted animals, $F(1, 38) = 72.43$, $p < 0.001$, but this contrast effect was not altered by CPZ [drug, $F < 1.00$, drug × shift, $F(3, 38) = 1.69$, $p > 0.15$]. These data are presented in the top panel of Fig. 1. The groups receiving saline on the first postshift day (but the drug on the second postshift day) showed an overall contrast effect, $F(1, 39) = 99.98$, $p < 0.001$, that did not differ as a function of drug condition assignment ($F < 1.00$). These data are not shown.

On the second postshift day, there was an overall contrast effect, $F(1, 39) = 43.58$, $p < 0.001$, that was not reliably influenced by the CPZ injection [drug, $F < 1.00$, drug × shift, $F(3, 39) = 2.48$, $p = 0.076$]. Inspection of the data presented in the bottom panel of Fig. 1 suggests that the nearly reliable drug × shift interaction might be primarily due to the decline

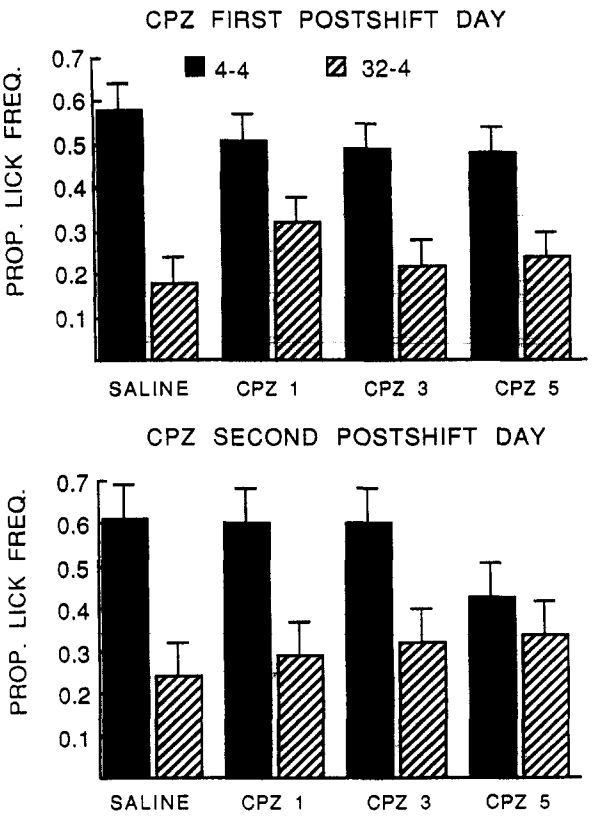

FIG. 1. Lick frequency during the postshift period expressed as a proportion of terminal preshift lick frequency [day 9/(day 8 + day 9) and day 10/(day 8 + day 10)] as a function of drug condition. Top, rats injected with chlorpromazine on the first postshift day (day 9); bottom, rats injected with chlorpromazine on the second postshift day (day 10). Groups labeled 32–4 received 32% sucrose for the first 8 days and were then shifted to 4% sucrose for the remainder of the experiment; groups labeled 4–4 were maintained on 4% sucrose throughout the experiment.

in lick frequency in the unshifted group administered the 5-mg/kg dose of CPZ. To verify this impression, the shifted and unshifted groups were analyzed separately. The results of this analysis revealed that there was no effect of the drug in the shifted animals ($F < 1.00$), nor was there a reliable effect of the drug in the unshifted animals, $F(3, 19) = 2.12$, $p = 0.13$. Thus, the tendency for the 5-mg/kg dose of CPZ to influence intake differentially in the unshifted group did not reach statistical reliability.

Analysis of the second postshift day data for the groups that had been injected with CPZ on the first postshift day revealed a reliable negative contrast effect, $F(1, 39) = 73.79$, $p < 0.001$, that was not affected by the drug administration on the previous day [drug, $F(3, 39) = 1.61$, $p > 0.20$, drug $\times$ shift, $F(3, 39) = 2.45$, $p = 0.078$]. These data are not illustrated. Examination of the drug $\times$ shift means, differences among which were only of marginal reliability, indicated no systematic residual effects of the previous drug treatment and analysis of the shifted and unshifted groups separately revealed that there was no reliable effect of previous drug administration in the shifted groups, $F(3, 20) = 2.49, p = 0.09$, or in the unshifted groups, $F(3, 19) = 1.51, p = 0.24$.

Analysis of all groups on the third postshift day, when no drug was administered, indicated that contrast was still maintained, $F(1, 69) = 124.05$, $p < 0.001$, and this contrast effect was unaltered by previous drug history ($F < 1.00$).

DISCUSSION

The acute administration of CPZ failed to influence negative contrast. The only effect of the drug was an apparent rate-dependent alteration in shifted and unshifted animals at the highest dose of CPZ on the second postshift day. This effect failed to attain reliability by conventional a priori tests, probably because the means obtained at the three lower doses are all quite similar, thus weighing against the deviation obtained at the high dose. Nevertheless, it is clear that the effect of CPZ was more to reduce the unshifted animals' lick frequency than to increase the shifted animals and, thus, could not be considered a contrast-reducing effect of the drug. The lack of influence of acutely administered CPZ on contrast is congruent with the failure of chronic administration of CPZ to influence negative contrast obtained in runway performance (32,33). The inability of CPZ to alter negative contrast, over a range of doses [1, 3, and 5 mg/kg in this study and in the Rosen and Tessel (33) study; 10 mg/kg in the Roberts and Pixely (32) study], is surprising given the many studies showing that the drug tends to disrupt reinforced behavior in general.

The one study that did demonstrate an effect of CPZ on contrast used a high dose (10 mg/kg) and the effect was to prevent the occurrence of positive behavioral contrast (4). Positive behavioral contrast involves an increase in rate of responding to one component of a multiple schedule when reinforcement level in the alternative component is decreased. The failure to find such positive contrast could be related to motoric or sedative effects of CPZ rather than to a specific effect of the drug on reinforcement relativity per se. Indeed, the CPZ-treated pigeons in Bloomfield's study (4) showed a lower level of overall responding and Bloomfield reported that the birds were "docile and sleepy" (p. 175).

Chlorpromazine has such a broad spectrum of activity (26,27) that its effects, or lack of effects, are difficult to relate directly to dopaminergic processes, the focus of the anhedonia hypothesis (48). It could be the case that a contrast-influencing effect of one aspect of CPZ's activity is offset by another aspect of the drug's activity. To obtain clearer evidence of the dopaminergic antagonist activity of neuroleptics on contrast, a second experiment was conducted using haloperidol (HAL).

EXPERIMENT 2

Haloperidol, a more potent and specific neuroleptic than CPZ (25), has been commonly used in studies of the dopaminergic basis of reward. The anhedonia hypothesis (48,49) stimulated many studies that attempted to analyze the effects of dopamine antagonists in regard to their ability to block reinforcement, blunt reinforcement, and produce performance deficits that mimic some aspects of reinforcement removal (13). Although disruption of the mesocorticolimbic dopamine system does interfere with the reinforcing effects of intracranial self-stimulation and aspects of cocaine self-administration and amphetamine or opiate place-preference learning, the data suggest that the relationship between dopamine and reward may not be a simple one (13). Furthermore, a number of studies have shown that treatment with pimozide or HAL produces behavior decrements that do not exactly simulate the effects of nonreinforcement [e.g., 30,36,39,42,43,46,47]. Other data also strongly suggest that dopamine blockers affect motor behavior per se [e.g., (20)].

However, some data also suggest that it is not possible to dismiss entirely the hypothesis that dopamine blockers affect reward value. For example, HAL administered intermittently during acquisition of a runway task to continuously reinforced rats led to increased resistance to extinction (in the absence of HAL). This result mimics the partial reinforcement extinction effect that develops after intermittent nonreinforcement in acquisition (10,11), suggesting that intermittent HAL administration acted like intermittent nonreinforcement. This result was replicated by Feldon et al. (12), who also showed that the administration of HAL in extinction decreased resistance to extinction in both continuously reinforced and partially reinforced animals. This outcome suggested to the authors that HAL has two reward-related effects: a lessening of the effectiveness of reinforcers and an enhancement of the effectiveness of nonreinforcers.

As yet, there appear to be no studies of the effects of dopamine blockers on the relative effects of reward, as demonstrated in the contrast paradigm. Gramling and colleagues (21,22) compared the effects of pimozide in rats maintained on a 32% sucrose solution to rats downshifted in sucrose concentration from 32 to either 4% sucrose or to tapwater. They reported that the response profiles (lick rate and across-session changes in lick rate, interlick interval, pauses, and lick duration) in the downshifted rats were similar to each other, but both were different from the pimozide-treated rats. The authors interpreted the effects of pimozide to reflect motoric deficits and suggested that pimozide treatment is not equivalent to a shift to reduced reward conditions. Although closely related to a contrast study, the experiments by Gramling and colleagues did not directly examine contrast or the effects of a dopamine blocker on contrast.

One other study showed that contrast could be produced by "blocking" the rewarding effects of saccharin by administration of HAL, but this study did not examine possible contrast-attenuating effects of HAL (35). The present experiment examined the effects of HAL (0.1, 0.5, and 1.0 mg/kg) on the contrast effect resulting from a shift from 32 to 4% sucrose. These doses are within the range found effective in reinforcement-related studies [e.g., (12,36)]. The drug was in-

jected on only the second postshift day because earlier experiments have suggested that contrast is more drug sensitive at this point [e.g., (16,19)].

METHOD

Animals

Fifty-four naive, male Sprague-Dawley-derived rats were used as subjects. Animals were maintained as in Experiment 1.

Apparatus

The apparatus was the same as that used in Experiment 1.

Procedure

Animals were assigned to eight groups. Half these groups received 4% sucrose throughout the experiment and half received 32% sucrose for the first 10 days and then 4% sucrose during the 3-day postshift period. Subgroups of the shifted and unshifted animals were injected with HAL (0.1, 0.5, or 1.0 mg/kg) or vehicle on the second postshift day. The drug was dissolved in 0.1 N acetic acid, neutralized to a pH of 5.5 with 1.0 m NaOH, and mixed in distilled water. The injections were given IP 30 min prior to the start of the session.

Other aspects of the procedure were the same as in Experiment 1.

RESULTS

On the last preshift day, animals receiving 32% sucrose licked at a higher frequency than animals receiving 4% sucrose, $F(1, 46) = 29.38$, $p < 0.001$.

The postshift data were analyzed in terms of proportion of preshift lick frequencies, as in Experiment 1. Analysis of the data across the postshift period showed that shifted animals licked proportionately less than the unshifted animals, $F(1, 46) = 50.15$, $p < 0.001$, and that HAL had an overall effect of suppressing licking, $F(3, 46) = 3.59$, $p = 0.02$, which was due to greater suppression in the 1.0-mg/kg group than in the vehicle or 0.1-mg/kg groups [least significant difference (lsd) test, $p = 0.05$].

Not surprisingly, this suppressive effect of HAL varied across days [drugs × day, $F(6, 91) = 14.32$, $p < 0.001$]. Analysis of this interaction was the lsd test ($p = 0.05$) showed that the effect of the drug was due to the two higher doses (0.5 and 1.0 mg/kg) and restricted to the day on which it was administered (second postshift day) with no residual suppressive effects on the third postshift day.

The data of particular interest, concerning the effects of HAL on contrast are presented in Fig. 2. A reliable shift × drug × day interaction, $F(6, 91) = 2.65$, $p = 0.02$, was further analyzed with the lsd test ($p = 0.05$). On the first postshift day, when drug was not injected, all groups showed statistically reliable and approximately equivalent contrast effects. On the second postshift day, HAL administration suppressed licking regardless of shift condition. This suppression was reliable for unshifted (4%) animals for the 0.5- and 1.0-mg/kg doses compared to the vehicle and 0.1-mg/kg doses. In the case of shifted animals, the suppression was reliable for the 0.5-mg/kg dose vs. the vehicle and 0.1-mg/kg doses and for the 1.0-mg/kg dose vs. all other drug conditions. Thus, HAL tended to suppress intake of shifted and unshifted animals to approximately the same degree, with some tendency for shifted animals to be more suppressed by the highest

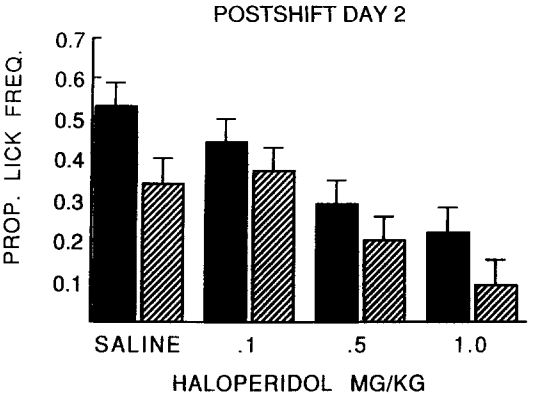

FIG. 2. Lick frequency on the second postshift day expressed as a proportion of terminal preshift lick frequency (as in Fig. 1) as a function of drug (haloperidol) condition. The drug was not injected on the first postshift day.

HAL dose. Contrast itself was reliable in all groups except the 0.5-mg/kg group, where it was marginally reliable ($p < 0.10$).

On the third postshift day, when the drug was no longer administered, contrast was reliable in all groups except the former 0.1-mg/kg group.

DISCUSSION

The anxiolytics CDP and midazolam alleviate contrast by increasing the lick frequency of shifted animals, but not unshifted animals, when the drug is administered on the second postshift day (17,18). Haloperidol did not have this pattern of action. Instead, the lick frequency of both shifted and unshifted animals was reduced in a dose-dependent manner. The fact that this reduction occurred proportionately in both groups and that contrast tended to be maintained at the highest dose of the drug indicates that haloperidol did not alter the *relative* effectiveness of the 4% sucrose solution in shifted and unshifted animals, even though it may have reduced the absolute effectiveness of the sucrose. However, on the basis of the literature cited previously, particularly the sucrose shift studies (21,22), a motoric deficit cannot be ruled out as the basis of the decline in lick frequency that occurred following HAL administration. Whatever the mechanism of lick reduction, it is clear that contrast was not greatly affected by the drug.

EXPERIMENT 3

Because CPZ and HAL were without clear effect on contrast, a benzodiazepine treatment was included as a positive control condition within this series of experiments. Since the effectiveness of CDP and midazolam have been demonstrated many times in our laboratory [e.g., (1,18,19)], a different benzodiazepine, flurazepam, was selected for use.

Flurazepam, like other benzodiazepines, enhances GABA-gated chloride ion flux (50) and potentiates the effects of the GABA agonist muscimol (14). However, flurazepam is less efficacious and less potent than CDP and diazepam in modulating GABA current (6). Flurazepam is an effective hypnotic and is often used in that role clinically (28,29,31), but it also has effective anxiolytic functions in some of the standard animal models of anxiety (8,9,24).

METHOD

Animals

Eighty male Sprague-Dawley-derived rats were used as subjects. Rats were about 100 days old at the start of the experiment and were maintained under the same conditions as animals in the previous experiments.

Apparatus

The apparatus was the same as that used in the previous experiments.

Procedure

The experiment was a 2 × 4 factorial in which shift condition [shifted (32–4) vs. unshifted (4–4)] and drug condition (saline, and flurazepam, 5, 10, and 20 mg/kg) were varied. Ten rats were randomly assigned to each of the eight groups defined by the factorial design. The drug treatment was administered IP on the second postshift day only, 30 min prior to the start of the 5-min session. Preshift training, in which half the animals received the 32% sucrose solution and half the 4% solution, was continued for 10 days and postshift training, in which all animals received the 4% solution, was continued for 4 days. The experiment was conducted in two complete replications. Other aspects of the procedure were the same as that used in Experiment 1.

RESULTS

Eight rats were dropped from the experiment for failure to lick the sucrose solution during the preshift period. Detailed data presentation will include only the second postshift day, the day on which flurazepam was injected. Analysis of the raw lick frequency data for the last preshift day and all postshift days indicated results that correspond to the proportion data presented below.

The proportion data showed an overall reliable negative contrast effect, $F(1, 55) = 88.58$, $p < 0.001$, and an overall effect of the drug, $F(3, 55) = 3.22$, $p < 0.03$. The latter term reflected an overall (shifted and unshifted groups combined) higher lick frequency in the 10-mg/kg group than in the vehicle group. Of most interest was a reliable shift condition by drug effect, $F(3, 55) = 3.95$, $p < 0.02$, subsequent analysis of which (lsd test, $p = 0.05$) indicated the following pattern of results: Contrast was maintained under all four drug conditions, but contrast was reliably reduced by the 10- and 20-mg/kg doses of flurazepam. This reduction was produced by increased responding in the shifted groups—the drug had no reliable effect on the unshifted control groups. These data are presented in Fig. 3.

DISCUSSION

Flurazepam, included as a positive control in this series of experiments, reduced negative contrast in a manner similar to that found with CDP and midazolam. Cross-experiment comparisons suggest that flurazepam is less effective than these other benzodiazepines in that CDP completely eliminated contrast with doses in the 6- to 8-mg/kg range and was marginally effective in the 4- to 5-mg/kg range (2,19) and midazolam substantially reduced contrast at a 1-mg/kg dose (1,18). Flurazepam, on the other hand, did not eliminate contrast at any dose and only reduced it at the higher doses of 10 and 20 mg/kg. These results may suggest that benzodiazepines that are primarily hypnotic are less effective in contrast than benzodiazepines that are more anxiolytic than hypnotic.

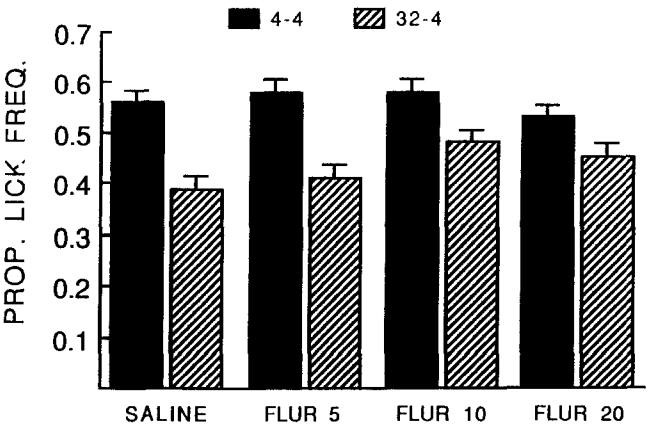

FIG. 3. Lick frequency on the second postshift day expressed as a proportion of terminal preshift lick frequency. Rats were injected with the various flurazepam doses on this day only.

GENERAL DISCUSSION

The failure of both CPZ and HAL to substantially alter contrast suggests that dopaminergic mechanisms are not involved in this behavior [as does the negative result obtained with buspirone in an earlier study (18)]. The results obtained with HAL were particularly striking—the drug produced dose-related decreases in licking, but these decreases were proportionate in shifted and unshifted animals, leaving contrast intact even with the low lick rates obtained with the 1.0-mg/kg dose of HAL. This result is consistent with the possibility that the effects of HAL on consummatory behavior are motoric or sedative (21,22,40).

The results may also have something more interesting to say about reward. Even though much of the data that has resulted from the study of dopaminergic blockers has suggested that the effects of these agents are often different from the effects of nonreinforcement, the possibility that dopamine antagonists affect reward value to some degree cannot be entirely eliminated (13,49). Particularly interesting are the data obtained by Ettenberg and Camp (10,11) and by Feldon et al. (12), who suggest that the effects of HAL on runway behavior are consistent with a two-pronged action of neuroleptics—the blunting of reward and the enhancement of the impact on nonreward (12). To the extent that this interpretation is correct, and to the extent that there is some validity to the anhedonia hypothesis as a whole, the results of the present experiments, particularly those obtained with HAL, imply that dopaminergic mechanisms are involved only in the absolute effects of reward, not in the relative effects. That is, the comparison of postshift rewards with the memory of preshift reward value, and the consequent decrement in performance that occurs when reward value has been decreased, remains unimpaired under the influence of HAL and CPZ, even though these drugs may reduce the absolute reward value of both preshift and postshift solutions.

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