Angiotensins
A Family That Grows From Within
Theodore L. Goodfriend

Hydrolytic cleavage of large, inert proteins into smaller, active products is a common event in biology. The active products usually enjoy brief useful lifespans before they themselves are cleaved into inactive fragments. Prototypic participants in this process include clotting factors, complement, and digestive enzymes. Angiotensin II (Ang II) was the first polypeptide hormone recognized as the active intermediate in a proteolytic sequence starting with an inactive precursor and ending in "inactive" fragments. It is now considered a universal feature of polypeptide hormones that they arise from larger precursors ("prepro-hormones") and are destroyed by further proteolysis. Insulin, parathyroid hormone, and atrial natriuretic factor are good examples.

Until the recent work of the group led by Carlos Ferrario at the Cleveland Clinic, one chapter of which is reported in this issue of *Hypertension*, it was conventional wisdom to regard the C-terminal amino acid residue of Ang II as crucial for biological activity. Phenylalanine in position 8 was found in traditional agonists, whereas aliphatic substitutions in that position yielded partial agonists or competitive antagonists. The fact that manipulation of the C-terminal residue could lead to formation of competitive antagonists was taken by many as proof of the crucial nature of that position. Cleavage at the C-terminus was assumed to be one step that created inactive fragments.

It has come as a surprise to most of us who work with angiotensins that complete removal of the C-terminal residue leaves a polypeptide that still exerts powerful effects in the brain. As shown by Ferrario and his coworkers, angiotensin-(1-7) (Ang-[1-7]), also called des-Asp'-Ang II, stimulates vasopressin release and modulates baroreceptor reflex sensitivity with a potency equal to that of Ang II. Therefore, it is incorrect to regard the C-terminal eighth residue of angiotensin as crucial, and it is simplistic to consider Ang-(1-7) as an inactive fragment.

Although Ang II remains by far the most powerful vasoconstrictor known to be produced by renin activation, cleavage of Ang II at either end yields fragments with significant potencies: des-Asp<sup>1</sup>-Ang II (also called angiotensin III) is a powerful stimulus of aldosterone secretion, and we now learn that des-Phe<sup>8</sup>-Ang II is a powerful stimulus of vasopressin release.<sup>2,3</sup> Both of these heptapeptides stimulate prostaglandin formation. The full list of active members of the angiotensin family probably is longer than we suspected. There are reports in the literature that the parent decapeptide angiotensin I (Ang I) exerts activities of its own, apart from those of its famous offspring.<sup>4</sup> At the other extreme, Chipens et al<sup>5</sup> showed that very small fragments of Ang II affect its degradation. We might well ask which, if any, fragments of angiotensin are truly inactive?

For that matter, it is probably presumptuous to dismiss angiotensinogen itself, and the large fragment of angiotensinogen that remains after removal of Ang I, as having no function beyond delivering its namesake. In the examples of proteolytic activation, such as clotting factors, cited above, the situation is opposite to that of angiotensin; the large fragment appears to be the most important product and the small peptides are relatively inert. Maybe, just maybe, angiotensinogen plus or minus Ang I is a potent protein whose other function presently eludes us. Poulsen and Jacobsen,<sup>6</sup> taking another view, thought of angiotensinogen as a protease inhibitor that restrains renin. What, then, is renin straining to do, if not make pressor peptides?

If the octapeptide Ang II and its two heptapeptide fragments are truly three distinct hormones with characteristic actions, they should have distinct receptors. The Cleveland Clinic group showed that Ang-(1-7) is apparently bound by receptors that also recognize Ang II. The two peptides displace each other from binding sites. Similar results have been observed with Ang II and des-Asp'<sup>1</sup>-Ang II (Ang III). The simplest hypothesis to explain these binding data is that the peptides all cross-react with a single angiotensin receptor. Conversely, use of nonpeptide inhibitors with greater selectivity has revealed distinct subtypes of binding sites that display preference for individual members of the angiotensin family. One site revealed by the use of these inhibitors has higher affinity for des-Asp'<sup>1</sup>-Ang II than the other site.<sup>7,8</sup> Perhaps there is a receptor subtype with particularly high affinity for Ang-(1-7). Cloning of...
angiotensin receptors will be the way these questions are answered in the near future.

Even if angiotensin receptors show no selectivity, pathways of proteolysis could determine which peptide was relevant in individual cells or regions of the body. In some regions, synthesis of Ang II would predominate; in others, Ang-(1–7) or Ang-(2–8). Ferrario and colleagues have used antibodies specific to individual peptides to localize these regions in the brain. Another approach could use labeled specific inhibitors of enzymes in one or another synthetic sequence, just as labeled angiotensin converting enzyme (ACE) inhibitors have been used to localize the traditional cascade.

We know that Ang-(1–7) can be formed by carboxypeptidase action on Ang II. Ferrario's group has shown that Ang-(1–7) can also be formed by endopeptidase action on Ang I, a pathway that would bypass Ang II and be unaffected by ACE inhibitors. One of their most interesting observations, reported in this issue, is the marked rise in the circulating level of Ang-(1–7) that follows administration of ACE inhibitor. This accumulation may have relevance to the mechanism of action of these drugs.

Discussions of angiotensin and its fragments usually assume that all congeners are pressors, elevating blood pressure by effects on vascular smooth muscle contraction, aldosterone secretion, vasopressin release, or neural function. Based on that assumption, the action of ACE inhibitors is explained by their ability to reduce the circulating levels of pressors of the angiotensin family (and to preserve kinins). However, it has been reported that during ACE inhibitor therapy, while the blood pressure remains low, levels of Ang II return to normal. The work of the Cleveland Clinic groups offers a possible explanation for this paradox: Ang-(1–7) may lower blood pressure. Ang-(1–7) could lower pressure in several ways: it could stimulate a depressor center in the brain; it could compete with Ang II for a pressor site and lower pressure because it is a weaker agonist; or it could stimulate release of depressor prostaglandins in the brain or elsewhere. A depressor angiotensin should not be viewed with surprise. The eicosanoids, catecholamines, and steroids are other hormone families that include pressor, depressor, and pressure-neutral members. Ang II itself lowers blood pressure in fowl.

The classical route for discovery of new hormones is to observe an effect of a natural product on a bioassay. That was a key technique in finding that Ang-(1–7) has activity in the nervous system. In addition, elucidation of the humoral effects of Ang-(1–7) was aided considerably by measurement of radioligand binding. Radioligand binding is now widely used in screening for new drugs. Its usefulness in finding new hormones is far from exhausted. That is only one lesson from the work on Ang-(1–7). The Cleveland Clinic group has also taught us to be extremely cautious before labeling any product of in vivo proteolysis inactive. Pro-opiomelanocortin is the best known example of a single precursor that yields a number of active products. We surely do not yet understand all the agonists, actions, and avenues of synthesis of the angiotensin family.

References


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T L Goodfriend

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