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Captopril Alters Schedule Induced Polydipsia, Urination, and Defecation in Rats

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BOWERS, R. L., J. HALBERDA, L. MULLEN AND K. MAY. *Captopril alters schedule induced polydispia, urinaation, and defecation in rats.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 353–359, 1997.—Schedule induced polydipsia, urination and defecation were examined in rats that received training on a fixed interval 2 min schedule of food reinforcement. In Phase I of the experiment, animals received peripheral injections of captopril (an angiotensin conversion enzyme blocker, 0.5 or 50 mg/kg), or equivalent volumes of 0.9% saline. The results showed that low doses of captopril (0.5 mg/kg) significantly increased both operant responding and the adjunctive behaviors. High peripheral doses of captopril significantly reduced responding and schedule induced behavior. In Phase II of the experiment, animals received either low peripheral doses of captopril (sc 0.5 mg/kg), or low doses that were coupled with central injections (i.e., 0.12 mg icv + 0.5 mg/kg sc). As observed in Phase I, low peripheral doses of captopril enhanced behavior, but the enhancement effect was eliminated with low (0.12 mg) central administration. The overall results are consistent with past research examining captopril effects on non-operant, meal-induced drinking. Yet since captopril affected operant responding and adjunctive behaviors similarly, the findings suggest that angiotensin plays a common role in the motivational processes that precede and follow the arrival of food. © 1997 Elsevier Science Inc.

Fixed interval schedules of reinforcement Operant responding Stress Angiotensin II Dopamine
Polydipsia Urination Defecation Adjunctive behavior Captopril

WHEN hungry rats are given extensive training on a fixed interval schedule of reinforcement, they typically respond more vigorously toward the end of the food interval, and then pause after reinforcement is delivered (3,22,24,40). During the pause animals engage in a number of striking behaviors. Polydipsia, urination, defecation, preening, aggression, and wheel running have been observed in variety of species (10,18,20,21,34,44,45,47,49,51). Since these responses occur beyond the requirements of reinforcement, they have been termed adjunctive behaviors (19,20,21,47). Although several theories have been advanced (11,19,29,47), recent evidence suggests that reinforcer-induced motivation plays a role (11,34).

A recent model (11,34) describes that schedule induced behavior emerges from two motivational states generated by the periodic delivery of food. Although the responses that occur in each state may be different, they are assumed to be controlled by a common, adaptive mechanism. For example, the model assumes that the first thing an animal does after reinforcement is to engage in behaviors that modulate stress. Stress is thought to ensue because of the removal of food, and the contingencies related to its return. Stress modulating behaviors are repetitive, stereotypical, and limited in duration by their ability to reduce physiological stress (4,5,37,38). If stress were the primary determinant we might expect these behaviors to develop with training; the removal of food cannot signal a period of extinction without adequate exposure to the contingencies (45). And this is precisely what numerous studies have shown. Polydipsia, pawlicking, and other reactions develop with training (34,35,45,47). Following stress modulation, motivation then shifts to food exploration. In this view behaviors such as timeout responding, turning away from the operandum, and wheel running may be hybrids of foraging (10,11,34). Although the two-state model has support (10,34, 35), the underlying physiological mechanisms remain unclear (6,12,38,39,49).

Recently, converging lines of evidence have encircled at least a portion of the mechanisms that control polydipsia. Behavioral studies have shown that eating and drinking are joined tightly as animals invariably seek water after eating (18,19,30,35,44,47). In fact, it has been shown that eating itself causes the release of a dipsogenic hormone called angiotensin

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II (31,32). When animals are administered captopril, a drug that blocks the conversion of angiotensin I to angiotensin II, drinking that normally accompanies feeding is abolished (31). Thus, a strong link exists between eating, the release of angiotensin II, and dipsia. Yet polydipsia emerges only after extended exposure to intermittent schedules of reinforcement (12,34,47). Can the angiotensin account explain drinking that develops with experience? Accumulating evidence now indicates that angiotensin II is released during stress (1,8,13,17, 26,27). And if intermittent schedules are stressful to animals (4,5,19,34,47), it is likely that angiotensin II plays a role in periodic drinking, and perhaps, other adjunctive behaviors.

With this in mind, the present study examined whether captopril alters three types of schedule induced behaviors. If captopril affects polydipsia, urination, and defecation, it would suggest that angiotensin plays a more common role. Since no research had yet examined the role of angiotensin on schedule induced behaviors, we proceeded by replicating the doses and administration routes used in the captopril research conducted by Fitzsimons and Elfont (23).

In the first phase of their study (23, Pp. 558-559), cavalligation-induced drinking was examined after rats were given high and low doses of captopril administered peripherally (i.e., sc 50 or 0.5 mg/kg). The results showed that 0.5 mg increased drinking six times over that shown after control injections. In the second phase of their study, animals received either low single injections of captopril (0.5 mg/kg), or low peripheral injections that were coupled with central administration (i.e., 0.12 mg icv + 0.5 mg/kg sc). As shown before, the single low dose produced robust drinking, but when 0.5 mg of captopril was coupled with central administration, drinking was nearly abolished. Interestingly, Fitzsimons and others have replicated these findings (14,15,16) and have determined that 0.5 mg of captopril increased peripheral levels of renin and angiotensin I. Although the authors suggest that peripheral accumulation of angiotensin I leads to heightened brain levels of angioten-sin II (23, P. 560), the mechanism underlying the dipsogenic effects remain unclear (22,46). Apparently high peripheral and central injections (sc 50 mg/kg, icv 0.120 mg) adequately block the formation of angiotensin II, and drinking (see 23 for further discussion).

Since drinking appears to be sensitive to captopril dose and injection route, the question in the present study was whether polydipsia and other adjunctive behaviors are affected similarly. If captopril alters schedule induced polydipsia, it would suggest that angiotensin II plays a common role in drinking that accompanies the consumption of food, and contingencies related to its return.

METHOD

Animals

Experimentally naive, male, Long–Evans rats were obtained from Charles River laboratories. All rats were maintained at 85% of their ad lib weights and were given continuous access to water in the home cages. Home cage room lighting was provided according to a 14:10 light-dark cycle.

Apparatus

Standard operant conditioning chambers were used that contained a response lever on the lower-right side of the intelligence panel, a food aperture located in the lower center of the panel, and single calibrated (ml) drinking spout (Pyrex) mounted against the back wall. Clean plastic trays were placed below the grated floors to catch the urine and fecal bolis emitted during test sessions. Timing of the fixed intervals and recording of the bar responses were accomplished by Med Associated interface systems connected to Apple IIE microcomputers.

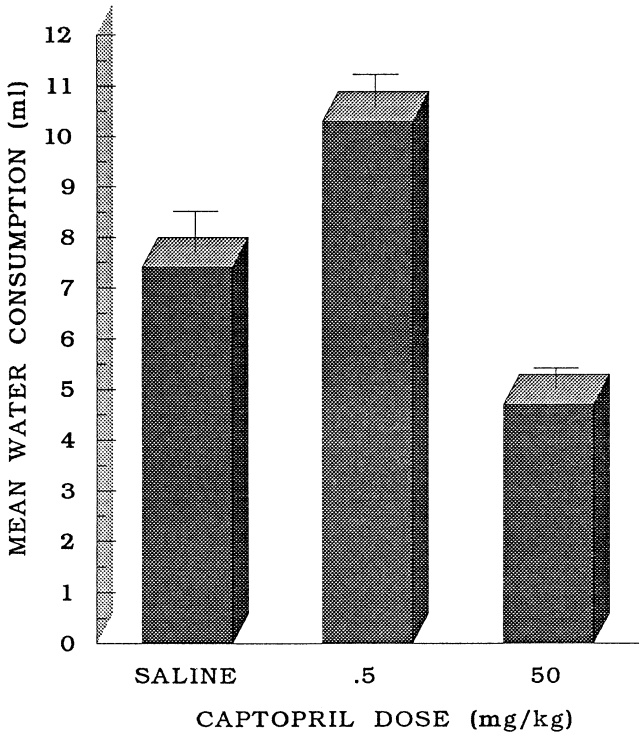

FIG. 1. Mean (± SEM) polydipsia following sc injections of 0.9% saline (N = 8), 0.5 mg/kg (N = 8), or 50 mg/kg (N = 8) captopril.

Procedure

All animals were shaped to barpress via successive approximations. After earning approximately 100 reinforcements (single Noyes pellets), rats were then exposed to a FI 2 min schedule of reinforcement for approximately 40 days. Each daily session began with five warmup trials and then 35 trials in which the overall responses per min, pause after reinforcement, and responses per min emitted within successive 20 s bins of each interval were computed. Polydipsia was assessed by measuring test chamber water consumption to the nearest 0.5 ml. Urine was weighted in milligrams, and fecal droppings were counted in discrete units. Following day 40 of training, operant responding and adjunctive behaviors were assessed after injections of saline or doses of captopril (see Injection Procedures described below).

Injection procedures: Phase I. Eight rats (weighing 430–550 g) were given injections of 0.9% physiological saline, 0.5 mg/kg, or 50 mg/kg of captopril administered subcutaneously. Each dose was administered twice to all animals, and the order of administration was randomized across subjects and days.

Phase II. Ten days prior to the training, nine rats (weighing 226–255 g) were fitted with 22-gauge stainless steel icv cannulas (Plastic Products). The cannulas were positioned unilaterally at: AP, 10.0 mm; L, 1.0 mm; V, 7.5 mm from dura inclined 10 degrees from the vertical coronal plane. Verification of placement was accomplished by inserting stylets into the can-

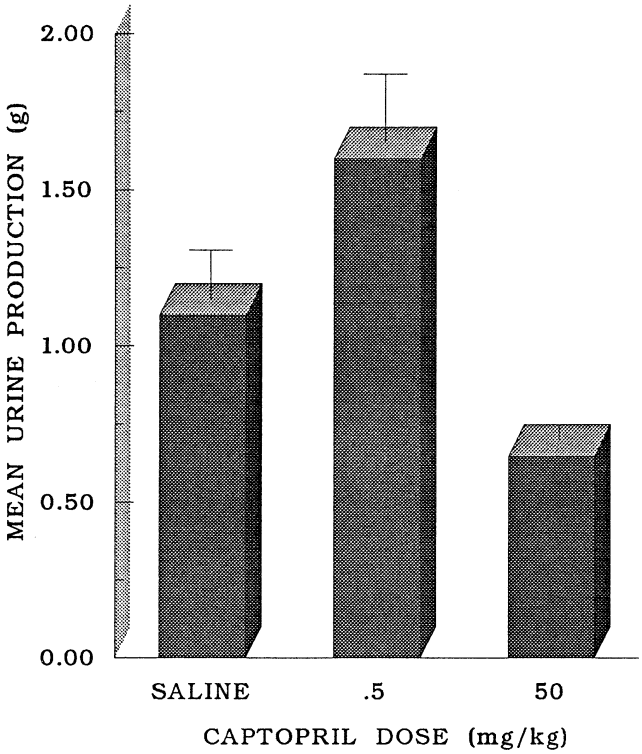

FIG. 2. Mean (± SEM) urine production following sc injections of 0.9% saline ($N = 8$), 0.5 mg/kg ($N = 8$), or 50 mg/kg ($N = 8$) captopril.

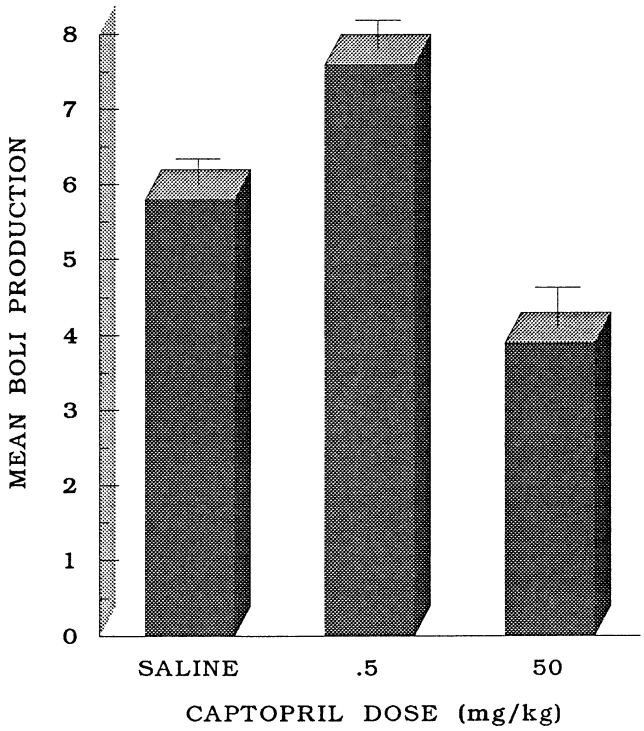

FIG. 3. Mean (± SEM) fecal production following sc injections of 0.9% saline ($N = 8$), 0.5 mg/kg ($N = 8$), or 50 mg/kg ($N = 8$) captopril.

nulas and observing ventricular fluid, and by injecting 1.0 μl of cresyl violet (5% solution) into the cannulas prior to histology. One of the nine rats failed to show correct placement and was eliminated from the study. After recovering from surgery, responding was then examined following three injections conditions administered twice to all animals in random order. The control condition involved administering animals three, 4 μl icv injections of isotonic saline followed by a sc injection (1 ml/kg) of 0.9% physiological saline (Condition: saline icv + saline sc). The first of three icv injections occurred 2 h before animals were placed in the test chamber. The second and third injections were given 1 and 0.5 h before testing. The sc injections occurred immediately before sessions began. The remaining two injection conditions were identical to the one described, except that captopril was administered in both the icv and sc injections (i.e. Condition: 0.120 mg Cap icv + 0.5 mg/kg Cap sc), or only before testing (Condition: saline icv + 0.5 mg/kg sc). Captopril was obtained through Sigma, lot 23H0783.

RESULTS

Figures 1–3 show the effects of captopril on polydipsia, urine, and boli production. As can be seen, low peripheral injections of captopril lead to a significant increase in polydipsia, urination, and defecation. High peripheral doses of captopril not only eliminated the enhancement effect, but they also reduced the adjunctive behaviors below the levels shown with saline controls.

More specifically, the animals drank an average of 10.3 (SD = 1.8) mls of water after low doses of captopril (0.5 mg/kg), while controls consumed 7.3 (SD = 2.3) mls; high doses reduced drinking to 4.7 (SD = 1.2) mls. The dose effects were replicated with urine and fecal production. Low doses of captopril enhanced urine and fecal production, and high doses led to a significant decline in gastric eliminations.

Figure 4 shows the effects of captopril on fixed interval responding. As illustrated, low doses of captopril led to a

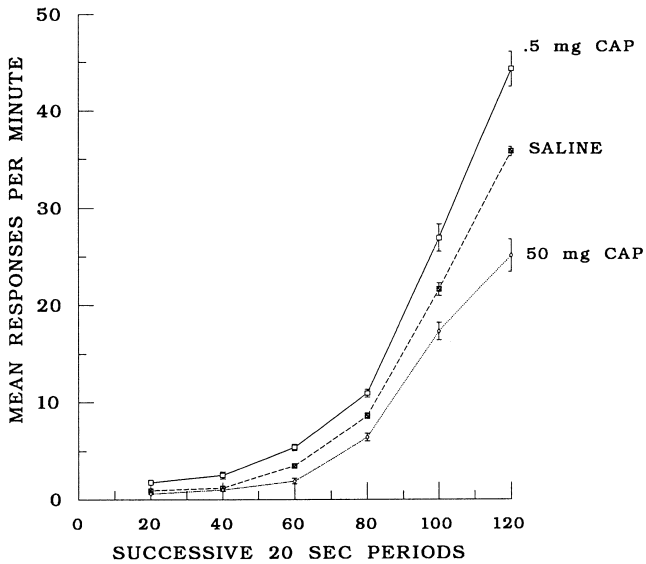

FIG. 4. Mean (± SEM) responses per minute within successive 20 s periods of the fixed interval for animals administered sc injections of 0.9% saline ($N = 8$), 0.5 mg/kg ($N = 8$), or 50 mg/kg ($N = 8$) captopril.

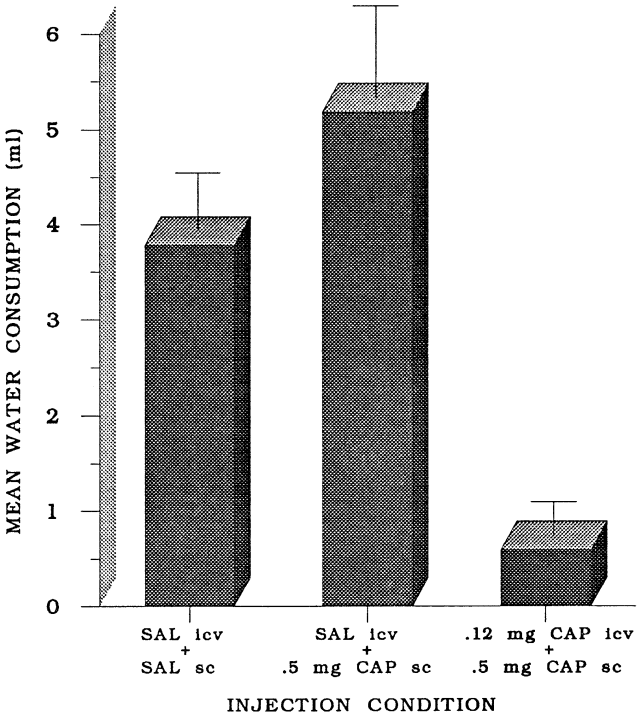

FIG. 5. Mean (± SEM) polydipsia following saline injections given icv + saline sc (N = 8); saline injected icv + 0.5 mg/kg captopril administered sc (N = 8), or 0.12 mg captopril injected icv + 0.5 mg/kg captopril administered sc (N = 8).

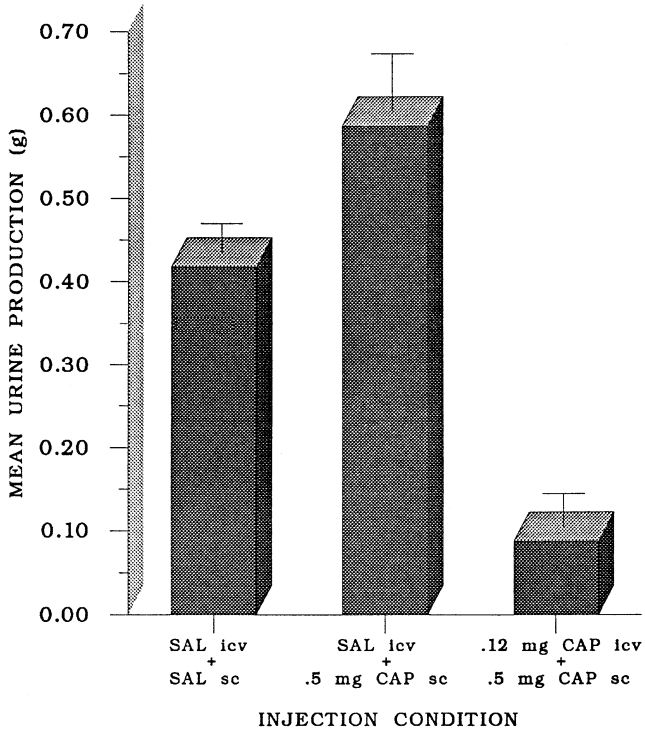

FIG. 6. Mean (± SEM) urine production following saline injections given icv + saline sc (N = 8); saline injected icv + 0.5 mg/kg captopril administered sc (N = 8), or 0.12 mg captopril injected icv + 0.5 mg/kg captopril administered sc (N = 8).

marked increase in mean response rate, particularly during last segment of the fixed internal (M = 44.3, SD = 5.1). Control injections produced an intermediate rate of response (M = 35.8, SD = 1.4), and high doses significantly reduced responding (M = 25.1, SD = 4.8) without altering the basic "scallop" pattern shown by all animals during the last portion of the interval.

Figures 5–7 illustrate the results obtained when captopril was administered through central and peripheral injections routes. As can be seen, polydipsia, urine and fecal production increased when low peripheral doses of captopril (0.5 mg/kg) were combined with icv injections of saline.

Rats that received low peripheral injections of captopril drank an average of 5.2 mls of water, while saline-saline injected animals consumed only 3.7 mls. The low dose enhancement effect was eliminated, however, when low peripheral doses were coupled with 0.12 mg administered icv. In fact, polydipsia was nearly abolished in this condition 0.12 mg CAP icv + 0.5 mg/kg CAP sc, M = 0.6 mls). Urine and fecal boli were similarly affected by the injection routes. The gastric measures increased significantly when captopril was administered peripherally; each declined below baseline when low peripheral doses were coupled with central administration.

Figure 8 shows that captopril altered operant responding in the same way that it affected the adjunctive behaviors. Low peripheral doses of captopril significantly increased the rate of response that occurred at the end of the fixed interval. Low peripheral doses coupled with central injection lead to lower response rates. More specifically, low peripheral doses (i.e., SAL icv + 0.5 mg/kg CAP sc) increased terminal responding by 15 percent above SAL-SAL controls. When captopril was added centrally (i.e., 0.21 mg CAP icv + 0.5 mg/kg CAP sc) terminal responding declined 50 percent.

Separate ANOVAs were performed on the results obtained in both phases of the experiment. The results revealed significant main effects for Polydipsia, Urine, and Boli production (all F's < 0.01). The ANOVAs also showed that significant interactions emerged between Responding within the fixed interval and Injection Conditions (F's < 0.001).

Ryans *post hoc* tests showed that low peripheral injections of captopril significantly increased the adjunctive behaviors above levels found after saline control injections (all comparisons $p < 0.05$). High peripheral doses of captopril (i.e., 50 mg/kg), and low doses (0.5 mg/kg) combined with central injections, decreased all adjunctive behavior ($p < 0.05$). Finally, the post-hoc analyses showed that terminal rates of responding were significantly enhanced (diminished) by low (high) doses of captopril (all comparisons significant $p < 0.01$).

DISCUSSION

The present study showed that captopril altered schedule induced polydipsia, urination, and defecation. Low peripheral injections of captopril (0.5 mg/kg) increased the adjunctive behaviors while high peripheral (50 mg/kg) and central administration (0.12 mg) reduced them. Since captopril blocks the synthesis of angiotensin II, the findings suggest that this hormone plays an important role in schedule induced behavior. Although angiotensin is traditionally linked to the control of normal drinking (23,31,41), the results suggest that angiotensin may influence behaviors that emerge following stress (1,12, 33,47).

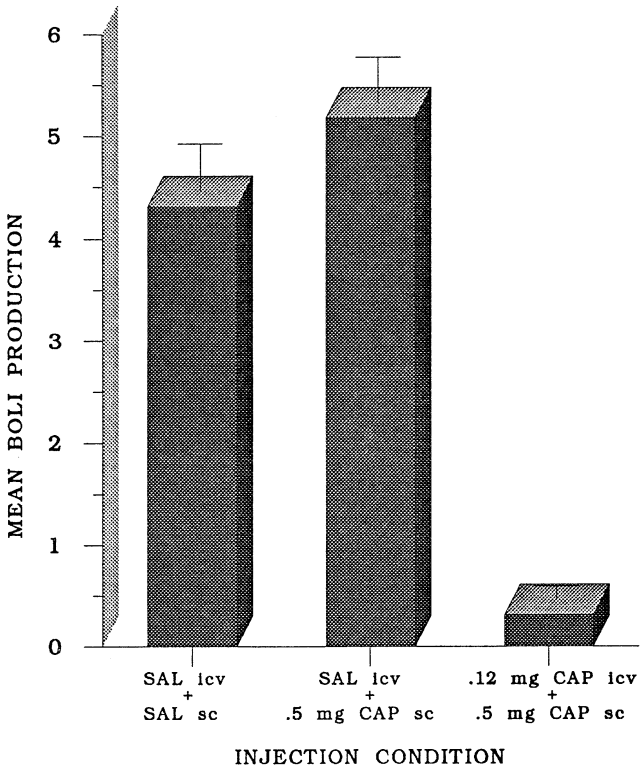

FIG. 7. Mean (± SEM) fecal production following saline injections given icv + saline sc ($N = 8$); saline injected icv + 0.5 mg/kg captopril administered sc ($N = 8$), or 0.12 mg captopril injected icv + 0.5 mg/kg captopril administered sc ($N = 8$).

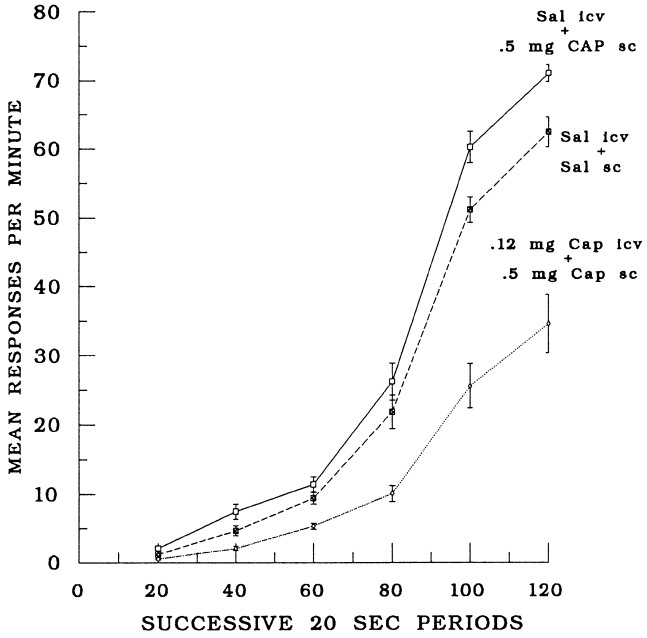

FIG. 8. Mean (± SEM) responses per minute within successive 20 s periods of the fixed interval for animals administered saline icv + saline sc ($N = 8$); saline injected icv + 0.5 mg/kg captopril administered sc ($N = 8$), or 0.12 mg captopril injected icv + 0.5 mg/kg captopril administered sc ($N = 8$).

Lawler and Cohen (34) recently suggested that a common mechanism may underlie a number of stress-induced adjunctive behaviors. Although the divergent nature of schedule induced behavior would seem to preclude a common mechanism, the physiology of angiotensin may provide a reasonable clue. For example, there is now growing evidence that angiotensin is released under stress (27,33,41,48). When angiotensin becomes active in the brain it interacts with three power output systems: endocrine, autonomic, and behavioral (7). The endocrine outputs affect the release of vasopressin and oxytocin (42). The autonomic connections comprise nuclei within the hypothalamus and brain stem that regulate sympathetic and parasympathetic arousal. In addition, angiotensin stimulates the lateral hypothalamus, zona incerta, and portions of the adrenal cortex that release aldosterone (7). Clearly these sites provide a possible link for the emergence of seemingly unrelated behaviors (e.g., polydipsia, urination, defecation, pawlicking, and aggression). Perhaps additional research will determine how angiotensin affects these behavioral reactions, and why some occur more frequently than others (34).

Although the results suggest that angiotensin influenced the adjunctive behaviors. There exists no direct evidence that intermittent schedules produce changes in angiotensin. Stress and arousal do increase the release of angiotensin (1,8,13,17, 27,33), but research suggests that stress may not provide the primary fuel that ignites schedule induced polydipsia (47, P. 132). Indeed, our results are similar to those obtained when captopril modified drinking in rats made thirsty by caval ligation (23), or the presentation of a palatable meal (30,31,32). In fact, had we not measured operant responding, urination, and defecation, the basic findings may not have revealed anything new about captopril effects on drinking. But captopril dose and injection route indeed affected operant responding in the same way that affected the adjunctive behaviors. Low peripheral doses significantly enhanced terminal responding (see Figures 4, 8); high peripheral and central injections reduced behavior. Clearly the combined results indicate that captopril affected more than simple ''thirst.''

In a pivotal review of schedule induced behavior, Staddon (47) summarized the variables that affect schedule induced polydipsia. Above all, food appears to be the fundamental instigator. Polydipsia is an increasing function of the presentation of food, level of food deprivation, magnitude of reward, and food palatability. Food-motivated rats, in other words, are thirsty, water-motivated rats. In fact, schedule induced polydipsia can be enhanced (or diminished) by altering both the amount and quality of food, and by manipulating the presence of water in the test situation (i.e., pre-loading the animals before sessions, or providing extra water in the reinforcer; 47, P. 138). However, even though polydipsia is strongly linked to food consumption, it appears that food is not crucial since schedule induced drinking occurs when animals merely ''anticipate'' food (47).

For many years it has been known that animals will drink in the presence of cues that signal food. For example, animals responding on DRL schedules drink after each non-reinforced temporally spaced response (47). Rats bar pressing under fixed interval schedules continue to drink even when water is presented later, rather than throughout the interval (47). These findings lead Staddon to conclude that, ''. . . the evidence is not sufficient to assert that deprivation-induced and schedule-induced ''thirst'' are identical, however, and it would be sur-

prising if they were in view of the different temporal properties of the two (47).'' Schedule induced polydipsia is therefore controlled by both internal and external factors. Certainly the presence of food influences the onset and quantity of schedule induced polydipsia, but the anticipation of food, its incentive value, also plays a role (44,47). If ''thirst'' emerges from separate sources (deprivation vs. schedule induced) it may be controlled by separate biochemical mechanisms. Although this notion sounds intuitive, the literature points toward a more common mechanism.

There is firm evidence that angiotensin contributes to post prandial drinking (30,31,32). Moreover, stress and arousal lead to the secretion of angiotensin, and angiotensin-based drinking (1,33). Since angiotensin is clearly linked to both types of ''thirst'' (i.e., internal and external), it seems reasonable to suggest that angiotensin may underlie the emergence of adjunctive behaviors. We offer the following account for the role angiotensin in schedule induced polydipsia.

We suggest that when hungry animals are first exposed to periodic schedules of reinforcement, drinking is initially influenced by internal factors (i.e., food-induced release of angiotensin). After several training sessions, rats learn that food is available, but that food is nested in time. When food appears periodically, animals learn that food occurs briefly, and that time must elapse again before its return. The consequence of introducing time is thus two fold: limited temporal access to reinforcement heightens both the incentive value of food, and the arousing aspects of the cues that precede its return (see 47 for further discussion). The result is that well trained animals begin to drink excessively because time has caused them to react more dramatically to food and its anticipatory cues (11,44,47). As stated above, animals that anticipate food, are also animals that seek water. Thus, we assert that polydipsia is controlled by angiotensin elicited by food, and angiotensin that is released in the presence of arousing (perhaps stress inducing) anticipatory cues. These cues may include the removal of food, the passage of time, the nature of responding within the interval, and interactions among these variables (47). Our results suggest that these factors are highly interdependent.

We found that polydipsia was an increasing function of terminal rates of responding. Yet how might the two variables be connected? We suggest that angiotensin, as affected by captopril, modified both fixed internal responding and polydipsia by altering cue-related motivation. For example, low doses of captopril (0.5 mg/kg), enhanced responding similar to animals administered amphetamine (3,28,39). Indeed, several reports show that angiotensin stimulates the release of dopamine in the nucleus accumbens (2,51). Since operant responding and adjunctive behaviors are both sensitive to dopamine levels (28,39), it seems reasonable to suggest that captopril may have altered behavior by changing the captivity of dopamine. Enhanced dopamine may have heightened operant responding by increasing the arousing aspects of food-related cues. Heightened arousal is clearly linked to a variety of conditioned and unconditioned responses that help animals find, defend, and process food (34,4,347,51). And as mentioned earlier, animals that anticipate food are ones that anticipate (and work to secure) water.

Although the angiotensin-dopamine hypothesis rests upon indirect evidence, the data are compelling since the gastric measures (i.e., fecal and urine production) were similar to those obtained with healthy, aroused animals (51). Clearly much research is needed to determine how angiotensin and dopamine interact as they readily alter operant responding and adjunctive behavior (28,39). For example, is it possible to alter cue-related motivation without changing internal motivation? Operant responding can serve as an anticipatory cue (47), but can dopamine-enhanced-responding increase polydipsia without altering the amount of water consumed after the ingestion of food? Animals have been shown to respond so vigorously that they allow reinforcers come and go within a test session (47). And there is evidence that the nature of drinking changes throughout the fixed interval (47). Perhaps additional research may reveal the common role played by angiotensin in the various kinds of ''thirst'' engendered by the periodic delivery of food.

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