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Effects of Angiotensin on Drinking[1]

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WAYNER, M. J., A. D. MERKEL, F. C. BARONE, F. B. JOLICOEUR AND D. B. RONDEAU. *Effects of angiotensin on drinking.* PHARMAC. BIOCHEM. BEHAV. 5: SUPPL. 1, 103–110, 1976. A series of four experiments was carried out to assess the effects of angiotensin II on drinking elicited by various types of stimulation. Experiment 1 examined the effects of the interaction of 2 cc/kg of 5% NaCl plus 0.2 mg/kg angiotensin II on ad lib eating and drinking. Results indicate that NaCl plus angiotensin produced an additive enhancement in water consumption. Experiment 2 was conducted to investigate the effects of 0.2, 0.4, 0.8, 1.2, and 1.6 mg/kg of angiotensin II on drinking and eating in 23 hr water deprived animals. Dose related increases in drinking alone were observed. In Experiment 3 the effects of 0.4, 0.8, 1.2, and 1.6 mg/kg of angiotensin II on schedule dependent lever pressing and schedule induced drinking and licking were determined. Results demonstrate that angiotensin II decreased lever pressing and increased schedule induced water consumption without a concomitant increase in licking. Experiment 4 examined the effects of the same doses of angiotensin II on prandial drinking in food deprived animals. Under these conditions angiotensin II increased water consumption. Results were discussed in terms of the differential effects of angiotensin II on drinking, eating, and schedule dependent lever pressing.

Drinking Angiotensin II Salt arousal of drinking Eating Water deprivation Licking
Schedule induced polydipsia Prandial drinking

ANGIOTENSIN is a hormone which stimulates the release of aldosterone and antidiuretic hormone and is thereby involved in the regulation of body fluids [5]. When kidney blood volume is reduced, renin is released and cleaves an α-2-globulin into the decapeptide angiotensin I. A dipeptidylcarboxypeptidase converting enzyme present in the lungs, kidneys and circulating plasma readily converts angiotensin I into the octapeptide angiotensin II. Shortly after entering the blood angiotensin II elevates blood pressure directly by vasoconstriction of systemic arterioles and indirectly by increasing the extracellular fluid volume via the effects of aldosterone and ADH [9]. Angiotensin II is rapidly inactivated by several enzymes, the angiotensinases. Since there is no unequivocal evidence that angiotensin crosses the blood brain barrier in significant amounts [10,11], any possible central effects are questionable when angiotensin II is administered peripherally. However, both peripheral and central administration of angiotensin II result in drinking. Early results on administration of angiotensin II to various parts of the brain by means of chronic implanted cannulae are confounded by the spread of the administered fluid along the shaft of the cannulae into the ventricles with possible action at some other tissue sites [6]. Because intraventricular administration of angiotensin II elicits drinking [4], an indirect route to central neurons via the choroid plexuses, cerebrospinal fluid and ventricles, and particularly into the walls of the third ventricle seems likely [7,14]. Angiotensin II therefore enters the brain in small amounts through the ventricular circulation and possibly through gaps in the blood brain barrier such as exist in the area postrema [8].

Some evidence indicates that the Na sensitive neurons of the lateral hypothalamus implicated in drinking are more sensitive to angiotensin II than cells of other parts of the brain [15]. In these experiments problems of blood brain barrier permeability were avoided by applying the angiotensin II directly by means of iontophoresis and assessing the effects in terms of the changes in spontaneous discharge frequency of the cells involved. All of the Na sensitive hypothalamic neurons tested were affected by angiotensin II. In these cells discharge frequency was enhanced greatly by the simultaneous administration of Na and angiotensin II. Since angiotensin II in higher doses also affected cells of the cerebral cortex and thalamus, it might have a more general nonspecific effect on some membrane mechanism in excitable cells. Angiotensin II definitely affects Na transport mechanisms in smooth muscle [13] which would also be consistent with the fact that the Na sensitive cells of the rat hypothalamus are the most sensitive to angiotensin II. A synergistic multiplicative facilitation between angiotensin II and Na was observed in drinking when both substances were administered intraventricularly [1]. A similar enhancement of the vasopressor effect of angiotensin II by Na was attributed to an increase in the biological activity of the angiotensin molecule due to a change in the steric conformation in the peptide chain by Na [3]. The increase in activity seems to be specific for Na because when angiotensin II is administered centrally with KCl, an enhancement in drinking does not occur [12].

Because of the obvious effects reported on drinking and the possible relations to central Na sensitive neurons, a more extensive investigation of the effects of angiotensin II on drinking induced by various types of stimulation seemed

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required. In general an attempt was made to examine in greater detail the effects of angiotensin II administered peripherally on drinking induced by several different methods. Specifically, the purposes of the present study were: (a) to determine the effects of simultaneous peripheral administration of hypertonic saline and angiotensin II on ingestive behavior in ad lib animals; (b) to measure the effects of peripherally administered angiotensin II on water deprivation induced drinking; (c) to assess the effects of angiotensin II on schedule induced polydipsia; and (d) to determine the effects of angiotensin II in animals treated similarly to those in schedule induced polydipsia except without the generator food reinforcement schedule. Results demonstrate that drinking appears to be increased by angiotensin II under all of the conditions studied and can be enhanced by the simultaneous administration of Na under some conditions, and some schedule dependent behaviors such as lever pressing are decreased by angiotensin II.

EXPERIMENT 1

Because of the synergistic interaction of angiotensin II and Na in drinking when administered centrally, the effects of combined intraperitoneal administration of threshold doses of hypertonic saline, 5% NaCl, and angiotensin II, 0.2 mg/kg, on ingestive behavior were studied. Results indicate that only drinking was enhanced by the combined treatment.

METHOD

Animals

Thirty female hooded rats, 194 - 233 g in weight and approximately 120 days old, were selected from our colony and allowed to adapt to individual living cages for 14 days. All animals were maintained on ad lib food and water for the duration of the experiment. An additional 10 female rats, 250 - 350 g in weight and approximately 180 days old, were selected and were studied later.

Procedure

Following the adaptation period the 30 animals were divided into 3 equal groups in order to study the effects of three injection treatments, NaCl, angiotensin II, and NaCl plus angiotensin II. Ten min prior to injection all animals were weighed, each cage was cleared of food and feces, water tubes were filled and 30 - 40 g of food were weighed for presentation to each animal. Rats were then injected intraperitoneally with 2 cc/kg body weight of 5% NaCl, 0.2 mg/kg angiotensin II (1-L-Asparginyl-5-L-Valyl angiotensin, Hypertensin, CIBA), or 0.2 mg/kg angiotensin II in 5% NaCl. All solutions were made from sterile distilled water. Seven days following the first injection the same injections and procedures were repeated again for these 3 groups. Latency to eat or drink and food and water consumption were recorded over a 2 hr period following the injections. The additional group of 10 female rats was injected once with 2 ml/kg of 0.9% NaCl to determine the approximate 2 hr food and water intakes following the administration of isotonic saline under the same conditions.

RESULTS

Two by three ANOVAs with repeated measures were used to analyze the 2 hr food and water intake data. The two factors were treatments of NaCl, angiotensin II, or angiotensin II + NaCl and injections, the first and second administration of the same treatments. The mean 2 hr water intakes following the two injections of each of the three solutions are presented in Fig. 1. The broken line indicates the mean response of the group which received only an isotonic saline injection. The group treatments were significant for water intake, $F(2,27) = 3.42$, $p < 0.05$. A Tukey A analysis indicated that the NaCl + angiotensin group consumed more water than the NaCl, $t = 7.39$, $df = 3,27$, $p < 0.01$, or angiotensin II, $t = 3.94$, $df = 3,27$, $p < 0.05$, groups. The NaCl and angiotensin II groups were not different from each other. The injections factor and the interaction of injection by groups were not significant for 2 hr water consumption. The mean 2 hr food intakes following the two injections of each of the three treatment groups are presented in Fig. 2. The broken line indicates the mean 2 hr food intake of the group which received only an isotonic saline injection. The effects of treatments, injections, and the treatment by injection interaction were not significant. Latencies to eat and drink were analyzed by means of a Kruskal-Wallis test and there were no significant differences between the three treatments. Therefore, the only significant effect of the combined treatment of NaCl and angiotensin II under these experimental conditions occurred in the enhancement of the 2 hr water intakes which appears to be additive and not multiplicative as expected.

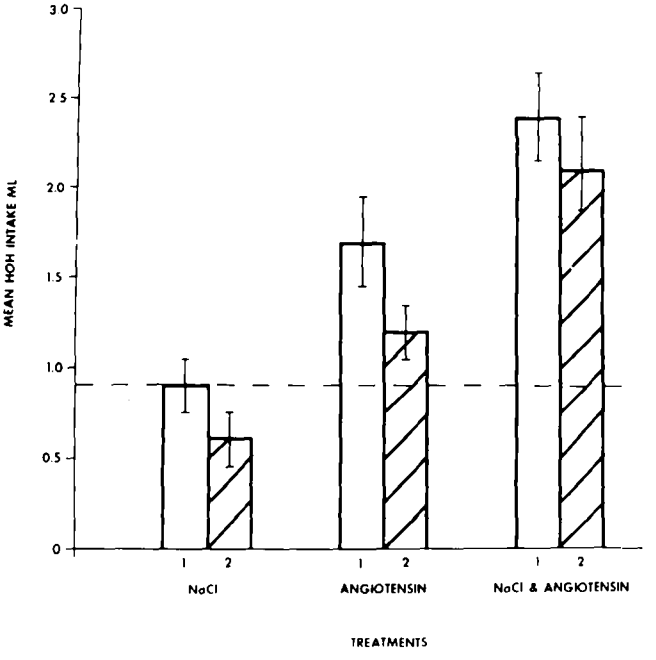

FIG. 1. Mean water intake in ml presented as a function of the different treatments. The open and striped bars represent the first and second determinations respectively. Mean water intake in ml following a single injection of 0.9% NaCl is illustrated by the horizontal broken line. Standard errors of the means are indicated by the vertical lines.

EXPERIMENT 2

The results of the previous experiment demonstrate that sodium and angiotensin II interact additively to produce

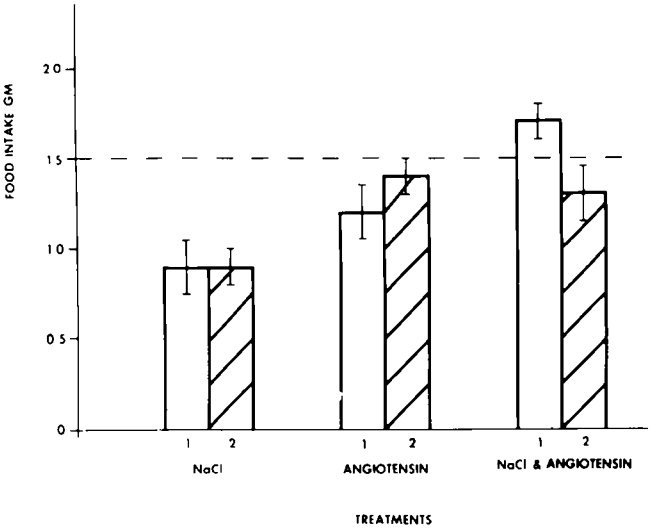

FIG. 2. Mean food intake in g presented as a function of the different treatments. The open and striped bars represent the first and second determinations respectively. Mean food intake in g following a single injection of 0.9% NaCl is illustrated by the horizontal broken line. Standard errors of the means are indicated by the vertical lines.

increased drinking. Since the interaction of peripherally administered angiotensin II and water deprivation on drinking has not been determined, the present experiment was carried out to examine the effects of 0.2, 0.4, 0.8, 1.2, and 1.6 mg/kg of angiotensin II on drinking induced by 23 hr water deprivation. Results indicate that angiotensin II enhances water deprivation induced drinking without any change in food consumption.

METHOD

Animals

Five female hooded rats, 260–290 g in weight and approximately 150 days old, were selected from our colony and placed in individual living cages.

Procedure

After 2 days of adaptation animals were placed on a 23 hr water deprivation schedule. At approximately the same time every day, tap water was presented for 1 hr in a graduated eudiometer tube equipped with a ball point stainless steel drinking spout. Body weights were recorded daily. Standard laboratory food blocks were available ad lib and the amounts of food ingested during the 1 hr drinking sessions were measured. After daily water intakes stabilized over a 5 day period, a series of injections was initiated. Intraperitoneal injections were made every third day immediately prior to the drinking session. Animals received 3 injections of 0.9% NaCl, then 5 doses of angiotensin II 0.2, 0.4, 0.8, 1.2, and 1.6 mg/kg were administered to each animal in a nonsystematic order. Following the administration of the various doses of angiotensin II, animals received three 0.9% NaCl injections. Results obtained on the first 3 days and the last 3 days due to the saline injections constitute the pre- and postdrug baseline data. Angiotensin II was dissolved in 0.9% NaCl solution and the injection volume was 1 ml/kg.

RESULTS

Two one-way ANOVAs with repeated measures were used to analyze both the 1 hr water intake and 1 hr food intake data. For the 1 hr water intakes, the main effect of angiotensin II was significant, $F(6,24) = 6.95$, $p < 0.01$. Specific comparisons between the predrug baseline data and the postdrug baseline and each of the angiotensin II doses were made by means of the Dunnett test. There was no difference between the predrug and postdrug 1 hr water intakes. The three largest doses of angiotensin II, 0.8, 1.2 and 1.6 mg/kg, did produce significant increases in 1 hr water intakes as compared to the predrug condition, $p < 0.01$. A linear test for trend as a function of increasing doses was also significant, $F(1,24) = 38.7$, $p < 0.01$. These results are illustrated graphically in Fig. 3 where the pre- and postdrug and the angiotensin II induced mean 1 hr water intakes are presented as a function of dose. A similar statistical analysis was performed on the 1 hr food intake data. Results were not significant. These data are presented in Fig. 4. Therefore, angiotensin II enhances water deprivation induced drinking under these experimental conditions in a linear way, without producing a change in food consumption.

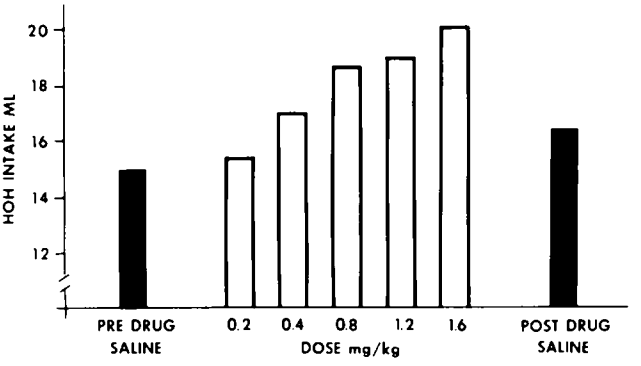

FIG. 3. Mean water intake in ml presented as a function of the pre- and postdrug baseline conditions (solid bars) and the 5 doses of angiotensin administered (open bars).

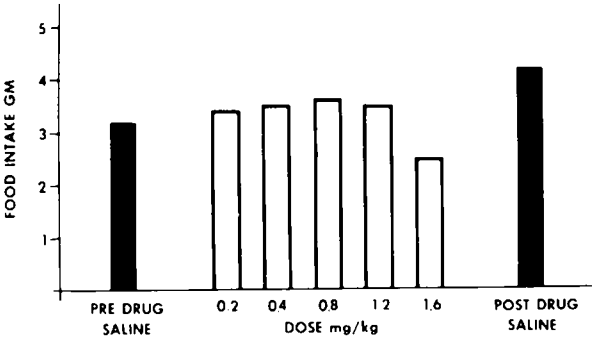

FIG. 4. Mean food intake in g presented as a function of the pre- and postdrug baseline conditions (solid bars) and the 5 doses of angiotensin administered (open bars).

EXPERIMENT 3

The results of the previous two experiments demonstrate that angiotensin II produced an additive interaction with the internal stimulation associated with the salt arousal and water deprivation induced drinking mechanisms. Since

schedule induced polydipsia is a nonregulatory drinking phenomenon which depends upon a nonspecific increase in motor excitability and since responsiveness to specific environmental stimuli is involved, this phenomenon provides a unique opportunity for studying the effects of angiotensin II on high water intakes in nonwater deprived animals. In addition, the effects of angiotensin II on schedule dependent lever pressing can also be determined simultaneously. Therefore, the purpose of the present experiment was to determine the effect of 4 doses of angiotensin II, 0.4, 0.8, 1.2, and 1.6 mg/kg, on schedule dependent lever pressing and schedule induced licking and water consumption for a fixed interval 1 min food reinforcement schedule in rats at 80% body weight due to partial food deprivation. Because only the largest 3 doses of the previous experiment produced increased drinking as compared to the saline injections, the smallest dose of 0.2 mg/kg was not employed. Results indicate a decrease in schedule dependent lever pressing and an increase in schedule induced drinking.

METHOD

Animals

Four male hooded rats, 310 350 g in weight and approximately 100 days old, were selected from our colony and placed in individual living cages.

Procedure

During a 10 day adaptation period food and water were available ad lib. The animals were reduced to 80% of their Day 10 body weight by gradually restricting food availability over a 7 day period. These weights were maintained throughout the experiment. Water intake and body weight data were recorded daily. Following 3 days of shaping to lever press for 45 mg Noyes pellets on a continuous schedule of reinforcement, animals were tested daily for 1 hr on a fixed interval 1 min generator schedule. The testing apparatus consisted of a standard LVE 1469 medium sized test cage and matching sound attenuating cubicle with a lever and pellet dispensing mechanism. A food cup, delivery mechanism, test lights, and lever were mounted in the standard fashion on one wall as provided by the manufacturer. A modified glass insulated stainless steel ball point drinking spout fitted to a glass eudiometer tube was placed in the center of the back wall of the test chamber, 4.0 cm above the grid floor. The spout protruded 1.5 cm into the cage. The number of lever presses, licks and water intake were recorded for each of the four 15 min intervals of the 1 hr session. When lever press rate and schedule induced polydipsia stabilized, a series of subcutaneous (SC) injections was initiated.

Drug

Angiotensin II was dissolved in 0.9% saline to obtain four doses - 0.4, 0.8, 1.2, and 1.6 mg/kg. The volume injected was 1 ml/kg. Because angiotensin II contains approximately 17% ammonium acetate, control injections were included in the drug procedure because of possible osmotic effects which might result in drinking. Control injections contained amounts of ammonium acetate identical to those found in each drug dose, 0.068, 0.136, 0.204, and 0.272 mg/cc of 0.9% saline. The results of these injections constituted baseline data to which data obtained from subsequent drug injections could be compared statistically. Saline-ammonium acetate and angiotensin solutions were kept under refrigeration. The 4 control injections were administered SC every third day in a random order immediately prior to the test session. Following the control injection sequence the drug injections were initiated. As with the control injections, the 4 drug doses were administered prior to the test session every third day in a random sequence.

RESULTS

Because angiotensin II has a rapid and relatively short duration effect the data were analyzed separately for the first 15 min interval and the total 1 hr test session. Since 2 × 4 ANOVAs with repeated measures for all data indicated that the 4 control injections did not produce differences, the control data were collapsed and the effects due to angiotensin II were evaluated by means of a one-way analysis. Individual one-way analyses were carried out for lever presses, licks, and water intakes for both the first 15 min and the total 1 hr test session.

A statistical analysis of 1 hr lever press data revealed a significant main effect, $F(4,12) = 2.49$, $p < 0.05$. However, individual specific comparisons were not significant as indicated by a Dunnett's test. When the 3 lowest doses were compared to the highest dose (0.4, 0.8, 1.2 vs 1.6 mg/kg), the highest dose produced a significant depression, Scheffe $p < 0.01$. A comparison of lever presses during the first 15 min interval revealed a significant main effect $F(4,12) = 8.38$, $p < 0.01$, with the 3 highest doses significantly depressing lever presses when compared to control injections by means of a Dunnett's test, $p < 0.01$. These effects are illustrated in Fig. 5 where the mean lever presses are presented for control and drug treatments for both the first 15 min interval and the totals for 1 hr.

One-way ANOVAs indicated that there were no significant differences in either the total 1 hr licks data or the first 15 min interval lick data. These results are presented in Fig. 6 by means of bar graphs for each of the different treatments.

There were no significant differences between the 1 hr water intakes for any of the experimental treatments. The analysis performed on the first 15 min intake data revealed a significant increase in water intake due to angiotensin II, $F(4,12) = 2.71$, $p < 0.05$. On the basis of a Dunnett's test only the 2 highest doses produced significant increases in water consumption as compared to control injections, $p < 0.01$. There were no significant differences between the intakes produced by the different doses of angiotensin II. These effects are illustrated in Fig. 7 where mean water intakes for the total 1 hr session and the first 15 min are presented as a function of the various treatments.

These data demonstrate a relatively clear, immediate, but short duration decrease in schedule dependent lever presses and a somewhat tenuous increase in schedule induced water consumption produced by angiotensin II. A more obvious effect occurred in the lick pattern which cannot be illustrated quantitatively at this time. However, the change in lick pattern explains the dissociation between the increases in water consumption and the licking data.

EXPERIMENT 4

Because the animals of Experiment 3 were subjected to a reduction in body weight due to partial food deprivation

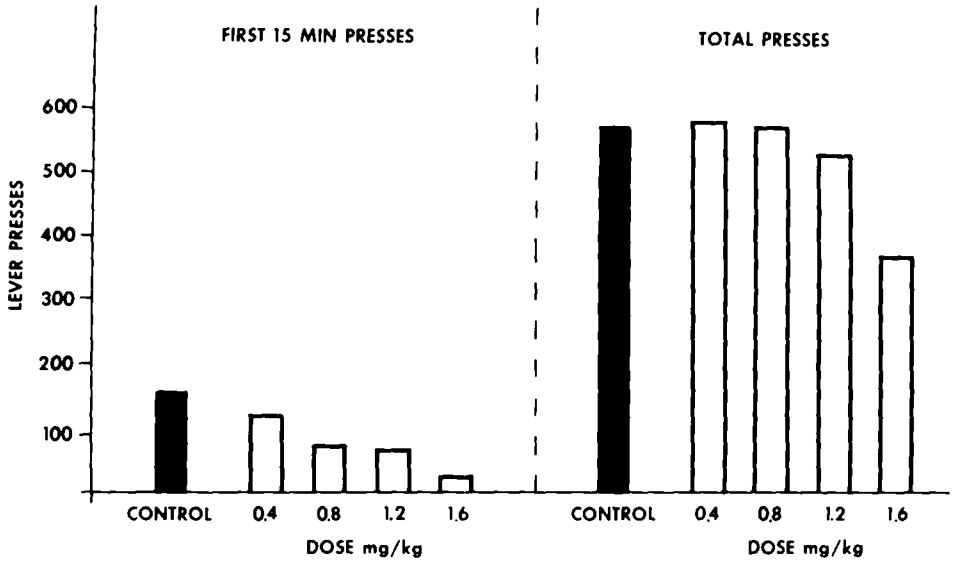

FIG. 5. Mean number of lever presses presented as a function of the control condition (solid bars) and the 4 doses of angiotensin (open bars) for both the first 15 min interval and the total 1 hr session.

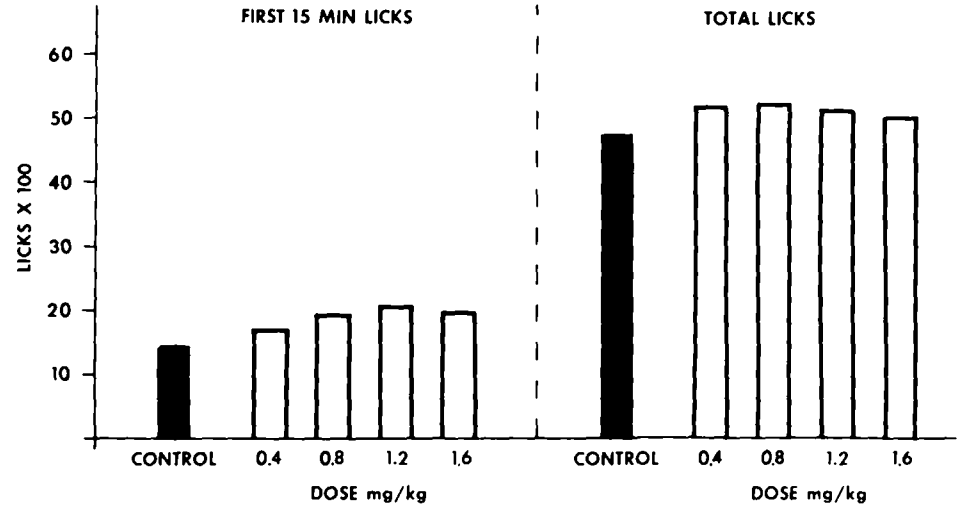

FIG. 6. Mean number of licks presented as a function of the control condition (solid bars) and the 4 doses of angiotensin (open bars) for both the first 15 min interval and the total 1 hr session.

and an intermittent schedule of food reinforcement, the effects of angiotensin II are confounded by both of these factors. The purpose of the present experiment was to determine the effects of the same doses of angiotensin II - 0.4, 0.8, 1.2, and 1.6 mg/kg - on rats reduced similarly to 80% body weight and not subjected to a food reinforcement schedule but permitted to eat the 60 pellets ad lib in the test chamber. Results indicate a clear, short duration enhancement of drinking under these conditions due to angiotensin II.

METHOD

Animals

Eight male hooded rats, 318-347 g in weight and approximately 100 days old, were selected from our colony and placed in individual living cages.

Procedure

During a 10 day adaptation period food was available ad lib. Water was continuously available in a graduated cylinder fitted with a glass insulated spout designed to conform with the spout to be used in the test apparatus. The animals were reduced to 80% of their Day 10 body weight by gradually limiting food rations. These weights were maintained throughout the experiment. Water intake and body weight data were recorded daily. The testing apparatus was identical to that described in Experiment 3. Prior to each experimental session sixty 45 mg Noyes pellets were placed in the food cup. The food delivery mechanism was disconnected and lever presses did not result in the delivery of a pellet. The number of licks and water intake were recorded for both the first 15 min and the total hour of each session. Lever presses were recorded when they did occur.

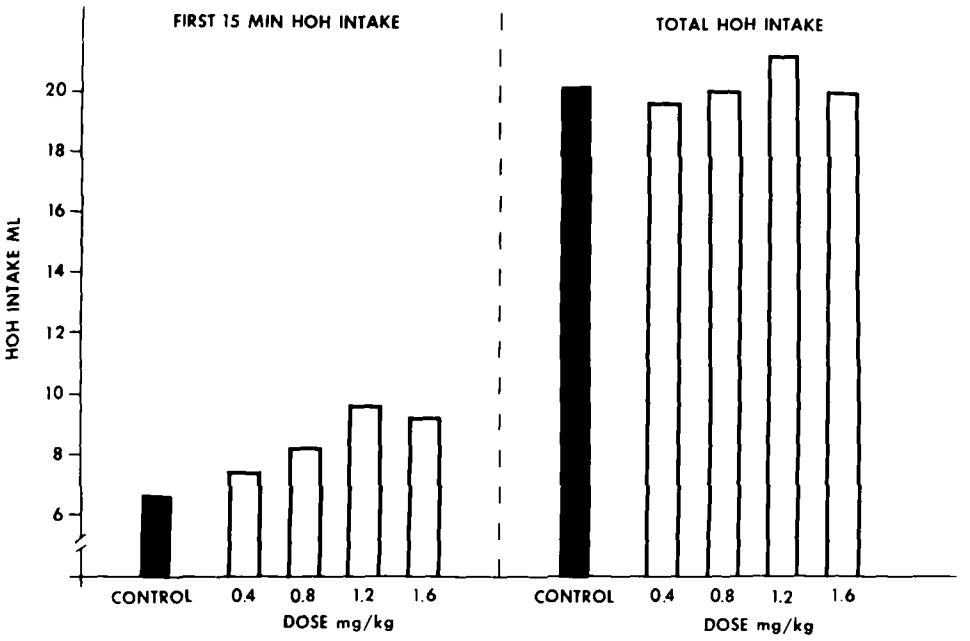

FIG. 7. Mean water intakes in ml presented as a function of the control condition (solid bars) and the 4 doses of angiotensin (open bars) for both the first 15 min interval and the total 1 hr session.

Drug

Angiotensin II doses, control treatments and injection procedures were identical to those in Experiment 3; i.e., 4 drug doses 0.4, 0.8, 1.2, and 1.6 mg/kg - with 4 corresponding control treatments. Animals were injected SC immediately prior to placement in the test chamber. Both the control injection sequence and the drug sequence were randomized.

RESULTS

Similar to Experiment 3, the data were analyzed in terms of both licks and water intake. Because the results of 2 × 4 ANOVAs revealed no differences between individual control injections, these data were collapsed and together constitute the predrug baseline condition. Therefore, the data were analyzed by one-way ANOVAs with repeated measures. Analysis of the total licks for 1 hr sessions indicated a significant main effect, $F(4,28) = 4.31$, $p<0.01$. The post hoc Dunnett's test revealed no significant differences from the control data. However, due to the significant main effect a post hoc Tukey A analysis was performed and revealed a significant difference between the total licks for the smallest vs the largest dose (0.4 and 1.6 mg/kg respectively). The analysis performed on the licks obtained during the first 15 min revealed a significant main effect, $F(4,28) = 8.47$, $p< 0.01$. A post hoc Dunnett's test revealed that only the largest dose, 1.6 mg/kg, produced a significant increase over baseline. These results are illustrated by the bar graphs in Fig. 8 where mean number of licks are presented for each condition.

The analysis of total 1 hr intake data revealed a significant main effect, $F(4,28) = 10.09$, $p< 0.01$. A post hoc Dunnett's test indicated that the two highest doses, 1.2 and 1.6 mg/kg, differed significantly from the control injections. Analysis of 15 min water intakes revealed a significant main effect, $F(4,28) = 14.03$, $p<0.01$. Post hoc testing indicated that all doses produced significant increases, $p<0.01$ when compared to the control injection by means of Dunnett's test but not when compared to each other by means of Tukey A tests. These results are illustrated in Fig. 9 where mean water intakes are presented for each condition. Although a schedule was not in operation, a small but insignificant amount of lever pressing did occur.

Angiotensin II appears to be effective in enhancing prandial licking and drinking in food deprived rats. The effects were not dose related but were more pronounced during the first 15 min of the 1 hr sessions. These results confirm the short term action of the peptide under these conditions and demonstrate a non-dose dependent increase in drinking.

DISCUSSION

In general, results seem to indicate that angiotensin II has a specific enhancing effect on drinking. Angiotensin II increased drinking due to salt arousal, following water deprivation, in schedule induced polydipsia, and it also enhanced prandial drinking. These effects were observed clearly in terms of water consumption during the various test periods. However, the results on licks were somewhat equivocal because the data were confounded by an angiotensin induced change in lick pattern. The potentiation of drinking under these experimental conditions due to the combined administration of NaCl and angiotensin II confirms the earlier work of others [2]. However, for peripherally administered threshold doses the combined effect was only additive. A synergistic multiplicative interaction could have been explained easily in terms of a similar action in lateral hypothalamic Na sensitive neurons implicated in drinking [15]. The linear increase produced by angiotensin II in water deprived animals indicates that the underlying physiological changes associated with these two

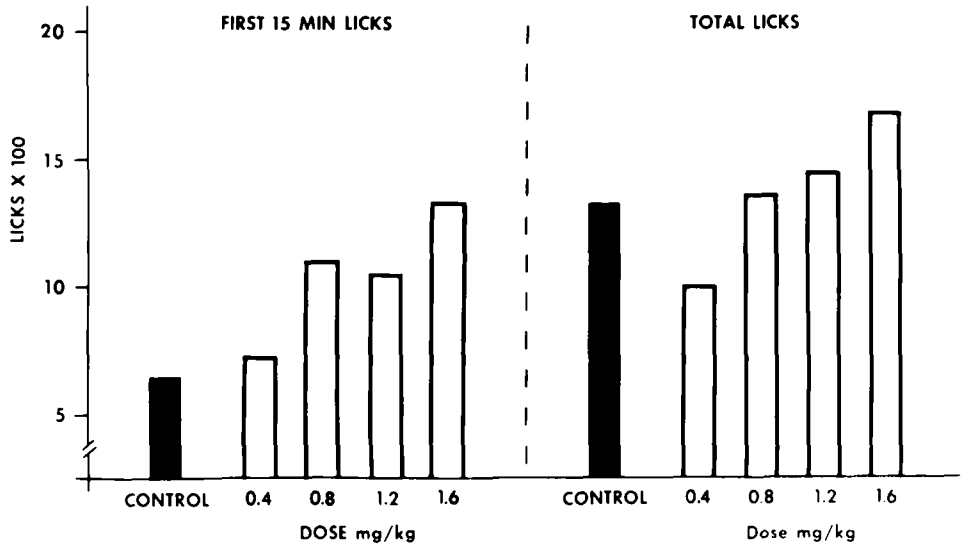

FIG. 8. Mean number of licks presented as a function of the control condition (solid bars) and the 4 doses of angiotensin (open bars) for both the first 15 min interval and the total 1 hr session.

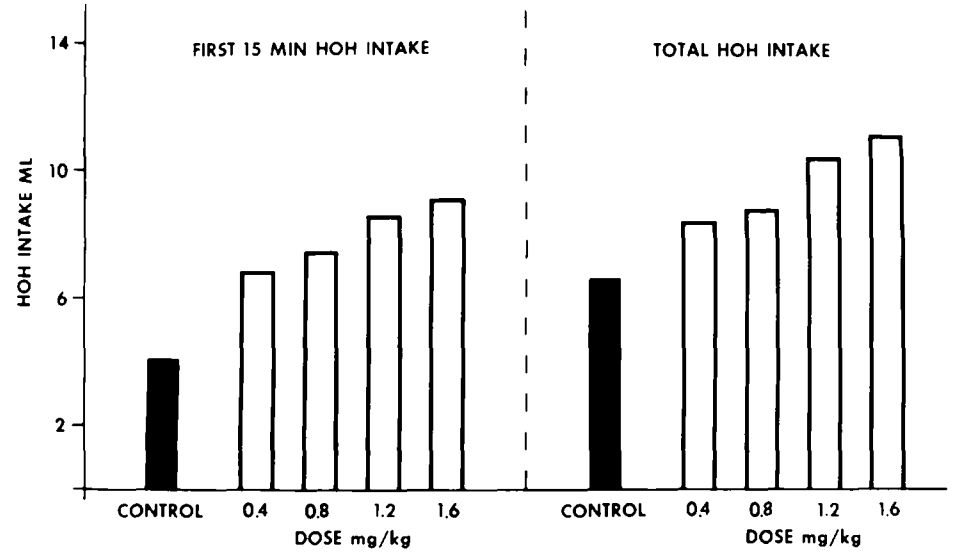

FIG. 9. Mean water intake in ml presented as a function of the control condition (solid bars) and the 4 doses of angiotensin (open bars) for both the first 15 min interval and the total 1 hr session.

treatments are also additive within certain limits. The results provide little clarification concerning the peripheral vs central issue of angiotensin II induced drinking.

The experiment on schedule induced polydipsia is important because the effects of angiotensin II were assessed simultaneously on schedule dependent and schedule induced behavior [16,17]. Although angiotensin II and angiotensin II plus Na enhance home cage ad lib drinking, they had no effect on home cage food consumption. Also, there was no effect of angiotensin II on eating in water deprived rats. These results indicate clearly that under these circumstances angiotensin II has no observable effect on eating. However, in the experiment on schedule induced polydipsia, angiotensin II significantly decreased schedule dependent lever pressing for food pellets. Under these same conditions angiotensin clearly increased water consumption without an associated increase in the number of licks. Both these effects were brief and support the fact that angiotensin II has a short half-life. Therefore, these effects were observed only during the first 15 min of the test session. It is interesting that in Experiment 4 when animals were tested under conditions similar to those which produce schedule induced polydipsia except that the generator food reinforcement schedule was not in operation and all the pellets were available at the beginning of the test session, angiotensin II did produce an increase in licking during the first 15 min of the test session for the highest dose (1.6 mg/kg). Although the remaining data suggest a dose related increase in licking, the differences when compared to the control condition were not significant due to the relatively large variability in licking under these conditions. The fact that the increases in

prandial drinking (Fig. 9) both during the first 15 min and for the entire hour in Experiment 4 are much more obvious than the increases in the schedule induced water drinking (Fig. 7) in Experiment 3 might be attributed to the lower water consumption in Experiment 4 under control conditions. There might also be a ceiling effect in the large number of licks and relatively high water intakes under conditions of schedule induced polydipsia as compared to considerably less licks and smaller water intakes in Experiment 4. Angiotensin II under these conditions would be having an effect similar to the so-called rate dependent effects of many other drugs. In addition, angiotensin II might produce a nonspecific increase in responsiveness which results in a small all-or-nothing increase in drinking under these conditions which is not related to any underlying mechanism of body fluid regulation.

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