Angiotensin II Type 1 Receptor–associated Protein
A Novel Modulator of Angiotensin II Actions in the Nephron

Jorge F. Giani, Sebastien Fuchs, Romer A. Gonzalez-Villalobos

See related article, pp 1203–1210

Most physiological actions of angiotensin (Ang) II are mediated by its binding to the Ang II type 1 receptors (AT\(_1\)R). These include, but are not limited to, vasoconstriction, increased renal sodium and water reabsorption, as well as the stimulation of aldosterone release, thirst, vasopressin secretion, and cell growth. Not surprisingly, the biochemistry of the AT\(_1\)R has been a subject of intense research for >30 years. These studies revealed that the cytoplasmic tail of the AT\(_1\)R is an important site for several protein-to-protein interactions, phosphorylation, and thereby the regulation of receptor signaling, desensitization, and endocytosis. Accordingly, considerable efforts have been made to identify and to study molecules with affinity to this region; one of such molecules is the angiotensin receptor–associated protein (ATRAP).

ATRAP is an 18-kDa protein that was first identified and cloned in 1999 using a yeast 2-hybrid assay. Successive in vitro studies showed that ATRAP lacks catalytic activity. Instead, ATRAP is a membrane protein with 3 predicted transmembrane domains and a cytoplasmic tail that is important for its interactions with the carboxyl terminal of the AT\(_1\)R. ATRAP colocalizes with the AT\(_1\)R mostly in intracellular compartments, it induces AT\(_1\)R internalization and reduces its signaling. Thus, available data indicate that ATRAP is a negative modulator of AT\(_1\)R activity. ATRAP is made by many organs, including the heart, testis, and adrenal glands. However, by far the kidneys are the site of highest expression.

Studies using gene targeting technology have provided valuable insights into the physiological role of ATRAP. For instance, the systemic knockdown of ATRAP elevates blood pressure by ≈8 mm Hg. Although vascular reactivity to Ang II was preserved, it was observed that ATRAP knockout mice have elevated plasma and body volume. These results indicated that ATRAP absence increased sodium and water retention by the kidneys. Accordingly, Ang II binding to the renal cortex, a surrogate for AT\(_1\)R surface abundance, was increased in the mutant mice. This was accompanied by increased carbonic anhydrase responsiveness, a measure of proximal tubule function. Hence, it was concluded that ATRAP was a blood pressure modulator because of its negative effects on proximal tubular AT\(_1\)R function and, consequently, sodium and water balance.

In this issue of Hypertension, Wakui et al\(^5\) analyzed the responses to Ang II infusion of transgenic mice overexpressing ATRAP predominantly in the distal nephron. Detailed analysis of renal ATRAP expression in their mutant strain revealed that distal regions of the nephron, from the distal to connecting tubules, were the sites of highest expression for the transgenic protein. The most important observation by Wakui et al\(^5\) is that ATRAP overexpression in the distal nephron blunted the pressor response to Ang II. In their experiments, the basal systolic blood pressure of the transgenic mice and wild-type mice was similar. However, during Ang II infusion, the blood pressure increase was 20 mm Hg lower in the mutant mice when compared with equally treated wild-type controls. This is no small feat considering that AT\(_1\)Rs in extrarenal tissues were presumably not affected by the genetic manipulation.

To investigate the consequences of ATRAP overexpression on renal function during Ang II infusion, the authors performed balance studies and explored the expression of several key sodium transporters along the nephron. Specifically, they measured the abundance of the proximal tubule Na+/H\(^+\) exchanger 3, the loop of Henle Na\(^+\)/K\(^+\)/2Cl\(^-\) cotransporter 2, the distal tubule NaCl cotransporter, and the epithelial sodium channel. Their balance studies indicated that the transgenic mice responded to Ang II infusion with less sodium and water retention. Importantly, the enhanced natriuresis of the mutant mice was associated with a failure to increase NaCl cotransporter phosphorylation and the \(\alpha\) subunit of epithelial sodium channel, indirect indicators of transport activity. Thus, the segmental ATRAP overexpression was associated with suppression of corresponding transporters and the consequent enhanced natriuresis. Accordingly, the authors concluded ATRAP protects against the Ang II–induced hypertension because it prevents the induction of sodium transport in distal segments of the nephron. These observations are novel because, although it is known that Ang II induces the activity and expression of NaCl cotransporter and epithelial sodium channel,\(^6,7\) it was not known that ATRAP can modulate such an effect (Figure).

The study by Wakui et al\(^5\) contains several conundrums. First, there is a discrepancy with previous reports as to where ATRAP is expressed within the kidneys. Although Oppermann et al\(^4\) reported that ATRAP is mostly expressed in the proximal tubule, the studies from Umemura’s group suggest a more extensive distribution.\(^8,9\) According to these authors, endogenous ATRAP is expressed in glomeruli, vasculature, proximal, and distal segments of the nephron.
Moreover, in their analyses, the distal nephron is the site of highest expression. The reason for such difference is unknown, and it should be a topic for future investigation. The second issue deals with the lack of an ATRAP effect on baseline blood pressure of the transgenic mice. The authors suggest that ATRAP is only important in pathological conditions, but a mechanistic explanation for this is missing. The third issue is that the impact of overexpressing ATRAP on the actual activity of NaCl cotransporter or epithelial sodium channel (ie, in vivo response to specific blockers) was not evaluated. Fourth, if the transgene is overexpressed predominantly in the distal nephron, it follows that it is probably under the control of a region-specific enhancer. Hence, it is possible that the transgene insertion disrupted the corresponding locus and its physiological role. Finally and most importantly, the fact that a very high ATRAP expression (33-fold mRNA increase in distal tubules and 10-fold protein increases in total kidney homogenates) was necessary to reduce the response to Ang II suggests that ATRAP effects may be minor.

Regardless of the previous observations, the study by Wakui et al{1} emphasizes the tremendous impact of the kidneys in the hypertensive response to Ang II, while highlighting the potential of ATRAP as a negative modulator. The authors present interesting evidence for the tuning down effect of ATRAP on Ang II actions to increase sodium avidity in the nephron. These results add to the mounting evidence in favor of an important role of AT$_1$R$_s$ expressed in various segments of the nephron in long-term blood pressure regulation{9,10}. The presented evidence and future details on how ATRAP affects AT$_1$R signaling may lead to a more comprehensive understanding of Ang II actions to regulate renal function. Finally, the possible effect of ATRAP on other renal processes is also intriguing. For instance, it is increasingly recognized that inappropriate activation of the intrarenal RAS is an important cause of hypertension{10}. However, the effects of ATRAP on the local pool of Ang II are unknown.

Only time will tell whether there is any usefulness in the pharmacological manipulation of ATRAP expression. Ultimately, the recent discovery of ATRAP and the ongoing elucidation of its effects remind us that we should not assume to possess the complete picture of Ang II actions in renal physiology and hypertension.

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References

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