Prorenin
Back Into the Arena

A.H. Jan Danser

Prorenin, the precursor of renin, exists in circulating blood at concentrations that are ≈5 to 10× higher than those of renin. For many years, prorenin was considered to be an inactive form of renin with no physiological role. Then, in the mid-80s of the last century, Luetscher et al reported that the levels of circulating prorenin (but not renin) are increased in diabetic subjects. Subsequent studies revealed that these high levels correlated with the presence of microvascular complications, and it was proposed that prorenin might be used to predict the occurrence of microalbuminuria. Simultaneously, high prorenin levels were observed in pregnant women, and evidence was obtained for the local synthesis of prorenin at extrarenal tissue sites such as the ovary and eye. Until today, however, the exact function of prorenin remains unknown.

An attractive concept is that in tissues not synthesizing renin locally, circulating prorenin, after its local conversion to renin, contributes to angiotensin (Ang) generation. This would not only provide a role for prorenin in vivo, but also explain why tissues, in contrast with plasma, contain predominantly renin. Studies in transgenic animals support this idea. Véniant et al described that transgenic rats expressing prorenin exclusively in the liver (resulting in a 400-fold rise in plasma prorenin) display cardiac hypertrophy and vascular damage in the absence of hypertension. Prescott et al detected increased cardiac Ang I levels in mice overexpressing human prorenin in the liver and human angiotensinogen in the heart.

The question then arises how tissues sequester and activate circulating prorenin. Sequestration may involve diffusion into the interstitial fluid and/or binding to a receptor. Activation can occur in 2 ways (Figure 1): the prosegment is proteolytically cleaved, or the prosegment unfolds from the enzymatic cleft, thus allowing intact prorenin to become catalytically active (nonproteolytic activation). The latter process is pH-dependent and might be enhanced at tissue sites (eg, in the extracellular matrix). A nonrenal prorenin-cleaving enzyme has not yet been demonstrated.

Two recent studies have provided the missing pieces of the above puzzle. First, Nguyen et al identified a renin receptor that bound renin and prorenin equally well. Interestingly, prorenin, when bound to this receptor, displayed enzymatic activity although there was no evidence for proteolytic cleavage of the prosegment. Thus, receptor binding per se may have resulted in a conformational change of the prorenin molecule, thereby enabling it to become catalytically active (Figure 2). Second, investigators in Japan developed a decoy peptide corresponding with the handle region in the prorenin prosegment (handle region peptide [HRP]). This region supposedly interacts with a receptor, thereby enabling prorenin to undergo nonproteolytic activation. HRP blocks this in a competitive manner. Consequently, any Ang I generation that is attributable to receptor-bound, nonproteolytically activated prorenin will be suppressed. Indeed, HRP reduced the renal content of Ang I and II and fully prevented the development of diabetic nephropathy in streptozotocin-induced diabetic rats. Surprisingly, HRP did not affect the plasma levels of Ang I and II in diabetic rats, nor the renal tissue Ang I and II levels in control rats. To explain the latter, the authors propose that the prorenin–renin ratio is altered in the diabetic rat kidney (for instance, attributed to a reduction in the prorenin-renin converting enzyme cathepsin B), thereby allowing more prorenin to bind to the receptor. The receptor identity was not investigated in this study.

In the current issue of Hypertension, Ichihara et al now bring the renin receptor described by Nguyen et al and HRP together. The authors treated 4-week-old stroke-prone spontaneously hypertensive rats (SHRsp) with HRP, and observed a reduced cardiac Ang content and fibrosis after 8 weeks of treatment, with no change in blood pressure or the levels of circulating Ang. HRP exerted no effect in Wistar-Kyoto (WKY) controls. Interestingly, at 8 weeks of age, when no organ damage was present in SHRsp, their cardiac renin receptor mRNA levels were ≈3× higher than in WKY controls. Since this difference disappeared at age 12 weeks, the authors propose that the interaction between prorenin and its receptor contributes to the development, but not the progression, of cardiac damage in the SHRsp.

To support the idea that HRP exerted its effects in SHRsp by blocking nonproteolytic activation of prorenin, Ichihara et al provide immunohistochemical data specific for the prosegment and the active site of renin. HRP did not alter prosegment immunoreactivity, and reduced active site immunoreactivity to WKY levels. The reduction in active site immunoreactivity paralleled the reduction in cardiac Ang content. Unfortunately, the study does not reveal whether the active site immunoreactivity represents nonproteolytically activated prorenin or renin, nor do the immunohistochemical studies provide a quantitative comparison between prosegment immunoreactivity and active site immunoreactivity. Thus, an

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alternative, although less likely, explanation of the data is that
HRP has reduced the uptake of renin. Future studies, aimed at
precisely quantifying the renin and prorenin content of the
heart (eg, by enzyme-kinetic assay), should solve this issue.
The total cardiac renin content reported by the authors
represents the sum of renin and prorenin and thus cannot be
used for this purpose. Such future studies should also inves-
tigate the mechanism of action of HRP: does it block binding,
or does it prevent the activation after binding? Given the fact
that the receptor recognizes both renin and prorenin, the
prosegment is not necessarily involved in the binding
process.6

Several issues remain unclear. First, why does HRP exert
no effect in WKY rats? Although the circulating renin and
prorenin levels in WKY rats are twice as low as in SHRsp,
their plasma prorenin–renin ratio equals that in SHRsp, and
thus some prorenin should bind to the receptor. The cardiac
renin receptor mRNA expression levels at the time of tissue
Ang measurement in both strains are identical, and yet HRP
only reduces the cardiac Ang content in SHRsp. Since high
pressure blocks prorenin-renin conversion in juxtaglomerular
cells,8 the authors speculate that the high pressure in SHRsp
has blocked prorenin-renin conversion in the heart. Conse-
sequently, more prorenin will bind to the receptor and contrib-
tute to cardiac Ang production. However, cardiac renin, in
contrast to renal renin, is largely plasma-derived,3 and it is not
known whether the same prorenin-renin conversion condi-
tions occur in both organs (ie, whether the heart responds the
same to high pressure as the kidney).

Second, why does HRP not lower plasma Ang I and II? It is
widely accepted that a major part of circulating Ang originates at
tissue sites (eg, the vessel wall, where renin receptors are
located on vascular smooth muscle cells6). There is no reason
to assume that the effect of HRP is limited to the heart, and
thus the peptide will also lower Ang levels in other tissues,
including the kidney. This should affect the Ang release from
tissue sites and, subsequently, renin release from the kidney
as well as blood pressure. Future studies investigating both
tissue Ang levels and Ang release from tissue sites during
HRP treatment might solve this issue.

Finally, based on the unaltered cardiac prosegment immu-
noreactivity during HRP treatment the authors conclude that
the majority of cardiac prorenin is not bound to the receptor.
Thus, unless HRP interferes only with the activation process
(and not binding), there may be more than one renin receptor.
Indeed, minimally one other candidate has been proposed: the
mannose 6-phosphate (M6P) receptor,9 which recognizes and
internalizes both renin and prorenin.

Summarizing, Ichihara et al8 have generated provocative
data using an elegant in vivo approach. This study puts
prorenin back on the map, finally providing a physiological role for this inactive renin precursor. This is of particular importance now that renin inhibition will soon become a clinical reality. Such inhibition is expectedly to block Ang generation by renin as well as nonproteolytically activated prorenin.

References
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