Pharmacology Biochemistry & Behavior, Vol. 20, pp. 323–326, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Force Requirements in Lever-Pressing and Responding After Haloperidol

KAREN E. ASIN[1] AND H. C. FIBIGER[2]

Division of Neurological Sciences, Department of Psychiatry, University of British Columbia 2255 Wesbrook Mall, Vancouver, B.C. V6T 1W5, Canada

Received 27 June 1983

ASIN, K. E. AND H. C. FIBIGER. *Force requirements in lever-pressing and responding after haloperidol.* PHARMACOL BIOCHEM BEHAV **20**(3) 323–326, 1984.—One hypothesis regarding the actions of neuroleptic drugs on operant responding is that they interfere in some manner with the motoric capability of the animal. To further explore this possibility, we investigated the effects of haloperidol on a bar press response after animals were trained on levers with different force requirements. In the first experiment, two groups of rats were trained to press levers having either low (30 g) or high (100 g) force requirements. The effects of haloperidol on bar pressing when both groups were responding on the light lever were then examined. Under these conditions, the groups showed similar declines in response rates, indicating little transfer between previous experience on the heavy lever and responding in the presence of haloperidol. In the second experiment, the same groups of rats received further training exclusively on either the heavy or the light lever; the rate of responding was similar for the two groups. The effects of haloperidol on pressing either the heavy or the light lever were then examined. It was found that the rate-decreasing effects of haloperidol were similar in both groups. However, when the lever-pressing response was subsequently extinguished, rats working on the heavy lever were significantly more resistant to extinction than the light lever groups. The results of these experiments fail to indicate that the putative motoric effects of haloperidol interact significantly with response force demands. Furthermore, the data provide yet further evidence that blockade of dopamine receptors and removal of reinforcement are not equivalent.

Haloperidol Lever-pressing Force requirements

THERE are a variety of mechanisms by which neuroleptics could decrease instrumental behaviors. One possibility [15] is that the decline in response rate seen after treatment with dopamine receptor blocking drugs such as pimozide or haloperidol reflects a reduction in the animals' subjective appreciation of reward (the "anhedonia" hypothesis). Others have indicated that impaired motoric capabilities may contribute significantly to this effect of neuroleptics [6].

There is no reason to assume that these two hypotheses must be mutually exclusive. Nevertheless, a number of studies have sought to evaluate the contribution of reward- and motor-related factors in the rate-decreasing effects of neuroleptics. Some have supported the view that neuroleptics interfere with reward mechanisms [15] even in tests requiring minimal response requirements [8, 9, 16]. On the other hand, although the decline in responding following neuroleptics has, under some circumstances, been shown to be similar to extinction [15], other studies have demonstrated differences between the two conditions. For example, when rats trained on a lever press response for food reward are extinguished and injected with pimozide, the effects of the two manipulations are additive [11]; that is, rats receiving pimozide during extinction show significantly less resistance to extinction than rats subjected to either manipulation alone. Furthermore, pimozide injections during training, unlike partial reinforcement, fail to produce the partial reinforcement extinction effect [11,13]. Finally, rats trained on long interval schedules of reinforcement can show a decline in response rate after neuroleptics that occurs prior to the delivery of the first reinforcement [12].

The experiments described here were concerned with investigating the effects of haloperidol on a lever press task in which the force requirements were varied. Specifically, inasmuch as it has been proposed that the rate-decreasing effects of neuroleptics may in some manner be related to drug induced increases in motoric demands [6], the effect of haloperidol on bar pressing rate was examined in rats trained on levers with different force requirements.

GENERAL METHOD

Subjects

Sixteen adult, male Wistar rats, weighing approximately 300 g served as subjects. All animals were experimentally naive and were individually housed and maintained on a 12 hr light:dark cycle, with water available ad lib. Rats were handled daily beginning one week prior to magazine training, at which time they were placed on a 23 hr food deprivation schedule. Lab chow was available for one hour a day in the animal's home cage after the operant session.

[1]Present address: University of Illinois, Department of Psychology, P.O. Box 4348, Chicago, IL 60680.
[2]Requests for reprints should be addressed to H. C. Fibiger.

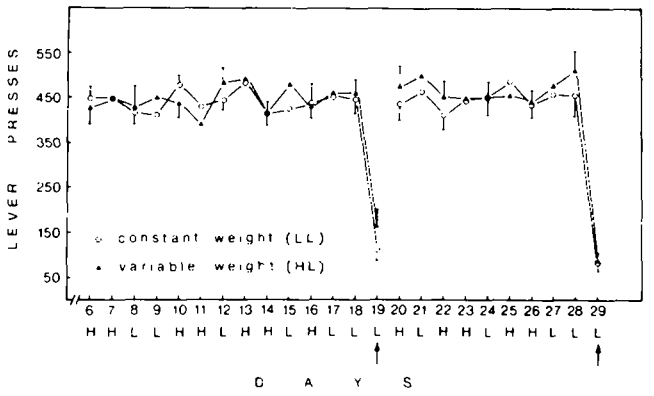

FIG. 1. Mean total number of lever presses per 15 minute session. Rats had either had experience exclusively with the light (L) lever (Group LL) or had had experience pressing both the light and heavy (H) levers (Group HL), as indicated. Rats were injected with haloperidol (0.1 mg/kg) on days indicated by the arrows, at which time both groups were tested on the light lever.

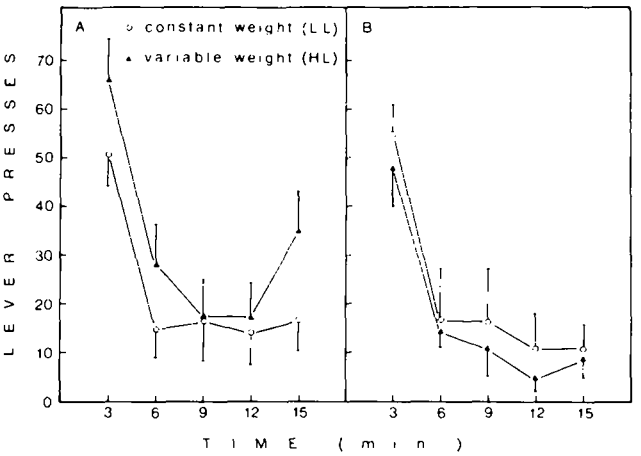

FIG. 2A, B. Mean number of lever presses 50 min following haloperidol (0.1 mg/kg) administration in three min blocks for LL and HL Groups as explained in Fig. 1 during two different test sessions, separated by 10 days.

Training

Rats were introduced to the operant chamber for 15 min with six 45 mg pellets (BioServ) available in the feeding trough. The next day, two pellets were placed in the trough, and the feeder was activated intermittently using a remote switch by the experimenter throughout the 15 min session. On the following day, rats which had not acquired the lever press response were shaped by the method of successive approximations. At this time, animals were on a continuous reinforcement schedule. During response acquisition, the weight required to depress the manipulanda of all four operant boxes was 30 g; all rats had acquired the response within 3 training sessions. The operant boxes were housed in light and sound attenuating chambers and were on-line with computer systems in another room. All sessions were 15 min long.

On the fourth day of training, rats were switched to an FR2 schedule of reinforcement and were allowed two days on this schedule before being divided into two groups. Rats were trained on the FR2 schedule so as to increase baseline response rates and resistance to extinction relative to a CRF schedule. This also allowed a closer comparison of rates between the experimental and control groups.

Drugs

Haloperidol (Haldol, 0.1 mg/kg) was injected (IP) on days of testing (see below). This dosage was chosen since pilot studies and other reports [12] indicated that it would produce a gradual, rather than abrupt, decline in response rate in control rats. Injections were made 50 min prior to the behavioral sessions.

EXPERIMENT 1

The first experiment sought to determine if previous experience with a lever press response requiring greater force would interact with the rate-decreasing effects of haloperidol during subsequent pressing on a light lever. More specifically, we sought to determine whether experience with increased force requirements on a lever press task would transfer to a response with lower force requirements in the presence of haloperidol. It was hypothesized that if haloperidol increases the perceived response force demands then animals that had learned previously to press a heavy lever at high rates might be resisitant to the rate decreasing effects of this drug.

Procedure

After the rats had been shaped, they were divided into 2 groups matched for response rates. One group (LL) continued to press exclusively on the light (30 g) lever, while the other group (HL) was trained for 4 days on an increasingly weighted lever on an FR2 schedule. Every day, additional weights were applied to the lever until the weight required to depress the lever was 100 g. These rats were then trained for 7 days on the 100 g heavy lever and thereafter were trained on either the light or the heavy lever according to the schedule indicated in Fig. 1 for 10 days. By this time, rats in the HL group displayed similar rates of responding regardless of the weight of the lever they were pressing, and these rates were equivalent to those of rats in the LL group. On the test day, all rats were weighed and injected with haloperidol and were tested only on the light lever (Test Session I). Following an additional 9 days of training (Fig. 1), the effect of haloperidol was evaluated again (Test Session II).

Results

Mean total baseline and test session response rates for groups LL and HL are shown in Fig. 1 where it may be seen that the rate of responding in the HL group did not vary as a function of force requirement the week prior to the injection of haloperidol. Mean lever pressing rates in three minute bins across the 15 min test sessions under haloperidol are shown in Fig. 2A, B. A Group × Time analysis of variance (ANOVA) with repeated measures on the time factor indicated significant time effects for test sessions I and II, $F(4,164)=24.24$ and 29.36, respectively, $p<0.01$. However, neither the Group effect ($p>0.1$) nor the Time × Group interaction was significant ($p>0.1$). Similar negative results were obtained when the data were analyzed in terms of percent baseline rate (data not shown).

These results suggest that the reduction in lever pressing rate seen after haloperidol is not influenced by prior experi-

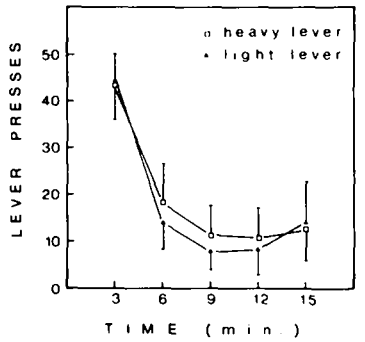

FIG. 3. Mean number of lever presses across three min blocks by rats pressing on either the heavy or the light lever following haloperidol (0.1 mg/kg).

ence with increased force requirements during food reinforced responding. Although it might be argued that the two differentially weighed levers did not, in fact, have different force requirements (i.e., they were less than one "just-noticeable difference" apart), we have observed in other experiments that when rats trained on the light lever are abruptly, rather than gradually, transferred to the heavier lever, the recorded response number is zero for the 15 min session, suggesting that increased effort is indeed required for responding on the heavy lever (unpublished observations). This finding also indicates that transfer between the earlier and later weighing conditions on this lever did occur. Therefore, although the HL group had learned to press the heavy lever at high rates, this experience failed to ameliorate the disruptive effects of haloperidol while responding on the light lever. This suggests that administration of haloperidol is not equivalent to increasing the force requirements of a lever press response.

EXPERIMENT 2

It has been suggested that neuroleptics may reduce lever pressing rates by increasing the motoric demands placed on the animal during operant responding [6]. According to this hypothesis haloperidol might be expected to have a greater effect on rats that are required to exert more effort during responding (i.e., those pressing a heavy lever). In contrast, if the halopridol-induced response decline is an extinction-like process, then rats pressing the heavier lever might show an attenuated response to haloperidol [10]. These hypotheses were addressed in the next experiment.

Procedure

Subjects were the same as those used in the previous experiment. After the completion of Experiment 1, rats in the HL group were trained exclusively on the heavy lever, while the other group (LL) continued to press on the light lever for 10 days. On the 11th day, rats were weighed and injected with haloperidol (0.1 mg/kg) 50 min before testing. Rats were given 4 more days of training and then the response was extinguished. During extinction, a lever press activated the food hopper but no pellet was delivered.

Results

On the 4 days prior to haloperidol administration, there was no significant difference in the rate of responding be-

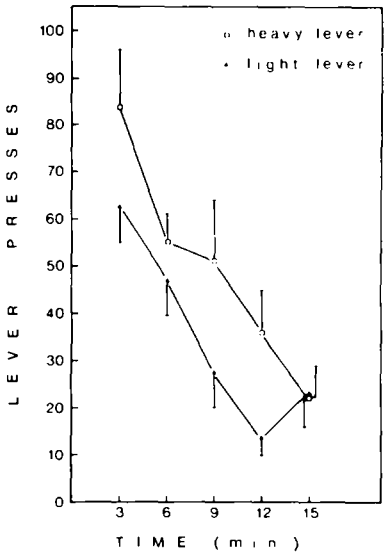

FIG. 4. Mean number of lever presses in 3 min blocks during extinction for rats pressing on either the heavy or light lever.

tween the HL and LL groups (data not shown). Figure 3 illustrates the effects of haloperidol on the rate of responding for rats pressing on either the light or heavy lever. A Group × Time ANOVA with repeated measures on the time factor indicated that the two groups failed to differ in their response to haloperidol ($F<1$) and showed a similar decline in response rate over time (interaction $F<1$). The time factor was statistically significant, $F(4,64)=22.77$, $p<0.01$.

A similar ANOVA conducted on the extinction data (Fig. 4) yielded different results. (Due to technical problems, the data from one rat in the LL group were excluded from the analysis.) Thus, the ANOVA indicated significant group, $F(1,13)=4.84$, $p<0.05$, and time effects, $F(4,130)=13.01$, $p<0.001$, but no significant interaction ($F<1$).

The results of this experiment suggest: (1) Increased force requirements during lever pressing do not influence the rate decreasing effects of haloperidol; and (2) the pattern of response decline under haloperidol differs qualitatively from that occurring after the withholding of reinforcement (i.e., during extinction).

GENERAL DISCUSSION

In assessing the effects of neuroleptics on behavior, it has become increasing apparent that distinctions between the motoric and "anhedonic" effects are difficult to test. In attempts to differentiate between these two mechanisms, investigators have utilized a variety of tasks which either include minimal response requirements or which test the ability of neuroleptics to mimic or substitute for extinction. As an example of the former, tests have been divised which only require nose poking or licking as the response. The results from these tests, however, have been largely equivocal. Chlorpromazine and pimozide have been reported to reduce both reinforced and nonreinforced nose poking [1,3]. Haloperidol has been found to be equipotent in reducing nose-poking or lever pressing for intracranial self-stimulation (ICSS) [8] whereas α-flupenthixol reduces lever pressing for ICSS with little effect on nose poking [4]. More convincing evidence for attenuation of reward by neuroleptics has been reported by Xenakis and Sclafani [16] who, used a model

of ingestive behavior [2], found that the lick rate and lick efficiency of pimozide-treated rats drinking a saccharin-glucose solution were similar to those seen in rats drinking a quinine adulterated solution. These results are consistent with a reduction in the perceived palatability of sweet tasting solutions in pimozide treated rats.

The first experiment described in the current study was designed to test whether rats with experience on a motor task requiring a low or high degree of effort during training would show different suppressant effects of haloperidol on operant responding. If haloperidol's effects were such that they required the organism to increase its "effort" in order to overcome the action of the drug, then transfer might be expected to occur between having learned to press on a heavy bar and subsequent pressing on a light lever in the presence of haloperidol. However, the results indicate that transfer between the two situations does not occur, at least under the conditions employed here. It remains possible that the motoric effects of haloperidol are related to an interference with quickly repeated movements rather than to force-related aspects of lever pressing. This possibility is suggested because pimozide does not reduce responding in rats trained on DRL 15 schedule [11].

The second study sought to determine whether the response requirements produced by increasing the force needed to depress a lever would interact with the rate-decreasing effects of haloperidol. The motoric hypothesis would predict that haloperidol would have a greater effect on rats responding on a heavy bar when compared to rats pressing on a light lever. On the other hand, if haloperidol produces extinction-like effects, rats on the heavier lever might be expected to show an equivalent, or even less of a response decline after haloperidol compared to rats trained on the light bar [10,17]. The results of the second experiment failed to provide evidence in support of the motoric hypothesis because rats responding on either the heavy or light lever were equally affected by haloperidol. Similar results have been reported by Ford *et al.* [7] who found that the rate-decreasing effects of the less specific dopamine receptor antagonist, chlorpromazine, were similar in groups of rats that were required to respond on manipulanda that differed in their force requirements. The present results also fail to support the view that haloperidol administration is equivalent to producing a state of non-reward because while response rates failed to differ under haloperidol, the HL group responded significantly more during non-reward (i.e., extinction) than did the LL group. The results obtained in the extinction condition are not without precedent [10], and it has been hypothesized that the increased resistance to extinction seen in rats trained and extinguished on a heavy lever may be a result of partial lever presses made during acquisition which are not reinforced (see [10]).

Other studies have also failed to find equivalence between neuroleptic treatment and extinction. Although it appears that behavior under these two conditions may be similar for rats on a continuous reinforcement schedule [15] they are not when other schedules of reinforcement are used [12,13]. Tombaugh *et al.* [13] reported that the decline in response rate produced by pimozide is greater than that produced by extinction on certain schedules and similar results were obtained in the current study. Other evidence also argues against the equivalence of extinction and responding under neuroleptics [5, 11, 14]. It is becoming increasingly apparent that the effects of central dopamine receptor blockade on instrumental behavior are complex and cannot be attributed exclusively either to a general disruption of reinforcement processes or to currently specifiable effects on motor function.

ACKNOWLEDGEMENTS

The authors thank M. Martin-Iverson for computer assistance. Karen E. Asin was supported by an NINCDS Post-Doctoral Fellowship No. 1F32NS06399-02. Supported by the Medical Research Council.

REFERENCES

1. Cleary, J., F. Gault and R. Sewell. Chlorpromazine effects on behavior under escape and fixed-time delivery of shock. *Pharmacol Biochem Behav* **15:** 43–47, 1981.
2. Davis, J. D. and M. W. Levine. A model for the control of ingestion. *Psychol Rev* **84:** 379–412, 1977.
3. Ettenberg, A., S. A. Cinasavich and N. White. Performance effects with repeated-response measures during pimozide-produced dopamine receptor blockade. *Pharmacol Biochem Behav* **11:** 557–561, 1979.
4. Ettenberg, A., G. F. Koob and F. E. Bloom. Response artifact in the measurement of neuroleptic-induced anhedonia. *Science* **213:** 357–359, 1981.
5. Faustman, W. O. and S. C. Fowler. Use of operant response duration to distinguish the effects of haloperidol from nonreward. *Pharmacol Biochem Behav* **15:** 327–329, 1981.
6. Fibiger, H. C. Drugs and reinforcement mechanisms: A critical review of the catecholamine theory. *Annu Rev Pharmacol Toxicol* **18:** 37–56, 1978.
7. Ford, K. E., S. C. Fowler and G. L. Nail. Effects of clozapine and chlorpromazine upon operant response measures in rats. *Pharmacol Biochem Behav* **11:** 239–241, 1979.
8. Gerhardt, S. and J. M. Leibman. Differential effects of drug treatments on nose-poke and bar-press self stimulation. *Pharmacol Biochem Behav* **15:** 767–771, 1981.
9. Grupp, L. A. Effects of pimozide on the acquisition, maintenance, and extinction of amphetamine-induced taste aversion. *Psychopharmacology (Berlin)* **53:** 235–242, 1977.
10. MacKintosh, N. J. *The Psychology of Animal Learning*. New York: Academic Press, 1974.
11. Mason, S. T., R. J. Beninger, H. C. Fibiger and A. G. Phillips. Pimozide-induced suppression of responding: Evidence against a block of food reward. *Pharmacol Biochem Behav* **12:** 917–923, 1980.
12. Phillips, A. G. and H. C. Fibiger. Decreased resistance to extinction after haloperidol: Implications for the role of dopamine in reinforcement. *Pharmacol Biochem Behav* **10:** 751–760, 1979.
13. Tombaugh, T. N., H. Anisman and J. Tombaugh. Extinction and dopamine receptor blockade after intermittent reinforcement: Failure to observe functional equivalence. *Psychopharmacology (Berlin)* **70:** 19–28, 1980.
14. Tombaugh, T. N., C. Szostak, P. Voorneveld and J. W. Tombaugh. Failure to obtain functional equivalence between dopamine receptor blockade and extinction: Evidence supporting a sensory-motor conditioning hypothesis. *Pharmacol Biochem Behav* **16:** 67–72, 1982.
15. Wise, R. A., J. Spindler, H. deWit and G. J. Gerber. Neuroleptic-induced "anhedonia" in rats: Pimozide blocks reward quality of food. *Science* **201:** 262–264, 1978.
16. Xenakis, S. and A. Sclafani. The effects of pimozide on the consumption of a palatable saccharin-glucose solution in the rat. *Pharmacol Biochem Behav* **15:** 435–442, 1981.
17. Young, A. F. Resistance to extinction as a function of number of nonrun forced trials and effortfulness of response. *J Exp Psychol* **72:** 610–613, 1966.