Putting the Brakes on Renin Release

Role of the A\textsubscript{1} Receptor

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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 al\textsuperscript{1} in this issue of Hypertension, showing that A\textsubscript{1} 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 Freeman\textsuperscript{2} and Keeton and Campbell,\textsuperscript{3} investigators recognized early on that 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 PGI\textsubscript{2} (mediating macula densa–induced and intrarenal baroreceptor–stimulated renin release).\textsuperscript{4} Subsequently, a third autocoid, adenosine (acting via A\textsubscript{1} receptors), was proposed to serve as a molecular brake on renin release and thereby to moderate the effects of catecholamines and PGI\textsubscript{2} on renin secretion.\textsuperscript{5} Because cAMP is a critical second messenger mediating the exocytosis of renin from juxtaglomerular cells, adenylyl cyclase unifies these concepts because \(\beta\)-adrenoceptors and PGI\textsubscript{2} receptors accelerate, whereas A\textsubscript{1} 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 A\textsubscript{1} receptors, mediates inhibition of renin release by high renal perfusion pressure.

An important aspect of Schweda et al’s experiments is the reliance on A\textsubscript{1} receptor knockout mice. In this context, it should be mentioned that studies in PGI\textsubscript{2} 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 mechanism\textsuperscript{4} but not by the \(\beta\)-adrenoceptor.\textsuperscript{6} Additional studies identified arachidonic acid (the precursor of PGs) as a renin secretagogue, found that PGI\textsubscript{2} and 6-keto-PGE\textsubscript{1} (metabolite of PGI\textsubscript{2}) are the most potent renin-releasing prostanoids,\textsuperscript{7} and discovered that renal artery hypotension increases renal production of PGI\textsubscript{2}.\textsuperscript{8} However, none of these studies were definitive, and knockout technology was required to more rigorously test the potential role of PGI\textsubscript{2} in renin release. In this regard, Fujino et al placed the capstone on the PGI\textsubscript{2} hypothesis by demonstrating that renin release and hypertension in response to renal artery clipping were attenuated in PGI\textsubscript{2} receptor knockout mice but not in mice with any of the four PGE\textsubscript{2} receptors deleted.\textsuperscript{9}

Testing of the hypothesis that adenosine importantly brakes renin release has lagged behind testing of the PGI\textsubscript{2} theory. Early studies showed that agonists and antagonists of A\textsubscript{1} receptors inhibit and stimulate renin release, respectively, suggesting that endogenous adenosine functions to brake renin release;\textsuperscript{5} 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 PGI\textsubscript{2} hypothesis, knockout technology was also the way forward with regard to more rigorous testing of the adenosine brake hypothesis. For example, Brown et al\textsuperscript{10} showed that in A\textsubscript{1} receptor knockout mice, basal plasma renin activity is twice as high as in wild-type mice. Intriguingly, Brown et al also found that A\textsubscript{1} knockout mice are mildly hypertensive. These seminal findings strongly suggest that A\textsubscript{1} receptors are critical for the proper regulation of renin release and arterial blood pressure.

Using Schnermann’s A\textsubscript{1} 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 A\textsubscript{1} knockout mice.\textsuperscript{11} This finding was totally unexpected because tubuloglomerular feedback (TGF) control of single-nephron glomerular filtration rate is
completely lacking in A1 knockout mice. Taken at face value, the data indicate that TGF regulation of afferent arteriolar tone (which is clearly a macula densa–dependent mechanism) is mediated by A1 receptors, whereas macula densa regulation of renin release apparently is not. This bifurcation of signaling by the macula densa seems unlikely, and perhaps additional studies are needed to secure this hypothesis. Be that as it may, Schweda et al also found that a low-sodium diet increases renal renin mRNA and renal renin content much more in A1 knockout mice compared with wild-type mice. The interpretation of this finding is open to discussion, but one possibility is that endogenous adenosine, acting via the A1 receptor, restrains sympathetically induced renin release, which of course would be activated in mice on a low-sodium diet. This explanation is consistent with a previous report demonstrating that selective antagonism of A1 receptors markedly increases β-adrenoceptor–induced renin release.12

In this issue of Hypertension, Schweda et al continue their exploration of the role of A1 receptors in the regulation of renin release by examining the modulation of renin release, in vitro and in vivo, in A1 receptor knockout mice in response to changes in renal artery perfusion pressure. In the current study, decreases and increases in renal perfusion pressure augmented and attenuated, respectively, renin secretion by the isolated perfused mouse kidney. Importantly, the increases in renin release in response to reductions in renal perfusion pressure were similar in kidneys from A1 receptor knockout mice compared with kidneys from wild-type mice. Consistent with this result, the selective A1 receptor antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) also failed to modify renin release changes induced by decreases in renal perfusion pressure in wild-type mice. In stark contrast, DPCPX blocked the reductions in renin secretion caused by increases in renal perfusion pressure, and pressure-induced reductions in renin release were completely absent in A1 receptor knockout mice. These findings strongly suggest that adenosine, acting via A1 receptors, mediates intrarenal baroreceptor–induced inhibition of renin release but not intrarenal baroreceptor–induced increases in renin secretion. It is conceivable that some of the inhibition of renin release in response to the increase in renal perfusion pressure was mediated by the macula densa mechanism. However, as mentioned above, these investigators showed previously that A1 receptors presumably are not involved in macula densa–induced changes in renin secretion (at least in mice). Therefore, it is unlikely (although still possible) that the lack of suppression of renin release in response to increases in renal perfusion pressure in A1 knockout mice or DPCPX-treated wild-type mice was attributable to a necessary role of adenosine in the macula densa pathway. Rather, these results seem to confirm a key role for endogenous adenosine, acting via A1 receptors, to mediate suppression of renin release by the intrarenal baroreceptor mechanism. Using phenylephrine to acutely and chronically increase renal perfusion pressure, Schweda et al showed that even in vivo, the A1 receptor is critical for proper functioning of the intrarenal baroreceptor system.

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, 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 hypotension in rats and humans.5 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


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