Molecular Mechanisms That Control Renin Secretion

It has long been appreciated that the plasma concentration of renin may vary over several orders of magnitude in response to some combination of changes in sodium intake, renal perfusion pressure, angiotensin II concentration, and adrenergic stimulation. There has been little insight, however, into the mechanism whereby these dramatic changes take place. The principal source of plasma renin is the kidney, where it is synthesized in the juxtaglomerular cells of the afferent arteriole and then apparently stored in intracellular granules. Histological observations indicate that prolonged stimulation of renin secretion, such as by sodium deprivation, increases the number of juxtaglomerular cell granules, while prolonged depression, such as by administration of excessive sodium, decreases granule numbers.

Do the same stimuli that increase renin release also promote storage to the same degree or are there conditions in which stimulation preferentially results in secretion with depletion of granular renin content? Morimoto et al. were able to isolate granules and measure their renin content. When rats were subjected to a low sodium intake over a 4-week period, a 12.4-fold increase in plasma renin activity was observed that was associated with only a 2.6-fold increase in granular renin activity. Thus long-term stimulation clearly resulted in a parallel directional change in secretion and storage, yet the former seemed to be favored quantitatively over the latter. Precise tools for dissecting mechanisms governing biosynthesis and secretion were not as yet available to these investigators.

What are the potential sites for control of renin secretion? As with all proteins, renin synthesis begins with RNA transcription. If transcriptional regulation were an important control point, it would be of exceptional interest. The identification of an inducer that regulates gene expression could provide the basis for exploring yet another avenue of intervention in the renin-angiotensin system. As with most secreted proteins, the first product of RNA translation bears a signal peptide at its amino terminus (prepro-renin) and is extremely short-lived, as evidenced by pulse-labeling studies. It is unlikely that the removal of the signal peptide by the endoplasmic reticulum to yield prorenin is a control step. At this point, there is little direct evidence as to what happens next in the juxtaglomerular cell.

Most observations have been made on tissues that were easier to study, such as the mouse submandibular gland or renin-secreting tumors, neither of which may accurately reflect events as they occur in the kidney. In the submandibular gland, prorenin is not secreted but processed to one-chain renin by removal of an amino-terminal peptide and then to two-chain renin by an internal proteolytic cleavage. Pratt et al. suggested that the two types of mature renin have different specific activities and may be secreted by different pathways, constitutive and regulated. The relationship between apparent plasma renin concentration and intracellular messenger RNA levels may vary with the pathway of secretion and the relative proportion of one- or two-chain renin released. Galen et al., on the other hand, have shown that both renin and prorenin are secreted by a renin-producing tumor, the latter by an independent pathway. Thus the potential sites for the posttranscriptional control of renin secretion include regulation of translation, prorenin-renin and renin maturation, glycosylation, release from storage granules, and selective transport of one or another species across the cell membrane.

While there is still a great deal to be learned, a report by Nakamura et al. in this issue of Hypertension casts considerable light on some of these questions. Utilizing a
complementary DNA probe from the mouse submaxillary gland, these investigators measured changes in renin-specific messenger RNA content of rat kidneys after prolonged marked stimulation of renin secretion as well as short-term inhibition of secretion in the stimulated animals. A 46-fold increase of plasma renin concentration was associated with only a 1.5-fold increase in intrarenal renin concentration and a 2.8-fold increase in the concentration of renin-specific messenger RNA. There clearly seems to be appreciable transcriptional control, and it is possible that this might, over time, account for all the observed rise in plasma renin concentration. The authors do not provide kinetic information that would allow us to evaluate whether a threefold rise in the rate of synthesis could support a 46-fold rise in plasma concentration (clearance rates of renin are, of course, an important determinant). Based on other information in the literature, however, the very rapid and marked changes in plasma renin concentration that can be observed in response to acute stimulation suggest that overall changes in the rate of synthesis greater than threefold are to be expected. This seems to point to additional posttranscriptional control.

In support of regulation at a later stage of biosynthesis is the observation that plasma renin concentrations fall within an hour of angiotensin II infusion without change in messenger RNA concentration and without an accumulation of active renin within the kidney. This excludes transcription as the sole control point and diminishes the likelihood that membrane transport rate governs secretion, since it is likely that inhibition at this step would cause an increase in the intracellular concentration of active renin. The results of this study, however, do not distinguish between translation and prorenin processing. This differentiation could be effected by comparing the concentrations of prorenin to renin before and after inhibition of renin secretion. Indeed, antibodies that recognize the human prorenin segment are currently available. If these antibodies cross-react with rat prorenin, a direct measurement of rat prorenin may be possible for these experiments. If prorenin did not accumulate, it would imply, but not prove, that translation rate regulates renin synthesis.

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