Modulation of renin release from juxtaglomerular cells is critical for appropriate adjustments of the cardiovascular and renal systems to internal and external stresses, and dysregulation of renin release participates in the pathophysiology of hypertension, vascular disease, heart failure, and chronic renal disease. This justifies investments in research to elucidate the fundamental mechanisms regulating renin release. These investments have yielded, and continue to yield, high returns, as exemplified by Schweda et al1 in this issue of Hypertension, showing that A1 receptors mediate high perfusion pressure–induced inhibition of renin release, whereas prostaglandins (PGs) participate in low perfusion pressure–mediated stimulation of renin release. The purpose of this commentary is to discuss how Schweda et al’s findings confirm and challenge present-day models of renin release.

As comprehensively reviewed by Davis and Freeman2 and Keeton and Campbell,3 investigators recognized early on that these three systems, namely the sympathetic nervous system, the macula densa apparatus, and the intrarenal baroreceptor, are the primary physiological mechanisms regulating renin release from juxtaglomerular cells. A key development was the recognition that the two most important biochemical accelerators of renin release are catecholamines (mediating sympathetically induced renin release) and PGI2 (mediating macula densa–induced and intrarenal baroreceptor–stimulated renin release).4 Subsequently, a third autocoid, adenosine (acting via A1 receptors), was proposed to serve as a molecular brake on renin release and thereby to moderate the effects of catecholamines and PGI2 on renin secretion.5 Because cAMP is a critical second messenger mediating the exocytosis of renin from juxtaglomerular cells, adenylyl cyclase unifies these concepts because β-adrenoceptors and PGI2 receptors accelerate, whereas A1 receptors brake the rate of cAMP production. The results reported by Schweda et al corroborate the accelerator/brake model of renin release because they report that PGs mediate stimulation of renin release by low renal perfusion pressure, whereas adenosine, via A1 receptors, mediates inhibition of renin release by high renal perfusion pressure.

An important aspect of Schweda et al’s experiments is the reliance on A1 receptor knockout mice. In this context, it should be mentioned that studies in PGI2 receptor knockout mice have also contributed critically to our knowledge of renin release control. Early studies demonstrated that inhibition of cyclooxygenase with NSAIDs (such as indomethacin) attenuated renin release induced by the macula densa apparatus and intrarenal baroreceptor mechanism4 but not by the β-adrenoceptor.6 Additional studies identified arachidonic acid (the precursor of PGs) as a renin secretagogue, found that PGI2 and 6-keto-PGE1 (metabolite of PGI2) are the most potent renin-releasing prostanoids,7 and discovered that renal artery hypotension increases renal production of PGI2.8 However, none of these studies were definitive, and knockout technology was required to more rigorously test the potential role of PGI2 in renin release. In this regard, Fujino et al placed the capstone on the PGI2 hypothesis by demonstrating that renin release and hypertension in response to renal artery clipping were attenuated in PGI2 receptor knockout mice but not in mice with any of the four PGE2 receptors deleted.9

Testing of the hypothesis that adenosine importantly brakes renin release has lagged behind testing of the PGI2 theory. Early studies showed that agonists and antagonists of A1 receptors inhibit and stimulate renin release, respectively, suggesting that endogenous adenosine functions to brake renin release;3 however, the medicinal chemistry of adenosine receptor agonists and antagonists was slow to develop, and specificity and water solubility of the available compounds remained serious impediments to testing the adenosine brake hypothesis. As with the PGI2 hypothesis, knockout technology was also the way forward with regard to more rigorous testing of the adenosine brake hypothesis. For example, Brown et al10 showed that in A1 receptor knockout mice, basal plasma renin activity is twice as high as in wild-type mice. Intriguingly, Brown et al also found that A1 knockout mice are mildly hypertensive. These seminal findings strongly suggest that A1 receptors are critical for the proper regulation of renin release and arterial blood pressure.

Using Schnermann’s A1 receptor knockout mouse, Schweda et al, in a study that predates their current Hypertension article, demonstrated that the macula densa regulation of renin release functions quite normally in kidneys from A1 knockout mice.11 This finding was totally unexpected because tubuloglomerular feedback (TGF) control of single-nephron glomerular filtration rate is...
As mentioned above, previous studies by Schweda et al suggest a bifurcation of signaling pathways by the macula densa (a different mediator for TGF versus modulation of renin release). In a similar vein, the current study suggests a bifurcation of signaling pathways by the intrarenal baroreceptor mechanism. In this regard, inhibition of cyclooxygenase with indomethacin (in wild-type and A1 knockout mice) abrogated the increase in renin secretion in response to a reduction in renal perfusion pressure, suggesting that PGs mediate the stimulatory limb of the intrarenal baroreceptor mechanism. However, because a reduction in renal perfusion pressure would be expected to decrease sodium delivery to the macula densa, the stimulation of renin release was in all likelihood mediated by the combined effects of the intrarenal baroreceptor and macula densa mechanisms. Therefore, it is not possible to conclude whether, in this study, PGs contributed to the intrarenal baroreceptor or macula densa mechanisms. But perhaps this is a moot point because previous studies have already confirmed a role for PGs in both mechanisms.

The current study by Schweda et al clearly demonstrates the importance of A1 adenosine receptors in the regulation of renin release. However, it is surprising that the increase in renin release induced by a reduction in renal perfusion pressure was not augmented in the A1 knockout mice. Because PGI2 stimulates renin release most likely by activating adenylyl cyclase, and because PGI2 mediates in part the increase in renin release induced by a reduction in renal perfusion pressure, removing the adenosine brake on adenylyl cyclase would be expected to augment renin secretion induced by activation of the intrarenal baroreceptor. Indeed, pharmacological blockade of adenosine receptors increases renin release responses to renal artery clipping in rats and hypertension in rats and humans. The variance in results could be related to species, or previous results may have been misinterpreted. Clearly, additional research is warranted.

Elucidating the role of A1 receptors in renin release is of immediate practical importance. Highly selective A1 receptor antagonists are being developed as renal-friendly, potassium-sparing diuretics. If A1 receptors brake renin release in humans, diuretic therapy with A1 receptor antagonists may cause unhealthy stimulation of the renin-angiotensin system. Although clearly speculative, the current study by Schweda et al suggests that A1 receptor antagonists may have to be combined with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to avoid unwanted activation of the renin-angiotensin system.

References


Putting the Brakes on Renin Release. Role of the A$_1$ Receptor
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