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Dopamine Receptor Blockade and Reductions in Thirst Produce Differential Effects on Drinking Behavior

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HORVITZ, J. C., W. B. RICHARDSON AND A. ETTENBERG. *Dopamine receptor blockade and reductions in thirst produce differential effects on drinking behavior.* PHARMACOL BIOCHEM BEHAV 45(3) 725–728, 1993.—The present study examined whether thirsty rats pretreated with the dopamine receptor blocker, pimozide, would show patterns of unconditioned drinking behavior similar to those produced by reductions in water deprivation. An examination of the drinking behavior of 23-, 16-, 12-, 4-, and 0-h water-deprived animals showed that reductions in thirst produced increased latencies to initiate drinking, changes in the within-session pattern of licking, and reductions in the total number of licks emitted. In contrast, administration of pimozide to 23-h deprived rats produced no effect on either initiation latencies or lick patterns, and only marginally reduced the total number of licks emitted during the session. Finally, pimozide produced no effect on either individual lick durations or interlick intervals. These results suggest that the primary motivational (i.e., "thirst") mechanisms and motoric processes underlying drinking behavior are relatively invulnerable to pimozide challenge.

Neuroleptics Pimozide Dopamine Drinking Thirst

NUMEROUS studies have shown that neuroleptic drugs produce patterns of reinforced behavior that resemble those seen in animals responding under either decreased reward or nonreward conditions (8,10,11,22,25). Furthermore, evidence suggests that this apparent disruption of reward-related processes observed in neuroleptic-treated animals cannot be accounted for solely on the basis of motor-impairing effects of the drug (3,6,7,15). While many investigators agree that neuroleptics, in some way, disrupt motivational or reward-related processes (2,4,16,19,23), investigators have *not* agreed upon a more specific characterization of this disruption. For example, neuroleptics may interfere with primary motivational states such as hunger and thirst (5,13,20), attenuate the behavior-activating effects of conditioned reward-related stimuli (4), or block the reinforcing effects of primary rewards such as food and water (7,14,15,24,25). As the nature of this neuroleptic-induced deficit becomes more specifically defined, the function of central dopamine systems in motivation/reward processes will become clearer.

In the present study, we were interested in determining whether a neuroleptic drug would attenuate a *primary* motivational state, thirst. We therefore examined both patterns of drinking behavior and latencies to initiate drinking in animals under various levels of water deprivation. These latencies and patterns of drinking were compared to those observed in thirsty rats drinking under the influence of a dopamine antagonist drug, pimozide. In addition, a microanalysis of individual lick durations and interlick intervals allowed an examination of possible subtle neuroleptic effects on motoric processes underlying drinking behavior.

METHOD

Subjects

Sixteen male albino Sprague-Dawley rats (300–325 g) obtained from Charles Rivers Laboratories served as subjects. Animals were individually housed in metal wire hanging cages, located within a temperature-controlled (23°C) 12L : 12D vivarium environment (lights on at 0700 h). All subjects were provided with ad lib access to food and water in their home cages for 1 week. For the remainder of the experiment, animals received free access to food, but were restricted to 15-min access to water per day. This schedule provided animals with sufficient fluids to maintain their health and body weights.

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On test days, animals received 5-min access to water in their home cages approximately 1 h after testing.

Apparatus

Test sessions took place within a chamber (20.5 × 24.2 × 28.0 cm high) constructed of wood walls, wire mesh floor, and Plexiglas ceiling. To gain access to water, an animal was required to place its head into a recess (5.4 cm deep, 4.0 cm wide, 7.3 cm high) located within one of the walls of the chamber. The recess was centered along the horizontal dimension of the wall, with its bottom surface 1.3 cm above the chamber floor. With its head inside the recess, the animal was required to lick downward through a circular hole (1.4 cm in diameter), the perimeter of which was located 1.2 cm beyond the chamber wall. A water trough (14.1 × 5.0 × 3.8 cm high) was located directly below the bottom surface of the recess, with the water surface 0.5 cm below the recess floor. Drinking behavior was monitored by a drinkometer circuit that was actuated each time the animal's tongue made contact with water. Data were collected on an IBM PC, equipped with a John Bell Engineering PC Universal I/O board. Custom software (written by Stephen Fowler) directed the A/D converter to sample the output of the drinkometer circuit at a frequency of 256 Hz, allowing licks to be recorded at a temporal resolution of approximately 5 ms.

Procedure

During a 1-week acclimation period, animals were placed under a 23-h deprivation schedule and were allowed to drink from the drinking apparatus for 10 min/day. Animals were then randomly assigned to either the deprivation or the pimozide condition (n = 8/condition).

Deprivation. Drinking behavior was recorded following 0, 4, 12, 16, and 23 h of water deprivation. Each animal was tested under each of the five deprivation levels, in a randomly assigned order, with at least 3 days separating each test session. To establish a particular water deprivation level, the animal was given free access to home cage water until the designated number of deprivation hours prior to testing. At the time of the test session, the animal was placed in the drink chamber where it had the opportunity to freely consume water for 10 min. Throughout each session, latency to initiate drinking, the time of occurrence of each lick, and the duration of each lick were recorded.

Pimozide. The drinking patterns of 23-h water-deprived rats were recorded following pretreatment with either 0, 0.5, 0.75, or 1.0 mg/kg of pimozide. Each animal was tested under each dose of pimozide, in a randomly assigned order, with at least 3 days separating each test session. Pimozide was dissolved in a warm vehicle solution of 0.002 M lactic acid. Intraperitoneal injections of pimozide or vehicle were administered in a volume of 1.0 ml per kilogram of body weight, 4 h prior to the test session. Test sessions were otherwise identical to those of the Deprivation group.

RESULTS

The mean latencies for animals to initiate drinking, upon placement in the test chamber, are illustrated in Fig. 1. Reductions in water deprivation level (left panel of Fig. 1) resulted in increased latencies to initiate drinking. In contrast, administration of pimozide to 23-h deprived rats produced little effect on initiation latencies (right panel of Fig. 1). Separate one-way ANOVAs conducted on the data shown in each side of Fig. 1 confirmed that initiation latencies were significantly affected by changes in water deprivation level, $F(4, 28) = 14.89$, $p < 0.0001$, but were unaffected by treatment with pimozide, $F(3, 21) = 0.35$, NS.

Figure 2 shows a comparison of drinking behavior (mean number of licks per minute) in animals under reduced water deprivation conditions (left panel) or following pretreatment with pimozide (right panel). As can be seen, reductions in deprivation level produced decrements in rates of licking that were evident from the very first minute of the session. In addition, reductions in deprivation produced changes in the pattern of licking over the course of the session. Animals under low-deprivation conditions (0, 4, and 12 h) showed relatively constant rates of licking throughout the session, while those under high-deprivation conditions (16 and 23 h) showed gradual reductions in lick rate over the course of the session. A two-factor deprivation × time analysis of variance (ANOVA) with repeated measures on both factors revealed a main effect for deprivation level, $F(4, 28) = 41.60$, $p < 0.0001$, confirming that reductions in deprivation level produced decrements in licking behavior; a main effect for time, $F(9, 63) = 5.61$, $p < 0.0001$, indicating that licking behavior

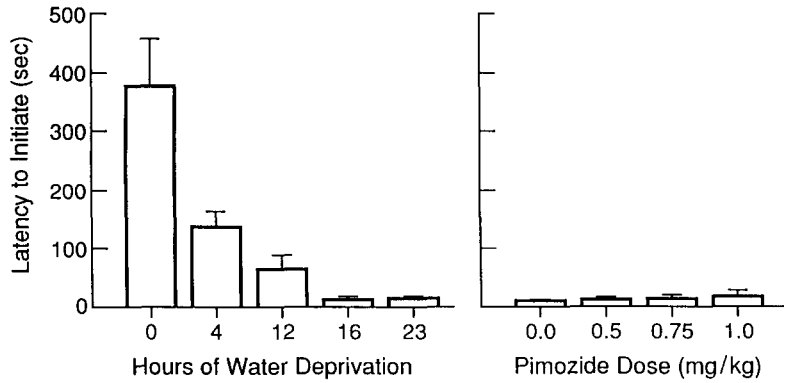

FIG. 1. Mean (+SEM) latency to initiate drinking following 0-, 4-, 12-, 16-, or 23-h water deprivation (left panel), and 23-h water deprivation and pretreatment with 0, 0.5, 0.75, or 1.0 mg/kg of pimozide (right panel). Reductions in thirst led to increased latencies to initiate drinking, while pretreatment with pimozide did not.

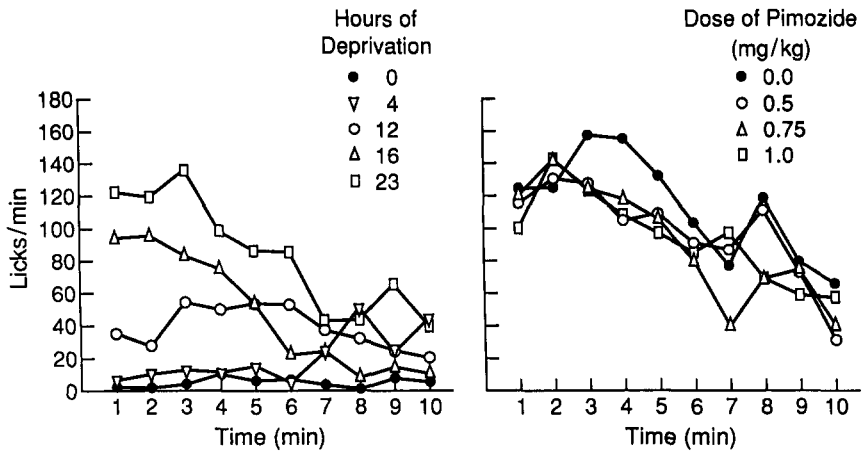

FIG. 2. Temporal pattern of licking in 0-, 4-, 12-, 16-, or 23-h water-deprived animals (left panel), and in 23-h deprived animals pretreated with either 0, 0.5, 0.75, or 1.0 mg/kg of pimozide (right panel).

decreased over the course of the session; and a significant deprivation × time interaction, $F(36, 252) = 3.31$, $p < 0.0001$, confirming that the magnitude of the within-session reduction in licking was influenced by deprivation level.

The 10-min drinking patterns for 23-h deprived animals pretreated with 0, 0.5, 0.75, or 1.0 mg/kg of pimozide are shown in the right panel of Fig. 2. In contrast to reductions in deprivation level, pimozide pretreatment produced relatively little attenuation of lick rates. In addition, the gradual within-session reductions in lick rate normally seen under high-deprivation conditions are evident in animals pretreated with even the highest (1.0 mg/kg) dose of pimozide. A two-factor drug dose × time ANOVA (with repeated measures on both factors) conducted on the pimozide data revealed only a marginal main effect for drug dose, $F(3, 21) = 2.89$, $p < 0.059$, suggesting that the drug did not produce reliable reductions in the total number of licks during the session; a significant main effect for time, $F(9, 63) = 12.04$, $p < 0.0001$, confirming the observation that lick rates decreased over the course of the session; and no significant drug × time interaction, $F(27, 189) = 1.23$, NS, indicating that these within-session changes in lick rate were similar in vehicle- and pimozide-treated rats.

Pimozide challenge was also ineffective in altering lick efficiency (i.e., the number of licks required for the animal to consume a given quantity of water). A one-way ANOVA computed on lick efficiency data (total number of licks in a 10-min session/total quantity of water consumed) in a subset of the vehicle- and pimozide-pretreated rats ($n = 5$/each dose) indicated that the neuroleptic produced no impairment in this behavioral index, $F(3, 16) = 0.23$, NS.

Finally, it was of interest to determine whether or not the neuroleptic produced changes in either individual lick duration or interlick intervals (ILI), since neuroleptic drugs have previously been shown to increase both response durations and interresponse times (9,12). A one-way ANOVA across drug conditions indicated that neither median lick duration, $F(3, 21) = 1.14$, NS, nor ILIs were affected by pimozide treatment, $F(3, 21) = 1.85$, NS. *Median* scores were used for the ANOVAs above, since these values most accurately reflect the rapid licking behavior that occurs during *bouts* of licking. In contrast, the *mean* interlick interval is strongly affected by pauses *between* bouts. Additional analyses conducted on mean values for duration and ILI data similarly revealed no effect of pimozide [$F(3, 21) = 0.97$; $F(3, 21) = 1.85$, respectively, NS].

DISCUSSION

The present study asked whether thirsty rats administered the dopamine antagonist pimozide would show patterns of drinking behavior similar to those seen following reductions in thirst (i.e., reductions in water deprivation). The results showed that pimozide did *not* produce the changes in drinking behavior observed following reductions in thirst. Specifically, 1) animals under reduced deprivation schedules (i.e., less thirsty animals) showed increased latencies to initiate drinking, while pimozide failed to increase initiation latencies; 2) reductions in water deprivation led to large decrements in rates of licking throughout the session, while pimozide produced only marginal reductions in lick rate; and 3) reductions in water deprivation produced changes in patterns of licking over the course of the session that were not observed in the pimozide subjects. In agreement with the present data, haloperidol (21) and pimozide (13) have previously been found to produce reductions in total licks emitted during a drinking session. However, additional measures, namely the latency to initiate drinking and the temporal pattern of licking, reveal that pimozide fails to mimic the effects of reduced deprivation level. Snodgrass and Allen (1987) come to a similar conclusion regarding the effects of haloperidol (21). These results support the view that thirst mechanisms are relatively invulnerable to dopamine receptor blockade.

Thirst mechanisms appeared intact, even during treatment with the high 1.0-mg/kg dose of pimozide. This finding is of particular significance, since the same dose of pimozide has been shown to disrupt both spontaneous and appetitive locomotor activity (16), and to block the reinforcing effects of food (14,24) and water reward (7) in an operant task. In fact, even at 0.6 mg/kg of pimozide, animals show approximately 90% reductions in responding for electrical brain stimulation to the medial forebrain bundle (17). Thus, doses of pimozide that have been shown to dramatically disrupt locomotor activity and reinforcement processes appear to be ineffective in disrupting thirst. It should be noted that higher doses of the

drug were not tested, for doses of pimozide greater than 1.0 mg/kg begin to produce indirect increases in noradrenaline (NE) activity (1), and produce substantial motor deficits (18).

In summary, the DA antagonist pimozide failed to produce the changes in drinking behavior seen in animals under reduced deprivation conditions. Thus, while neuroleptics have been shown to produce disruptions in various aspects of reward/motivational functions (2,4,7,8,10,11,16,19), the present data suggest that a primary motivational state, namely thirst, remains intact during treatment with the dopamine antagonist pimozide.

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