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Renal actions of angiotensin-(1-7)

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Abstract

The heptapeptide angiotensin-(1-7) is considered to be a biologically active endproduct of the renin-angiotensin system. This angiotensin, which is devoid of the most known actions of angiotensin II such as induction of drinking behavior and vasoconstriction, has several selective effects in the brain and periphery. In the present article we briefly review recent evidence for a physiological role of angiotensin-(1-7) in the control of hydroelectrolyte balance.

Key words
- Angiotensin antagonists
- Angiotensin II
- Hydroelectrolyte balance
- Renin-angiotensin system
- Kidney
- Water transport

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Introduction

The classical view that angiotensin II (Ang II) mediates all actions of the renin-angiotensin system (RAS) has been modified in the past few years by the demonstration that other angiotensin peptides (Figure 1), especially angiotensin-(1-7) (Ang-(1-7)) may selectively mediate actions of the RAS (1-3). Ang-(1-7) can be formed by an angiotensin converting enzyme (ACE)-independent pathway (4), and exerts important biological effects. *In vitro* this peptide is a potent vasopressin secretagogue (5) and possesses a potent prostaglandin-releasing activity in several cell lines (6,7). Microinjection of this angiotensin into the dorsomedial or ventrolateral medulla produces significant changes in mean arterial pressure and heart rate, comparable to those produced by Ang II (8-11). Furthermore, intracerebroventricular infusion of Ang-(1-7) in rats increased baroreceptor reflex sensitivity, an effect that was opposite to that observed with Ang II infusion (12). Other findings have indicated that Ang-(1-7) can act as an osmoregulatory peptide. Immunohistochemistry demonstrated that this peptide is present in brain areas related to the control of hydromineral balance (13). Additional studies in our laboratory have demonstrated that Ang-(1-7) has a potent antidiuretic effect in water-loaded rats (14) and that its plasma concentration is increased by hemorrhage or by maneuvers known to increase plasma osmolality such as water deprivation and salt load (15). A natriuretic effect of Ang-(1-7) in isolated rat kidneys (16) or in denervated rat kidneys *in vivo* (17) has also been described. Ongoing studies strongly suggest that these biological effects are mediated by specific receptors (10,11). These data indicate that Ang-(1-7) could be involved in the mediation of important central and peripheral actions of the RAS.

As documented above, in the past few years a large body of evidence has been accumulated suggesting a role for Ang-(1-7) in the control of hydroelectrolyte balance. However, due to several factors discussed below there is no consensus regarding the major action of Ang-(1-7) in the kidney. Several studies suggest a major role of Ang-(1-7) as a natriuretic peptide (16-18) while other studies, including ours, point to a major role of this angiotensin in water transport (19-22). It should be pointed out, however, that, even when apparently contradictory, these studies clearly show that the renal ac-

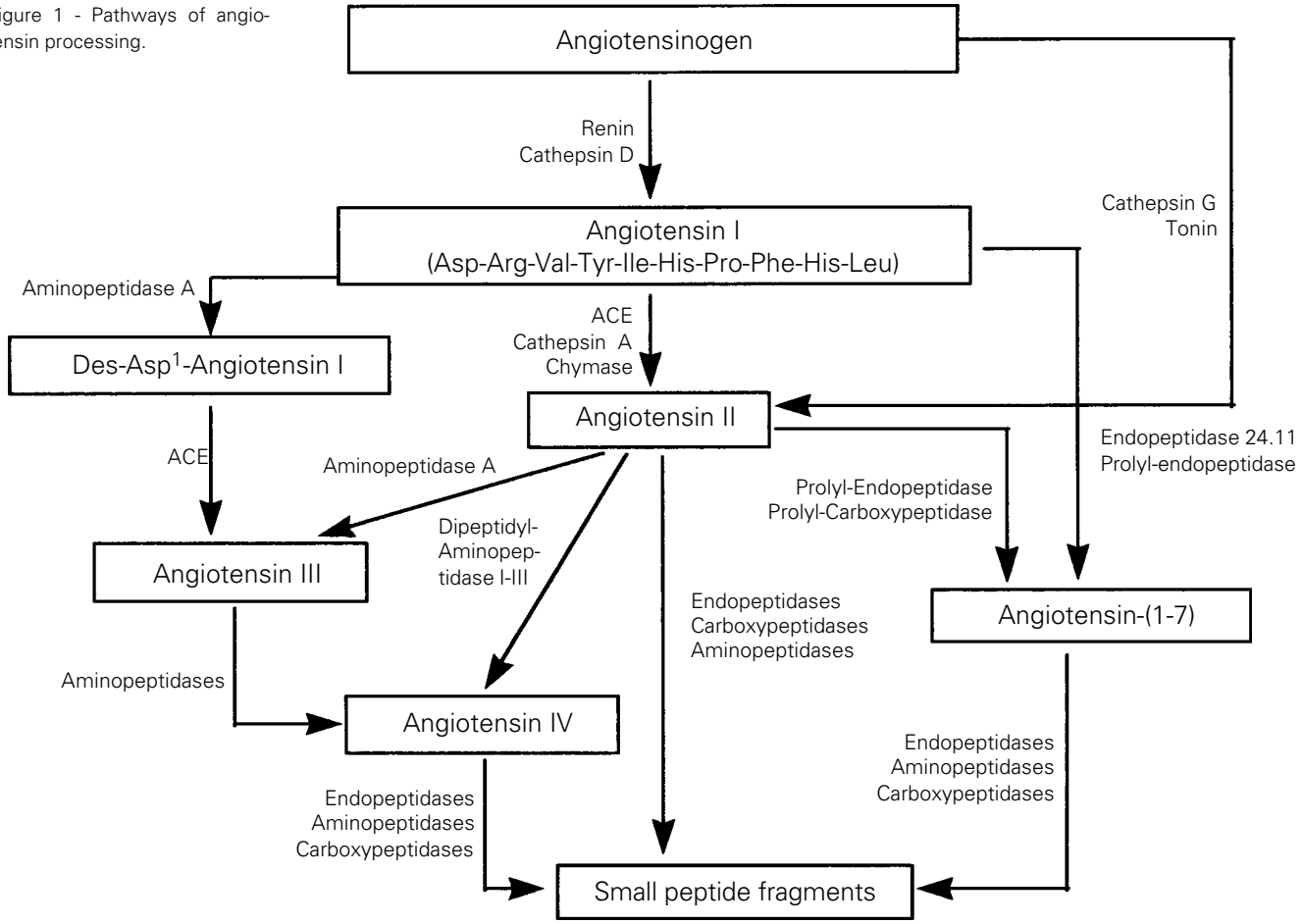

Figure 1 - Pathways of angiotensin processing.

tions of Ang-(1-7) are very complex, apparently involving both the proximal and distal nephron as is also the case for Ang II.

In the present article we briefly review the main evidence for a physiological role of Ang-(1-7) in the control of hydroelectrolyte balance, especially that dealing with water and sodium transport in the kidney.

Renin-angiotensin system and the kidney

The association of the renin-angiotensin system with kidney function is one of the most established concepts in physiology. The importance of the most active peptide of the RAS, Ang II, in hydroelectrolyte balance and cardiovascular homeostasis is due to its wide spectrum of biological activity.

Ang II is a potent vasoconstrictor that increases peripheral vascular resistance and thus mean arterial pressure. In situations of extracellular fluid volume contraction, Ang II reduces renal sodium excretion via alterations in renal hemodynamics, direct enhancement of proximal tubule sodium bicarbonate reabsorption, and aldosterone-mediated increases in late distal tubule and cortical collecting duct reabsorption (23,24). Ang II also increases thirst, salt appetite and intestinal sodium absorption, all of which increase the extracellular fluid volume. There is growing evidence, however, that besides Ang II the heptapeptide Ang-(1-7) also plays a physiological role in the control of hydroelectrolyte balance, mainly through its activity on the kidney (14,16,17,22).

In the following sections, we first briefly

summarize the renal actions of the RAS mediated by Ang II and then discuss a variety of experimental findings that point to an important role for Ang-(1-7) in modulating renal function.

Renal actions of angiotensin II

Ang II is one of the most powerful regulators of sodium excretion, operating through extrarenal mechanisms, such as the stimulation of aldosterone secretion, as well as intrarenal mechanisms (23). In the physiological concentration range, Ang II acts mainly as an antinatriuretic hormone by directly or indirectly producing changes in renal hemodynamics and in sodium reabsorption (25). Considerable evidence suggests that the intrarenal actions of Ang II are quantitatively more important than the extrarenal mechanisms in the normal day-to-day regulation of sodium and water excretion (23,26).

The extrarenal actions of Ang II include stimulation of the sympathetic nervous system and aldosterone secretion (23). The antinatriuretic effect of Ang II could be mediated in part by increased renal sympathetic nerve activity that in turn could increase renal tubular sodium reabsorption directly or indirectly by causing renal vasoconstriction (27). The other well-known extrarenal mechanism by which Ang II controls sodium and water excretion is through its indirect renal effect mediated by aldosterone. Aldosterone biosynthesis and secretion are strongly influenced by Ang II, which acts directly on adrenal glomerulosa cells to stimulate both early and late steps in the steroid biosynthetic cascade (28).

Two intrarenal effects of Ang II that may contribute to fluid retention and that occur at very low concentrations include the constriction of efferent arterioles and increased sodium transport by the renal tubules. Ang II markedly raises efferent glomerular arteriolar resistance (29) and does not change afferent arteriolar resistance unless the renal perfusion pressure rises (29). The consequence of the disproportionate increase in efferent (over afferent) resistance is a marked increase in the mean transcapillary hydraulic pressure, which results in an increase in mean transcapillary ultrafiltration pressure. Thus, the Ang II-induced decrease in renal plasma flow is offset by the increase in mean transcapillary ultrafiltration pressure and this maintains the glomerular filtration rate (GFR) by increasing the filtration fraction. Besides its effect on efferent arteriolar resistance, Ang II has a marked influence on glomerular mesangial tone. Ang II promotes mesangial cell contraction and thus a decrease in the glomerular capillary ultrafiltration coefficient (Kf) (30,31). The Kf-lowering effect of Ang II is attenuated by the stimulatory effect of Ang II on the production of vasodilatory prostaglandins (32). Thus, the final effect of Ang II is a stable GFR despite the changes in renal perfusion pressure.

The vasoconstrictor effect of Ang II on efferent arterioles causes changes in peritubular capillary dynamics that could increase renal tubular fluid reabsorption (33). The efferent arteriolar vasoconstriction would reduce the peritubular capillary hydrostatic pressure as well as increase peritubular capillary colloid osmotic pressure due to an increase in the filtration fraction. Both of these changes would tend to decrease renal interstitial fluid hydrostatic pressure and raise interstitial fluid colloid osmotic pressure, thereby increasing the driving force for fluid reabsorption (26,34).

Another mechanism by which Ang II-mediated changes in renal hemodynamics could increase tubular reabsorption is by decreasing renal medullary blood flow (35). The constriction of efferent arterioles of juxtaglomerular nephrons or a direct action on the vasa recta may lower renal medullary blood flow and increase medullary interstitial fluid osmolality. The increased osmolality could raise the urine-concentrating abil-

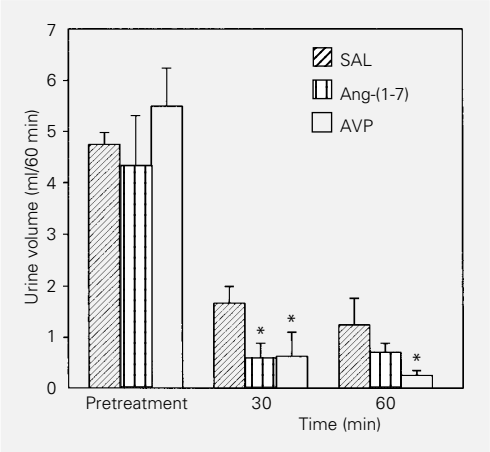

Figure 2 - Effect of angiotensin-(1-7) and vasopressin on water diuresis. Male Wistar rats (280 to 320 g) were submitted to a water load (5 ml/100 g body weight, gavage) and immediately housed in metabolic cages with no water or chow. Within 60 min of the water load the urinary volume was measured and the rats were immediately injected intraperitoneally with vehicle (0.9% NaCl, SAL, 0.05 ml/100 g body weight, N = 6), Ang-(1-7) (44 pmol/100 g body weight, N = 6), or AVP (20 pmol/100 g body weight, N = 4). Following injection, the animals were returned to the metabolic cages and diuresis was measured 30 and 60 min after completion of the treatment. Data are reported as mean ± SEM and were analyzed by one-way ANOVA, followed by the Newman-Keuls test. *P<0.05 compared to the vehicle-treated group.

ity and tend to enhance passive sodium chloride reabsorption in the thin ascending limb of Henle's loop (36).

Micropuncture and microperfusion studies have shown that the effect of Ang II on proximal tubule sodium transport is bimodal (37). Ang II at concentrations of 1 to 100 pM significantly stimulates proximal sodium reabsorption, whereas higher concentrations of 0.1 to 1 µM inhibit transport (37). Various studies suggest that at physiological concentrations (1 to 100 pM) Ang II promotes sodium bicarbonate reabsorption by activation of Na^+-H^+ exchange (38). Ang II also participates in the regulation of distal nephron acidification by stimulating the Na^+-H^+ exchange in early and late distal segments via activation of AT_1 receptors, as well as vacuolar H^+-ATPase in the late distal segment (39).

In contrast to its antinatriuretic actions, Ang II produces natriuresis when infused at supraphysiological concentrations that increase mean arterial pressure (25). This natriuretic effect of Ang II is mainly due to an increase in renal perfusion pressure and, additionally, to a direct inhibitory action on proximal tubular reabsorption. This effect, called pressure natriuresis, is thought to involve changes in peritubular Starling forces or interstitial pressures increasing back-leakage of fluid into the tubule lumen (25). Ang II-associated pressure natriuresis appears to serve as a negative feedback system on sodium retention produced by Ang II. The physiological importance of this mechanism is illustrated by the observation that if renal perfusion was prevented from rising by a servo control device during Ang II infusion, renal sodium reabsorption continued to rise to the point of pulmonary edema (40). Even with continued Ang II infusion, release of the renal clamp led to increased urinary sodium excretion with resolution of pulmonary edema (40). Thus, the net effect of different levels of Ang II on sodium and water excretion depends critically on the balance between the antinatriuretic actions of Ang II and the effect of increased renal perfusion pressure that tends to cause natriuresis.

Most of the known actions of Ang II in the kidney and other organs are mediated by angiotensin receptors of the AT_1 subtype coupled to various signal transduction pathways through pertussis toxin-sensitive and pertussis toxin-insensitive G proteins (41). There is evidence that in the proximal tubule Ang II is coupled to a pertussis toxin-sensitive G_i, reducing adenylate cyclase activity and cAMP accumulation. This appears to be the mechanism by which Ang II stimulates proximal tubule bicarbonate absorption (26). In addition, G protein-coupled activation of phospholipase A_2 with subsequent metabolization of arachidonic acid by cytochrome P450 epoxygenase to epoxy-eicosa-trienoic acids (EET) apparently mediates the natriuretic effect of Ang II acting on luminal angiotensin receptors (42). In contrast, the activation of phospholipase C, which in most tissues is the major mediator of the biological actions of Ang II, in the kidney appears to be limited to the mediation of Ang II hemodynamic effects (41).

Angiotensin-(1-7) and hydroelectrolyte balance

One of the major differences between

Ang II and Ang-(1-7) is the inability of the heptapeptide to stimulate drinking when injected centrally or peripherally (12,43,44). Thus, unlike Ang II, the participation of Ang-(1-7) in fluid homeostasis appears to be restricted to changes in the renal handling of fluid and salt. The role of Ang-(1-7) in the intestinal absorption of water and/or electrolytes has not yet been investigated.

The first description of an effect of Ang-(1-7) on water excretion was provided by Santos and Baracho (14) who demonstrated a potent dose-dependent antidiuretic action of Ang-(1-7) in water-loaded rats. This antidiuresis was associated with an increase in water reabsorption and a decrease in creatinine clearance (22). The antidiuresis produced by Ang-(1-7) occurred even when the peptide was administered 60 min after water load, when water diuresis was fully established. As shown in Figure 2, administration of Ang-(1-7) produced a significant decrease in urinary volume 30 min after its injection (0.58 ± 0.30 *vs* 1.67 ± 0.33 ml/30 min in the control group, $P<0.05$). Sixty minutes after treatment with Ang-(1-7), a slight decrease in urinary volume was observed, which, however, was not significant when compared with vehicle-treated rats (0.70 ± 0.18 *vs* 1.25 ± 0.51 ml/60 min, respectively, $P>0.05$). Similar results were observed in the group treated with avian vasopressin (AVP). Intraperitoneal injection of this peptide produced a significant reduction in water diuresis 30 min after its administration (0.63 ± 0.47 *vs* 1.67 ± 0.33 ml/30 min in vehicle-treated rats, $P<0.05$). The antidiuretic effect produced by AVP was also observed 60 min after water load (0.25 ± 0.10 *vs* 1.25 ± 0.51 ml/60 min in the control group, $P<0.05$). This observation ruled out the possibility that the antidiuretic effect produced by Ang-(1-7) in water-loaded rats was due to the interference with gastrointestinal water reabsorption. The physiological relevance of these data was substantiated by the utilization of the selective Ang-(1-7) antagonist, A-779 (11). This compound antagonizes several actions of Ang-(1-7), including its antidiuretic effect (11,45). The acute administration of A-779 in conscious rats produced a diuretic effect (1.12 ± 0.32 ml/h *vs* 0.13 ± 0.03 ml/h in vehicle-treated rats, $P<0.05$) which was associated with an increase in creatinine clearance (1.09 ± 0.35 ml/min *vs* 0.34 ± 0.04 ml/min in vehicle-treated rats, $P<0.05$) and a decrease in urinary osmolality (556 ± 88 mOsm/kg *vs* 1990 ± 149 mOsm/kg in vehicle-treated rats, $P<0.05$), as shown in Figure 3. The acute administration of a vasopressin V_2 receptor antagonist produced a similar diuretic effect (Figure 3). However, the diuresis produced by vasopressin blockade was also associated

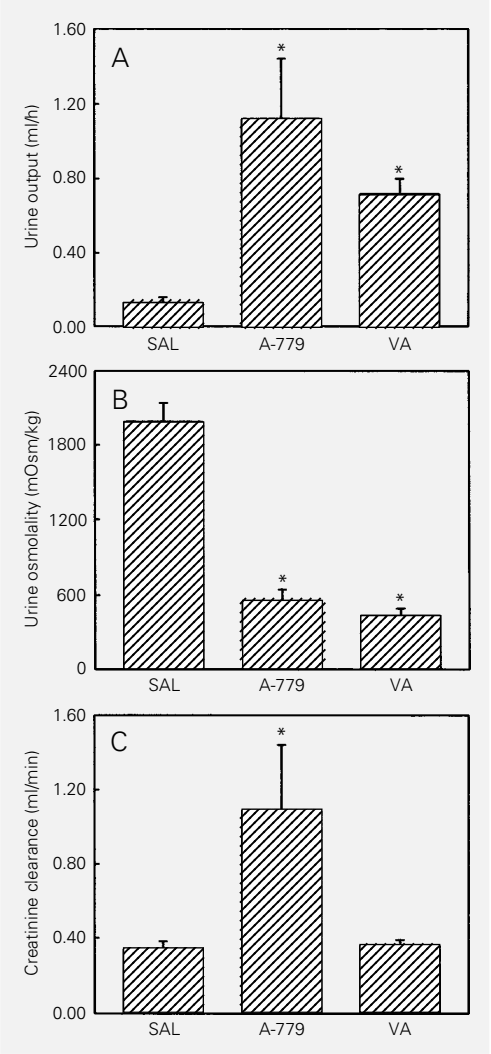

Figure 3 - Effect of D-Ala^7-angiotensin-(1-7) (A-779) and an AVP-V_2 antagonist on urine output, urine osmolality and creatinine clearance in awake rats. Male Wistar rats (280-320 g) were transferred to metabolic cages with tap water and standard chow. Twenty-four hours later, the animals were treated subcutaneously with A-779 (4.6 nmol/100 g body weight, N = 5), a vasopressin V_2-receptor antagonist (adamantaneacetyl O-Et-D-Tyr^2, Val^4, aminobutyryl^6, Arg^{8,9}-vasopressin (VA, 3.2 nmol/100 g body weight, N = 5)), or vehicle (0.9% NaCl, SAL, N = 10). Immediately after the treatments, the animals were transferred to metabolic cages and the volume of urine was measured and collected for 6 h. Blood for determination of the effect of A-779 or VA on renal function was obtained under anesthesia immediately after urine collection. The effect of A-779 and VA on basal urinary output (A), urinary osmolality (B) and creatinine clearance (C) is shown. Data are reported as mean ± SEM. *$P<0.05$ compared to vehicle-treated animals (ANOVA, followed by the Newman-Keuls test).

with an increase in water excretion, but not with changes in creatinine clearance as shown in Figure 3. These results suggest that, in contrast to vasopressin, endogenous Ang-(1-7) influences water reabsorption also acting at the glomerular level. Pawloski-Dahm and Fink (19) also observed an antidiuretic effect in normal rats chronically infused with Ang-(1-7). In contrast, a natriuretic and diuretic effect of Ang-(1-7) was observed in other studies (16,17). Using isolated perfused rat kidneys, Dellipizzi et al. (16) observed a natriuretic effect associated with an increase of urinary volume following infusion of Ang-(1-7). Handa et al. (17) also reported an increase in sodium and water excretion after intrarenal injection of Ang-(1-7) in Na^+-replete anesthetized male Wistar rats with denervated kidneys. In addition, an inhibitory effect of Ang-(1-7) on Na^+ transport in cultured renal epithelial cells was previously demonstrated by Andreatta-Van Leyen et al. (18).

Neither the antidiuretic action of Ang-(1-7) in water-loaded rats (14) nor the natriuretic/diuretic effect observed in anesthetized/kidney denervated animals (17) was substantiated by infusion of high doses of Ang-(1-7) (46) in euvolemic rats. No changes in urinary volume or in urinary osmolality were observed in these experiments. However, chronic infusion of the Ang-(1-7) antagonist A-779 produced sustained diuresis in conscious male Wistar rats (47), suggesting that the possible physiological role of Ang-(1-7) is mainly as an endogenous antidiuretic peptide.

Angiotensin-(1-7) and vasopressin

Schiavone et al. (5) provided the first demonstration of a biological action of Ang-(1-7) by showing that Ang-(1-7) was equipotent to Ang II in releasing vasopressin from hypothalamo-neurohypophyseal explants. These data were substantiated by the observation of immunoreactivity against Ang-(1-7) in brain areas associated with hydromineral balance, the hypothalamus and neurohypophysis (13). However, other studies did not provide conclusive data regarding the possible central Ang-(1-7)-AVP interaction suggested by these early reports. Mahon et al. (44) reported that intracerebroventricular injections of Ang-(1-7) had no effect on vasopressin release, and induced a pattern of *c-fos* protein expression in the forebrain which is significantly different from that obtained with Ang II injection. For example, Ang-(1-7) did not induce *c-fos* expression in paraventricular or supraoptic nuclei. On the other hand, unlike Ang II, peripheral administration of Ang-(1-7) failed to change plasma AVP levels (22,46). The antidiuretic effect of Ang-(1-7) in water-loaded rats was not blocked by a vasopressin V_2 receptor antagonist at doses that abolished the antidiuresis produced by vasopressin, and was not associated with changes in plasma vasopressin levels (22). As mentioned before, a similar finding was previously obtained in normal rats chronically infused with Ang-(1-7) in which a dissociation of the antidiuresis and the increase of plasma AVP was observed (19). Benter et al. (46) also reported no changes in plasma levels of vasopressin in Wistar Kyoto or Sprague-Dawley rats during Ang-(1-7) infusion. Interestingly, a significant reduction in plasma vasopressin levels was observed in spontaneously hypertensive rats infused with Ang-(1-7). Taken together, these observations indicate that the release of vasopressin did not contribute to the renal actions of Ang-(1-7). However, the possibility that in situations of chronic osmotic imbalance Ang-(1-7) may contribute to changes in plasma AVP levels cannot be ruled out.

Glomerular actions

The effects of Ang-(1-7) on the GFR are apparently dependent on the experimental conditions. In water-loaded conscious rats,

Ang-(1-7) administration significantly reduced creatinine clearance (22). However, in further experiments carried out in our laboratory, no significant changes in the GFR (estimated by inulin clearance, Cl_{In}) were observed in thiopental-anesthetized rats submitted to acute extracellular volume expansion. In these experiments, infusion of Ang-(1-7) (30 ng min^{-1} 100 g body $weight^{-1}$) reduced the Cl_{In} from 0.61 ± 0.1 to 0.56 ± 0.01 ml min^{-1} 100 g body $weight^{-1}$. Chronic (47) or acute (Figure 3, Ref. 22) administration of the selective Ang-(1-7) antagonist A-779 to conscious rats produced a significant increase in creatinine clearance. Conversely, small increases in GFR following Ang-(1-7) infusion were reported in isolated rat kidneys (16,48). The results obtained in our laboratory using anesthetized rats, and by others in isolated rat kidneys suggest that the glomerular actions of Ang-(1-7) are significantly blunted by kidney denervation and anesthesia. In addition, differences in the sensitivity to Ang-(1-7) among rat strains should be considered when interpreting these results (22). The presence of angiotensin receptors with a relatively high affinity for Ang-(1-7) (30 nM) in the mesangium (49) probably accounts for the glomerular effects of the heptapeptide, since there is no evidence for significant changes in renal blood flow produced by Ang-(1-7) (17).

Tubular effects

Several studies have provided evidence that Ang-(1-7) can influence proximal and distal tubular transport mechanisms. In perfused proximal straight tubules, Garcia and Garvin (20) found that Ang-(1-7) at a concentration of 1 pM increased fluid and bicarbonate absorption. The increase in bicarbonate reabsorption could not be attributed to an increase in the maximum bicarbonate absorption rate or to changes in bicarbonate permeability. Conversely, at a high concentration (10 nM) Ang-(1-7) decreased fluid absorption. On the other hand, using isolated rat proximal tubules, Handa et al. (17) found that Ang-(1-7) induced only a dose-dependent decrease in O_2 consumption over a large range of concentrations (0.1 to 10 nM). Besides other explanations for the apparent divergent results of Handa et al. (17) and Garcia and Garvin (20), including the presence of straight and convolute tubules in Handa's proximal tubule preparation, the extensive handling of the kidney tissue used in the study of Handa et al. (17) to prepare the crude proximal tubule preparation probably accounts for the observed differences.

In accordance with the data obtained by Garcia and Garvin (20) using a high concentration of Ang-(1-7) and those obtained by Handa et al. (17), an inhibitory role of Ang-(1-7) in sodium reabsorption was described by Andreatta-Van Leyen et al. (18), using primary cultures of rabbit proximal tubular cells.

The data available about the actions of Ang-(1-7) on the distal nephron are restricted to the inner medullary collecting ducts (IMCD). At a 10 nM concentration Ang-(1-7) increased water conductivity 4-fold in the rat IMCD (22). The stimulatory effect of Ang-(1-7) on water permeability in this nephron segment is dose-dependent, can be blocked by A-779 and, interestingly, also by an AVP-V_2 receptor antagonist (Magaldi AJ, personal communication). Regarding this last observation, it would be interesting to explore the involvement of the recently described AVP-angiotensin receptor (50) in the renal effects of Ang-(1-7). In contrast to the dose-related increase of water reabsorption induced by Ang-(1-7) in IMCD (22), in the frog skin the heptapeptide alters osmotic permeability biphasically, increasing it at low concentrations (1 nM) and decreasing it at higher concentrations (10 nM) (21). Indirect evidence for an action of Ang-(1-7) on the collecting ducts has also been provided by Santos and Baracho (14) and Santos et al. (22).

Angiotensin-(1-7) and renal prostanoids

There are few data about the possible interaction between Ang-(1-7) and prostanoids in the kidney. A significant prostaglandin-releasing activity of Ang-(1-7) was demonstrated in the vasa deferentia (51) and cultured endothelial cells (7). This prostaglandin-releasing activity of Ang-(1-7) may also be involved in the renal actions of the heptapeptide. We provided *in vivo* evidence of a possible modulatory effect of prostaglandins on the antidiuresis produced by Ang-(1-7) in water-loaded rats (22). In that study pretreatment with the cyclo-oxygenase inhibitor indomethacin potentiated the antidiuretic effect of Ang-(1-7) (22). In addition, *in vitro* studies also provided evidence for an interaction between Ang-(1-7) and prostaglandins at the renal tubular level (18,48). Using cultured renal epithelial cells, Andreatta-Van Leyen et al. (18) observed that Ang-(1-7) significantly increased phospholipase A_2 activity and suggested that this heptapeptide may be involved in the regulation of electrolyte transport in proximal tubular epithelium by phospholipase A_2 activation. Hilchey et al. (48), using isolated perfused kidney, reported that Ang-(1-7) selectively stimulated renal PGI_2 and suggested that this effect may be related to the natriuresis observed during Ang-(1-7) infusion.

Taken together, these findings suggest that prostaglandins released by Ang-(1-7) from endothelial cells (7) or through activation of phospholipase A_2 at the tubular level (18) could modulate the effects of Ang-(1-7) on water and sodium transport.

Angiotensin-(1-7) and angiotensin receptors

There is growing evidence that the actions of Ang-(1-7) in the kidney or other sites are mediated by specific receptors (3,10,11, 17,22,45,52,53). In the kidney the antidiuretic action of Ang-(1-7) in water-loaded rats is blocked by the selective Ang-(1-7) antagonist A-779 which shows very low affinity for classical angiotensin II receptors (AT_1 and AT_2 subtypes) (22). On the other hand, Garcia and Garvin (20) found that the effects of Ang-(1-7) on fluid and bicarbonate absorption in isolated proximal tubules were blocked by the AT_1 receptor antagonist losartan. A similar observation was made by Simões e Silva et al. (54) who noticed the blockade by losartan of the antidiuretic effect of Ang-(1-7) in water-loaded rats. A partial blockade of the effect of Ang-(1-7) on O_2 consumption in rat proximal tubules was also observed by Handa et al. (17). We suggest that these findings should be interpreted as evidence that losartan can bind to a subtype of Ang-(1-7) receptors rather than that, under these conditions, Ang-(1-7) acts through AT_1 receptors. The main reason for this interpretation is that Ang-(1-7) lacks two of the most classical actions of Ang II mediated by AT_1 receptors, i.e., vasoconstriction and induction of drinking. Furthermore, Ang-(1-7) binds poorly to AT_1 receptors (3,11). Obviously, other explanations can be proposed, including conformational changes of the AT_1 receptors which permit Ang-(1-7) binding to occur. However, these possibilities are less likely than losartan binding to an Ang-(1-7) receptor.

Although further studies are obviously needed to demonstrate the existence of specific Ang-(1-7) receptors, the observations made with the Ang-(1-7) analogue D-Ala^7-Ang-(1-7) (A-779) in the brain (10,11,45,55) and in the periphery (22) strongly suggest that a non-AT_1, non-AT_2 receptor mediates the biological actions of Ang-(1-7).

Angiotensin-(1-7) signal transduction

There are few studies dealing with signal transduction associated with the actions of Ang-(1-7) in the kidney or other organs. Ang-(1-7) was as potent as Ang II in terms of prostaglandin release but did not activate

phospholipase C or mobilize intracellular calcium in human astrocytoma cell lines (56). Evidence for the existence of an Ang-(1-7) receptor linked to phospholipase A_2 was also obtained by Jaiswal et al. (6,7,57) in C6 glioma cells, endothelial cells and human astrocytes. These studies confirmed the original observation of Trachte et al. (51) in isolated rabbit vasa deferentia. Evidence for the participation of a signal transduction pathway for Ang-(1-7) mediated by phospholipase A_2 in the kidneys was provided by Andreatta-Van Leyen et al. (18). Indirect evidence for such pathway was obtained by Hilchey et al. (48) and Santos et al. (22) (see above). The observation that the increase in water permeability induced by Ang-(1-7) in IMCD is blocked by the protein-kinase A inhibitor H8 (Magaldi AJ, personal communication) suggests that a signal transduction pathway mediated by adenylate cyclase also contributes to the effects of Ang-(1-7) in the kidney. There is an inverse relationship between cAMP and Na^+ and bicarbonate reabsorption probably related to changes in the phosphorylation of the Na^+-H^+ exchanger on the luminal cell surface (41). Thus, an attractive hypothesis is that Ang-(1-7) stimulates adenylate cyclase which may explain both its natriuretic action in the proximal tubule (16,17) and its effect on water permeability in the collecting ducts (22), reducing plasma osmolarity.

In summary, Ang II and Ang-(1-7) can be formed locally (58) and influence several aspects of kidney function. The novel activities described for Ang-(1-7) in this organ suggest that this angiotensin peptide may be responsible for an important subset of angiotensinergic effects influencing the hydroelectrolyte balance.

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