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Review

Bench-to-bedside pharmacology of adrenomedullin

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ABSTRACT

The bioactive peptide adrenomedullin (AM) exerts pleiotropic actions in various organs and tissues. In the heart, AM has an inhibitory effect on ventricular remodeling, suppressing cardiomyocyte hypertrophy and the proliferation of cardiac fibroblasts. This pharmacological property was shown not only in rat models of acute myocardial infarction, but also clinically in patients with this cardiac disease. An originally characterized feature of AM was a potent vasodilatory effect, but this peptide was found to be important for vascular integrity and angiogenesis. AM-induced angiogenesis is involved in tumor growth, while AM inhibits apoptosis of some types of tumor cell. A unique pharmacological property is anti-inflammatory activity, which has been characterized in sepsis and inflammatory bowel diseases; thus, there is an ongoing clinical trial to test the efficacy of AM for patients with intractable ulcerative colitis. These activities are assumed to be mediated via the specific receptor formed by calcitonin receptor-like receptor and receptor activity-modifying protein 2 or 3, while some questions remain to be answered about the molecular mechanisms of this signal transduction system. Taking these findings together, AM is a bioactive peptide with pleiotropic effects, with potential as a therapeutic tool for a wide range of human diseases from myocardial infarction to malignant tumors or inflammatory bowel diseases.

Contents

1. Introduction

The integrity of the biological functions of mammals is maintained by various mechanisms, in which a number of bioactive

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substances play pivotal roles. These substances are classified into subgroups by their molecular features, and of these, a group of biologically active peptides are of particular importance in cell-to-cell, tissue-to-tissue, and organ-to-organ signaling systems. Either dysfunction or malfunction of these mechanisms results in human diseases; however, we have been able to establish pharmacotherapy methods by exploring the mechanisms of action of these bioactive peptides. For example, pharmacotherapy agents for patients with cardiovascular and renal diseases, such as angiotensin receptor blocker and angiotensin-converting enzyme inhibitor, were introduced by understanding cascades of the renin–angiotensin system (Dzau, 2005; Weber, 1999).

As a member of the biologically active peptides, adrenomedullin (AM) was discovered from tissue extract of pheochromocytoma, by monitoring cyclic AMP (cAMP) levels in platelets (Kitamura et al., 1993). Despite its discovery in tumor tissue, this peptide was found to be produced in various human organs and tissues, including the heart, lungs, kidneys, adipose tissue, and vascular endothelium, which contributes to AM circulating in the human blood (Kato and Kitamura, 2013; Kitamura et al., 2002). AM belongs to the calcitonin gene-related peptide (CGRP) superfamily, together with amylin and the AM isoform peptide AM2/intermedin, because of similarities in their molecular structures as shown in Fig. 1 (Cooper et al., 1987; Kato and Kitamura, 2013; Roh et al., 2004; Takei et al., 2004). Since the discovery of AM, a substantial number of pharmacological experiments have been performed, revealing that it is involved in mechanisms regulating or modulating biological functions in various types of cell, tissue, or organ through its pleiotropic actions (Ashizuka et al., 2013a; Kato et al., 2005, 2003a; Kitamura et al., 2002). In that process, basic research was often necessary to interpret phenomena observed clinically in patients, and indeed, these clinical findings have promoted basic pharmacological research on AM. On the basis of the pharmacological properties of AM, clinical trials have been carried out to test the efficacy of this peptide in the treatment of human diseases including acute myocardial infarction, primary pulmonary hypertension, and ulcerative colitis (Table 1) (Ashizuka et al., 2013b; Kataoka et al., 2010; Nagaya et al., 2004).

In this review article, we discuss what has been achieved in the bench-to-bedside pharmacology of AM, along with occasionally mentioning the bedside-to-bench process, as well as what we can see on the horizon when utilizing this pleiotropic peptide for the pharmacotherapy of human diseases.

2. Cardiovascular actions

Many researchers have measured the plasma AM levels of human patients with various diseases, revealing elevation of the plasma levels in heart failure, myocardial infarction, atherosclerotic arterial diseases, and pulmonary hypertension (Kakishita et al., 1999; Kato et al., 1996; Kobayashi et al., 1996; Suzuki et al., 2004). These clinical findings promoted basic research clarifying the roles of AM in regulating or modulating the biological functions of the heart and blood vessels.

Table 1
Possible therapeutic applications of pharmacological actions of AM to human diseases.

Pharmacological action	Target disease	Clinical study or trial
Cardiac remodeling inhibition	Myocardial infarction	Kataoka et al. (2010)
Vascular protection	Pulmonary hypertension	Nagaya et al. (2004)
Angiogenesis	Peripheral arterial disease	Not reported
Anti-inflammation	Inflammatory bowel diseases	Ashizuka et al. (2013b)

2.1. Heart protection

Cardiac ventricles and atria were found to produce AM, and this production was augmented in rodent models of hypertension and acute myocardial infarction (Nagaya et al., 2000; Shimokubo et al., 1996). Meanwhile, in vitro experiments with cultured cardiac cells showed that AM released from those cells acts in an autocrine or paracrine manner to suppress cardiomyocyte hypertrophy and fibroblast proliferation (Tsuruda et al., 1999, 1998). On the assumption that AM has protective roles in the heart, Nakamura et al. (2004, 2002) intraperitoneally infused synthetic AM into a rat model of myocardial infarction induced by coronary ligation during the acute stage of the disease. In their in vivo study, AM not only reduced the mortality rate of the rats, but also inhibited left ventricular remodeling and deterioration of cardiac function (Nakamura et al., 2004, 2002). Similar protective effects of AM were observed by using rodent models of myocardial infarction or injury induced by ischemia–reperfusion of the coronary artery (Hamid and Baxter, 2006; Kato et al., 2003b; Okumura et al., 2004). Multiple mechanisms appear to be involved in the protective effects on infarcted or injured heart: suppressed oxidative stress, phosphorylation of Akt and endothelial nitric oxide synthase, and inhibited myocyte apoptosis (Hamid and Baxter, 2006; Kato et al., 2003b; Nakamura et al., 2004; Okumura et al., 2004).

The clinical benefits of AM as a therapeutic agent for patients with myocardial infarction were tested in a bedside study by Kataoka et al. (2010), in which those with acute myocardial infarction received continuous, intravenous infusion of AM commenced prior to the reperfusion therapy. In this study, significant improvement of left ventricular function and reduction of infarct size were observed at 3 months (Kataoka et al., 2010), although this was a single-armed, pilot study; therefore, a randomized controlled study is necessary to verify the beneficial effect of this AM therapy.

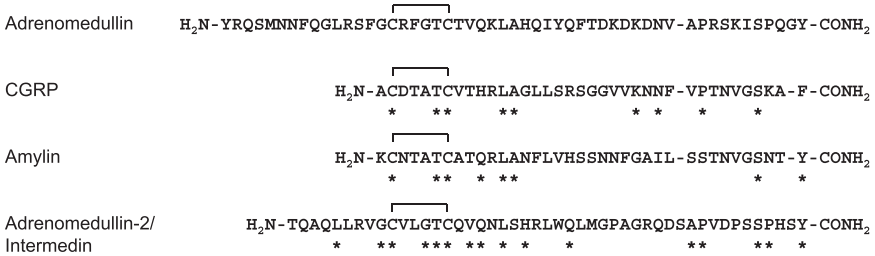

Fig. 1. Amino acid sequences of human adrenomedullin (AM), calcitonin gene-related peptide (CGRP), amylin, and AM2/intermedin. Asterisks indicate amino acids identical to those of AM.