Dogmas and surprises about the renin–angiotensin system and sodium reabsorption*

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Introduction

After many years of studies on the renin–angiotensin system (RAS), one of the central concepts is that the RAS forms an effective defence mechanism against low-sodium states and hypotension. Low-perfusion pressure sensed by the afferent arteriole, low-distal delivery sensed by the macula densa and low blood pressure sensed by the sympathetic nervous system increase renin release, leading to angiotensin generation and sodium retention, vasoconstriction and restoration of blood pressure. About 15 years ago, the first reports appeared indicating angiotensin concentrations in the proximal tubule of higher magnitude than in the plasma [1,2]. Attempts to relate intraluminal angiotensin II (Ang II) concentrations to the functionality ascribed to the RAS were not very successful: the intratubular system did not seem to be adapting synchronously with the systemic RAS. What is the matter here? Is there a local RAS that acts independently from the systemic RAS? What would be the physiological relevance? In a recent article, Thomson et al. [3] explore the possibility that the local proximal tubular RAS functions in an opposite fashion to the systemic RAS: salt loading increased proximal tubular Ang II levels and sodium reabsorption. In this commentary, we attempt to place these recent findings in perspective with previous studies on the systemic and local RAS.

The classical view: the RAS is a sodium-retaining mechanism

Infusion of Ang II to humans and animals leads to sodium retention [4–6]. In vivo micropuncture and microperfusion studies [7,8] have confirmed that Ang II can strongly enhance proximal tubular reabsorption. Stimulation of proximal reabsorption by Ang II diminishes distal delivery; this would deactivate the tubuloglomerular feedback (TGF) system and consequently would increase GFR and filtered load. Ang II also enhances the responsiveness of the TGF system and, therefore, actions of Ang II on proximal reabsorption and the TGF system are synergistic and permit a decrease in distal delivery [9]. Translated to a clinical situation, a decrease in blood pressure will lead to RAS activation, enhanced proximal tubular reabsorption and a decrease in sodium excretion.

The proximal tubular angiotensin system; what do we know?

In 1990, the first report appeared that proximal tubular concentrations of Ang II were much higher than plasma concentrations [2]. We have confirmed and expanded these findings: when artificial tubular fluid is infused into the early proximal tubule, and collected downstream, the Ang II concentration is extremely high, in the nanomolar range [1], suggesting proximal tubular secretion of Ang II. Since then, similarly high intraluminal Ang II concentrations have been published in Ang II-infused hypertensive rats [10] and in one-clip, two-kidney Goldblatt hypertensive rats [11]. Interestingly, we failed to demonstrate diminished proximal tubular Ang II levels during volume expansion [12]. Reduced renal perfusion pressure, however, resulted in a parallel increase in systemic and proximal tubular Ang II levels [12]. In these studies, we failed to demonstrate a decrease in proximal tubular Ang II concentrations upon intraluminal angiotensin-converting enzyme (ACE) inhibitor administration [1] and failed to show diminished maximum TGF
responses upon intraluminal administration of the AT1 receptor antagonist losartan [13]. Renin, albeit in low concentrations, and angiotensinogen message have demonstrated in proximal tubular cells [14]. The brush border contains ACE and angiotensinogen and Ang I concentrations are also high in the proximal tubular fluid [15–17]. AT1 receptors have been described on both the luminal and basolateral membranes [18]. Thus, the proximal tubule contains all the components of the RAS and could thus function in a paracrine fashion.

The surprise: sodium loading in rat increases intratubular Ang II levels and is associated with maintained Ang II-dependency of proximal tubular reabsorption

Recently, Thomson et al. [3] investigated the long-held hypothesis that the RAS contributes to sodium retention. Male Wistar rats were maintained on a regular diet or a 1% NaCl high-salt diet for 7 days. Proximal tubular reabsorption was assessed prior to and following acute, intravenous administration of the angiotensin AT1 receptor antagonist losartan (10 mg/kg i.v.). Using micropuncture, late proximal tubular fluid flow was measured during a deactivated (zero perfusion of the loop of Henle) or a fully activated TGF system, to obtain variations in single nephron GFR (SNGFR). During a fully deactivated system, the TGF system dilates the afferent arteriole and maximizes SNGFR, while during full activation of the system, SNGFR is decreased. SNGFR and late proximal tubule flow were assessed prior to and following losartan administration, and plasma, kidney and proximal tubular Ang II concentrations assessed using radioimmunoassay. The key observations were that: (i) a high-salt diet increased GFR and proximal tubular sodium reabsorption, (ii) the TGF response was not suppressed by the high-sodium diet, (iii) losartan decreased proximal tubular sodium reabsorption to the same extent in sodium depleted and replete animals and (iv) sodium loading decreased plasma and kidney Ang II levels, but increased proximal tubular Ang II levels [3]. The authors' view is that Ang II, by enhancing proximal tubular reabsorption during the sodium-replete state and the associated higher GFR, stabilizes the sodium load to the macula densa. This is further illustrated in Figure 1A: at any SNGFR, Ang II blockade results in an increase in late proximal flow, irrespective of the sodium diet. It is not of note that when GFR is higher, absolute reabsorption is higher (as will be excretion), which is glomerulotubular balance. What is noteworthy, however, is that proximal tubular reabsorption remains so dependent on Ang II.

There are some methodological issues that can be raised to question the approach. One is that blood pressure changes accompanied the changes in proximal reabsorption; still, when related to the blood pressure changes, the change in fractional proximal reabsorption was not different between normal and sodium-loaded animals (Figure 1B) while plasma Ang II levels were significantly decreased. Second, no early distal tubular fluid collections were performed. Acute ACE inhibition in humans on a low-, intermediate- and high-sodium diet suppressed plasma Ang II levels in all three groups, and increased fractional sodium excretion in subjects on low and medium salt intake [19]. Interestingly, urinary sodium concentration increased after ACE inhibition, indicating actions of Ang II beyond the proximal tubule in the diluting segment. Unfortunately, Thomson et al. [3] did not report urinary sodium concentration or excretion. A third concern would be that the salt loading was not very rigorous.

What could be the physiological implication of a local and a systemic RAS with opposing functions?

The researchers propose that an additional mechanism operates to stabilize distal delivery, on top of glomerulotubular balance and the TGF system (Figure 2). In this way, the adaptation of the proximal tubular angiotensin system will prevent an increase in distal delivery by sodium loading, even when the function of the TGF system is attenuated. What would be the physiological meaning of such a mechanism?
The mechanism will not interfere with regaining overall sodium balance after a change in sodium intake. However, the compartmentalized, proximal tubular Ang II system would change the time frame in which balance is regained after a change in sodium intake: by maintaining high-proximal tubular reabsorption, the mechanism will oppose the other systems that aim to excrete that sodium load, and delay the moment at which balance is regained. Teleology could help to find a function for this mechanism: if environmental circumstances are such that there is incidental food (and sodium) available, it would not be logical to immediately excrete such a sodium load. Strauss et al. [20] observed that a normal individual, in balance on a very low-sodium intake, responds to administration of a small amount of sodium with natriuresis within hours. However, if more sodium is ‘squeezed’ out, by means of a diuretic or excessive sweating, administered sodium is retained quantitatively until this additional amount is replaced, after which any further sodium administered is treated as surplus to the body, i.e. excreted. The concept that Thomsom et al. [3] propose would be compatible, despite the fact that a time frame of a week of sodium loading is too long to remain in a sodium-depleted state.

It should be mentioned that we demonstrated that during a decrease in renal perfusion pressure, intraluminal Ang II increases in parallel to the systemic and whole kidney levels. Thus, the intraluminal system seems to be able to respond both parallel and opposite, depending on the exact stimulus. It would be interesting to study how different levels of sodium intake affect the luminal Ang II levels, and, conversely, how Ang II inhibition affects the time course of excretion of a sodium load.

Fig. 2. Systems that stabilize distal delivery (SNGFR, single nephron glomerular filtration rate).

What implications could be envisioned of the intratubular Ang II system for clinical syndromes?

Given the activation of the systemic RAS during sodium depletion, ACE inhibitors and AT1 receptor antagonists are widely believed to have more consequences in low, than in high-salt states. The presented scheme would indicate that in sodium-replete states, such as volume-mediated hypertension, the (adult) nephrotic syndrome and diabetic nephropathy, Ang II blockade would also be effective for volume regulation. Indeed, high-glucose levels have been shown to stimulate angiotensinogen gene expression in proximal tubular cells [21], and proximal tubular renin expression was enhanced in streptozotocin-induced experimental diabetes mellitus in vivo [22]. Similarly, intraluminal Ang II levels have been reported to be increased in experimental hypertension, as noted earlier. One can only speculate on other clinical states such as the nephrotic syndrome; this remains to be investigated.

Conclusions

Taken together, the recent report by Thomson and other data indicate that during a high-sodium intake, proximal intraluminal Ang II does not function in parallel to the systemic RAS and may even function in an opposite fashion. The proximal tubular renin–angiotensin system could thus act to stabilize distal delivery in the face of GFR increases upon sodium loading (in the present study even up to 20%). The high GFR in this situation may be meant to adapt to a high-caloric intake. Although this needs still to be unraveled, such a mechanism would at least allow GFR changes, i.e. upon changes in caloric intake, and leave delivery to the fine-tuning, low-capacity distal tubular mechanisms stable. With currently available information, the proximal tubular system seems to act in parallel with the systemic RAS during strong sodium depletion and/or low blood pressure, but opposite during exaggerated sodium intake. The suggestion here may be that this system serves sodium preservation during low-sodium conditions, and serves metabolic adaptation during high-sodium states.

References


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