AT₂, Judgment Day
Which Angiotensin Receptor Is the Culprit in Cardiac Hypertrophy?

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As reviewed recently in these pages,¹ the vasoconstrictor angiotensin II (Ang II) is one of the circulating peptide growth factors, and clinically the most relevant, that fulfill many of Koch’s postulates for having additional effects locally in the myocardium. These criteria include local production of Ang II within the heart, its upregulation there by hypertrophic signals, its release from cardiac cells after mechanical load, the presence of its receptors on the surface of cardiac cells, and the responsiveness of both cardiac myocytes and cardiac fibroblasts to provocation by this peptide.¹² This local circuit of Ang II production, release, binding, and transduction within the myocardium itself is the most cogent explanation for the effectiveness of ACE inhibitors in heart failure, even at doses that do not alter loading conditions.¹²

A credible body of work even argues that AT₂ opposes cell growth, a position dichotomous with the present study. AT₂ is reported to interfere with Ang II signals that work through AT₁, including both short-term responses and long-term growth. AT₂ receptor stimulation suppresses hypertrophy in ventricular myocytes⁶⁷ in part by induction of MKP-1, a phosphatase that antagonizes the mitogen-activated protein kinase growth cascade.⁷ Likewise, AT₂ reportedly suppresses growth of cardiac fibroblasts.⁶

Context makes a difference. In isolated perfused hearts, blocking AT₁ had no effect on normal myocardium (in which AT₂ is sparse) but amplified the response to Ang II in hypertrophic hearts (in which AT₂ is increased).⁸ Analogously, blocking AT₁ interfered with the antihypertrophic, antifibrotic effects of AT₂ blockade in experimental myocardial infarction,⁹ AT₂ also is upregulated in failing human hearts, where it can inhibit activation of mitogen-activated protein kinases; some ascribe this to induction of AT₂ in cardiac fibroblasts rather than myocytes.¹⁰

A more direct challenge arises from divergent results by others who also used AT₂-null mice. Akishita et al¹¹ subjected AT₂-null and wild-type mice to suprarenal aortic banding and observed the same increase in cardiac mass and myocyte cross-sectional area, regardless of genotype. The reported paucity of AT₂ in normal ventricular myocytes suggests why deleting AT₂ might have no effect on the initial response to cardiac fibrosis induced by a 3-week infusion of Ang II. The authors rely heavily on echo-Doppler methods to assess cardiac structure, and left ventricular weight was not reported. The authors have addressed one of the important caveats for any perturbation of the renin-angiotensin system: elevation of systolic pressure by Ang II was not impeded by lack of AT₂. An obligatory role of AT₂ for hypertension induced by load also was inferred by these authors.⁴

Genetic technologies, however, do not guarantee a clear-cut answer or even concurrence with presumptively identical models. The authors’ work is difficult to reconcile with certain other evidence, including related gene deletion (“knockout”) studies. Two uncertainties in the present report should be noted in particular. In the absence of mean and diastolic pressure, one cannot fully distinguish between Ang II as a cardiac trophic factor versus a trigger for hypertension; and the lack of hypertrophy in the right ventricle after Ang II was infused is not explained. Even in the absence of increasing blood pressure, Ang II stimulates cardiac hypertrophy in vivo, which is inhibited by selective AT₁ antagonists.⁵ If AT₂ were ordinarily the mediator for this, Ang II might be expected to stimulate hypertrophy even if its other receptors were blocked. Alternatively, AT₂ might be necessary, even if not sufficient.

Three related receptors exist for Ang II: AT₁a, AT₁b, and AT₂, which communicate with a complex cell-wide web of signaling cascades through GTP-binding (G) proteins as the proximal transducer. The operation of a local circuit for Ang II within the myocardium poses two questions, which have attracted much recent experimental effort, and an even larger share of controversy. First, given that multiple receptors exist for Ang II, which type or types are responsible for pathobiology provoked by the local circuit? Second, given that cardiac muscle and nonmuscle cells are both potential targets for Ang II, what is the respective role of each?

Genetic models that altogether lack the receptors individually provide an invaluable experimental tool beyond what is achievable by use of pharmacological inhibitors alone. Surprisingly, the Ang II receptor AT₁a was superfluous for hypertrophy induced by a hemodynamic load, as well as by the reductionist surrogate, stretching cardiac cells in tissue culture (reviewed in References 1 and 2). Although adverse effects that were specifically contingent on AT₁a were identified later in mouse models of infarction,¹ the paradox remained, what about hypertrophy?

As reported by Ichihara et al¹ in this issue of Circulation, an obligatory requirement for AT₂ is suggested, from studies of mice lacking this gene, in left ventricular hypertrophy and

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load. Conversely, AT₂ deletion led to increased coronary artery thickening and perivascular fibrosis, consistent with the growth-inhibitory functions cited above. Abdominal aortic banding was used in both studies, with some difference in severity. Differences in the vectors used for gene deletion can matter, too, as a consequence of the fragment remaining or other technical issues. For AT₂, one of the null constructs could theoretically encode a small amino-terminal fragment of the receptor, although there is no proof that this is made or is stable.

Disparities in genetic background (FVB/N versus C57BL/6) could also influence physiological outcomes. Even the pressor response to Ang II, arguably a simpler test of receptor function, differed between these AT₂-null lines. This points to differences in the extracardiac effects of AT₂ deletion, which could be naive on the discrepant cardiac growth response or help pinpoint a mechanistic difference that occurs in both locations. Paracrine factors that mediate several actions of Ang II and could differ between strains include nitric oxide and heparin-binding epidermal growth factor; AT₂ activates the kinin–nitric oxide pathway but blocks the cleavage and activation of heparin-binding epidermal growth factor in response to AT₁.

Understanding the role played clinically by AT₂ in human heart failure begins with knowing that this receptor is upregulated in diseased myocardium, which differs from decoding its role in normal physiology. Clinical trials can also provide insight into the respective roles of AT₁ and AT₂ in humans. In a study of the ELITE I trial, an AT₁ antagonist and an ACE inhibitor led to comparable reverse remodeling, including reduced left ventricular diastolic volume. In ELITE II, by comparison with ACE inhibitors, no apparent exacerbation of all-cause mortality resulted from AT₁ antagonists, i.e., from the unopposed action of AT₂. At the least, these studies suggest a larger role for AT₁ in chronic human heart failure than do short-term mouse banding studies.

The specific role of AT₁ in humans thus poses several unsolved questions. No data are yet available from large randomized trials comparing AT₁ antagonists versus ACE inhibitors for regression of hypertrophy or for potential effects of AT₂ antagonists (or agonists) in human heart disease. Ligands, receptors, and transducers often play context-specific roles and are not intrinsically “good” or “bad.” In patients with infarction or heart failure, conceivably the increase in AT₂ may be salutary at first, opposing hypertrophy and fibrosis and perhaps promoting nitric oxide production. Conversely, chronic stimulation of AT₂ in myocardium by the high local and systemic levels of Ang II could have cumulative deleterious effects, including potential stimulation of apoptosis. Conventional knockouts rely on gene deletion from the fertilized egg onward, with possible compensatory adaptations. Methods to provoke gene deletion only in cardiac muscle, just after birth, should help address this concern. A gain-of-function mutation in mice also could be informative, to mimic the increase in AT₂ seen in heart disease. Mice may differ from humans, but one take-home lesson is that mice also differ from mice.

References

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