Our fragmentary knowledge of the regulatory functions of ANG II “fragments”: are we beginning to see the light?

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TWO ARTICLES IN THIS ISSUE of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology address the importance of angiotensin hormone “fragments.” Before focusing on the angiotensin “fragments,” the main functions of the renin-angiotensin system (RAS) are briefly outlined.

The control of total body sodium and water by the kidney has a pivotal role in the long-term control of mean arterial blood pressure (MAP; 4, 10). Whereas the function of the arterial baroreceptor reflex seems to be limited to the sensing and the correction of rapid short-term pressure changes around long-term MAP (5, 16), the cardiopulmonary receptors in the low-pressure system provide important information on the degree of vascular filling (16). It seems unlikely that by using the latter afferents the central nervous system (CNS) can detect changes in total body sodium or water, a prerequisite for the necessary long-term correcting adjustments. However, there are two fundamental mechanisms, serving as input and output, which are driven directly by MAP via renal perfusion pressure: 1) the acute pressure-natriuresis mechanism affecting sodium and water excretion and 2) pressure-dependent renin release, which functionally characterizes the strongest stimulus for renin synthesis (18) and release (9, 11). However, both mechanisms are modulated effectively by neural, hormonal, and intrarenal paracrine and endocrine influences (4, 7, 12); therefore the kidney actually integrates many different inputs. By providing circulating ANG II, which acts on the CNS via the circumventricular organs, the kidney even determines the set point of the neural control mechanisms. There is evidence that a chronic infusion of ANG II (1, 2) or a 2-h servo-controlled fall of renal perfusion pressure (for literature, see Ref. 11) resets the arterial baroreceptor reflex toward a higher level of MAP. A chronic infusion of ANG II can also attenuate the arterial baroreceptor reflex toward a higher level of perfusion pressure (for literature, see Ref. 11); therefore the renal effects of ANG IV-(3–8) may differ from those of ANG II-(1–8) (for literature, see Refs. 3, 20). Endogenously formed ANG III-(2–8) seems to exert its effects mainly on the CNS, and the action of ANG II-(1–8) on vasopressin release may depend on the previous conversion of ANG II-(1–8) to ANG III-(2–8) (3, 20, 23). ANG III-(2–8) is more sensitive to the enzymatic hydrolysis by aminopeptidase N and therefore is less potent than ANG II-(1–8) (for literature, see Ref. 3).

ANG IV-(3–8) formed by the cleavage of ANG III-(2–8) by aminopeptidase N can bind AT1 receptors, albeit with lower affinity than ANG II-(1–8) and ANG III-(2–8). A hypothetical AT4 receptor (better “binding site,” because the gene encoding for this receptor has not been cloned) was found in kidneys, adrenals, heart, and endothelium. In vitro experiments have shown nitric oxide (NO)-dependent vasodilatation in the porcine pulmonary vascular bed (15). Renal effects have been described, although some evidence indicates that the renal effects of ANG IV-(3–8) may differ from those induced by ANG II-(1–8). However, the results are conflicting (proximal tubular sodium reabsorption, renal vasoconstriction, renal vasodilatation? for literature, see Ref. 22).

ANG-(1–7) is either formed from ANG I-(1–10) by the tissue-specific endopeptidases 24.11, 24.15, or 24.26 or due to the cleavage of ANG II-(1–8) by carboxypeptidase P. Further evidence suggests that in the kidney ANG-(1–7) might be formed from ANG I-(1–10) or ANG II-(1–8) by the ACE-related enzyme ACE2 (6, 21). As endopeptidases are present in epithelial, neuroepithelial, endothelial, and smooth muscle cells, this peptide might have mainly an autocrine/paracrine role. In humans, the plasma concentrations of ANG-(1–7) are lower than those of ANG II-(1–8) and ANG III-(2–8) (1:14 and 1:3, respectively [14]). Because the effects of ANG-(1–7) can be abolished by high doses of AT1 antagonists, they might be mediated in part by AT1 receptors. Whether high-affinity binding sites different from AT1 receptors characterize a specific receptor different from AT1 remains controversial (3). The major effect of ANG-(1–7) in the CNS is vasopressin release. The mechanisms of the cardiovascular vasodilatory effects of ANG-(1–7) are complex and may, de-
pending on the vascular bed, rely on a receptor-mediated facilitation of NO or prostaglandin release. It also was suggested (8) that this peptide has a counterbalancing effect to ANG II–(1–8). The renal effects of ANG–(1–7) were recently reviewed in detail (19). Briefly, ANG–(1–7) locally interacts with the bradykinin–kinin system. There also may exist an interaction between ANG–(1–7) and ANG II–(1–8) at the renal level, but it is poorly understood. The primary route of degradation of ANG–(1–7) is via ACE (for literature, see Ref. 8).

In companion papers in this issue (17, 22), the cardiovascular, endocrine, and renal effects of ANG III–(2–8), ANG IV–(3–8), and ANG–(1–7) are compared with those of ANG II–(1–8) under physiological conditions in conscious dogs and in humans. The angiotensins were applied in equimolar physiological concentrations while the RAS was acutely blocked by converting enzyme inhibition, and the effects of endogenously formed aldosterone were prevented by an aldosterone antagonist. Because most of the previous investigations on the biological effects of the angiotensin fragments either were in vitro studies or were made in anesthetized animals, these two publications make an important contribution to the integrative physiology of angiotensins. However, there are still many open questions. Further research in this area will hopefully tell us soon which of these fragments we may call biologically active hormones.