Over the last 2 decades, it has become clear that angiotensin can be generated not only in the systemic circulation but also in multiple tissue sites, where its production can be regulated by local factors. Given the ability of angiotensin II to influence target cell proliferation, hypertrophy, and apoptosis, tissue angiotensin systems potentially play an important role in a wide variety of physiological processes. In this issue of *Hypertension*, De Mello and Danser review the evidence for the synthesis of angiotensin II in the heart and discuss its possible role in health and disease. Their review complements other recent reviews of this subject, such as that by Dostal and Baker. Uniquely, however, the present review discusses the potential role of intracellular angiotensin II, called intracrine angiotensin II, in intercellular signaling and calcium flux in the heart. These findings are based on De Mello’s studies of renin, angiotensin I, and angiotensin II dialedyzed into rat cardiac cells. The evidence for the influence of an intracellular AT1-like angiotensin II receptor on intercellular communication is compelling and supports the concept of an intracrine angiotensin II system in the heart, with possible implications for cardiac conduction and contractility in health and disease. Also, the review emphasizes the potential importance of the uptake of prorenin by cells and its subsequent activation in the intracellular milieu, as demonstrated by De Mello and Danser. However, a more complete discussion of the role of locally synthesized renin must be found elsewhere.

In some cases, nucleolar binding is noted. In some cases, large amounts of peptide hormone can be demonstrated in parathyroid hormone–related protein and FGF-2), relatively poorly understood.

The concept of intracellular peptide hormone action, ie, intracrine action, remains foreign to most. Our laboratory introduced the term intracrine on the basis of extensive studies of the intracellular actions of angiotensin II, including its interactions with specific nuclear receptors to regulate gene transcription. The term intracrine was applied to the actions of hormones synthesized intracellularly as well as to the intracellular actions of hormone internalized from the extracellular space. In the case of angiotensin II, a small but growing body of evidence has developed to indicate that angiotensin II does indeed bind to intracellular receptors with effects on the transcriptional regulation of renin and angiotensinogen and with effects on calcium ion fluxes. The latter findings parallel those previously reported by De Mello and Danser involving intracellular calcium currents and intercellular communication in the heart. Also possibly related is the observation that some effects of angiotensin on sodium transport by renal tubular cells appear to require hormone internalization. Thus, evidence is emerging to indicate that angiotensin II can perform a variety of physiologically relevant intracrine actions, including influencing cardiac conduction and contractility.

Do other intracrine systems exist? Over the last 20 years, evidence has accumulated to indicate that many, and perhaps all, peptide growth factors and hormones operate in part through an intracrine mode of action. Included among these growth factors, hormones, and proteins are the following: insulin, fibroblast growth factor (FGF) A and FGF B (FGF-1 and FGF-2, respectively), platelet-derived growth factor, nerve growth factor, epidermal growth factor, growth hormone, prolactin, parathyroid hormone–related protein, angiotensin, tat protein, interferon-γ, hepatoma-derived growth factor, and a wide variety of other protein hormones. Of note is the fact that in some cases (eg, parathyroid hormone–related protein and FGF-2), relatively large amounts of peptide hormone can be demonstrated in association with intracellular organelles such as the nucleus. In some cases, nucleolar binding is noted. In some cases, intracellular hormone appears to be associated with specific high-affinity receptors (eg, angiotensin II), whereas in other cases (eg, FGF-2), lower specificity binding is found. Finally, intracrine hormone can be synthesized in situ or act after internalization. Thus, intracrine function is complex and poorly understood.

Are there any principles of intracrine peptide hormone action? The existence of intracellular regulatory peptide factors influencing gene transcription or other intracellular functions is well established. Indeed, intracellular peptide feedback loops have been associated with the regulation of cellular processes such as the establishment of biological rhythms. If intracellular peptide hormones can similarly form feedback loops, might they not play a role in such processes as cellular differentiation and memory? The answer to this question will have to await further experimentation. However, there are even now observations that may bear on this issue. For example, it has been reported that the treatment of spontaneously hypertensive rats early in life with a converting enzyme inhibitor produces a long-lasting normalization of blood pressure and long-lasting effects on angiotensin receptor number in specific cells. A similar phenomenon has been reported after AT1 antisense therapy. How is this effect produced? Clearly, a long-lived change has been produced in these animals at either the tissue or cellular level, and among the possible explanations is the idea that the
interuption of intracrine systems could play a role; ie, if intracrine angiotensin II stimulates the cellular production and secretion of angiotensin II with a resulting upregulation of intracrine angiotensin II in nearby target cells, the interruption of this process with a converting enzyme inhibitor could lead to long-lasting downregulation of tissue angiotensin. Other forms of angiotensin-induced memory could result from a similar mechanism.\textsuperscript{15} Likewise, the apparent amplification of physiological effects that is associated with some forms of gene therapy could be due to the upregulation of similar intracrine hormone systems, with resulting stimulation of nearby cells to operate at a higher level of activity.\textsuperscript{15,16}

In this process, the intracrine pool of hormone would serve as a reservoir to maintain hormone action in the face of short-term variations in ambient extracellular concentrations of hormone. Thus, the introduction of genes for vascular endothelial growth factor (VEGF) in relatively few cells could, through an intracrine action in those cells, stimulate the enhanced secretion of VEGF, which (after internalization) could, through an intracrine action in those cells, stimulate VEGF production in surrounding cells, thereby producing a wave of long-lived VEGF production and, ultimately, the formation of new vessels.

These latter mechanisms must remain conjecture, but the review of De Mello and Danser\textsuperscript{1} clearly marks a step forward in the ultimate elucidation of intracrine action and its role in biology and medicine. Their review should also stimulate new investigation into the effects of angiotensin on cardiac conduction and contractility in health and disease.

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References


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