Renal Angiotensin-Converting Enzyme Upregulation: A Prerequisite for Nitric Oxide Synthase Inhibition–Induced Hypertension?

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doi: 10.1681/ASN.2014060549

Angiotensin II (Ang II) production at tissue sites is well established. Interference with such local generation, rather than with Ang II generation in the circulation, is believed to underlie the beneficial cardiovascular and renal effects of renin-angiotensin system (RAS) blockers. Infusion studies with 125I-Ang I and II, allowing the quantification of tissue uptake of circulating angiotensins, have unequivocally confirmed that most tissue Ang II is not derived from blood but is of local origin. For instance, in the kidney, >95% of tissue Ang II is generated at renal tissue sites from locally synthesized Ang I. This generation depends on renal angiotensin-converting enzyme (ACE), and not chymase, as evidenced by ACE knockout studies and studies with ACE inhibitors. Initially, it was thought that the angiotensinogen required for this local production was also kidney derived because angiotensinogen production had been observed in the proximal straight tubule. However, elegant studies by Matsusaka et al. selectively knocking out angiotensinogen synthesis in the kidney or liver revealed that only hepatic deletion affected renal Ang II, under both normal and pathologic conditions. Apparently, therefore, kidney-derived angiotensinogen does not contribute to renal Ang II production and appears unconverted in urine. In humans, urinary angiotensinogen closely follows albumin excretion and is therefore exclusively plasma (i.e., liver) derived.

Despite their common source of angiotensinogen, circulating and renal Ang II production do not always run in parallel. For instance, in patients with diabetes, plasma renin is low, and yet their renal plasma flow response to RAS blockade is greatly enhanced, suggesting an overactive intrarenal RAS. The opposite occurs after treatment with very high doses of a renin inhibitor. RAS blockers, by interfering with the negative feedback loop between Ang II and renin release, normally upregulate renin synthesis. Particularly after high doses this upregulation may be >100-fold. Renin inhibitors selectively accumulate in renal tissue, and, therefore, after stopping treatment, renal RAS suppression will continue, so that renin release stays high. At the same time the inhibitor starts to disappear from plasma, and thus insufficient renin inhibitor is around to block all renin molecules that continue to be released. As a consequence, plasma renin activity will increase, and extrarenal Ang II and aldosterone levels may even rise to levels above baseline.

The hypertension occurring in animals during inhibition of nitric oxide synthase (NOS) with L-NG-nitroarginine methyl ester (L-NAME) is also believed to involve a discrepancy between the circulating and renal RAS. This concept is based on the observation that RAS blockers lower BP in this model, despite the fact that circulating renin is suppressed. This renin suppression, however, appears to be transient because long-term L-NAME treatment increases plasma renin levels.

In this issue of JASN, Giani et al. report on the importance of renal ACE in the NOS inhibition model. Their aim was to obtain further evidence for the independency of renal Ang II production (by renal ACE) as a determinant of hypertension. To this end, they used mice that, via targeted homologous recombination, expressed ACE only in myelomonocytic cells (ACE 10/10 mice). Such mice are phenotypically normal (i.e., they have normal BP and display no renal abnormalities). In fact, according to the authors, the renal Ang II levels of these mice were similar to those of wild-type animals at baseline and remained unchanged during treatment with L-NAME, even though their renal ACE levels were reduced by 90% or more. This is a surprising finding that merits further discussion. The most logical explanation of these findings is that these mice, like humans during ACE inhibitor treatment, display increased renin levels. In humans the return of Ang II to baseline levels, despite ongoing ACE inhibition, is called Ang II escape. In case of 90% ACE inhibition, a 10-fold rise in renin is sufficient to achieve this, and as described above even renin increases of >100-fold are feasible.

Although the authors emphasize that renal ACE is completely absent in ACE 10/10 mice, there appears to be residual renal ACE staining with immunoblot. In addition, macrophages of ACE 10/10 mice have upregulated ACE and produce more NO, thus potentially compensating for the absence of renal ACE.

Importantly, Giani et al. demonstrate that NOS inhibition in the low-renal ACE mice does not result in hypertension, cardiac hypertrophy, or proteinuria. In addition, L-NAME did
not lead to the acute reduction in GFR or sodium retention that was observed in wild-type mice. If anything, they displayed an acute natriuresis and no change in GFR. The authors meticulously studied all relevant sodium transporters, including the sodium hydrogen exchanger, sodium potassium chloride cotransporter, sodium chloride cotransporter, and epithelial sodium channel. Although the natriuresis in the ACE 10/10 mice occurred during the first week of L-NAME treatment, most transporters still showed a greater downregulation after 4 weeks of L-NAME. The authors attribute this to the fact that the wild-type mice, unlike the ACE 10/10 mice, displayed a rise in renal Ang II after L-NAME. Such a global effect on sodium transporters is uncommon and intriguing, but the proposed model of tubular Ang II affecting sodium transporters via apical Ang II type 1 receptors requires experimental proof.14 The authors assume the rise in renal Ang II to be due to the approximate 2-fold rises in both renal ACE and angiotensinogen, which did not occur in the ACE 10/10 mice. Surprisingly, however, Giani et al. did not study renal renin expression, which usually displays much larger rises (as discussed above) than the modest rises observed here for ACE and angiotensinogen. On this basis, renin is actually more likely to determine the changes in (renal) Ang II levels. Indeed, a study of the ACE insertion/deletion polymorphism in humans observed that the 60%–70% higher tissue ACE levels in DD participants versus II participants had no effect whatsoever on renin or Ang II.16 This implies that normal ACE levels are non–rate-limiting. The doubling of angiotensinogen in wild-type mice is in full agreement with the doubling of proteinuria after L-NAME and supports the enhanced leakage of circulating angiotensinogen from plasma proposed by Matsusaka et al. as the source of increased renal Ang II generation.5,6

Of interest, renal angiotensinogen in the ACE 10/10 mice was lower than in wild-type mice. This is also suggestive for the upregulation of renin that has most likely occurred in these mice to overcome the consequences of >90% ACE disappearance. Here it should be noted that in humans the levels of angiotensinogen are within the range of its Km, while in mice they are much lower. Thus, in mice, much more than in humans, fluctuations in angiotensinogen levels have immediate consequences for the degree of angiotensin generation. An alternative explanation of the data is therefore that the ACE 10/10 mice already used their maximum capacity to normalize renal Ang II at the expense of angiotensinogen and were unable to increase Ang II even further after L-NAME. Moreover, NO was recently demonstrated to be of vital importance for the recruitment of renin-expressing cells along periglomerular vessels (i.e., the usual site of renin cell upregulation during ACE inhibition). In other words, L-NAME might have interfered with the delicate balance in the ACE 10/10 mice that allowed the restoration of the renal Ang II levels. From this point of view it would have been no surprise if the ACE 10/10 mice had shown no change in renin or even a renin decrease after treatment with L-NAME. To partially address this point, the authors measured total renin in plasma. Unfortunately, this measurement involved the simultaneous detection of prorenin, the inactive precursor of renin, and thus no clear conclusions can be drawn on the actual changes in plasma renin. The variation in total renin is much larger in the ACE 10/10 mice, and although neither BP nor total renin significantly decreased after L-NAME treatment, total renin levels did correlate with change in systolic BP in these animals. This is difficult to understand and might imply that BP in these animals is more renin-dependent, again supporting the renin upregulation in this model.

In summary, the impressive studies by Giani et al. confirm the importance of renal Ang II upregulation for the hypertensive effects after L-NAME infusion. This obviously depends on ACE, as all Ang II generation does, but to what degree renal ACE—rather than renin upregulation—is the permissive factor cannot yet be said. The ACE 10/10 model most likely is a high-renin model, at least in the kidney, and may thus be less responsive to agents that induce hypertension by inducing renal renin expression. An important question is why NOS inhibition would increase renal Ang II at all. The answer may lie in the complicated consequences of nonselective NOS inhibition, affecting endothelial, inducible, and neuronal NOS simultaneously, thereby reducing not only the effect of NO on renin release and renin cell recruitment but also its capacity to suppress the sympathetic nervous system.11,12 The sympathetic nervous system interacts at various levels with the RAS, for example by increasing renin release, but also directly with kidney sodium transport.18 Therefore, to fully understand these issues, we need to know not only the changes in renal and plasma renin but also the degree of sympathetic nervous system activation in this model.

DISCLOSURES
None.

REFERENCES


