Is (Pro)Renin Receptor a Multifunctional Receptor?

Qiuhong Li, Mohan K. Raizada

The existence of various components of the renin-angiotensin system in the eye has been known for more than a decade, and the importance of this system in ocular pathophysiology is a subject of active investigation. It has long been recognized that prorenin, an inactive precursor of renin, is elevated in the ocular fluids of patients with diabetic retinopathy. However, the pathophysiological implications of these elevated levels remained a mystery until the discovery of a specific receptor for renin and prorenin: the (pro)renin receptor [(P)RR].

(P)RR is a 350–amino acid transmembrane protein which has been proposed to function by two distinct mechanisms: (1) by binding to (pro)renin, (P)RR activates renin’s enzymatic activity inherent in prorenin, leading to the generation of angiotensin II by a traditional renin-angiotensin system pathway at the cell/tissue level; and (2) (pro)renin binding to (P)RR initiates a cascade of signaling events that are associated with profibrotic and proliferative actions, independent of angiotensin II.

Although the action of (P)RR in the generation of Ang II is documented, its coupling to signaling pathways leading to vasodeleterious effects remains to be fully elucidated. This is, in part, due to lack of a reliable and selective (P)RR antagonist. A peptide segment corresponding to amino acids 10 to 19 of the prorenin segment, called handle region peptide (HRP), has gained significant interest as a (P)RR antagonist. HRP has been shown to inhibit prorenin binding to (P)RR, and thus nonproteolytic activation, and to be capable of preventing diabetic nephropathy and cardiac fibrosis. In the eye, HRP has also been shown to be beneficial in preventing ocular inflammation induced by endotoxin and diabetes, as well as pathological angiogenesis. However, the potential of HRP as a specific antagonist of (P)RR for treating these pathological conditions has met with skepticism, because several studies have failed to reproduce the inhibitory effects of HRP either in vivo or in vitro.

It is in this context that the study of Wilkinson-Berka et al in this issue of Hypertension is relevant. They present exciting observations indicating that systemic administration of HRP reduces angiogenesis in developing rodent retina, diminishes pathological angiogenesis, and reduces leukostasis and expression of inflammatory markers in rodents with oxygen-induced retinopathy. Thus, HRP exhibits a protective effect in retinal vasculature similar to the angiotensin II type 1 receptor blocker valsartan.

These findings confirm previous reports by Satofuka et al. However, in contrast to previous reports on (P)RR’s cellular localization, in which it was detected mainly in the retinal vessels, Wilkinson-Berka et al found more abundant expression of (P)RR in retina neuro-glia. Moreover, they also revealed that HRP treatment in normal animals resulted in reduced electroretinogram responses. Because treatment with valsartan did not have any effect on electroretinogram, the detrimental effect of HRP on retinal function is likely mediated by an angiotensin II–independent mechanism, presumably via (P)RR. The cellular localization of (P)RR in retina neuro-glia reported in this study is consistent with its involvement. Also consistent with this interpretation is the observation that elevated levels of (P)RR mRNA and phosphorylated extracellular-signal–related protein kinase (ERK) 1/2 immunolabeling in oxygen-induced retinopathy are reduced with HRP treatment. However, HRP was shown to increase (P)RR mRNA and phosphorylated ERK1/2 immunolabeling in the normal retina, an effect opposite that seen in the oxygen-induced retinopathy retina. These findings demonstrate the involvement of (P)RR in retinal pathophysiology and suggest that (P)RR may be multifunctional, exerting distinct actions with opposing effects in a cell-type specific manner.

This study raises important questions that will determine the future direction in establishing the role of (P)RR and HRP. First, how does HRP exert its actions in the retina? The observation that no HRP is detectable in the circulation following continuous subcutaneous administration of the peptide, which contradicts a previous study, may indicate a methodological issue, as suggested in this study. However, a selective increase in the local HRP cannot be ruled out; if this is the case, the transport of HRP across the blood-retina barrier needs to be addressed. Furthermore, the possibility of a compromised blood-retina barrier under pathological conditions, such as diabetes, endotoxin presence, and pathological angiogenesis, would enable circulating HRP to accumulate in retinal tissue at concentrations appropriate for its actions.

Second, do the opposing effects of HRP, ie, beneficial in retinal vasculature but detrimental in retina neuro-glia, involve (P)RR? The observation that reduced electroretinogram following HRP treatment correlates with increased (P)RR mRNA and increased phosphorylated ERK1/2 immunostaining in the normal retina, but with reduced (P)RR mRNA and ERK1/2 immunolabeling in retinas with oxygen-induced retinopathy, supports the involvement of (P)RR. However, direct evidence that these effects are indeed mediated through

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(P)RR is needed. Furthermore, the possibility that HRP may act as a partial agonist to the (P)RR should be considered because it also elicits weak activation of ERK1/2 in the absence of prorenin in human vascular smooth muscle cells. The dual effects of HRP in the retina, ie, reduced (P)RR activation under pathological conditions but increased activation under normal conditions, may be explained by the fact that it may act as an antagonist to block (P)RR activation when the prorenin level is high under pathological conditions, but as an agonist to activate (P)RR when the prorenin level is low, as in normal physiological conditions.

Third, are renin and prorenin the only ligands for (P)RR? There is evidence suggesting that (P)RR may act as multifunctional receptor. Recently, Cruciat et al14 demonstrated that (P)RR, as a component of the Wnt receptor complex, functions as an adaptor between Wnt receptors and vacuolar H+-ATPase (V-ATPase) complex. Although this report showed that the requirement of (P)RR in Wnt signaling activation is renin-independent, the possible effect of HRP was not investigated in this experimental paradigm. Wnt signaling is one of the fundamental mechanisms that control cell proliferation, polarity, and fate determination during embryonic development and tissue homeostasis. Mutations in this pathway are linked to diverse human diseases.15 Thus, the association of (P)RR with this pathway suggests that the function of (P)RR may be more complex than was previously suggested.

The C-terminal fragment of (P)RR, composed of the transmembrane and cytoplasmic domain of (P)RR, presumably generated by furin cleavage of the full-length protein, was previously reported to be a protein associated with V-ATPase.16 V-ATPase plays a vital role in many physiological and biochemical processes by control of the cellular and intracellular vesicle pH. A functional link between (P)RR and V-ATPase activity was recently demonstrated by Advani et al,17 who showed that (pro)renin can increase V-ATPase activity via activation of (P)RR. Whether or not this mechanism exists in other tissues with a local renin-angiotensin system, such as the eye, and whether it is angiotensin II dependent or independent remains to be determined. Furthermore, if (P)RR function involves Wnt/β-catenin signaling and/or V-ATPase-associated functions, does HRP have any effect on these pathways other than as a competitive antagonist for (pro)renin binding? Is it possible that the opposing effects of HRP on retinal vascular and neuro-glia functions reported in this study are due to its effect on these pathways independent of the (pro)renin-(P)RR pathway? Resolving these issues would be critical before HRP and (P)RR could be considered as a target for therapeutic interventions in retinal, renal, central nervous system, and other cardiovascular pathophysiology.

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