

EDITORIAL

Role of Angiotensin and its Inhibition in Hypertension, Ischemic Heart Disease and Heart Failure

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ABSTRACT

Suppression of the renin-angiotensin system (RAS) has proven efficacy not only in the treatment of hypertension, but it also greatly benefits and protects patients with ischemic cardiomyopathy and heart failure. This inhibition not only leads to symptomatic and functional improvement but it also prolongs life. The role of angiotensin inhibition in cardiovascular disease is herein briefly discussed.

RENIN-ANGIOTENSIN SYSTEM AND HYPERTENSION

The renin-angiotensin system (RAS) was extensively investigated and characterized throughout the first half of the 20th century. However, its contribution to the maintenance of high blood pressure in essential hypertension and to the development of hypertensive cardiac complications remained under debate until the advent of the first pharmacologic probes capable of blocking its actions, namely the angiotensin receptor blocker (ARB) saralasin and the angiotensin-converting enzyme inhibitor (ACEI) teprotide in the early 1970's.^{1,2} Using these probes, we could demonstrate that even in normal-renin and low-renin hypertension, blockade of the RAS produced a fall in blood pressure. And this fall was maximized if the patient had been previously submitted to sodium depletion by diuretics or low salt diet, which might produce only a small blood pressure fall by itself, but rendered the hypertension RAS-dependent and far more responsible to RAS blockade.

ISCHEMIC CARDIOMYOPATHY AND HEART FAILURE

In parallel, we had found that excess angiotensin II, either exogenous, in experimental animals, or endogenous, in various clinical settings, could produce significant cardiac and renal tissue damage, because the vasculature of these organs is particularly sensitive to the constricting effects of angiotensin.³ In particular, angiotensin excess was shown to produce widespread foci of necrosis and scarring of the myocardium, leading to replacement of myocardial tissue by fibrotic tissue, eventually progressing

LIST OF ABBREVIATIONS:

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin-receptor blocker
CVD = cardiovascular disease
RAS = renin angiotensin system
SAGE = serial analysis of gene expression

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to ischemic cardiomyopathy and heart failure.

Treatment of congestive heart failure with saralasin or with teprotide (both suitable for intravenous use only, in acute clinical experiments) resulted in significant hemodynamic improvements in terms of increased cardiac output, decreased peripheral arterial resistance, decreased heart rate, increased coronary blood flow and diminished myocardial oxygen consumption. These small clinical trials offered the “proof of concept” in support of the notion that blockade of the RAS is beneficial in the treatment of ischemic cardiomyopathy and heart failure. This concept formed the basis for subsequent large randomized long-term outcome trials with oral ACEIs or ARBs, such as the HOPE, EUROPA, LIFE, CHARM, etc, which have now established treatment with an ACEI or ARB as mandatory therapy for patients with ischemic heart disease, as well as congestive or chronic heart failure.⁴⁻⁹

It is now universally accepted that initiation of RAS-suppressing therapy with an ACEI or ARB in patients with multiple cardiovascular risk factors, not necessary including hypertension, offers long-term protection from ischemic heart disease, diastolic and systolic cardiac dysfunction, arrhythmias, as well as protection from renal insufficiency, cerebrovascular accidents and new onset type 2 diabetes mellitus.

GENOMICS

The molecular events triggered by angiotensin excess and leading to these complications are still poorly understood. We have conducted a number of genomic analyses on tissues of target organs from animals exposed to exogenous angiotensin excess using either the microarray technique (which reveals changes in expression of selected candidate genes placed on the microarray chips), or the serial analysis of gene expression (SAGE) technique, which does not require a priori knowledge of genes. The former revealed significant changes in expression of various genes related to the structure and function of cardiomyocytes, including growth factors, enzymes, receptors, etc. The latter revealed among others, a striking increase in expression of a hitherto unknown gene, the cardiomyopathy

associated 3 (Cmya 3) gene which we were able to sequence and characterize, but whose product(s) remain still unknown.¹⁰

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