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Role of Angiotensin in Thirst

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ROLLS, B. J. AND R. J. WOOD. *Role of angiotensin in thirst.* PHARMAC. BIOCHEM. BEHAV. 6(3) 245–250, 1977. – Angiotensin is a potent dipsogenic substance and causes elevated water intake in some pathological conditions but as yet no physiological role for angiotensin in normal thirst has been proven. If angiotensin is important in normal drinking, then it should contribute to the drinking which follows water deprivation. The rehydration of bilaterally nephrectomized rats, rats with bilateral ureteric ligation and control rats was compared after 21 hours of water deprivation. The total intake during the 6 hour rehydration was the same in the 3 groups despite the differences in the level of circulating angiotensin. Thus the renal renin-angiotensin system is not essential for deprivation-induced drinking. Another way to test any contribution to drinking by angiotensin is the administration of the competitive angiotensin inhibitor, saralasin acetate. In a control experiment saralasin acetate was found to block the dipsogenic effect of intravenous angiotensin. The infusion of saralasin acetate in a wide range of doses did not, however, affect the drinking following ligation of the inferior vena cava. Thus angiotensin is not essential for drinking following caval ligation. Two possible explanations for these results are that angiotensin is not normally involved in these types of thirst or that there is redundancy in the control of drinking with compensation for blocked mechanisms.

Angiotensin Saralasin acetate Water intake

ANGIOTENSIN has been shown to be a potent dipsogenic substance. Intravenous infusions of angiotensin stimulate copious drinking [7, 10, 12] as does the injection of angiotensin directly into the brain [6,27]. The doses of angiotensin needed are small. Injections made directly into the subfornical organ, which is thought to be a receptive site for the dipsogen are effective in concentrations of 0.1 to 1.0 picograms [28]. This dose of angiotensin is within the physiological range and such levels probably occur after water deprivation [1, 7, 12] and acute thirst challenges such as ligation of the inferior vena cava [14].

Elevated angiotensin appears to lead to excessive drinking in some pathological conditions. The uncontrollable thirst observed in patients with chronic renal failure occurs in spite of reduced plasma sodium, and appears to be correlated with elevated renin. Bilateral nephrectomy reduces both renin levels and thirst in these patients. Thirst and elevated renin are also found in hyperaldosteronism, and secondary hyperaldosteronism accompanying pregnancy, anorexia nervosa, hemorrhage and sodium depletion [5]. We have also shown that two pathological conditions in the dog are associated with both elevated angiotensin and excessive water intake. Constriction of the thoracic inferior vena cava to produce congestive cardiac failure, elevates water intake which leads to excessive oedema. The elevated intake is probably due to increased levels of circulating angiotensin since the competitive angiotensin inhibitor, saralasin acetate, reduced water intake [18]. Water intake is also significantly increased in dogs with one-kidney Goldblatt hypertension [25]. The elevation of endogenous angiotensin in some pathological conditions may play an important role in maintaining plasma volume through increased water intake.

Thus angiotensin is a potent dipsogenic substance and causes elevated water intake in some pathological conditions, but as yet no physiological role for angiotensin in normal thirst has been proven. This is a difficult problem because it is not yet entirely clear whether plasma changes play an important role in initiating drinking in rats with free access to water. At least some of the drinking anticipates any real physiological need [9]. However, if plasma changes are critical in normal drinking these changes would be similar to, though probably of smaller magnitude, than those seen after water deprivation. Plasma volume is significantly decreased in water-deprived rats and dogs and this hypovolemia contributes to deprivation-induced drinking [19,20]. Hypovolemia might stimulate drinking in two ways. First, a low venous return will lead to a reduction in the rate of stimulation of both cardiac distension receptors and arterial baroreceptors [11]. Secondly, a reduction in blood volume may stimulate the release of renin and the formation of angiotensin.

In these experiments the possibility that angiotensin contributes to deprivation-induced drinking and drinking following ligation of the inferior vena cava was examined.

GENERAL METHOD

Animals

Male rats were housed in individual cages at a temperature of 72 ± 2°F with the lights on from 7 a.m.–7 p.m. Water and food were available ad lib at all times except during deprivation periods and experiments. Before the experiments began the rats were accustomed to drinking from calibrated drinking tubes. No food was available during experiments which were always conducted in the rat's home cage.

Statistics

Means and standard errors of means are represented in the results. Significances were calculated by a Student's *t*-test.

EXPERIMENT 1

The Effect of Nephrectomy on Deprivation-Induced Drinking

In this experiment the possibility that angiotensin plays an essential role in deprivation-induced drinking was investigated by comparing bilaterally nephrectomized rats, rats with bilateral ureteric ligation and control rats. The level of circulating angiotensin should be markedly different in these three groups of rats since nephrectomy will eliminate the main peripheral source of renin and ureteric clamping has been shown to increase renin levels [13].

Method. Male hooded Lister rats were deprived of water, but not food at 12 noon the day before an experiment. The experiments were started between 9 and 10 a.m. Nineteen rats, which served as the unoperated controls (mean weight 343 ± 13 g), were lightly anesthetized with ether. Eighteen rats (mean weight 288 ± 4 g) were anesthetized with ether and both kidneys were removed through dorsal incisions. Twelve rats (308 ± 7 g) were anesthetized with ether and both ureters were ligated through dorsal incisions. Surgical procedures took 5–10 min. The rats were placed back in the home cage and given access to tap water from calibrated drinking tubes. Intake was recorded over the next 9 hr. At the end of the experiment autopsies were performed on the rats which had undergone surgery.

Results. The results are shown in Fig. 1. During the first hour the rats which had undergone nephrectomy or ureteric ligation drank significantly less ($p<0.001$) than the unoperated controls. This was probably due to the surgery since during the second and third hours they compensated for the reduced intake during the first hour. After the first two postoperative hours the total intake of the three groups was the same. Urine output was not measured in the intact rats, but urinary loss would tend to increase the intake of the controls. The most important comparison is between the nephrectomized rats and those in which the ureters were ligated since there could be no renal modification of serum sodium or osmolality in either group. Both groups drank exactly the same amount throughout the experiment although the nephrectomized rats would have a much lower level of circulating angiotensin.

EXPERIMENT 2

Intravenous Saralasin Acetate and Angiotensin

Another way to test any contribution to drinking by angiotensin is the administration of the competitive angiotensin inhibitor, saralasin acetate or P-113. Since nephrectomy did not affect deprivation-induced drinking and since in preliminary experiments saralasin acetate did not influence deprivation-induced drinking, the effect of the blocker on thirst stimuli which were definitely thought to be angiotensin-dependent was determined. First, the intravenous infusion of angiotensin was combined with saralasin acetate. This was a control experiment to ensure that the intravenous administration of the inhibitor does block the dipsogenic effect of angiotensin. Epstein and Hsiao [7,12]

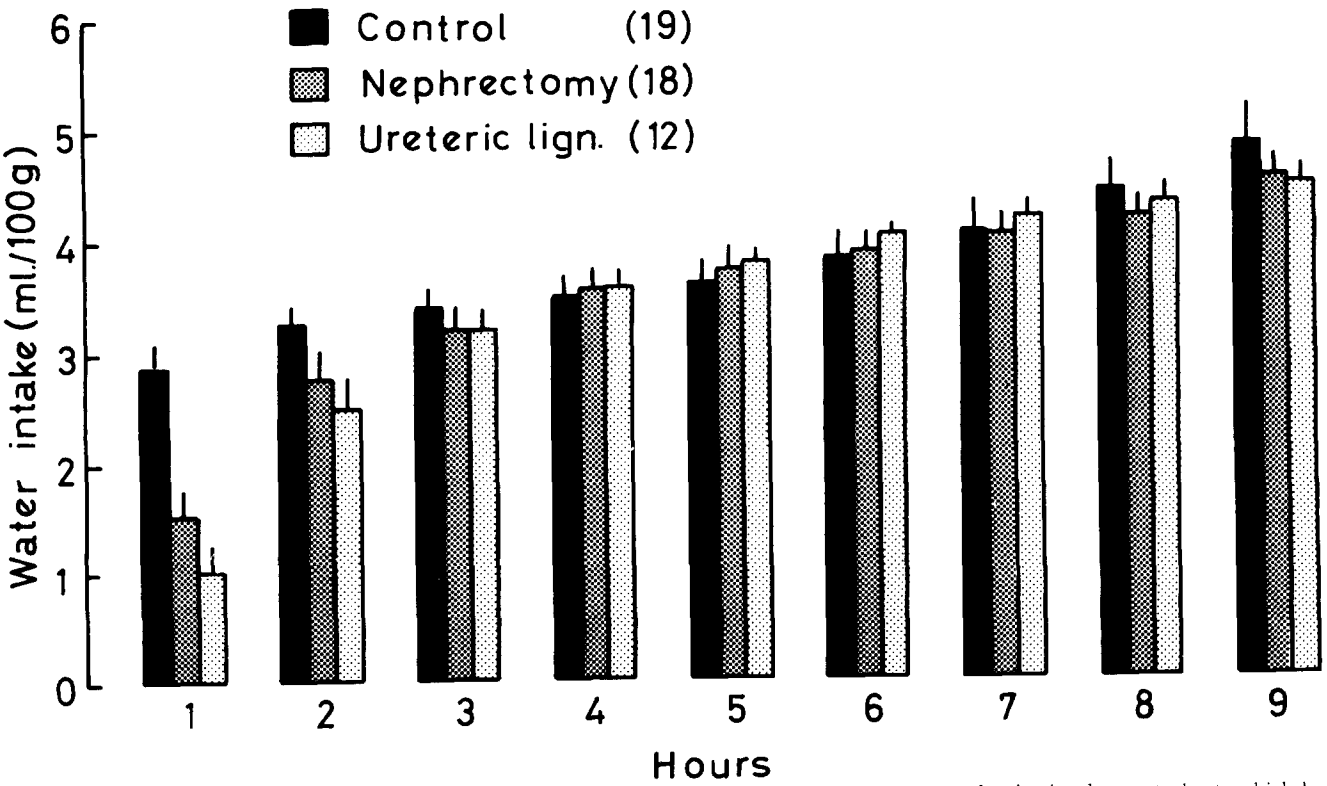

FIG. 1. The mean cumulative hourly water intake (ml/100 g initial body wt.) after 21 hours water deprivation by control rats which had not undergone surgery, by rats which were bilaterally nephrectomized, and by rats with both ureters ligated. The vertical bars show the S.E. of the mean. The number of rats in each group is given in parentheses.

showed that with low rates of infusion of angiotensin, saralasin acetate blocked the dipsogenic response when infused at 10 times the molal dose of the hormone. Tang and Falk [30] have also shown that intravenous saralasin acetate attenuated drinking due to intravenous angiotensin. In this experiment we infused angiotensin at a high rate which had been shown to elicit a copious and reliable drinking response [10].

Method. Twenty male Sprague Dawley rats (354 ± 7 g) were accustomed to the experimental procedure. Following overnight water deprivation they were allowed to rehydrate from calibrated drinking tubes for one hour. This was simply to ensure that at the time of the experiment all of the rats were familiar with the test situation. After this practice run, the rats were anesthetized with ether, and a soft polyvinyl chloride tube (o.d. 1 mm) filled with sodium heparin (10 unit per ml) was inserted through the external jugular vein to the right atrium. After surgery the rats were returned to ad lib food and water for two days before the experiment began. Between 10 and 11 a.m. the animals were infused with one of the following five solutions (N = 4 for each condition) via the jugular catheter: (1) 0.15 M NaCl; (2) angiotensin (Hypertensin, CIBA) at a rate of 0.8 μg kg^{-1} min^{-1}; (3) angiotensin (0.8 μg kg^{-1} min^{-1}) with saralasin acetate (P-113 or Sar^1-Ala^8-angiotensin II, Norwich Pharmacal) at a rate of 0.08 μg kg^{-1} min^{-1}; (4) angiotensin (0.8 μg kg^{-1} min^{-1}) with saralasin acetate (0.8 μg kg^{-1} min^{-1}); (5) angiotensin (0.8 μg kg^{-1} min^{-1}) with saralasin acetate (8.0 μg kg^{-1} min^{-1}).

All solutions were made up using 0.15 M NaCl. Infusions were at a rate of 0.3 ml/hr for three hours. Infusions were carried out in the home cage and the rats were unrestrained. The jugular catheter was connected to a 15 cm length of stainless-steel tubing (o.d. 0.75 mm) which projected through the top of the cage. This metal tube was connected by 1.5 m of polyvinyl chloride tubing to an infusion pump. During the 3 hr infusion, water intake was recorded and urine was collected. The protein content of the urine was determined using a biuret test.

Results. The results in Fig. 2 show that the intravenous infusion of saralasin acetate at a rate of 0.8 μg kg^{-1} min^{-1} ($p<0.001$) or 8.0 μg kg^{-1} min^{-1} ($p<0.01$) blocks the dipsogenic effect of intravenous angiotensin. The intakes of those two groups of rats did not differ nor were they different from the intake of the controls that were infused just with isotonic saline. The effect of the saralasin acetate was dose related in that the infusion of the inhibitor at 0.08 μg kg^{-1} min^{-1} did not significantly reduce the dipsogenic effect of angiotensin. The rate of angiotensin infusion was high and in the rats not infused with saralasin acetate or with saralasin acetate infused at a rate of 0.08 μg kg^{-1} min^{-1} protein was found in the urine. The higher rates of infusion of saralasin acetate blocked the proteinuria as well as reducing water intake.

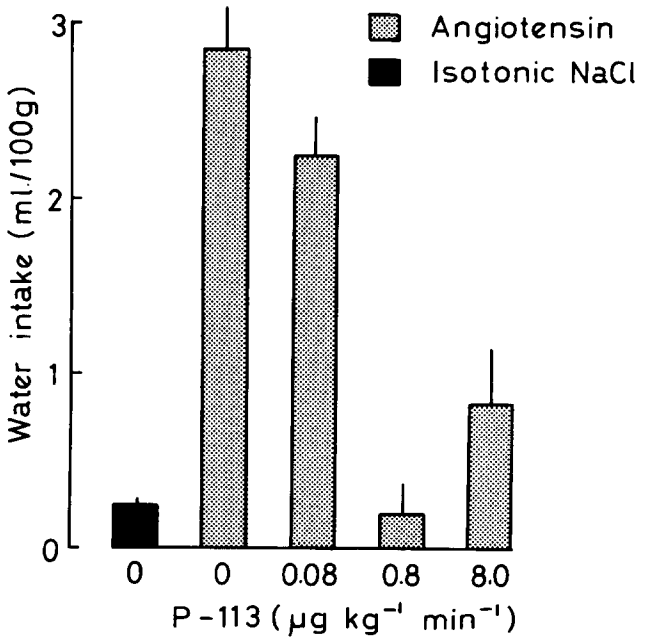

FIG. 2. The mean water intake (ml/100 g initial body wt.) by rats infused just with isotonic saline or with angiotensin (0.8 μg kg^{-1} min^{-1}) alone or in combination with saralasin acetate (P-113). Each block represents the total intake during a 3 hr infusion. The vertical bars show the S.E. of the mean.

EXPERIMENT 3

Intravenous Saralasin Acetate and Caval Ligation

In Experiment 2 it was shown that the intravenous infusion of saralasin acetate blocks the dipsogenic response produced by intravenous angiotensin. In this experiment the effect of intravenous saralasin acetate on the drinking following ligation of the inferior vena cava was investigated. The drinking which usually follows caval ligation is thought to be renin-dependent since it is almost eliminated by nephrectomy and is restored by intravenous angiotensin [8,10].

Method. Sprague-Dawley male rats ranging from 250–400 g body weight were used. Albino rats were found to drink more reliably after caval ligation than hooded rats which did not tolerate the operation well. Two days before the experiment the rats were accustomed to the experimental procedure. They were deprived of water overnight and were allowed to rehydrate using calibrated drinking tubes. Immediately after this practice run the rats were anesthetized with ether and a catheter similar to the one described in Experiment 2 was implanted in the jugular vein. The rats were put back on ad lib food and water and two days later they were again anesthetized with ether. Through a dorsal incision the inferior vena cava was ligated above the entry of the renal veins and below the hepatic veins. The surgery took 5 to 10 min. The rats were returned to the home cage.

In preliminary experiments we found that the rats drank most reliably if access to water was delayed for three hours after surgery. Thus after three hours the infusion of P-113 (Saralasin acetate, Norwich Pharmacal) in 0.15 M NaCl was begun. The rate of infusion ranged from 0.0008 μg kg^{-1} min^{-1} to 50.0 μg kg^{-1} min^{-1}. The infusion lasted for 75 min. The total volume infused did not exceed 1.75 ml. Control ligated rats were infused with a similar volume of isotonic saline. Another control group had a sham caval ligation and was infused with isotonic saline. During the first 15 min of the infusion the rats were not allowed access to water since at the start of an infusion saralasin acetate may have an angiotensin-like effect as shown by an increase in blood pressure [3]. To check for possible angiotensin-like effects of saralasin acetate on intake during the remainder of the infusion period, a sham cavally ligated

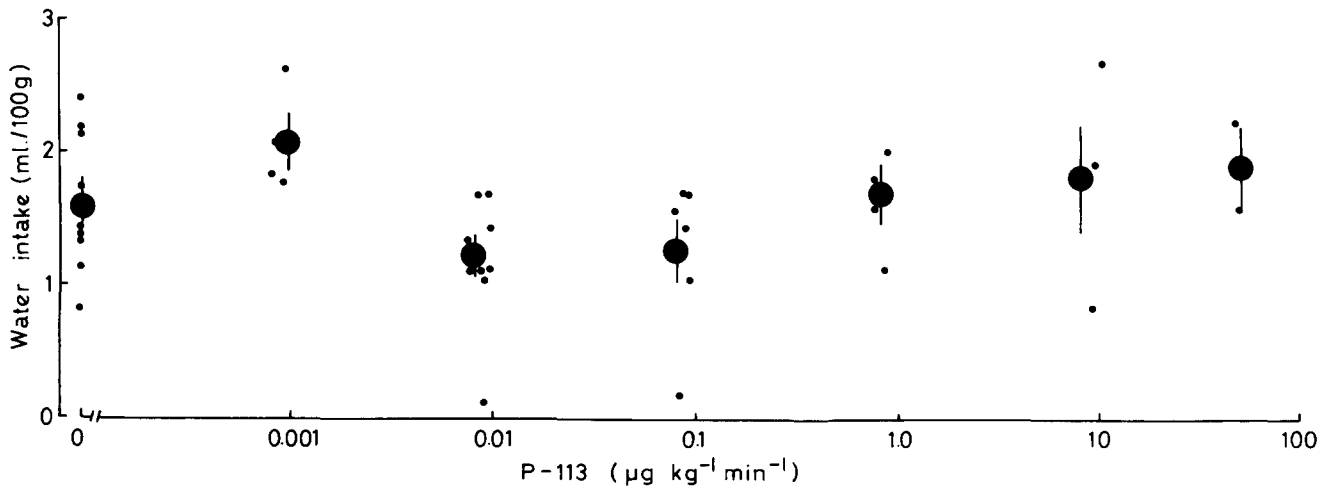

FIG. 3. The water intake (ml/100 g initial body wt.) by rats with the inferior vena cava ligated during an infusion of isotonic saline or the angiotensin inhibitor saralasin acetate (P-113). The small circles show the intakes for individual animals during the hour when water was given with the infusion on. The large circles indicate the mean intake for all the rats at a given dose of P-113. The vertical bars show the S.E. of the mean. Control rats which had a sham caval ligation and which were infused with isotonic saline drank 0.04 ± 0.03 ml/100 g initial body wt. (N = 5) during the same period.

group of 16 rats also received infusions of saralasin acetate at rates ranging from 0.0008 μg kg^{-1} min^{-1} to 0.8 μg kg^{-1} min^{-1}. Fifteen minutes after the start of the infusion all rats were allowed to drink for 2 hr. The infusion of saralasin acetate was terminated halfway through the drinking period. Water intake was recorded. The rats were autopsied at the end of the experiment to ensure that the caval ligation was successful.

Results. The results are shown in Fig. 3. Although a wide range of infusion rates was employed, there was no significant reduction of the drinking following caval ligation during the infusion period of one hour. Similarly we observed that the saralasin acetate infusions had no effect on water intake during the hour after the infusions were terminated, compared to the isotonic saline infused animals. In the sham ligated animals, infusions of saralasin acetate did not significantly change water intake with respect to control levels (isotonic saline infusion = 0.04 ± 0.03 ml/100 g, n = 5; saralasin acetate 0.8 μg kg^{-1} min^{-1} = 0 ml/100 g, n = 4; 0.008 μg kg^{-1} min^{-1} = 0.16 ± 0.1 ml/100 g, n = 4), so that there was no evidence of an angiotensin-like effect on drinking due to the saralasin acetate infusion (analysis of variance, $F(4,16) = 1.3$ n.s.). Thus the angiotensin inhibitor saralasin acetate does not inhibit the drinking which follows caval ligation.

DISCUSSION

There is suggestive evidence that angiotensin may play a role in normal drinking. Doses of angiotensin found to be dipsogenic when injected into the subfornical organ are within the physiological range [27]. Also, the effect of angiotensin on behavior is highly specific. For example, feeding is inhibited [6, 16, 24] and highly motivated drinking is induced [23]. Furthermore, angiotensin has been found to be dipsogenic in every species tested.

The renin-angiotensin system may mediate the drinking which follows depletion of the extracellular fluid compartment. Following a period of water deprivation extracellular fluid volume is significantly decreased [19] and levels of circulating renin are increased [1,17], yet in the present study bilateral removal of the kidneys which would eliminate the main peripheral source of renin did not influence deprivation-induced drinking. Furthermore, injections or infusions of saralasin acetate into the third ventricle of the dog [17] or sheep [2] do not affect deprivation-induced drinking. Two different conclusions can be drawn from these experiments. First, angiotensin may not contribute to the drinking which follows water deprivation, and may only act in pathological conditions such as congestive heart failure or renal hypertension and is therefore an emergency mechanism for maintaining plasma volume. However, circulating renin and angiotensin are elevated after water deprivation to levels similar to those which probably occur with dipsogenic doses of exogenous angiotensin [1, 7, 12, 17].

A second possibility is that there is redundancy in the control of drinking so that when one mechanism is removed other mechanisms take over. There is no direct evidence for redundancy but it is theoretically possible. Sibly and McFarland [26] summarize their theoretical analysis of motivational systems "... different processes act in parallel, their effects are additive, but at the same time the success of one mechanism obviates the necessity for another." After water deprivation the changes in the body fluids are complex and it is likely that various receptor mechanisms are involved in rehydration. For example, osmosensitive cells in the forebrain may detect changes in cell size; receptors in the subfornical organ, the preoptic area and the anterior third ventricle, may respond to changes in the level of circulating angiotensin; and receptors in and around the heart may monitor changes in blood volume. As it is essential to maintain fluid balance, redundancy in the controlling mechanisms would be an advantage. A possible example of redundancy may be found in rats with lesions in the preoptic area. These animals drink normally after water deprivation although they do not respond to hypertonic saline, polyethylene glycol, or isoproterenol [4, 21, 31]. Also, subfornical organ

lesions which abolish drinking to angiotensin and carbachol have only a transient effect on normal drinking [28].

In spite of the possibility of redundancy, it was expected that angiotensin blockade with saralasin acetate would reduce the drinking following ligation of the inferior vena cava because nephrectomy had been shown to significantly decrease the drinking and intravenous angiotensin had been shown to bring it back to normal levels [10]. Following caval ligation in the rat, renin levels are up 5–10 times above control values but the increases in renin do not correlate closely with the elevation of water intake. This may be due to a reduction of the dipsogenic property of angiotensin by osmotic dilution [14] or extracellular fluid volume expansion [22,24] following ingestion of water.

In Experiment 2 it was shown that the intravenous infusion of saralasin acetate completely blocked the dipsogenic effect of intravenous angiotensin. Therefore, if drinking following caval ligation depends solely on increases in the level of circulating angiotensin then an intravenous infusion of saralasin acetate should block the response. The intravenous infusion of saralasin acetate at a wide range of rates did not, however, affect the drinking following caval ligation. Lehr, *et al.* [15] also found that chronic renin depletion with DOCA did not affect drinking following caval ligation. Since caval ligation is unlikely to cause cellular dehydration and since angiotensin is not essential for the dipsogenic response, some as yet unidentified thirst mechanism is probably involved, for example, the cardiac distension receptors and arterial baroreceptors [11]. If this is so, it seems likely that bilateral nephrectomy not only reduces angiotensin levels but also causes circulatory changes which influence distension and baroreceptors, since nephrectomy almost abolishes the drinking following caval ligation.

The drinking which follows isotonic depletion of the extracellular fluid compartment with polyethylene glycol is thought to be independent of the renin-angiotensin system since nephrectomy has little effect on polyethylene glycol-induced drinking [29]. However, renin levels are elevated following polyethylene glycol treatment and water intake is correlated with both plasma renin activity and plasma deficits [1,14]. Thus if the redundancy argument put forward for water deprivation and caval ligation is valid, hypovolemic thirst may also depend on angiotensin.

These experiments show that angiotensin is not essential for the drinking following water deprivation and caval ligation. Two possible explanations for these results are first that angiotensin is not normally involved in these types of thirst or second that there is redundancy in the control of drinking with compensation for blocked mechanisms. If there is redundancy, it will be difficult to determine whether angiotensin has a physiological role in normal thirst in addition to its probable role as an emergency mechanism in some pathological conditions.

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