On the Origin of Urinary Angiotensin II

To the Editor:

With great interest we read the publication by Shao et al., who propose that angiotensin (Ang) II type 1 (AT₁) receptor stimulation in the kidney results in urinary Ang II excretion. The authors have used an elegant approach, infusing rats with Val⁵-Ang II to allow a clear distinction from endogenous Ile⁵-Ang II, here denoted as Ang II. Val⁵-Ang II is believed to have the same properties as Ang II.

We have followed a similar approach and infused ¹²⁵I-labeled Ang II in pigs to distinguish it from endogenous Ang II. In these studies, ¹²⁵I-Ang II accumulation in the kidney, largely if not exclusively, depended on AT₁ receptors, as demonstrated by a >90% reduction in the renal tissue/plasma concentration ratio of ¹²⁵I-Ang II after pretreatment with the AT₁ receptor blocker eprosartan. Recent experiments showing low or undetectable renal Ang II levels in AT₁ receptor knockout animals further support the dependency of renal Ang II accumulation on AT₁ receptors. In addition, the porcine renal tissue/plasma concentration ratio of endogenous Ang II decreased by ~90% after eprosartan pretreatment, thus confirming that renal ¹²⁵I-Ang II accumulation fully resembles that of endogenous Ang II.

In the study by Shao et al., the renal tissue/plasma ratio of endogenous Ang II decreased by >90% after candesartan treatment (from 358/24 to 21/157), identical to our results in pigs. Yet, the ratio of Val⁵-Ang II was virtually unchanged after candesartan treatment (385/283 versus 242/217). This demonstrates that the renal accumulation of Val⁵-Ang II, unlike that of Ang II and ¹²⁵I-Ang II, largely occurs in an AT₁ receptor–independent manner, at least when infused at a rate of 80 ng/min. One explanation for this discrepancy may be that this rate is above the rate required to obtain (near) complete renal AT₁ receptor occupancy. In agreement with this concept, Val⁵-Ang II suppressed plasma renin activity by >95%. Yet, endogenous plasma Ang II was either unaltered or increased.

According to Figure 6,1 urinary Val⁵-Ang II excretion without candesartan amounted to 3 to 7 pmol/24 hours. Urinary volumes ranged from 11 to 38 mL/24 hours, and thus the urinary Val⁵-Ang II concentrations were 80 to 636 fmol/mL. This equals the Val⁵-Ang II concentration range in plasma. Because Val⁵-Ang II cannot be made in the kidney, and assuming that circulating Val⁵-Ang II reaches urine to the same degree as circulating Ang II, it appears that urine minimally contains the same Ang II levels as plasma based on filtration and/or tubular secretion of circulating Ang II. Consequently, by using the Val⁵-Ang II urine/plasma concentration ratio, it should be possible to distinguish plasma- and kidney-derived Ang II in urine. The same procedure might be followed during candesartan treatment so that one gets an indication of the AT₁ receptor blockade-induced changes in the urinary washout of circulating Ang II and renal Ang II. Given the identical urinary excretion rates of Val⁵-Ang II and Ang II during candesartan treatment, as well as their comparable plasma levels during such treatment, it can already be predicted that candesartan reduces the net release of Ang II from renal tissue sites into urine to 0.

Disclosures

None.

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