A positive feedback loop contributes to the deleterious effects of angiotensin

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When a basic scientist looks at heart failure, he sees a disease that appears to originate from any damage that causes low cardiac output, is progressive, and elicits a variety of physiological responses that attempt to correct the depressed cardiac function. Furthermore, these reflex physiological responses to low cardiac output—increased sympathetic-adrenal tone, increased activity of the renin–angiotensin system and other systems that maintain blood pressure, left ventricular remodeling, and cardiac hypertrophy—seem deleterious, because the pump is overworked and failing and cannot be expected, in the long run, to respond well to increased load or increased inotropic stimulation. The disease looks like a downward spiral, a spiral that therapy must interrupt. Models of heart failure have provided rationales for therapy and experimentation. A cardio-renal model viewed heart failure as a problem of salt and water retention originating with alterations in renal blood flow; a cardio-circulatory, or hemodynamic, model ascribed heart failure to vasoconstriction and reduced pumping capacity of the heart. These models provided rationales for the use of diuretics, vasodilators, and inotropic agents as therapies but mechanistically did not account for the progressive worsening of the disease or the fact that inotropic interventions produce improvements in cardiac contractility but do not slow the progression of the disease or reduce mortality. More recently, attention has focused on some of the neural/paracrine/autocrine mechanisms that constitute the reflex responses to low output and on the importance of signaling pathways regulating cell growth, apoptosis, and cell survival (1–3). Mann and Bristow (4) have suggested a synthesis, the biomechanical model, that emphasizes that the components of altered cardiac function and cardiac remodeling interact, such that one will invariably cause the other, and both will be sustained by neurohumoral responses. Among the humoral factors involved, much attention has been focused on the renin–angiotensin–aldosterone axis and on therapies that lower the levels of renin [β-adrenergic antagonists, some of which may also cause vasodilation via β1 receptor activation of NO production (5)], that reduce levels of angiotensin II (Ang II) [angiotensin-converting enzyme (ACE) inhibitors], or that antagonize Ang II binding to the G protein-linked type I Ang II receptors (AT1 receptor blockers) (6). These drugs inhibit the immediate, intermediate, and long-term effects of Ang II, reducing the pressure against which the heart pumps, slowing the progression of remodeling, and reducing mortality caused by heart failure (Fig. 1). ACE inhibitors and AT1 antagonists have also been useful in demonstrating that Ang II is a growth and apoptotic factor (6, 7). Myocyte apoptosis has been demonstrated in late-stage human heart failure and may constitute an important and progressive component of the disease. The article by Ding et al. (8) in this issue of PNAS suggests a putative molecular mechanism that may contribute to myocyte apoptosis in response to Ang II.

Angiotensin activates a great variety of signaling pathways (6). Via the AT1 receptor, Ang II activates three G proteins (Gi, Gq, and G12/13) that couple to the activation of a plethora of protein kinase cascades, causing immediate responses and longer-term responses that occur via transcriptional regulation. An apoptotic response to angiotensin has been reported (2, 4, 7), but neither the mechanism nor the involvement of specific signaling pathways is clear, although the participation of p38 mitogen-activated protein kinase, NFAT3, and reactive oxygen species has been proposed. The Gq–PLC–Ca2+–PKC pathway is implicated in the cardiovascular effects of Ang II. Moderate overexpression of Gq (or of PKC isoforms) causes hypertrophy and cardiac dysfunction (9–11); high levels of Gq activity cause heart failure. Gq activity has been inhibited in transgenic mice by overexpression of the carboxyl-terminal peptide of Gq; inhibitor-expressing transgenic mice have a reduced hypertrophic response to aortic constriction (12), demonstrating that Gq activation is necessary for this hypertrophic response. Overexpression and knockout of the AT1 receptor produce phenotypes that are consistent with the Gq data (13, 14).

What Ding et al. (8) have found builds on previous work from their laboratory. They have reported that a cyclic nucleotide phosphodiesterase, PDE3A, is downregulated in tissue taken from failing heart.
human heart and from a mouse model of pressure overload hypertrophy/failure (15). The consequences of less PDE3A activity would be similar to the effects of a specific inhibitor of PDE3, such as milrinone: reduced degradation of cAMP, with an exaggeration of responses when cAMP synthesis is stimulated, possibly confined to a specific subcellular compartment (16, 17). They have also shown that, in cultured cardiac myocytes, down-regulation of PDE3A is associated with apoptosis and induction of ICER (the inducible cAMP early repressor), a proapoptotic transcriptional repressor. Furthermore, exposure of cultured heart cells to a β-adrenergic agonist or Ang II induces a prolonged down-regulation of PDE3A and an up-regulation of ICER, suggesting that regulation of the two factors might be coordinated. Ding et al. have characterized the relationship between PDE3A and ICER in adult neonatal rat myocytes. The data are carefully and systematically presented, and there is no need to repeat them here. What is worth emphasizing is the overall picture that the data give (Fig. 2). Ang II, presumably acting via an AT1 receptor, activates an isoform of PKC. With concurrent activation of PKA, Ang II leads to a persistent up-regulation of ICER expression. Elevated ICER, in turn, transcriptionally represses PDE3A gene expression, reducing cAMP degradation, elevating cAMP, and activating PKA, completing the feedback loop. Sustained elevation of ICER results in apoptosis through inhibition of cAMP response element-binding protein (CREB)-mediated transcription and down-regulation of Bel-2 (18).

These data raise some interesting questions. How is such a positive feedback loop restrained from working at all times? Once started, can it be shut off? Ding et al. (8) suggest that apoptosis resulting from this loop is a matter of degree of activation, much as has been observed with Gs4 overexpression (9–12). Other signaling pathways also influence the elements of the feedback loop. Mitogen-activated protein kinase targets ICER for ubiquitination, whereas ICER is stabilized by the PKA pathway by inhibition of the mitogen-activated protein kinase pathway (19), and, indeed, PKA–CREB activation is needed for sustained activity of the cycle. The picture is clouded by the multiple effects of CREB-mediated signaling on cell survival: CREB up-regulates ICER in the model (Fig. 2) but also, at appropriate stages in a cell’s life, may up-regulate Bcl-2 and apoptosis inhibitor protein 2 (20), as though there is a balance between proapoptotic and antipapoptotic forces that can be upset by pathological conditions. Sustained activation of the AT1 and β1 receptors may upset this balance. One wonders about the effect of β2 stimulation, which reportedly has antiapoptotic effects (21). It seems likely that ICER and PDE3A are under additional transcriptional and posttranslational regulation, such that the feedback loop does not become deadly in “normal” cells. It will be interesting to discover those additional controls. It will also be important to examine transgenic animals lacking PDE3A. Mice lacking PDE3A are viable and without cardiac abnormalities (22), posing a challenge to the simplicity and universality of Fig. 2.

The experiments of Ding et al. (8) were performed in cultured neonatal myocytes. These cells have less intracellular structure and possibly a different complement of G protein-linked receptors than adult rat cardiac myocytes. Not all workers find Gs4-linked AT1 receptors on adult rat ventricular myocytes (23), and an effect of Ang II on adult myocytes might then be mediated, in a paracrine fashion, by an angiotensin-responsive cell, such as the ventricular fibroblast. Extrapolating from data in neonatal rat cells to adult rat myocytes is an inductive leap; extrapolating to human disease is a much greater leap. It is not clear to what extent the ICER–PDE3A–PKA cycle operates in human heart failure, although the early data suggest that aspects of the cycle are present (15). In addition, the cycle is consistent with data from several laboratory and clinical studies. β-Adrenergic agonists and inhibitors of PDE3A produce positive inotropic effects in cardiac cells and relaxation in vascular smooth muscle but do not improve mortality in heart failure. Does this dichotomy reflect the operation of the feedback loop when cAMP is pharmacologically elevated? If so, we can predict that treatments for heart failure that elevate cAMP or stimulate the Gs and Gq pathways are not likely to slow the progressive nature of heart failure and could accelerate apoptosis. Furthermore, regimens that elevate myocyte cGMP could also be deleterious, because cGMP is a competitive inhibitor of cAMP hydrolysis by PDE3A.

It is far too soon to make predictions of the relevance of these findings (summarized in Fig. 2) to human heart failure. Nonetheless, the findings of Ding et al. (8) in the neonatal rat myocyte model are provocative and should provide a focus for additional research on mechanisms of the deleterious effects of Ang II on the progress of heart failure.


Fig. 2. Proposed positive feedback loop activated by Ang II and leading to myocyte apoptosis. ISO, isoproterenol.