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Adrenomedullin: regulator of systemic and cardiac homeostasis in acute myocardial infarction

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Abstract

During and following acute myocardial infarction, a variety of endogenous mediators are elevated, one of which is adrenomedullin (AM). AM is a multifunctional peptide that has been identified as having a putative beneficial role following an ischemic insult at both systemic and local levels. Classically described as a potent vasodilator, natriuretic, and diuretic agent, experimental infarct models also demonstrate AM to exhibit antiproliferative and antiapoptotic functions in the myocardium, counterregulating the effects of mediators such as angiotensin-II and endothelin-1. Less well documented are the angiogenic and inflammatory modulating potentials of AM, which may also contribute toward reducing adverse ventricular remodeling. The review examines clinical and experimental studies, looking at the effects of AM and cellular mechanisms that could be involved in mediating cardioprotective effects and ultimately optimizing left ventricular remodeling. Finally, the possibility of enhancing endogenous actions of AM by pharmacological intervention is considered.

Keywords: Adrenomedullin; Myocardial infarction; Ischemia-reperfusion; Ventricular remodeling; Cardioprotection

Abbreviations: ACE, angiotensin converting enzyme; AM, adrenomedullin; ANP, atrial natriuretic peptide; AT-II, angiotensin-II; BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CGPP, calcitonin gene-related peptide; CL, calcitonin receptor-like receptor; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; FGF, fibroblast growth factor; GSK, glucose synthase kinase; HUVEC, human umbilical vein endothelial cell; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccaride; LV, left ventricular/left ventricle; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; NAD(P)H, nicotinamide-adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; PAMP, pro-adrenomedullin N-terminal 20 peptide; PKA, protein kinase A; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; RAMP, receptor activity modifying protein; TF, tissue factor; TGF-α, transforming growth factor-α; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

Contents

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1. Introduction

Since the discovery of adrenomedullin (AM) a little over a decade ago (Kitamura et al., 1993), potential roles of this peptide in various aspects of cardiovascular regulation have been examined. Although originally isolated from human pheochromocytoma, AM is widely expressed and exerts a multitude of actions, predominantly although not exclusively, in the cardiovascular system. The myocardium and vascular endothelium are recognized as the principal sites of expression (Eto et al., 2003). Clinical and experimental studies of AM have shown that the peptide has marked influences on pressure and volume homeostasis, which come into play during many pathophysiological conditions. However, there is abundant evidence that AM plays important roles in regulating local tissue responses to several physiological and pathological factors, including hypoxia, mechanical loading, inflammation, and pressor mediators such as aldosterone, endothelin-1 (ET-1), and angiotensin-II (AT-II; Eto et al., 2003). This review focuses on the systemic and local autocrine/paracrine actions of AM in the ischemic myocardium where local expression of the peptide is markedly up-regulated. AM may act in several ways, influencing the acute and long-term outcomes of an acute ischemic episode through cytoprotective actions and through actions regulating systemic hemodynamics, neurohormonal responses, inflammatory mediators, oxidative stress, and cellular proliferation and growth.

2. Sources of the adrenomedullin family of peptides

Human mature AM is a 52-amino acid peptide containing a 6-amino acid ring and a C-terminal amidation sequence, which are highly conserved, sharing moderate sequence homology to the calcitonin family of regulatory peptides (calcitonin, CGRP-α and -β, and amylin; Champion et al., 1999). The porcine sequence is similar to that of human AM with a single substitution (Kitamura et al., 1994), whereas in the rat and mouse the sequence contains 50 amino acids (Sakata et al., 1993).

The human AM gene is localized to a single locus on chromosome 11 with 4 exons and 3 introns, as shown in Table 1 (Ishimitsu et al., 1994). Post-translational regulation of the gene product, a 185-amino acid preproAM sequence, results in the biologically inactive, 53-amino acid peptide C-terminal glycated AM (Sakata et al., 1993). Enzymatic amidation of glycated AM results in mature AM, which is biologically active and chemically less