Does Angiotensin Receptor Recycling Regulate Blood Pressure?

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For more than a century, the renin–angiotensin system (RAS) has been recognized as an important part of the physiological system that regulates sodium and water homeostasis, renal function, and systemic blood pressure. The RAS consists of an enzyme/substrate cascade generating angiotensin II (Ang II). Initially the RAS was considered an endocrine system. By activating cellular receptors, circulating Ang II influences blood pressure and electrolyte balance through its effects on vascular tone, aldosterone secretion, renal sodium handling, and water intake. Nowadays, Ang II is thought to also act as a paracrine factor. Various tissues can generate Ang II, although not all RAS components are locally synthesized. Despite recently detected roles of other RAS components, such as prorenin, (pro)renin receptors, angiotensin IV, and angiotensin 1 to 7, the octapeptide Ang II is still considered the main actor of both the endocrine and paracrine RAS.

Circulating and tissue concentrations of Ang II may vary markedly. For the kidney, a model has been designed to describe the kinetics of Ang II production, distribution, and disposal. The model distinguishes between endocrine Ang II mainly acting in the glomerular tissue regions, whereas peritubular tissue regions are exposed to Ang II generated by the conversion of intrarenally produced angiotensin I. The model explains why the kidney is responsive to low levels of endocrine Ang II, despite its high paracrine Ang II content.

Ultimately, Ang II has its biological effects by activating signaling pathways through specific receptors. Various cellular Ang II receptor subtypes have been distinguished, with the Ang type 1 receptor (AT1R) and AT2 receptor as the most important ones. The G-protein–coupled AT1R mediates most of the known physiological and pathological actions of Ang II. Activation of the AT1R elicits a rapid response through various signaling mechanisms. However, the C-terminal cytoplasmatic domain of the AT1R not only binds a variety of signaling proteins. After agonist stimulation, the AT1R undergoes rapid desensitization and internalization. Several molecules are thought to play a role in these processes. Specifically associated with the AT1R are AT1R-associated protein (ATRAP), also known as AGTRAP, and Ang II receptor–associated protein (ARAP1). The molecular structure of ARAP1 is identical to that of angiopoietin-related protein 2 (ARP2), also known as ANGPTL2 (Note that the AT1R binding protein, ARAP1, should not be confused with ARAP1 present in genomic databases [www.ensembl.org]). ARAP1 then relates to Arf-GAP, Rho-GAP, Ankyrin repeat, and Pleckstrin homology domain containing protein 1, which again is identical with CENTD2, ie, centaurin-δ2, or STARD10, ie, Start domain containing 10. This ARAP1 protein is a PIP3-dependent Arf-GAP that regulates Arf-, Rho-, and Cdc42-dependent cell activities. Both intracellular AT1R-binding proteins seem to act differently. Although ATRAP enhances AT1R internalization and acts as modulator of Ang II signaling, ARAP1 seems to enhance recycling of the receptor to the plasma membrane.

Do these AT1R-associated proteins play a role in blood pressure regulation and hypertension? One way to learn more about the relevance of a candidate gene is to modify its expression. Genetic modification can be achieved by gene targeting techniques leading to reduced or increased gene expression. In addition, gene expression can be modified selectively, that is, developmentally or tissue specifically. The role of the RAS genes has been intensively investigated by these techniques. Collectively, these studies indicate that changing the expression of RAS components, including renin, angiotensinogen, angiotensin-converting enzyme, and AT1R, does influence blood pressure. Notwithstanding the overwhelming experimental evidence, linkage studies so far have provided no solid evidence that allelic variation in RAS constituents plays an important role in human essential hypertension or animal models of (genetic) hypertension.

In the middle of this uncertainty about a possible role of the various RAS components in human essential hypertension and animal models of genetic hypertension, a new player emerges. In the current issue of Hypertension, Guo et al describe the development of hypertension in transgenic mice overexpressing the AngII receptor-associated protein ARAP1 in the kidney. Using a construct containing rat-ARAP1 cDNA coupled to the kidney androgen-related promotor, transgenic mice were generated to produce proximal tubule-specific rat ARAP1 expression. Overexpression of rat ARAP1 in male mice resulted in an elevation of the systolic blood pressure (SBP) by 20 to 25 mm Hg (ie, 130 to 135 in transgenic compared with 110 mm Hg in nontransgenic mice). Female mice showed an increase in SBP only when treated with testosterone to activate the kidney androgen-related promotor. The increased SBP of ARAP1-transgenic mice could be normalized by angiotensin-converting enzyme inhibition (perindopril) or AT1R blockade (losartan), indicating a direct involvement of AngII in the SBP increase. Gene expression studies indicated that mRNA expression of the α-subunit of the epithelial sodium channel was significantly increased in the kidney of ARAP1-transgenic mice. Inhibition of epithelial sodium channel with amiloride reduced SBP to 120 mm Hg. Furthermore, the blood pressure (SBP) by 20 to 25 mm Hg (ie, 130 to 135 in transgenic compared with 110 mm Hg in nontransgenic mice). Female mice showed an increase in SBP only when treated with testosterone to activate the kidney androgen-related promotor. The increased SBP of ARAP1-transgenic mice could be normalized by angiotensin-converting enzyme inhibition (perindopril) or AT1R blockade (losartan), indicating a direct involvement of AngII in the SBP increase. Gene expression studies indicated that mRNA expression of the α-subunit of the epithelial sodium channel was significantly increased in the kidney of ARAP1-transgenic mice. Inhibition of epithelial sodium channel with amiloride reduced SBP to 120 mm Hg. Furthermore, the blood

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pressure of the ARAP1-transgenic mice was salt sensitive. A high-salt diet increased SBP from 130 to 145 mm Hg, whereas a low-salt diet reduced SBP from 130 to 112 mm Hg.

What mechanisms are involved in the blood pressure elevation? The observed findings are compatible with a kidney tubule–specific increased activation of AT1R by AngII to enhance renal salt retention. This increased activity could be the result of an enhanced recycling of the AT1R by the ARAP1-transgene. Unfortunately, no data were reported on differences in AT1R density between the transgenic mice and controls. On the other hand, it has not been unequivocally established that increased AT1R expression leads to hypertension. Although AT1R (type 1A)-deficient mice showed a reduced blood pressure,10 an increase in mice with 3 or 4 copies of the Agtr1a gene was present only in females but not in males.11

In the present study, kidney (proximal tubule)-specific ARAP1 overexpression was studied, raising the question about the effect of a generalized overexpression of ARAP1 or overexpression in other organs or cell types, such as the heart, the central nervous system, or vascular smooth muscle cells. Furthermore, it would be relevant to know the effects of altering the expression of AGTRAP, the second AT1R binding molecule, and of other molecules involved in the intracellular trafficking of AT1R, as well as other components of the paracrine RAS. A wide range of molecules are involved in directing newly synthesized molecules to their site of action; for example, receptors have to become incorporated into the plasma membrane. Additionally, after agonist activation, receptors are rapidly internalized by endocytosis via vesicular uptake mechanisms. Internalized receptors are then processed in endosomal compartments and either recycled back to the plasma membrane (recycling endosomes) or entered into compartments where the receptor molecule is degraded (lysosomes), again involving many molecules, most of them receptor specific, and eventually leading to recycling or degradation.12 Theoretically, alterations in each of them could influence receptor density at the cellular membrane and the physiological responsiveness to their respective agonists. Thus, the current findings by Guo et al.9 may open a new field of research focusing on the effects of genes that play a secondary role in the regulation of the RAS.

Disclosures

None.

References

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