Ang II-independent prorenin/(pro)renin receptor signaling pathways in the central nervous system

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The renin-angiotensin system (RAS) is important in the physiological and pathophysiological regulation of blood pressure (BP) and cardiovascular function. The (pro)renin receptor (PRR, also called ATP6AP2), is one of the newer member of the RAS(10, 20). Emerging evidence indicates that the PRR not only mediates formation of Ang II, the key bioactive peptide of the RAS, in various tissues and organs including the kidney(6), macula(26) and the brain(14), by enhancing renin activity or activating prorenin, it also mediates Ang II-independent signaling. This latter signal transduction pathway involves activation of the mitogen-activated protein kinases (MAPKs) p38 and ERK (extracellular signal-regulated kinase, p40/42) and downstream targets, such as heat shock protein 27 (HSP27)(9, 25), tumor growth factor (TGF)-β, c-Jun N-terminal kinase (JNK)(11) and NADPH oxidase (22), enhancing the production of pro-inflammatory cytokines(27, 35) and Wnt-mediated promyelocytic zinc finger protein (PLZF) expression(3, 4). Importantly, Ang II-dependent and -independent PRR signaling pathways have been linked to the pathogenesis of neurogenic hypertension, diabetic nephropathy and cardiomyopathy, glomerulosclerosis, and choroidal neovascularization.

Although the PRR was only identified as a receptor for renin and prorenin 14 years ago(20), its history has been turbulent. An important obstacle for research in the PRR field has been the lack of effective knockout animal models and related tools. For example, global knockout of the PRR in mice(28) or zebrafish(1) is lethal. Moreover, deletion of the PRR specifically in various tissues, including cardiac myocytes(12), podocytes(21, 24), and the ureteric bud and medullary collecting duct cells(29), results in developmental defects in the respective organs and the death of mice at 3–4 weeks of age. These studies illustrated the importance of the PRR in embryonic development, demonstrating its role as an accessory subunit for vacuolar-type H+-ATPase (V-ATPase) and in Wnt signaling pathways. This early research in the field also raised important questions(19): why does the PRR bind renin and prorenin, and is this interaction physiologically or pathologically relevant? Better tissue-specific PRR-knockout (KO) models or antagonists capable of blocking (pro)renin binding to the PRR without interfering with V-ATPase activity and Wnt signaling are the key to resolving these unanswered questions.

Fortunately, several recently developed models and tools allow us to bypass the embryonic developmental phase, facilitating the investigation of the physiological and pathophysiological roles of the PRR, especially in hypertension.
and cardiovascular end-organ damage. These tools include the PRR peptide antagonists HRP (handle region peptide) (8, 31) and PRO20 (15), as well as neuron-specific (14) and nephron-specific PRR-KO mouse models (23). Several groups have reported that blocking prorenin activation with HRP exerts beneficial effects in PRR-related diseases models (6, 7, 9, 30, 32). However, the antagonistic effect of HRP on the PRR has not been consistently replicated (5, 16, 18). Two research groups even reported a partial agonistic effect of HRP on the PRR (2, 33, 34), casting doubt on the efficacy of this decoy peptide. The newly reported PRR antagonist PRO20 represents an encouraging development because of its dual effects, blocking both Ang II formation and Ang II-independent signaling through ERK activation (15). Testing this new PRR antagonist in other organ systems is warranted. Cell type-specific PRR-KO models have similarly proven their worth. Notably, neuron-specific PRR-KO mice survive and are resistant to the development of hypertension induced by DOCA-salt. This latter observation supports the critical importance of the PRR in mediating central nervous system (CNS) Ang II formation and the pathogenesis of hypertension. Very recently, a second nephron-specific PRR-KO mouse model was reported (23). These mice, which exhibit normal survival to about 1 year of age with no histological defects, allow investigation of the PRR in renal function. Thus, in addition to early support for the importance of the PRR in development, clear evidence provided by more recently developed experimental tools has demonstrated essential roles for the PRR in physiology and pathophysiology.

PRR-mediated Ang II formation in the CNS has been implicated as a major contributor to the regulation of BP and neurogenic hypertension (13, 14). Notably, however, the importance of Ang II-independent, direct PRR signaling pathways in the CNS in the regulation of cardiovascular function has remained undefined. The study by Huber (Ref) and colleagues from the Shan laboratory reported in this issue of the *American Journal of Physiology Heart and Circulatory Physiology* sheds new light on the role of Ang II-independent, direct PRR signaling pathways in sympathetic nerve activity in anesthetized rats. To separate direct PRR signaling events from Ang II-mediated pathways in regulating sympathetic activity in rats, Huber et al. made elegant use of human prorenin to activate the rat PRR in the paraventricular nucleus (PVN) of the hypothalamus, taking advantage of the fact that human prorenin has minimal ability to cleave rodent angiotensinogen (17). They found that direct PRR signaling in the PVN contributes to sympathoexcitation through a pathway that involves reactive oxygen species (ROS) signaling. Using a hypothalamic neuron culture model, this group also found that activation of the PRR by prorenin is associated with AP1 (activator protein 1)-mediated activation of inducible nitric oxide synthase (iNOS). On the basis of these observations, they proposed that AP1-iNOS signaling might contribute to elevated sympathetic activity in vivo. Notable in this context, increased sympathetic outflow has been implicated in the etiology of hypertension. Whether iNOS is involved in regulating PRR-mediated sympathetic nerve activity and whether this contributes to the development of hypertension will require further study. Because the study by Huber et al. was
performed in normotensive, anesthetized rats, further investigation will also be required to assess the role of direct PRR signaling pathway in conscious hypertensive animal models and, possibly, hypertensive patients.

The studies undertaken by Huber and colleagues advance our understanding of the role of direct PRR signaling in the PVN in the regulation of sympathetic nerve activity in anesthetized, normotensive rats, showing that this direct PRR signaling pathway may act through ROS signaling to promote sympathetic tone, and thereby contribute to hypertension development. Future studies should dissect the contribution of PRR-mediated signaling pathways—both Ang II-dependent and -independent—in different forms of hypertension and other cardiovascular diseases involving autonomic disorders. With the development of effective tools for studying the PRR, described above, such studies are now possible.

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**References:**


