ISSN 0025-7680

MEDICINA (Buenos Aires) 200; 63: 489

SIMPOSIO
"MOLECULAR PHYSIOLOGY OF VASOACTIVE PEPTIDES"

MECHANISMS REGULATING NATRIURETIC PEPTIDE GENE EXPRESSION

HEIKKI RUSKOAHO

Department of Pharmacology and Toxicology, University of Oulu, Biocenter Oulu, Finland

The natriuretic peptides are a group of structurally similar but genetically distinct peptides. A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are of cardiac origin and C-type natriuretic peptide (CNP) is of endothelial origin. The principal stimulus controlling synthesis and release of both ANP and BNP from the atria and ventricles is wall stretch. Accordingly, ventricular levels of natriuretic peptides are substantially increased in response to chronic cardiac overload. Interestingly, an acute increase in both atrial and ventricular BNP mRNA levels by pressure overload in vivo occurs within 1 hour, and mimics the rapid induction of proto-oncogenes in response to hemodynamic stress. Experiments using cultured neonatal rat ventricular cells have further shown that cardiac myocytes are able to respond to mechanical stretch by increasing BNP secretion and gene expression without neurohumoral control. However, in addition to wall stretch, a variety of endocrine, paracrine and autocrine factors that are activated in congestive heart failure (e.g. norepinephrine, angiotensin II, endothelin-1 and cytokines), have been shown to affect ANP and BNP gene expression and release. By using direct gene injection into rat ventricular myocardium we have identified several elements of the natriuretic peptide promoters that are required for transcriptional responsiveness to hemodynamic overload. A major finding is that hemodynamic stress increases BNP reporter expression through a GATA-dependent pathway. Furthermore, activation of p38 kinase is sufficient for GATA-dependent B-type natriuretic peptide gene expression. Finally, our results also suggest that posttranscriptional mechanisms may contribute to BNP mRNA levels in the ventricles.