REVIEW ARTICLE

An Expanded View of Progressive Cardiorenal Disorders

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ABSTRACT

Chronic renal diseases and congestive heart failure are progressive disorders, which cannot be completely controlled by established therapies. It has been argued that intracrine biology involving the formation of self-sustaining intracrine regulatory loops accounts for the progression of these disorders and for the inability of standard therapies to stop disease spread. The renin-angiotensin system is a prime candidate to be involved in any such process, and an amplifying role for mineralocorticoid activation is also consistent with this view. Here, the notion of intracrine participation in congestive heart failure and chronic renal disease is expanded to include consideration of the participation of other intracrines including transforming growth factor beta 1, parathyroid hormone–related protein and vascular endothelial growth factor among others. The possibility that intracrine expression patterns account for disease phenotypes is explored. The therapeutic implications of this view are discussed.

Key Indexing Terms: Congestive heart failure; Chronic renal disease; Intracrine; Angiotensin; TGF-B1; PTHrP; VEGF. **[Am J Med Sci 2016;351(6):626–633.]**

INTRODUCTION

This laboratory has investigated the intracellular actions of the peptide vasoactive hormone angiotensin II (AII) and based on these studies, and the work of others in different systems, has proposed that some extracellular signaling proteins act in what we call an intracrine fashion.[1-26] By this we meant the action of an extracellular signaling protein or peptide in its cell of synthesis or in a target cell, after internalization. Intracrines can traffic between cells following secretion, atypical secretion, by means of exosomes or microsomes or possibly by means of nanotubes. Surprisingly, various peptide moieties such as hormones, growth factors, cytokines, enzymes and DNA-binding proteins can operate in an intracrine mode.[14-29] In addition, we developed principles of intracrine actions. For example, intracrines often upregulate their own synthesis or that of their signaling cascades and so produce feedforward positive feedback loops. Angiotensin II, vascular endothelial growth factor (VEGF) and the homeodomain transcription factor pancreatic and duodenal homeobox 1 have all been shown to upregulate their own synthesis in one cell line or another.[19,27-29] This capability coupled with the ability to spread between cells either in the fluid phase or by means of exosomes or nanotubes enables intracrines to potentially establish these feedforward loops in multiple cells and indeed throughout a tissue.[1-29] For example, the homeodomain transcription factor pancreatic and duodenal homeobox 1 can spread between cystic duct cells, can upregulate its own synthesis and can induce an insulin-producing phenotype.[27-31] Also, we proposed that intracrines can operate in the intracellular milieu in either a canonical (using a traditional cognate receptor, usually in a lipid environment) or in a noncanaonical fashion (either acting without interaction with a cognate receptor or involving a cognate receptor functioning in an atypical fashion).[25] For example, AII can bind to angiotensin II type 1 receptors (AT-1R) on cell nuclei and mitochondria and can generate nitric oxide.[16,18] This is a canonical intracrine action. The AII can also bind directly to electron transport proteins in mitochondria generating reactive oxygen species.[30,31] This action, independent of an established AII receptor, is noncanonical.

Recently, we extended these ideas to an investigation of the pathogenesis of chronic kidney disease and systolic congestive heart failure (CHF).[32] We based these arguments on the clinical finding that interruption of renin-angiotensin system (RAS) action with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin 1 receptor blocker (ARB) slowed the progression of diabetic and other forms of chronic renal disease, and also slowed the progression of systolic CHF. Also mineralocorticoid antagonism slowed progression of these disorders. But neither of these therapeutic modalities arrests disease. They only modestly slow them. The diseases progress even if the causative factor such as hyperglycemia is reasonably controlled and these drugs are given. These facts led us to suggest that stressors such as hyperglycemia, if sufficiently severe and prolonged, can upregulate intracrines in renal and cardiac cells such that pathology-causing self-upregulating intracrine systems can spread between cells and therefore cause disease progression.[32] As AII, ACE, angiotensinogen and renin are all intracrines, the potential role of RAS intracrines in progressive cardiorenal disease could be complex. This, coupled with the partial effectiveness of renin system–suppressing

drugs, suggests that an RAS, and very likely an AII or angiotensinogen, intracrine system is operative in these disorders. To be sure, other possible explanations for this partial effectiveness include involvement of such mechanisms as the direct action of renin as well as angiotensin (1-12) serving as a substrate for AII formation; these mechanisms are considered elsewhere, whereas possible intracrine mechanisms are considered here.[32]

To the extent RAS intracrines traffic between cells in exosomes or RAS intracrines such as renin or angiotensinogen traffic between cells in the establishment of disease-causing intracrine loops, ACE inhibitors and ARBs would be ineffective. We have also proposed a role for mineralocorticoid receptor (MR) activation, resulting either from local aldosterone upregulation, or direct MR activation by AII or oxidative stress, in amplifying an RAS intracrine mechanism by upregulating ACE and AT-1R.[33] We also suggested that other intracrines, such as transfrorming growth factor beta 1(TGF-B1), parathyroid hormone–related protein (PTHrP) and VEGF, which are known to be upregulated in renal cortical cells in some forms of chronic renal disease and also in cardiac cells in some circumstances, could play a role in establishing pathologic intracrine feedforward loops.[32,33] Here the notion that RAS components, TGF-B1, VEGF, PTHrP and possibly other intracrines collaborate in CHF and chronic renal disease and that the relative activity of these intracrine systems can alter disease presentation is suggested. Moreover, one can speculate that differences in the activities of these intracrine loops cause the differing pathologies of diastolic heart failure (heart failure with preserved ejection fraction) and systolic heart failure.

POTENTIAL CARDIORENAL INTRACRINE LOOPS

In attempting to define intracrine loops in renal or cardiac cells it is important to note in regard to intracrines such as RAS components, VEGF, TGF-B1 and PTHrP that (1) that the effects of expression of these factors can vary dramatically depending on cell type and (2) the interactions between these factors can also be cell-type specific. Here, plausible loops are described based on established intracrine interactions in specific cell types on the assumption that in some cases such interaction could occur in cardiac and renal cells and participate in pathogenesis. Indeed, some of the variation that is observed in the incidence of chronic renal disease and CHF could be the result of variation in the tendency for target cells to generate the proposed loops in specific patients. However, until such time as they are demonstrated to exist in cardiac and renal cells, these intracrine interactions must be considered tentative or potential. Nonetheless, their consideration likely can point to productive lines of research and can suggest novel schema for disease progression. An additional point is that the intracrine loops proposed here may involve intracellular or extracellular signaling or both as well as canonical or noncanonical intracrine action or both. Although each of the factors to be discussed has been shown to act in cell interiors, in only a handful of cases has intracellular intracrine action been shown to act in ways consistent with participation in specific loops, and so the extent to which intracellular action is involved in this biology is yet unknown. Intracellular intracrine action has been shown in specific cases of AII upregulation of renin, and angiotensinogen; in AII upregulation of TGF-B1 and in the AII upregulation of PTHrP.[6,8,34,35] Each of these actions is consistent with participation in one or another of the intracrine loops described here. All other loops or interactions between the intracrines discussed could involve intracellular signaling, extracellular signaling or both. The argument that intracellular intracrine action is integral to the propagation of the hormonal loops to be described, rests on several observations like (1) the major intracrines proposed to be involved in pathologic intracrine loops, AII, TGF-B1 and PTHrP, have been shown to act in the intracellular space in ways consistent with the described loops; (2) the only partial effectiveness of RAS interruption or blockade suggests that intracellular intracrine action, or the action of atypical intracellularly active intracrines such as angiotensinogen or renin, is involved; (3) all the proteins involved in these loops are intracrines and have been shown to act in cell interiors; (4) intracrines frequently participate in positive feedback loops of the type described here and (5) cell autonomous intracrine upregulation associated with local intracrine trafficking and intracellular action is consistent with the slow, focal nature of disease progression seen in these disorders. Finally, this formulation of the pathophysiological mechanisms involved in chronic renal failure wand CHF suggests seeking factors that can influence the expression of various intracrines and intracrines loops, thereby modifying disease phenotype. The available data suggest a large number of potentially relevant intracrine loops existing, but also suggests that several are predominant. These would be considered initially and then other possible modifiers would be discussed.

ANGIOTENSIN—TGF-B1—PTHRP LOOP

The first loops to be considered is what can be called the angiotensin—TGF-B1—PTHrP network that consists of 3 distinct interacting loops (Figure 1). Angiotensin II has been shown to upregulate renin and angiotensinogen in isolated nuclei and has been shown to upregulate and maintain its own synthesis in cardiomyocytes derived from diabetic rats and in stretched myocytes.[6,8,36-39] Other observations support the existence of RAS-angiotensinogen upregulation in disease and these are discussed elsewhere in more detail.[32,33] At the same time, AII upregulates TGF-B1.[34,40-45] In some renal cells, this can be accomplished by intracellular AII