Adrenomedullin
An Autocrine/Paracrine Factor for Cardiorenal Protection

Toshihiro Tsuruda, John C. Burnett, Jr

Since 1993, with the discovery of adrenomedullin (AM) by Kitamura and coworkers,1 we have gained many insights into the biology of this new peptide. Although AM was originally found in human pheochromocytoma, preproAM gene expression and its immunoreactivity are widely distributed in humans and rodents and found in cardiovascular tissues, kidney, digestive organs, nervous system, and tumor cells.2–4 While this ubiquitous AM distribution has prompted many investigators to clarify the role of AM, we advance the concept that the role of endogenous AM is especially important in cardiovascular and renal homeostasis. We now know that AM circulates in plasma and is present in organs and tissues with increases in AM activity in heart failure, hypertension, and renal dysfunction.5,6 Although AM was originally found by Kitamura and coworkers,1 we have gained many insights into the biology of this new peptide. Although AM circulates in plasma and is present in organs and tissues with increases in AM activity in heart failure, hypertension, and renal dysfunction.5,6 Although AM was originally found by Kitamura and coworkers,1 we have gained many insights into the biology of this new peptide.

AM synthesis may be mainly regulated by lipopolysaccharide (LPS) and cytokines, it has been reported that hormones as well as physical stimuli, stimulate AM synthesis in smooth muscle cells (SMCs), endothelial cells (ECs), and cardiomyocytes.7–12 It is also accepted that AM has multiple functional properties linked to intracellular cyclic adenosine monophosphate (cAMP) elevation. Indeed, exogenous AM administration induces vasodilation and natriuresis with cAMP elevation, resulting in beneficial cardiorenal response in humans with heart failure.13 Although AM was originally found by monitoring cAMP elevation in platelets,1 supporting a key role for cAMP, it has been reported that the nitric oxide (NO)-cGMP pathway also contributes to actions of AM.14 In addition, a third pathway might mediate the AM signal.15

**AM as an Autocrine or Paracrine Factor**

To date, the role of AM as an autocrine or paracrine factor has been studied using receptor antagonists, such as calcitonin gene–related peptide (CGRP), type 1 receptor antagonist [human CGRP (8-37)], the N-terminal–deleted form of AM [human AM (22-52)], and AM monoclonal antibodies for neutralizing AM biological activity.16–21 However, the effects of these former two antagonists to inhibit AM differ among studies, indicating the presence of AM receptor subtypes or differences of AM receptors in organ-specific or species-specific conditions. Several earlier studies have demonstrated the role of AM as an autocrine or paracrine factor but mainly in in vitro environments. The Figure illustrates the mechanism of action of AM as an autocrine or paracrine factor in the vasculature. For instance, Michibata et al20 have reported neutralization of endogenous AM by monoclonal antibodies’ reduced basal production of cAMP and increased DNA synthesis in ECs. In addition, Kato et al21 have shown AM is antiapoptotic via a paracrine mechanism that can be neutralized by monoclonal antibody. These data indicate AM may act as a local factor as well as an endocrine factor.

**Lessons From Transgenic and Knockout Mouse**

In the present issue of *Circulation Research*, studies by Nishimatsu and coworkers22 have importantly demonstrated the protective properties of endogenous AM on renal injury, using transgenic and knockout mouse models. They concluded that AM has a cytoprotective property and that the beneficial “endogenous” effects of AM are mediated, in part, by the enhanced production of NO. This group has shown previously that in mice with AM overexpression, blood pressure was lower and there was resistance to LPS-induced hepatic injury and an increased mortality rate.23 On the other hand, AM gene knockout mice have also been established by two independent groups.24,25 In these studies, AM-deficient mice (heterozygous) had higher blood pressure compared with wild types and, importantly, homozygous mice were associated with death at midgestation and demonstrated cardiovascular abnormalities. From these gene engineering studies, endogenous AM clearly regulates blood pressure by controlling vascular tone and has cytoprotective properties that are in part mediated by an NO-cGMP pathway. These studies establish a critical role for endogenous AM in organogenesis. Further studies are warranted to clarify the role of endogenous AM, especially on the remodeling process in the cardiovascular system.

**Therapeutic Potential of Local AM in Cardiovascular and Renal Disease**

The work by Nishimatsu et al22 supports the development of AM as a potential therapy in cardiorenal disease. McLatchie et al26 have isolated and cloned a receptor-modifying protein (RAMP) accessory protein that induces three isoforms (RAMP1, RAMP2, and RAMP3), and coexpression of RAMP2 or RAMP3 and calcitonin receptor–related receptor (CRLR) functions as a specific AM receptor. Kuwasako et al27 have recently defined the critical step for stimulating AM action inside RAMP2 and RAMP3. This finding indicates that development of receptor agonists or antagonists may modulate the action of endogenous AM and might be a useful means for treatment. Another therapeutic strategy comes
Autocrine and paracrine pathways for endogenous AM actions in the vasculature. Action of AM is mainly mediated by cAMP and NO-cGMP pathway. See text for details. AM indicates adrenomedullin; NOS, nitric oxide synthase; NO, nitric oxide; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; LPS, lipopolysaccharide; CAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; and PKA, protein kinase A.

from our understanding of modulating AM by degradation. To date, AM lacks oral activity and has a short plasma half-life so that intravenous infusions are required to achieve and maintain therapeutically effective levels. An emerging concept of treatment is to potentiate “endogenous” AM by inhibiting its degradation. AM is now thought to be a substrate for neutral endopeptidase (NEP), a membrane-bound zinc metalloprotease that is abundantly present in the kidney. Indeed, inhibition of NEP augments the natriuretic and diuretic action of AM in physiological conditions as well as in experimental heart failure.\(^{28,29}\) In addition, enhanced local production by AM gene delivery may be another strategy for treatment of cardiovascular and renal disease.

As discussed, AM is present throughout the body and its action is mainly mediated by cAMP but also by cGMP elevation. When the AM molecule is given systemically, stimulation of intracellular cAMP and/or cGMP may result in elevation. When the AM molecule is given systemically, action is mainly mediated by cAMP but also by cGMP strateg for treatment of cardiovascular and renal disease.

**Summary**

In summary, the study by Nishimatsu and coworkers advances our understanding of the biology of endogenous AM and supports the role of endogenous AM as an autocrine or paracrine factor in cardiorenal regulation. Furthermore, endogenous AM contributes a cytoprotective effect against organ damage, indicating that AM is a potential therapeutic candidate for the treatment of cardiovascular and renal disease.

**References**


Key Words: adrenomedullin transgenic knockout autocrine paracrine
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Circ Res. 2002;90:625-627
doi: 10.1161/01.RES.0000015462.11528.28
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/90/6/625

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