(Pro)renin Receptor as a Therapeutic Target for the Treatment of Hypertension?

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It is now well established that the intrinsic brain renin–angiotensin system (RAS) is an integral constituent of the neural regulatory machinery on cardiovascular functions; hyperactivity of this system contributes to neural mechanisms of hypertension. Whereas all components of the RAS have been identified in the brain,1 exactly how the bioactive angiotensin II (Ang II) is synthesized from an extremely low level of renin in brain2 remained for decades a debate. This debate was resolved when the (pro)renin receptor (PRR), a specific receptor for renin and (pro)renin, was discovered in 2002.2 This discovery prompted a reevaluation of the brain RAS signaling in cardiovascular homeostasis.

PRR is a 350-amino acid protein with a single transmembrane domain.3 When bound to (pro)renin, PRR initiates a nonproteolytic activation of (pro)renin that mediates Ang II formation via the classical RAS pathways. In addition, binding of (pro)renin to PRR activates a RAS-independent intracellular signal transduction pathway that results in the production of reactive oxygen species,4 proinflammatory and profibrotic factors, as well as cellular proliferation.5

Accumulating evidence supports an important role for brain PRR in local generation of Ang II. Incubation of cultured neuronal cells with human (pro)renin and angiotensinogen results in augmented generation of Ang I and Ang II.6 In human neuroblastoma cells overexpressed with human PRR, (pro)renin mediates Ang II formation in a dose-dependent and captopril-reversible manner, confirming the derivation of Ang II from Ang I.4 Conversely, brain-targeted PRR knockdown using PRR short hairpin RNA significantly decreases Ang II levels in the hypothalamus of human renin and angiotensinogen double transgenic mice.7 In addition, both baseline and (pro)renin-induced increase in Ang II levels in the hypothalamus and brain stem are significantly decreased in neuron-specific renin-induced increase in Ang II levels in the hypothalamus and brain stem are significantly decreased in neuron-specific renin–angiotensinogen double transgenic mice.8

Accumulating evidence also supports an important role for brain PRR in neural regulation of blood pressure. Both PRR mRNA and protein are distributed in key brain regions that are involved in the regulation of blood pressure and body fluid homeostasis, with a significant increase in their expressions under hypertensive conditions.7,8 A definitive role for brain PRR in neural control of blood pressure was established when gene knockdown of brain PRR attenuates Ang II–dependent hypertension,7 retards age-dependent increase in blood pressure in spontaneously hypertensive rats,6 and prevents the development of salt-sensitive hypertension,3

Despite gene knockdown studies established a role for PRR in neural control of blood pressure, whether this class of receptors presents itself as a promising therapeutic target in the treatment of hypertension remains elusive. This is, in part, because of the lack of a reliable and selective PRR antagonist. Ichihara et al9 developed in 2004 a PPR-inhibiting peptide called handle region peptide (HRP). This peptide mimics amino acid residues 10 to 19 of the (pro)renin prosegment and functions as a decoy peptide. Long-term administration of HRP to salt-fed spontaneously hypertensive rats inactivates the RAS in cardiac tissues and attenuates the development of cardiac fibrosis and hypertrophy.9 In a sheep model of heart failure, HRP produces sustained reduction in blood pressure in association with attenuation of circulating Ang II and improvement of renal function.10 However, HRP exhibits no direct inhibitory effect on the binding of (pro)renin to the PRR,7 and the antagonistic effect of HRP on PRR has not been consistently duplicated under other pathological conditions.11,12 Several recent studies even suggested a partial agonistic effect of HRP on the PRR,13,14 casting doubt on the potential of HRP as a treatment for hypertension.

In this issue, Li et al15 reported the design and development of a new PRR inhibitory peptide, PRO20, which corresponds to the first 20 amino acid residues of the (pro)renin prosegment, directly inhibits the binding of (pro)renin to PRR. They found that this peptide not only binds to PRR in mouse and human brain tissues, its binding to PRR is blocked by coinubation with excessive (pro)renin and is diminished in brain-specific PRR-knockout mice. Furthermore, these authors demonstrated that PRO20 reduces (pro)renin-induced and Ang II–dependent calcium influx in a human neuronal cell line (SH-SY5Y) and attenuates Ang II–dependent hypertension induced by intracerebroventricular infusion of (pro)renin or oral treatment with deoxycorticosterone acetate–salt, and in renin–angiotensinogen double transgenic mice.

These exciting results reinforce the proposed role of (pro)renin and PRR in the formation of Ang II in the brain and in hypertension associated with the elevated brain RAS. Nevertheless, they also raise several important issues that will ultimately determine the applicability of PRO20 as a potential treatment of RAS-associated hypertension. First, PRR is present on the cell membrane as well as in the cytoplasm.4 It is unclear as to how a peptide with 20 amino acids in length might cross the cell membrane to block the binding of (pro)
renin to intracellular PRR? How inhibition by PRO20 of the binding of (pro)renin to the PRR on the cell membrane might affect Ang II formation in the cytoplasm also remains to be demonstrated? In addition, whereas the study by Li et al13 focused on neuronal PRR, the contributions of PRR in glial cells to the inhibitory effects of PRO20 on generation of Ang II also await further clarification.

Second, the effect of PRO20 on Ang II formation and RAS function in tissues where renin activity is high has to be resolved. Li et al13 reported that subcutaneous administration of PRO20 exerts no protective effect on the development of deoxycorticosterone acetate–salt hypertension. Based on these findings, they argued that Ang II specifically decreases Ang II formation in brain and that brain PRR plays an important role in the pathophysiology of deoxycorticosterone acetate–salt hypertension. However, these same observations raise the issue of whether the effectiveness of PRO20 as a PRR inhibitor is restricted to tissues where renin activity is low. This is a valid concern because the tissue level of (pro)renin and renin is known to increase under several cardiovascular disease conditions.19 A reasonable question is therefore whether PRO20 will be as effective as, if not better than, renin inhibitor, angiotensin-converting enzyme inhibitor, or angiotensin receptor blockers in blunting RAS overactivation under those pathological conditions.

Third, the inability of PRO20 to prevent the development of neurogenic hypertension after its subcutaneous application also points to the need for structural modification of the peptide to cross the blood–brain barrier, if the site of action for this antagonist is the central nervous system. Finally, binding of (pro)renin to PRR mediates Ang II–independent activation of mitogen-activated protein kinases and production of reactive oxygen species in neuronal cells.4 Given a pivotal role of brain oxidative stress in the pathogenesis of neurogenic hypertension, would this new compound promote antihypertension via alleviation of PRR-dependent brain oxidative stress?

A decade after the report of the first PRR antagonist, it is exciting to the RAS field that a new peptide that possesses the pharmacological property to block the binding of (pro)renin to PRR in brain tissue is developed. Although further studies are required to validate the pharmacological actions of PRO20 and to address the issues posted above, the article by Li et al13 is timely in moving forward the concept of targeting PRR as a new therapeutic strategy for the treatment of hypertension associated with brain RAS hyperactivity.

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