EFFECTS OF HALOPERIDOL ON SCHEDULE-INDUCED POLYDIPSIA¹

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In dose-related amounts, the drug haloperidol attenuated schedule-induced drinking by rats prefed with 0.01-mg drug added to 0, 25, 50, 75 or all of 100 Noyes 45-mg pellets. Drug pellets also induced less drinking than did regular Noyes pellets by rats that obtained these pellets at 1-min intervals by bar pressing. Haloperidol also reduced bar pressing and, temporarily, rate of reinforcement. The results appeared not to be due to a general sedative effect of haloperidol but to its selective power to reduce angiotensin-induced drinking. Thus, schedule-induced drinking, which is abnormal in not causing satiation, is controllable by a drug that interferes with the renin-angiotensin hormone system thought to regulate normal drinking.

Key words: polydipsia, adjunctive behavior, haloperidol, bar press, rats

Schedule-induced polydipsia is a phenomenon wherein rats intermittently fed small pellets of food consume extraordinary amounts of water by drinking after each pellet that they eat (Falk, 1961, 1971). Explanations of the phenomenon focus either on drinking behavior—as an operant controlled by reinforcement and punishment (Bond, Blackman, and Scruton, 1973; Clark, 1962; Cohen, 1975; Hawkins, Schrot, Githens, and Everett, 1972; Hymowitz and Freed, 1974) or as an adjunctive interim activity (Falk, 1971; Staddon and Simmelhag, 1971; Wuttke and Innis, 1972)—or on water consumption induced by thirst (Stein, 1964). Of numerous studies in the first of these categories (*cf.* Falk, 1971; Segal, 1972) only a few relate schedule-induced drinking to other determinants of “thirst” (Burks and Fisher, 1970; Keehn and Matsunaga, 1971).

Traditional theories of thirst are about the origins of thirst sensations in water-deprived organisms. Modern theories of thirst are about determinants of drinking; they include intracellular fluid depletion, extracellular volume reduction, cholinergic centers in the brain, and “a renin-angiotensin hormone system” (Fitzsimons, 1972, 1973). The effectiveness of these mechanisms is supported by the elicitation and “blockage” of drinking by water-sated

animals with appropriate stimulation (*cf.* Fisher, 1973; Fitzsimons 1972, 1973 for reviews). Intermittent feeding stimulates drinking by sated animals (Colotla and Beaton, 1971), so it is possible to relate schedule-induced drinking to other determinants of drinking by seeking common blocking agents. Haloperidol is a drug that selectively reduces drinking induced by angiotensin (Setler, 1973). The present study shows that this drug also reduces drinking stimulated by intermittent feeding.

GENERAL METHOD

Subjects

Eight male Wistar rats supplied by High Oak Ranch, Guelph, Ontario, were used in three experiments. They were approximately 120 days old at the beginning of the experiments and had been trained to bar press in a manually controlled operant chamber.

All subjects were individually housed and maintained at 80% of their free-feeding weights, which averaged 380 g at 120 days of age. Water was freely available in home cages. Animals J9 through J12 were used in Experiments I and III, J5 through J8 in Experiment II.

Apparatus

Two standard Grason-Stadler two-bar boxes Type E 3125B were used. In each box, the left-hand bar was removed and its housing covered

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by a metal plate mounted flush with the wall. A force of 19 g (0.19 N) on the remaining bar activated electromagnetic scheduling and recording apparatus housed in an adjacent room. A calibrated filled water-bottle was mounted on the outside of the door of each box such that the outlet tube was 5 cm above floor level and 9 cm from the wall containing the lever and food cup. Licks at the tube were monitored by Grason-Stadler Model E 4690A-1 drinkometers. The experimental boxes were enclosed in standard Grason-Stadler ventilated, sound-attenuating chambers. Data were collected on electromechanical counters and Gerbrands cumulative recorders.

EXPERIMENTS I AND II

In these experiments, different methods of oral administration of haloperidol were used. Subjects were given 0.01 mg haloperidol in standard 45-mg Noyes rat pellets in both cases. In Experiment I, the pellets were prefed 30 min before testing sessions; in Experiment II, they were used as reinforcers during testing sessions. The prefeeding method gave a standard massed dose a specified time before testing; the reinforcer method provided an accumulating drug dose spaced over the time of testing. Imipramine and propranolol were also used (see Table 1) but had no effect.

Procedures

The conditions of Experiments I and II are summarized in Table 1. Each subject was given

Fig. 1. Mean five-day bar-press, eating, and drinking rates after prefeeding with 100 45-mg pellets, each containing 0.01 mg haloperidol (H), 0.01 mg imipramine (I), 0.01 mg propranolol (P), or no drug (N).

five 1-hr sessions of magazine approach and bar-press training in which the reinforcement schedule was adjusted until bar presses were reinforced at fixed intervals of 60 sec (FI 60-sec). This terminal condition was maintained for a further 13 1-hr sessions. After this, the subjects of Experiment I were given 100 pellets 30 min before each experimental session. In blocks of five sessions the prefed pellets were: standard formula 45-mg Noyes pellets; standard pellets with 0.01 mg propranolol (P); standard pellets; standard pellets containing 0.01 mg haloperidol (H); standard pellets; standard pellets containing 0.01 mg imipramine (I); standard pellets; standard pellets containing 0.01 mg haloperidol (H); standard pellets.

Reinforcers in Experiment I were always standard pellets. In Experiment II, they were standard pellets through Session 18. Then, for five sessions each, reinforcers were: standard pellets; standard pellets with 0.01 mg imipramine; standard pellets; standard pellets with 0.01 mg haloperidol; standard pellets; standard pellets with 0.01 mg propranolol; standard pellets; standard pellets with 0.01 mg haloperidol; standard pellets.

Sessions normally lasted 90 min or until 60 reinforcers were secured, whichever came first. Water was freely available during all sessions, and water consumption, cumulative licks, and bar presses were recorded.

Table 1

Experimental Conditions

Sessions	Experiment I	Experiment II
1-5	Magazine and bar trained to FI 60-sec with standard (N) pellets	
6-18	N-pellets earned on FI 60-sec	
19-23	Prefed 100 N-pellets	N-pellets as reinforcers
24-28	Prefed 100 P*-pellets	I*-pellets as reinforcers
29-33	Prefed 100 N-pellets	N-pellets as reinforcers
34-38	Prefed 100 H*-pellets	H-pellets as reinforcers
39-43	Prefed 100 N-pellets	N-pellets as reinforcers
44-48	Prefed 100 I-pellets	P-pellets as reinforcers
49-53	Prefed 100 N-pellets	N-pellets as reinforcers
54-58	Prefed 100 H-pellets	H-pellets as reinforcers
59-63	Prefed 100 N-pellets	N-pellets as reinforcers

*P-pellets are standard 45-mg Noyes pellets containing 0.01 mg propranolol.

*I-pellets are standard 45-mg Noyes pellets containing 0.01 mg imipramine.

*H-pellets are standard 45-mg Noyes pellets containing 0.01 mg haloperidol.

RESULTS

Experiment I

During prefeeding, all subjects consumed all available pellets within the time allowed, re-

gardless of pellet composition. Subjects J9 and J10 exhibited polydipsia with the usual pattern of eat-drink behavior. Animals J11 and J12 drank less reliably after pellets, but all subjects showed markedly less drinking follow-

Fig. 2. Bar-press, eating, and drinking rates on successive days after prefeeding with 100 45-mg Noyes pellets each containing no drug (A) or 0.01 mg haloperidol (B).

ing prefeeding with haloperidol than following prefeeding with other pellets. Drinks occurred only about half as often after haloperidol prefeeding (35.9 and 37.2% on first and second determinations) as under the other experimental conditions.

Rates of bar pressing, reinforcer deliveries, and drinking for each rat under each condition appear in Figure 1. In each case, drinking was reduced only by haloperidol. However, as Figure 1 also shows, bar pressing and rates of reinforcer delivery were also depressed by haloperidol. Thus, the effect of haloperidol on drinking could have been a byproduct of the drug's effect on bar pressing and eating.

A more detailed picture of haloperidol's effect is shown in Figure 2, which illustrates session-by-session bar pressing, reinforcer delivery, and drinking rates during the second five-session block with haloperidol prefeeding (Sessions 54 to 58). Fluid and bar-press rates

remained depressed for the five days that haloperidol was prefed, but food intakes recovered almost to baseline levels (except for J12) after an abrupt drop on the first day of haloperidol prefeeding. These data contradict the hypothesis that haloperidol reduces drinking because it reduces eating, but leave open the possibility that it decreases drinking because it depresses activity in general. Figure 3 contains typical cumulative licking records after prefeeding with standard and haloperidol pellets. Notice that pellets were secured regularly through drug and no-drug sessions, and that the subject stopped drinking after securing only four or five reinforcers when prefed with haloperidol but continued licking throughout the session when prefed with the same number (100) of standard Noyes pellets. Record A, a no-drug record, covers 65 min in which 60 reinforcers were secured. Records B and C are records of drug sessions, in which 46 reinforcers were

Fig. 3. Cumulative records of licking with food reinforcement scheduled at fixed 1-min intervals. One hundred 45-mg regular Noyes pellets were fed before record A; 100 45-mg Noyes pellets each containing 0.01 mg haloperidol were fed before records B and C. Record A is 65 min long and a complete vertical excursion of the record requires 1100 licks. Spurs on the record indicate pellet deliveries.

secured in 60 min, and 60 reinforcers were secured in 73 min, respectively.

Experiment II

All four animals became polydipsic and drank after more than 90% of the reinforcer pellets they consumed, except when they contained haloperidol. Figure 4 shows how haloperidol affected drinking: postpellet drinks occurred normally at first, but after about 25 reinforcer pellets (each containing 0.01 mg haloperidol), drinking stopped. Subject J7 ate three pellets after it finished drinking, and Subject J5 ate 11, six immediately after stopping drinking and five later in the session. The percentage of haloperidol pellets followed by drinking therefore reflects the time between termination of drinking and termination of bar pressing. This was not the case in Experiment I, where standard Noyes pellets were used as reinforcers, because subjects continued to eat pellets throughout sessions.

EXPERIMENT III

Comparison of the cumulative licking records of J12 from Experiment I (Figure 3) with those of J5 and J7 from Experiment II (Figure 4) shows that the effect of haloperidol on drinking is dose-dependent: J12 was prefed 100×0.01 mg haloperidol and drank very little; J5 and J7 drank more but consumed only about 25×0.01 mg of the drug. However, as these dose-response results are contaminated by many other experimental differences, the animals of Experiment I were used to obtain additional dose-response data. Only the prefeeding method of drug administration was possible in this experiment because drug doses with the reinforcer method of Experiment II are not under experimenter control.

Procedure

The procedure of Experiment I was used, except that the 100 pellets fed before experi-

Fig 4. Cumulative records of licking with reinforcer pellets containing 0.01 mg haloperidol, each scheduled at fixed intervals of 1 min. Spurs on the record indicate pellet deliveries.

mental sessions contained 0, 25, 75, or 100 45-mg standard Noyes pellets. The remainder were regular pellets with 0.01 mg haloperidol per pellet. Haloperidol dose orders were balanced across subjects in a Latin square design (*cf.* Table 2), with five zero-dose sessions intervening between five-day blocks with each drug dose.

Experiment III followed Experiment I without interruption. Sessions normally lasted for 90 min or until 60 standard pellet reinforcers scheduled at 1-min fixed intervals were secured, whichever came first. Water was freely available in all sessions, and water consumption, cumulative licks, and bar presses were recorded.

RESULTS

Table 2 shows mean rates of bar presses, reinforcer deliveries, and millilitres of water drunk for each rat over the five days of each drug dose. Zero dose rates are means from all of the sets of five drug-free sessions that separated drug doses. Average and individual

Table 2
Dose-response effects of haloperidol on water intake, pellet delivery, and bar-press rates.

Subjects	Number per Minute			Drug Order
	Water (ml)	Pellets	Bar Presses	
Dose 0 mg				
J9	0.39	0.94	21	—
J10	0.26	0.90	14	—
J11	0.25	0.98	34	—
J12	0.26	0.93	13	—
Dose 0.25 mg				
J9	0.27	0.88	14	1
J10	0.16	0.90	12	3
J11	0.22	0.98	24	4
J12	0.16	0.90	11	2
Dose 0.50 mg				
J9	0.21	0.86	12	2
J10	0.08	0.90	9	1
J11	0.17	0.97	19	3
J12	0.20	0.89	9	4
Dose 0.75 mg				
J9	0.16	0.76	4	4
J10	0.10	0.76	4	2
J11	0.09	0.92	7	1
J12	0.07	0.54	3	3
Dose 1.0 mg				
J9	0.12	0.86	5	3
J10	0.08	0.80	4	4
J11	0.06	0.90	5	2
J12	0.14	0.61	4	1

dose-response relationships between haloperidol dose and millilitres of water drunk per food pellet consumed over the five days of each of the drug doses appear in Figure 5. Generally, attenuation of drinking is a direct function of dose, whether water intake is expressed per minute (Table 2), or per pellet consumed (Figure 5), although results of J12 are less regular than those of the other subjects.

DISCUSSION

Schedule-induced drinking is interesting on two counts: first, it is an orderly behavior exhibited when food reinforcers are scheduled periodically, although it is not a behavior specified by the schedule; second, it results in extraordinarily high fluid intakes—hence schedule-induced polydipsia (Falk, 1961)—when sessions continue beyond the time when satiation would normally occur. Thus, one mystery with schedule-induced polydipsia concerns the drinking that occurs after eating; a second concerns the fact that sated animals continue to drink. The present results pertain to the second mystery by showing that a drug that attenuates physiologically induced drinking by sated animals (Fitzsimons, 1972; Setler, 1973) also reduces schedule-induced drinking, suggesting the possibility of a common mechanism in the two kinds of drinking.

Fig. 5. Dose-response curves of schedule-induced water intake per food pellet and amount of haloperidol eaten 30 min before an experimental session. Dose orders were balanced across subjects (*cf.* Table 2).

Experiments I and II together, and Experiment III alone, showed that oral administration of haloperidol attenuates schedule-induced drinking by rats in direct proportion to drug dose. The drug also affected rates of bar pressing and reinforcer delivery, so the reduction of drinking could have been an artifact. First, schedule-induced drinking is a postpellet phenomenon, and fluid intake depends not directly on session time but on pellets consumed per session (Keehn, 1972). Therefore, the reduced drinking with drug pellets as reinforcers in Experiment II could have occurred because the subjects "lost their appetites" and stopped bar pressing for food after 20 to 30 pellets. This explanation cannot apply to Experiment I, however, because animals predrugged with 100 pellets eventually ate standard Noyes pellet reinforcers at almost their normal rates. But they did not drink after eating, and their bar-press rates were depressed. Second, bar pressing and drinking rates could have been depressed because the animals were sedated. They were not noticeably lethargic after haloperidol, but sedative effects of haloperidol have been reported for rats (Sayers and Kleinlogel, 1974). However, the drug dose at which subjects stopped bar pressing in Experiment II (about 25×0.01 mg haloperidol) reduced mean bar-pressing rates in Experiment III only from 20.5 to 15.25 responses per minute (reinforcers were drug pellets in Experiment II, standard pellets in Experiment III). Animals capable of making 15 bar presses per minute can hardly have been too sedated to drink.

A third possibility is that haloperidol directly affected drinking, perhaps by blocking the renin-angiotensin hormone system (Fitzsimons, 1972), and that the absence of drinking reduced the reinforcing value of standard pellets and hence the rate of bar pressing. Evidence against this possibility is that bar-pressing rates are higher without than with water present in the experimental chamber (Colotla and Keehn, 1975; Knutson and Schrader, 1975), but bar-pressing rates in these cases did not allow for time spent drinking when water bottles were present, so the data are not decisive. Results of experiments in our laboratory have also been inconclusive on this matter. Thus, although the present experiments clearly show a dose-related suppression of schedule-induced drinking by haloperidol, the fact that

the drug also depressed rate of bar pressing leaves the question of its mode of action open.

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