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An Examination of Methodological Refinements, Clozapine and Fluphenazine in the Anhedonia Paradigm

WILLIAM O. FAUSTMAN[1] AND STEPHEN C. FOWLER[2]

Department of Psychology, University of Mississippi, University, MS 38677

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FAUSTMAN, W. O. AND S. C. FOWLER. *An examination of methodological refinements, clozapine and fluphenazine in the anhedonia paradigm.* PHARMAC. BIOCHEM. BEHAV. 17(5) 987–993, 1982.—Previous work has shown that the reduction in operant response rate in rats treated repeatedly with pimozide is similar to the pattern of decline in rate occasioned by nonreward. This similarity, usually observed with a continuous reinforcement (CRF) schedule, has been interpreted in terms of the neuroleptics' reducing the rewarding quality of the reinforcer, i.e., anhedonia. Although retaining the CRF schedule, the present work departs from earlier methodologies in three major ways: retraining days were not interposed between drug or extinction days; the operant measure, response duration, was used to complement response rate in describing the drug and extinction effects; and, in addition to using pimozide (0.5 and 1.0 mg/kg), two other neuroleptics, clozapine (5.0 and 10.0 mg/kg) and fluphenazine hydrochloride (0.125 mg/kg), were examined in the anhedonia paradigm. Omission of the retraining days still resulted in declines in response rate and increases in response duration that were graphically similar for pimozide and extinction, but were significantly different in degree, with pimozide producing greater reductions in rate and lesser increases in duration than did extinction. Although clozapine, a low-motor-effect neuroleptic, reduced rate and elevated duration, no change was observed for repeated dosing at the 5.0 mg/kg dose level. The 10.0 mg/kg dose yielded a significant across-session increase (i.e., tolerance effect) in rates, an effect entirely the opposite of what would be indicative of anhedonia. Fluphenazine, a high potency, high-motor-effect phenothiazine, did produce a pattern of declining rate and increasing duration across the four days of dosing, and the 0.125 mg/kg of fluphenazine hydrochloride yielded greater effects than 1.0 mg/kg of pimozide. The extinction-like pattern of responding produced by fluphenazine and pimozide, but not by clozapine, suggests that anhedonia per se is insufficient to account for these results and that an as-yet-to-be-elucidated motor and/or associative process is involved.

Anhedonia Pimozide Clozapine Fluphenazine Response rate Response duration Rats

RECENT investigations have found apparent similarities in operant responding between rats administered neuroleptics (e.g., haloperidol, pimozide) and previously-rewarded animals which are exposed to a no reward condition [9, 10, 28]. These results have been interpreted as evidence that neuroleptics may reduce operant response rates by creating a decrement in the rewarding qualities of primary [28] or secondary reinforcers [14]. Though there is increasing evidence for the role of dopamine in brain reward mechanisms [16,20], other studies have placed greater emphasis upon the motor effects of neuroleptics in producing operant rate reduction [8, 17, 19].

In one of the most widely cited studies supporting the anhedonia hypothesis, Wise *et al.* [28] demonstrated that repeated dosing of rats with pimozide brought about a pattern of responding for food on a continuous reinforcement schedule that was indistinguishable from a no reward condition for previously rewarded animals. Assessments of effects were made on four occasions with two nondrug "retraining days" placed between each drug or extinction session. Results showed that the animals in both the drug and no reward conditions displayed a monotonic decline in responding across the four assessments. Accordingly, since responding in the presence of pimozide was indistinguishable from responding during no reward, these and other data were interpreted as evidence that pimozide diminishes the reinforcing properties of reward. In demonstrating that the effect may not generalize to other experimental conditions such as intermittent reinforcement schedules, additional studies [14,23] have employed a similar testing procedure which included the use of retraining days between assessments.

By alternating retraining sessions with drug or extinction treatments, one introduces a discrimination training procedure which makes the results of such experiments more difficult to interpret. For animals given the drug vehicle with no reward on testing days, this allows for the development of a simple reward-no reward discrimination, a condition which is quite different from continuous no reward (i.e., extinction)

[1]Current address: Psychology Service, Veterans Administration Medical Center, Palo Alto, CA 94034.

[2]Requests for reprints should be addressed to Stephen C. Fowler, Department of Psychology, University of Mississippi, University, MS 38677.

across consecutive sessions. The use of a continuous reinforcement schedule, which offers salient cues regarding reinforcement availability after the first few responses in a session, accentuates the possibility of the development of a rapid discrimination. Also, the use of retraining days in the drug treated animals introduces the chance for confounding due to possibly unique discriminative stimulus properties which may be associated with the drug [21]. In light of these problems, the purpose of the first experiment in the present paper was based primarily on these methodological concerns related to the determination of whether four consecutive days of pimozide (with no retraining days) were distinguishable from four consecutive days of no reward.

An additional feature of previous anhedonia studies is that all the investigations supporting [9, 14, 28] or attempting to refute [8,19] the anhedonia hypothesis have made exclusive use of one of two high-potency neuroleptics, pimozide or haloperidol. In view of the possibility that neuroleptics may reduce operant rates through both their motivational and motor effects, it would be of interest to determine whether the anhedonic effect can be observed with a low-potency neuroleptic possessing dopamine blocking properties but having few motor effects per se. Accordingly, the purpose of a second experiment was to determine if the anhedonic effect extends to clozapine, an effective dopamine blocking neuroleptic which produces few, if any, extrapyramidal motor effects [4]. Also, the second experiment examined the possible anhedonic qualities of fluphenazine hydrochloride, a high-potency phenothiazine with strong extrapyramidal effects [12]. This allows for an assessment of the anhedonic effects of a high-potency phenothiazine—a class of compound not heretofore used in the anhedonia paradigm.

An important feature of the present experiments was the addition of the operant response variable, response duration, to characterize drug and no reward effects. Response duration is presumed to reflect characteristics of individual responses, and previous work has shown that it is influenced by extinction [18] and by various pharmacological agents [11] and that it provides behavioral information about drug effects not available from the exclusive reliance upon a rate of response measure [26]. Recent work [6] has shown that this measure may be particularly valuable in detecting the possible differences between no reward and neuroleptic treatments.

EXPERIMENT 1

METHOD

Subjects

Thirty-three male Sprague-Dawley rats (Holtzman Co.), averaging approximately 320 g in weight, were water deprived and were allowed access to water for three minutes each day approximately one hour after data collection. Food was continuously available in the individual home cages.

Apparatus

The four simultaneously-operative experimental chambers measuring 23 cm long, 20 cm wide, and 19 cm high had front panels constructed of aluminum while the remaining sides and tops were clear Plexiglas. Stainless steel rods running parallel to the front of the chamber served as a grid floor. The top of the manipulandum (Gerbrands Co., Rat Lever G6312) was 8 cm above the grid floor and was positioned in the center of the front panel extending 1.5 cm beyond the panel wall. The lever was calibrated for a 0.196 nt (20 g) force requirement. A brass water cup was positioned in the lower left corner of the front panel. A solenoid valve was calibrated daily to deliver a reinforcer volume of 0.05 ml water.

Programming of contingencies and recording of data were accomplished with a laboratory computer (PDP 8/e) and associated peripherals. This system recorded the number of lever press responses and the amount of time that the lever microswitch was held in the closed position.

Procedure

Responding was initially shaped by the method of successive approximations and all animals were subsequently placed on a continuous reinforcement schedule of water reinforcement with 20-minute sessions. Following four weeks of daily operant training, stable rates of responding had been obtained. (Stability of responding shown for the four daily sessions for Group A in Fig. 1 was typical for all groups for both measures.) At the termination of baseline (i.e., the final days of training prior to drug administration) animals were randomly assigned to one of four different treatment conditions.

One group (Group A, N=9) served initially as a saline control and later for the no reward condition. During the last four days of baseline for all animals this group was injected with 0.9% saline solution (1 ml/kg IP) four hours prior to data collection. On the four subsequent days these animals were injected with saline four hours prior to an operant session in which the water reinforcer was withheld (the solenoid click was still present). On the same four consecutive days a second group (Group B, N=8) of rats received a 0.5 mg/kg (IP) injection of pimozide four hours before reinforced operant exposure. Pimozide (McNeil) was mixed prior to the start of experimentation in a mixture of tartaric acid and water. A third group (Group C, N=8) of animals was administered 1.0 mg/kg (IP) of pimozide four hours prior to data collection for four consecutive days. The presently-employed dose levels for pimozide are the same as those used by Wise *et al.* [28]. A final group (Group D, N=8) received 1.0 mg/kg injections of pimozide during the same four consecutive days as the other groups. However, during the first three days these animals did not receive operant exposure, but rather, they remained in their home cages. During the fourth day these animals received reinforced operant exposure four hours after their 1.0 mg/kg pimozide administration. This procedure, which was used by Wise *et al.* [28], serves as a control to assure that the decrease in operant responding observed across test sessions in pimozide-treated animals is due to some effect other than a cumulative drug effect carried-over across sessions. In addition, following the fourth day test session, these "home cage control" animals received two days of retraining in which they were injected with saline four hours prior to data collection, and, on the next day they were administered pimozide (1.0 mg/kg, IP) four hours before the operant session. These additional test days allow for a partial replication of the intermittent retraining procedure used by Wise *et al.* [28].

On several occasions during the four-day assessment period certain animals received either a greatly diminished amount of water from operant responding (i.e., due to the rate reducing effects of pimozide) or no water at all during an

operant session (e.g., the no reward and home cage control animals). In these cases the daily home cage water access was increased by approximately two minutes. This procedure assured relatively stable weights during the four day testing sequence.

Drug effects were characterized by the number of bar press responses and average response duration. The later dependent variable was obtained for each animal by dividing the amount of time the manipulandum switch was held in the closed position by the number of responses in a session. Data were analyzed by means of t-tests and split plot factorial analyses of variance with post-hoc Tukey's test for differences between means [15].

RESULTS AND DISCUSSION

Four consecutive days of pimozide with reinforcement (Groups B and C) or saline with no reward (Group A) resulted in decreases in responding and increases in response duration (see Fig. 1, compare columns 2, 3, and 4). The data for the two dose levels (Groups B and C) and the no reward animals (Group A, no reward) were entered into a split plot factorial analysis of variance. The across days repeated measures variable yielded statistical significance for both a decrease in the amount of responding, $F(3,66)=33.85$, $p<0.001$, and an increase in average response duration, $F(3,66)=10.609$, $p<0.001$.

An examination of Fig. 1 reveals that the 1.0 mg/kg pimozide dose brought about a greater reduction in responding than did no reward and that pimozide, especially at the 0.5 mg/kg dose, tended to produce smaller effects upon response duration than no reward. The between groups comparison (Groups B, C, and A—no reward) for the analysis of variance yielded a significant difference for number of responses, $F(2,22)=6.85$, $p<0.01$, and the response duration data were not quite statistically significant, $F(2,22)=2.876$, $p=0.076$. In addition, for the rate data, the split plot analysis yielded a significant interaction, $F(2,66)=2.855$, $p<0.01$, indicating that the pattern of decline in response rate was dependent upon group membership. A post-hoc Tukey test showed that the overall amount of responding by the 1.0 mg/kg pimozide group (Group C) was significantly lower ($p<0.05$) than the no reward group (Group A, no reward). Thus, when dosing and no reward are performed on consecutive days, there is a detectable difference between a 1.0 mg/kg dose of pimozide and animals receiving extinction. A comparison between the two dose levels was not significant (Groups B and C), nor was a comparison between the 0.5 mg/kg group (Group B) and the no reward animals (Group A, no reward).

The home cage control animals emitted a relatively large number of responses and low duration when given their first operant exposure on the fourth day of drug treatment (see Day 4, Group D). Based on independent-group t-tests, the fourth day comparisons between Group C and Group D showed that number of responses, $t(14)=2.478$, $p<0.05$, and response duration, $t(14)=3.678$, $p<0.05$, were significantly less affected by pimozide (1.0 mg/kg) in Group D. This result rules out the possibility that changes in the two dependent variables for Group C across the 4 days were produced merely by drug accumulation since both groups received the same amount of the drug and differed only in whether or not they were given operant exposure. A comparison between Day 4 of the home cage control data (Group D) and the next pimozide dosing for these same animals (Day 7) revealed a

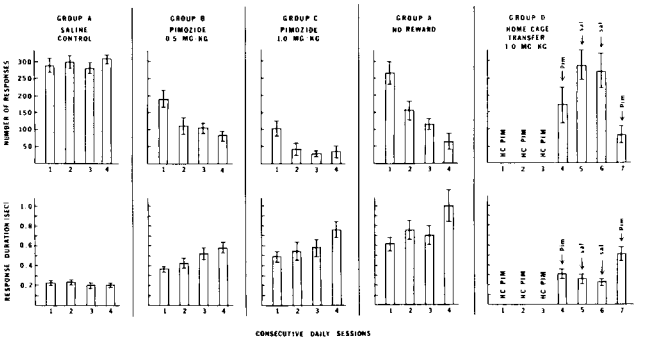

FIG. 1. Mean number of responses in a 20-min session (top) and mean response duration for 4 separate groups of rats. The vertical bars represent ±SEM. One group (Group A, saline control, N=9) received saline (1.0 ml/kg) during the last 4 days of baseline for all animals. On the next 4 consecutive days these animals were given saline and exposed to no reward (Group A, no reward). Other animals (Groups B and C, N=8) received 4 consecutive days of pimozide (0.5 and 1.0 mg/kg) with reward maintained. The home cage rats (Group D, N=8) received pimozide (1.0 mg/kg) for 4 days but remained in the home cage for the first 3 days. Reinforced operant exposure was initiated on day 4, followed by 2 retraining days (with saline) and another assessment with pimozide.

significantly lower level of responding on Day 7 (paired observation—$t(7)=2.475$, $p<0.05$, and a lack of statistical significance for the duration data, $t(7)=0.908$, NS. This result may be taken as further evidence for some combined effect of repeated pimozide dosing and operant exposure which produces declining response levels.

The results of the first experiment do not unequivocally support a simple anhedonia hypothesis. The home cage control group tended to support an anhedonia explanation; this is demonstrated in that there were significantly fewer responses made on the fourth day of pimozide plus operant exposure (Group C, Day 4) than there were on day four for the home cage animals (Group D, Day 4). Both groups of animals had received the same amount of the drug and differed only in that one was exposed to the operant setting while the others remained in their home cages. Accordingly, this difference in response levels may be accounted for by some combined effect of pimozide and operant exposure, although the effect of 3 non-drug home cage days per se cannot be ruled out completely. Additional research is needed to specify the pharmacological and behavioral parameters of this effect. One recent work [14] has speculated that pimozide decreases food associated apparatus cues. Though such an explanation may partially account for the decline in responding observed across repeated pimozide sessions, it is important to note that data to assess directly such a hypothesis are somewhat lacking. In a study relevant to this explanation [2], it has been demonstrated that pimozide effectively blocks the acquisition of conditioned reinforcement. Yet, it [22] has been shown that pimozide does not influence a simple discrimination in a two-bar operant chamber even when dose levels are employed that produce substantial decreases in responding. Therefore, conclusions regarding the effect of pimozide on reinforcement-related external stimuli appear to be somewhat equivocal at present.

In interpreting the findings of Experiment 1 it should be noted that there were two methodological differences be-

tween the present work and the research of Wise *et al.* [28]. The present study employed a CRF schedule of water reward rather than the food reinforcer used by Wise *et al.* [28]. However, in view of the recent findings [13] which demonstrated that the anhedonic effect extends to water reward, it would appear that differences between the type of primary reward are not of great importance. An additional difference, and one whose effects are somewhat more difficult to speculate on (e.g., there may be related differences in deprivation levels, magnitude of the reinforcer, satiation effects), involves the present use of 20-minute sessions rather than the 45-minute sessions used by Wise *et al.* [28]. Yet, the failure of the present work to replicate the results of Wise *et al.* [28], which found pimozide (0.5 and 1.0 mg/kg) and no reward to be indistinguishable, may be at least partially related to the removal of retraining sessions. By using 4 consecutive extinction days and 4 consecutive drug days the present experiment provides a stronger test of the anhedonia hypothesis than that given by similar experiments employing intervening retraining sessions. This follows from the fact that retraining days introduce a discriminative training procedure in addition to the simple extinction procedure. Although a "pure" extinction procedure is probably impossible to achieve (e.g., during shaping some previously rewarded responses are purposefully extinguished), the procedure used here is less open to discrimination training effects than the ones having retraining days.

Drug dosing with retraining days between assessments may also enhance discriminative drug effects not specifically related to either anhedonia or to reward-no reward discriminations. Use of retraining days gives the animal alternating drug and no-drug experiences in the operant chamber. Thus, four consecutive treatment days may lessen (but not abolish) these discriminative effects. Of course, use of consecutive dosing days increases the likelihood of obtaining a cumulative drug effect across the test sessions, yet the results of the home cage control group demonstrated that cumulative drug effects were probably not an important confound in the present investigation.

EXPERIMENT 2

The results of Experiment 1 demonstrated that though pimozide dosing did induce several patterns of responding that are consistent with an anhedonia explanation, pimozide and extinction were not equivalent. These findings, taken alone, still do not offer clear evidence as to the relative role of motor/motivational effects in producing these results. By using neuroleptics with differing degrees of motor side effects Experiment 2 was undertaken to assess the relative contribution of this type of motor effect in producing the anhedonia-like pattern of responding. Using the same test procedure as in Experiment 1, a comparison was made between clozapine, a neuroleptic producing few, if any extrapyramidal motor effects [4], and fluphenazine hydrochloride, a high potency phenothiazine agent with strong extrapyramidal motor effects [12]. It should be noted that phenothiazine agents have not been previously tested in the anhedonia paradigm.

METHOD

Subjects and Apparatus

Thirty-eight male Sprague-Dawley rats (Holtzman Co.), averaging approximately 340 g in weight, were water deprived, and, similar to Experiment 1, were allowed access to water for three minutes each day about one hour after data collection. The apparatus was the same as that used in Experiment 1.

Procedure

Responding was shaped by the method of successive approximations, and all animals were subsequently placed on a continuous reinforcement schedule of water reinforcement (0.05 ml) with 20 minute sessions. Stable baselines had been established after 4 weeks of daily training, and the animals were then randomly assigned to one of four different treatment conditions. On four consecutive days animals received either 5.0 mg/kg (Group B, N=8) or 10.0 mg/kg (Group C, N=6) injections of clozapine (Sandoz) 1 hour before a session with reinforcement maintained. Another group (Group D, N=8) was injected (IP) with 0.125 mg/kg (expressed in terms of the salt) of fluphenazine hydrochloride (Squibb) 3 hours before a session in which reinforcement was available. The final two groups were given clozapine (5.0 mg/kg, IP, Group E, N=8) or fluphenazine hydrochloride (0.125 mg/kg, IP, Group F, N=8) on 4 consecutive days but remained in their individual home cages for the first three days of dosing (operant exposure in the drugged state was initiated on the fourth day of dosing). Similar to Experiment 1, animals in the home cage conditions received three additional days of testing following the assessment performed on the fourth day. On day 5 and 6 these animals were injected with saline (0.9%, 1.0 ml/kg). On the seventh day the animals in the clozapine group received a 5.0 mg/kg clozapine injection 1 hour prior to the session, and the fluphenazine animals were given the drug (0.125 mg/kg) 3 hours prior to data collection. Data from the combined saline-extinction animals in Experiment 1 (Group A, saline and no reward) were used as control data for the present experiment.

The dose level and injection time for the fluphenazine animals were determined from pilot work with separate animals and were aimed at establishing initial rate reductions essentially equivalent to those obtained with pimozide in Experiment 1. The clozapine dose and injection time were derived from previous behavioral work with this drug [7]. Clozapine was mixed daily immediately prior to injection and due to its poor water solubility was dissolved in 0.9% saline solution with 0.1 N HCl. Fluphenazine hydrochloride was furnished in injectable form and was mixed with 0.9% saline to achieve the appropriate injection volume. Similar to Experiment 1, drug effects were characterized by the number of responses in the 20-min session and by average response duration.

RESULTS AND DISCUSSION

Mean response rate and duration data are shown in Fig. 2. Similar to the no reward condition (Group A, no reward), fluphenazine treated rats (Group D) demonstrated a decline in responding and an increase in duration across the four consecutive daily sessions. The results for the two clozapine groups appear to differ greatly from those obtained with fluphenazine. Though the 5.0 mg/kg group displayed a decrease in responding from control levels, there was no apparent across-session decline in responding. Moreover, the 10.0 mg/kg dose (Group C) produced a tolerance effect in that low rates were obtained during initial assessments and there was an increase in rate across the four assessments. A randomized block ANOVA revealed that the across-session

increase for the 10.0 mg/kg clozapine response rate data was statistically significant, $F(3,15)=3.924$, $p<0.05$. Low response rates (less than 5 responses in most animals) during the first assessments resulted in unavailable or unreliable duration data at the 10.0 mg/kg dose and therefore precluded analysis of these data. Two split plot ANOVA's were employed to provide a further analysis of the 5.0 mg/kg clozapine data, the fluphenazine group, and the no reward data (4 sessions × 3 conditions—i.e. groups B, D, and A no reward). The results revealed a significant decline in rate, $F(3,66)=23.65$, $p<0.01$, and an increase in duration, $F(3,66)=4.99$, $p<0.01$, across the four sessions. Also, the analysis yielded a significant difference between the three treatment groups for both rate, $F(2,22)=7.206$, $p<0.01$, and duration, $F(2,22)=5.551$, $p<0.05$. As evidenced by a significant interaction effect for the rate measure, $F(2,66)=4.794$, $p<0.05$, the pattern of change in rate across the sessions differed among the three groups. The interaction effect was not significant for the duration variable, $F(2,66)=1.683$, $p<0.10$.

The results for Group F showed that fluphenazine-treated animals displayed relatively high rates and low durations when given their first operant exposure on the fourth day of treatment (similar to pimozide in the first experiment). Independent group t-tests showed a significant difference between Day 4 of the home cage control animals and Day 4 of the fluphenazine animals (Day 4 for Groups D and F) for both response rate, $t(14)=6.481$, $p<0.01$, and duration, $t(14)=2.646$, $p<0.05$. Similar comparisons for the clozapine data (Day 4 of Group B vs Day 4 of Group E) failed to demonstrate significance for both rate, $t(14)=0.223$, $p>0.05$, and duration, $t(14)=1.325$, $p>0.05$.

A comparison between Day 4 of the fluphenazine home cage control data and the next drug dosing for these same animals (Day 4 vs Day 7 of Group F) failed to attain statistical significance for either rate, $t(7)=0.358$, $p>0.10$, or duration, $t(7)=0.415$, $p>0.10$. A similar comparison between Day 4 and 7 for the clozapine home cage group (Group E) also was not significant, Rate, $t(7)=1.164$, $p>0.10$; duration, $t(7)=1.951$, $p>0.10$. Visual inspection of the fluphenazine transfer data (Group F) in Fig. 2 reveals a failure to replicate the decline in responding following retraining days which was obtained with pimozide in Experiment 1. In view of the fact that fluphenazine showed anhedonic-like patterns in other aspects of this experiment of (e.g., a steady decline across 4 assessments, relatively high rates on Day 4 of the home cage group), it would appear that the use of retraining days may be an important variable in the observation of anhedonic effects.

The present results demonstrated that fluphenazine, a high-potency phenothiazine possessing strong motor effects [12], produces an anhedonic-like response pattern similar to that obtained with pimozide in Experiment 1. Both drugs produced a decline in rate and an increase in duration across the consecutive test sessions. Moreover, the home cage control group for fluphenazine demonstrated that the results were probably not due to an cumulative drug effect (i.e., rates were high and durations low on day 4 of dosing for these animals), but rather, can be accounted for only by some combination of drug dosing and operant exposure. Clozapine, an effective dopamine antagonist (and effective antipsychotic) with few motor effects, (e.g., [3,7]) failed to demonstrate typical anhedonic-like qualities at either a 5.0 mg/kg or 10.0 mg/kg dose. Thus the ability to produce dopamine blockade per se may be insufficient to produce

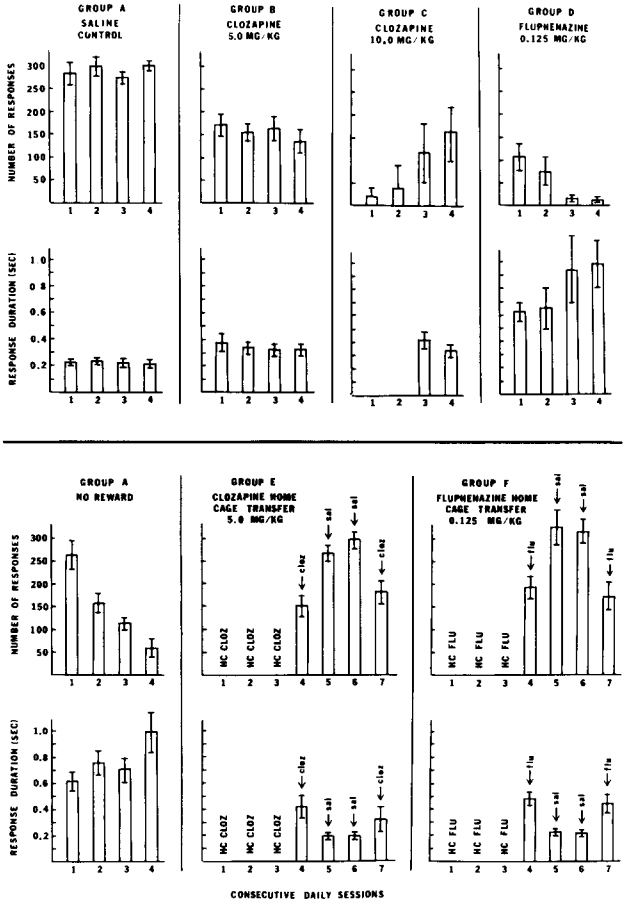

FIG. 2. Mean number of responses in a 20-min session and mean response duration for 6 separate groups of rats. The vertical bars represent ±SEM. Data from the combined saline-no reward animals (Group A, N=9) in Experiment 1 were used for control data for the present study. Groups B (N=8) and C (N=6) received clozapine (5.0 mg/kg and 10.0 mg/kg) on 4 consecutive days with reward maintained. Response duration data for the first 2 days of dosing in Group C are not displayed due to a lack of data resulting from numerous animals showing very low (less than 5 responses) response rates. Group D (N=8) received fluphenazine hydrochloride (0.125 mg/kg) with reward maintained. Groups E and F (N=8) were given clozapine or fluphenazine for 4 consecutive days but remained in the home cage for the first 3 days. On day 4 these animals received the drug with rewarded operant responding, followed by two saline-retraining days and then another assessment with the drug.

anhedonia. Accordingly, the present results suggest that the supposed "anhedonia effect" may be a manifestation of a motor effect of high-potency neuroleptics rather than a direct effect of these drugs on reward mechanisms.

GENERAL DISCUSSION

In review, the results of the first experiment showed that with certain methodological refinements relating to the operational definition of no reward, pimozide dosing produced several anhedonic-like patterns of responding, but, these effects do not directly parallel an ongoing extinction condition. Experiment 2 found that this anhedonic-like pattern of response extends to a 0.125 mg/kg dose of fluphenazine hydrochloride, a high potency neuroleptic of a drug class

(phenothiazine) not previously examined in anhedonic testing procedures. Also, a 5.0 mg/kg dose of clozapine, a drug having few extrapyramidal motor effects, failed to induce demonstrable anhedonic-like patterns of response, despite the fact that this dose produced definite reductions in response rate (cf, [3]) and elevations in response duration relative to the saline control group. In addition, the 10.0 mg/kg clozapine dose led to behavioral tolerance (lessening of rate reducing effects across the 4 sessions), a pattern which is the opposite of what would be expected if this agent possessed demonstrable "anhedonic" qualities at this dose. It should be noted that prior work [7] has shown that clozapine may produce behavioral tolerance effects with repeated administration. The behavioral differences between clozapine and the conventional neuroleptics, pimozide and fluphenazine, may be related to biochemical differences observed by others [1,29].

The present data offer further information on the apparent complexity of the "anhedonia" phenomenon. There does appear to be some combined effect of dosing with high-potency neuroleptics and operant exposure which brings about a decline in reinforced responding. Since clozapine failed to produce this pattern and at one dose produced a behavioral tolerance effect, the present results suggest that the neuroleptic-operant interaction may not be due to dopamine blockade per se, but rather, to some property related to dosing with high-potency agents which tend to produce strong motor effects.

Recent work [24] has advanced the idea that pimozide may reduce operant rates by making it more difficult for the rat to respond (e.g., a result of motor effects). Additionally, it has been hypothesized that motoric feedback resulting from responding may produce an aversive condition which affects an animal's motivation to respond [24]. The across-session decline in response rate may be attributed to a classical conditioning process in which the aversiveness of the drug-induced feedback is paired with the environment of the test session [24].

Although the results for the duration measure in the present work largely parallel those for the rate measure, previous work did not presage this outcome. An earlier study [6] showed that one can observe duration differences between haloperidol and no reward groups even when fixed ratio 10 response rates were approximately equal. Hence, in the context of this previous work, duration data reported herein indicate that the schedule of reinforcement (FR10 vs CRF) may be a determinant of whether or not the duration variable will provide information complementary to rate. Moreover, another FR study [7] suggested that for conditions of approximately equal rates of responding haloperidol may affect response duration more than does clozapine—the latter drug having relatively low extrapyramidal effects. With the CRF schedule used here evidence for such an effect did not emerge (compare Experiment 1, Group B, Day 1 with Experiment 2, Group B, Day 1 for both rate and duration measures). Finally, since no duration data have been previously reported for fluphenazine, the present results show that this high potency phenothiazine affects response duration in a manner similar to pimozide.

In contrast to the results of Wise *et al.* [28], the present investigation generally showed that with certain methodological refinements, the effects of pimozide on CRF responding are not equivalent to extinction. There does appear to be some type of interaction between repeated dosing with pimozide or fluphenazine that produces declining response levels, but this interaction does not appear to extend to a neuroleptic which does not produce strong motor side effects. Thus, although dopaminergic reward mechanisms may play a role in the operant rate reduction by neuroleptics the present results suggest that motor and associative effects may also be importantly involved in these drug-induced changes in operant behavior.

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