Nitric Oxide Can Directly Mediate Renin Cell Recruitment

Pontus B. Persson

In this issue of Hypertension, Neubauer et al fit missing pieces into the puzzle of how renin production is controlled, when the demand for renin is high. Our understanding of the acute release of renin is much more complete than what we know about the long-term adaptations to stimuli of renin. Our scarce knowledge of the mechanisms mediating long-term renin stimulation is remarkable with regard to the clinical importance of renin. Hypertension, fluid and electrolyte homeostasis, as well as inflammation and fibrosis all may involve chronic renin stimulation.2

More than 400 million years ago, renin first appeared in organisms,3 and renin is often seen as the first hormone discovered. Shortly before the 20th century, Tigerstedt and Bergman showed that kidney extracts can elevate blood pressure, when intravenously infused.4 Today, we recognize that the actions of renin go far beyond that of controlling blood pressure, and we have detailed insight into how renin is released into the circulation.5 The major stimuli of short-term renin release are blood pressure decreases, β1-adrenergic stimulation, and low salt, whereas the latter may require prostaglandin formation.6 When stimuli for renin release persist over a longer period, 2 major distinct adaptations take place. The first is an induction of renin expression in the juxtaglomerular region. The second mechanism is metaplastic transformation of smooth muscle cells of preglo merular vessels. Metanephric mesenchymal cells are the origin of vascular smooth muscle cells and of renin precursor cells.7 Interestingly, these renin precursor cells give rise to juxtaglomerular cells (JGCs) during ontogeny, and also to a subset of arteriolar smooth muscle cells. Of particular importance in the context of the study by Neubauer et al is that smooth muscle cells originating from the renin precursors are capable of undergoing metaplasia to renin-producing cells.7

Increased renin gene expression along with hypertrophy of JGCs is found during long-term, enhanced renin release. In addition to the hypertrophy of juxtaglomerular cells, the abovementioned metaplastic transformation of preglo merular vascular smooth muscle cells into renin-producing cells can take place (Figure). How this is controlled remains largely unclear. It is here where Neubauer et al add to our understanding. Their work targets a novel role of endothelium-derived nitric oxide (NO), via its second messenger cGMP, on, what they term, renin recruitment in the afferent arteriole. In various different mouse models, low-salt diet was combined with angiotensin-converting enzyme inhibition to dramatically stimulate renin release, as well as to stimulate kidney renin mRNA expression. In consequence, renin-producing cell recruitment took place in the juxtaglomerular apparatus, as well as upstream along the renal afferent arterioles.

When the NO system was inhibited unspecifically by L-NAME, (L-Nitro-Arginine Methyl Ester), or specifically by targeted inhibition of NO using eNOS−/− (endothelial NOS) mice, the metaplastic transformation of upstream arteriolar progenitor cells into renin-producing cells no longer took place. However, inhibiting the NO system failed to fully eliminate hypertrophy of the juxtaglomerular cells, and only blunt ed the recruitment of renin-producing cells in the vicinity of the glomerular pole.

Obviously, a relevant role of endothelium-derived NO for renin cell recruitment can be assumed. To narrow down the signaling pathways along which NO could exert its effect on renin expression, mice lacking NO-sensitive guanylate cyclase (NO-GC) in renin-expressing cells and their descendents (via Cre-lox recombination system [Ren1d-Cre−/−NO-GC−/− mice]) were investigated. Again, no recruitment of renin cells along afferent arterioles was found in these mice, after the renin stimulus of low-salt diet in combination with enalapril. However, juxtaglomerular hypertrophy developed similarly as in wild-type mice. This finding in mice lacking NO-GC in renin-expressing cells underscores the importance of the NO-GC for upstream recruitment of vascular smooth muscle cells.

How does this fit into our current understanding that activation of the cAMP signaling pathway is crucial for transforming vascular smooth muscle cells? The answer to this question may be analogous to the regulation of renin secretion. Various groups have shown that NO-derived cGMP inhibits cAMP via phosphodiesterase-3 (for review, see Kim et al8). An increase in cAMP levels is a fundamental mechanism for renin secretion and renin gene transcription.5 As made clear by the article of Neubauer et al, a similar interaction may take place to stimulate renin recruitment.

The highlighted article by Neubauer et al provides conclusive evidence that it is endothelial NO that is important for renin cell recruitment. The recruitment of renin-producing cells may have, by far, more important clinical implications than the stimulation of short-term renin release. Naturally, one must keep in mind that it is difficult to prove a direct causal effect of NO on renin cell recruitment, as NO may also be a permissive effect. What is more, various maneuvers to modify NO activity often perturb blood pressure, perhaps the most potent stimulus of renin.4–10 Therefore, changes in renal hemodynamics constitute a major confounding factor, which can only be ruled out indirectly.
Considering the several disorders that constitute NO production by the endothelium, and taking into regard the manifold possibilities to attenuate endothelial NO production pharmacologically, these are very important findings. The understanding of renin cell recruitment is now taking place!

Disclosures

None.

References

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