



Translational studies of adrenomedullin and related peptides regarding cardiovascular diseases

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Abstract

Adrenomedullin (AM) is a vasodilative peptide with various physiological functions, including the maintenance of vascular tone and endothelial barrier function. AM levels are markedly increased during severe inflammation, such as that associated with sepsis; thus, AM is expected to be a useful clinical marker and therapeutic agent for inflammation. However, as the increase in AM levels in cardiovascular diseases (CVDs) is relatively low compared to that in infectious diseases, the value of AM as a marker of CVDs seems to be less important. Limitations pertaining to the administrative route and short half-life of AM in the bloodstream (<30 min) restrict the therapeutic applications of AM for CVDs. In early human studies, various applications of AM for CVDs were attempted, including for heart failure, myocardial infarction, pulmonary hypertension, and peripheral artery disease; however, none achieved success. We have developed AM as a therapeutic agent for inflammatory bowel disease in which the vasodilatory effect of AM is minimized. A clinical trial evaluating this AM formulation for acute cerebral infarction is ongoing. We have also developed AM derivatives that exhibit a longer half-life and less vasodilative activity. These AM derivatives can be administered by subcutaneous injection at long-term intervals. Accordingly, these derivatives will reduce the inconvenience in use compared to that for native AM and expand the possible applications of AM for treating CVDs. In this review, we present the latest translational status of AM and its derivatives.

Keywords Adrenomedullin · Translational research · Clinical trial · Adrecizumab · PEGylated adrenomedullin

Introduction

Cardiovascular diseases (CVDs) are a major public health problem worldwide. For instance, heart failure (HF) is a therapy-resistant cause of death, with a relatively high incidence of 1–2% in developed countries [1]. Surprisingly, the lifetime risk of developing HF for individuals 55 years of age is 33% for men and 28% for women [1]. The pathogenesis of HF is quite complicated, and thus, versatile approaches are needed for its treatment. Innovative agents, such as angiotensin receptor neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter-2 inhibitors, have been recently introduced for the treatment of HF; [2, 3] however, an unmet need for HF remains.

Adrenomedullin (AM or ADM) is an endogenous vasodilatory peptide that has many diverse effects and functions, including organ protection, anti-inflammatory effects, and tissue repair. AM and AM receptors are ubiquitously present in various tissues and are highly expressed in blood vessels. Furthermore, constitutive expression of AM and AM receptors has been confirmed in the heart, kidneys, brain, lungs, and adrenal glands of humans and various animals [4–6]. Due to its vasodilatory effect and constant expression in the cardiovascular system, AM was initially expected to be a candidate therapeutic agent for CVDs, including HF. However, the potential exploitation of AM to treat various CVDs has not been as thoroughly explored as expected.

AM is ubiquitously expressed in many organs, which should be an advantage for its use to treat many diseases in various organs. However, this ubiquitous expression may be a disadvantage, as it makes it difficult to focus on organ-specific effects of AM. Furthermore, care will be needed in using AM considering its potential systematic effects. In contrast, great success has been achieved using natriuretic peptides in treating HF. Specifically, brain natriuretic

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peptide (BNP) and the N-terminal fragment of pro-BNP (NT-pro-BNP) have been used as clinical markers of HF, while atrial natriuretic peptide (ANP) has been employed as a therapeutic agent for treating acute HF. Both ANP and BNP levels are markedly increased in patients with HF, indicating that they are critically involved in the pathogenesis of HF. Generally, native peptides achieve their maximum potential mostly under the required conditions. Unfortunately, the increase in AM levels in CVDs is limited. As a result, AM may not be capable of preventing or controlling CVD progression. In contrast, levels of AM are drastically increased during severe infections, such as sepsis and severe pneumonia [7–19]. Therefore, the development of AM as a clinical marker and therapeutic agent in severe infections, including coronavirus disease 2019 (COVID-19), is highly expected. However, the nature of the AM peptide restricts its application for CVDs, as the method of administration requires continuous intravenous injection. To overcome this limitation, we have developed long-acting AM derivatives for use in treating various diseases, including CVDs. In this review, we highlight early studies on AM regarding CVDs, describe the issues and challenges related to AM, present information on a current clinical trial of AM, and discuss the future prospects of AM.

Biosynthesis of AM and its receptors

AM is composed of 52 amino acids, has a ring structure containing a disulfide bond between Cys¹⁶ and Cys²¹ and is amidated at the C-terminal Tyr⁵² [20]. Both disulfide bonds and amidation are crucial for bioactivity and are highly conserved in calcitonin (CT) and the two forms of calcitonin gene-related peptide (CGRP), amylin and adrenomedullin2/intermedin [21, 22]. Therefore, AM is considered a member of the CT/CGRP superfamily [21, 22]. The AM gene, which consists of four exons, is located on chromosome 11 [23]. AM is synthesized as a large prohormone and processed to proadrenomedullin (proAM), including amino acid residues 22–185, which is then fragmented into four segments, namely, proAM N-terminal 20 peptide (PAMP)-Gly, mid-regional proadrenomedullin (MR-proADM, 45–92), AM-Gly, and C-terminal proAM (adrenotensin) [20]. Both PAMP and AM are initially processed as intermediate forms (C-terminally glycine-extended forms), which are biologically inactive. The C-terminal glycine of these peptides is subsequently amidated by an amidation enzyme, and the peptides are then converted to their mature bioactive forms; however, only a portion of the peptides are converted [24]. MR-proADM is a nonbioactive fragment that is stable in the bloodstream and is therefore useful as a biomarker of AM synthesis [25].

The receptors for the CT/CGRP family consist of two different types of molecules, G protein-coupled receptors (GPCRs) and chaperone molecules called receptor activity-modifying proteins (RAMPs). For the CT/CGRP family, there are two forms of GPCRs, calcitonin receptor (CTR) and calcitonin receptor-like receptor (CRLR), and three forms of RAMPs (1, 2, and 3). CTR functions independently as a CT receptor, but the other receptors require the assistance of the RAMPs. For instance, CTR + RAMPs serve as the amylin receptor, CRLR + RAMP1 serves as the CGRP receptor, CRLR + RAMP2 serves as the AM1 receptor, and CRLR + RAMP3 serves as the AM2 receptor [26]. AM has equal affinity for both AM1 and AM2 receptors. AM and AM2/intermedin exhibit a similar high affinity for AM2 receptor [26]. Models have shown that the knockout (KO) of AM is lethal at mid-gestation due to serious vascular abnormalities and causes extreme hydrops [27, 28]. CRLR KO in mice is also lethal, but interestingly, CGRP KO mice appear to be normal, and only the KO of RAMP2 causes lethal abnormalities, such as those observed upon the KO of AM [29, 30]. These findings suggest that AM and AM1 receptors are crucial for angiogenesis and vascular homeostasis, while the AM2 receptor has been shown to be important for lymph vessel function [31].

Cardiovascular effects of AM

AM is present in both the endothelium and vascular smooth muscle cells. The most important functions of AM in the vasculature are vasodilation and the maintenance of vascular integrity. AM is thought to maintain vascular tone through direct action on vascular smooth muscle cells and the formation of nitric oxide [32]. The vasodilative ability of AM is as strong as that of ANP [33]. The administration of AM decreases blood pressure in vessels but increases blood flow [34]. This vasodilative effect of AM may be beneficial for congestive HF and pulmonary hypertension [35, 36]. In contrast, this vasodilation also causes unwanted decreases in blood pressure during the application of AM because of its pleiotropic effects on other targets, such as in inflammatory bowel disease (IBD) [37].

AM plays an important role in maintaining vascular integrity. AM KO and RAMP2 KO mice experience lethal edema due to vascular abnormalities [27, 28, 30]. Furthermore, endothelial cell-specific RAMP2 KO (E-RAMP2^{-/-}) mice die during the perinatal period due to edema, wherein the malformation of endothelial cells and the detachment of endothelial cells from the basement membrane are observed. Only 5% of E-RAMP2^{-/-} mice survive until adulthood, and they show the same vascular abnormalities and marked accumulation of inflammatory cells along the blood vessels of major organs [38]. AM is an endogenous key factor that

Table 1 Various effects of adrenomedullin

Ogan	Effects	References
Blood vessels	Vasodilation	[42]
	Inhibition of excessive proliferation of SMCs	[43, 44]
	Inhibition of apoptosis	[45, 46]
	Angiogenesis	[47, 48]
	Reduction of endothelin production	[49, 50]
Heart	Increase of coronary flow	[51]
	Stimulation of ANP production	[52, 53]
	Inhibition of cardiac hypertrophy	[54, 55]
	Reduction of myocardial fibrosis	[55, 56]
Lung	Pulmonary artery dilatation	[36]
	Antifibrotic effect	[57, 58]
Adrenal gland	Reduction of aldosterone production	[59, 60]
Kidney	Diuretic and natriuretic effects	[61, 62]
	Inhibition of excessive proliferation of mesangial cells	[63]
CNS	Increase of cerebral blood flow	[64, 65]
	Inhibition of water-drinking	[66]
	Inhibition of salt intake	[67]
RAA system	Counteraction against the RAA system	[144]

SMCs smooth muscle cells, ANP atrial natriuretic peptide, CNS central nervous system, RAA renin-angiotensin-aldosterone

maintains vascular endothelial barrier function and decreases vascular permeability during severe inflammation [39]. For example, AM decreases lung permeability and suppresses lung injury in lipopolysaccharide (LPS)-induced pneumonia in mice [40]. AM may counteract acute HF-induced overload of tissue fluid by stabilizing endothelial barrier function. Indeed, AM levels increase in acute HF, proportional to the severity of pulmonary congestion [41].

Pleotropic effects of AM have been reported in cardiovascular and renal systems [36, 42–67] and are shown in Table 1. Generally, AM counteracts the renin-angiotensin-aldosterone system and oxidative stress [68, 69] and suppresses excessive tissue proliferation. Consequently, AM decreases tissue injuries in organs caused by various pathogenic stimuli.

Plasma levels of AM

Several systems for measuring the plasma concentration of AM and related peptides have been reported. The intermediate inactive form and mature active form of AM have been confirmed to be present in the bloodstream, with levels of the intermediate form being almost ten times higher than those of the mature form [24]. In early studies, total AM (intermediate + mature forms) levels in various disease

states were found to be two- to three-times higher than the basal levels in a healthy state [70]. However, even plasma levels of total AM were markedly increased during systemic inflammatory response syndrome, including that caused by sepsis [71]. A specific system for measuring the levels of mature AM was subsequently established by Ohta et al. [72], followed by the development of a similar system by Weber and colleagues [73] for measuring the levels of mature AM, which they called bioactive ADM or “bio-ADM.” The plasma levels of AM in healthy individuals were reported to be 7.08 ± 3.9 pg/mL using the system of Ohta et al. and 15.6 ± 9.2 pg/mL using the system of Weber et al. [72, 73]. Our group used an automated enzyme immune assay analyzer (AIA-1800, Toso, Tokyo, Japan). In our phase 1 trial employing this system, using the same antibodies as those used by Ohta et al., we determined the plasma levels of AM in healthy males to be 7.2 ± 1.4 pg/mL [74]. As mature AM is bioactive, these measured levels should reflect the dynamic state of AM in various diseases. Recently reported plasma levels of bioactive ADM are shown in Fig. 1, which includes our data from recent clinical trials [37, 74–79]. These studies employed a one-step luminescence sandwich immunoassay (SphingoTec GmbH, Hennigsdorf, Germany) [73], and the median plasma levels in healthy individuals were reported to be 20.7 pg/mL (43 pg/mL, upper range of the 99th percentile) [15]. The increase in AM levels in the absence of major injury and/or overload to the endothelium, such as that seen during subarachnoid hemorrhage, is limited [75]. However, significant increases in AM levels are observed in conjunction with major injury and/or overload to the endothelium, such as during acute HF or shock, with the level of AM increasing according to the severity of disease [41, 76, 77]. Importantly, the addition of inflammation markedly enhances the level of AM, similar to that associated with sepsis [19, 78]. The highest concentrations (C_{\max}) of AM observed during our clinical trials are shown in the lower part of Fig. 1. As our assay system showed lower AM values than the bio-ADM values reported by Weber et al., the dosage of AM chosen for use in our trials covered the ranges of bioactive ADM in various diseases, including sepsis and COVID-19 (Fig. 1).

Based on findings from early research, MR-pro ADM is a stable, nonbioactive fragment that is easy to assess in blood samples and is expected to serve as a biomarker of AM synthesis [25]. Many reports have been published regarding MR-pro ADM during various infectious diseases, especially sepsis [7–14, 17]. Meta-analysis showed that MR-pro ADM has high sensitivity and specificity as a prognostic marker of sepsis, at 0.83 (95% CI: 0.79–0.87) and 0.90 (95% CI: 0.83–0.94), respectively [79]. The relatively high sensitivity and specificity of MR-pro ADM levels as a prognostic indicator was confirmed even for

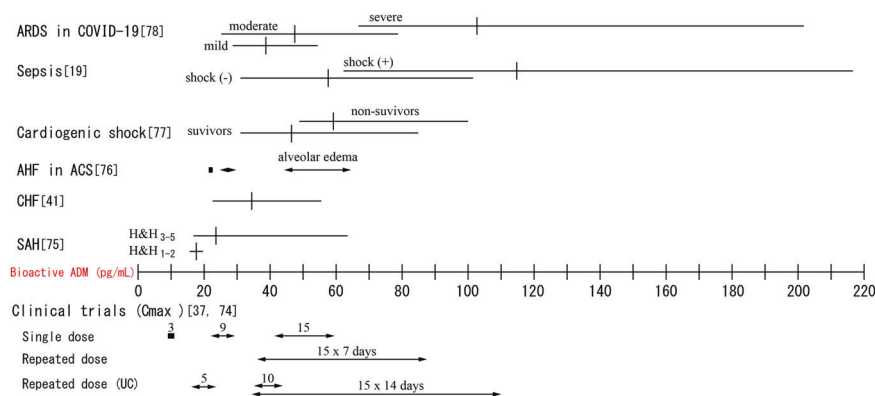
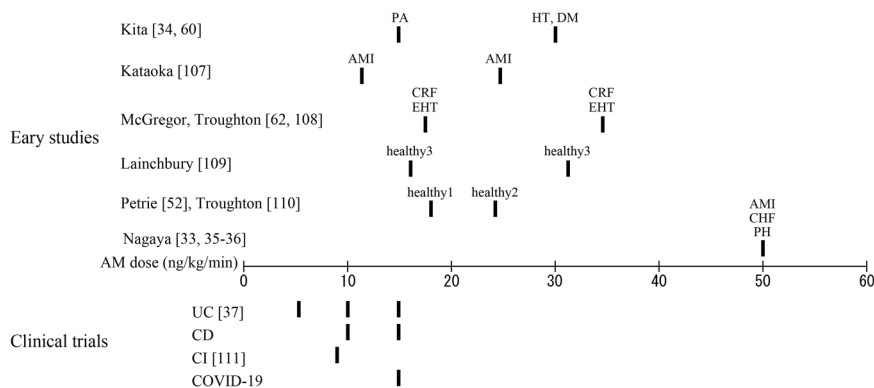


Fig. 1 Plasma concentrations of bioactive adrenomedullin (ADM) in various diseases and the maximum concentration (C_{max}) used in our current trials. The assay systems used in the studies referred to in the upper and lower parts of the figure used different antibodies. As a result, AM concentrations in studies shown in the lower section of the figure are lower than those shown in the upper section. Plasma

concentrations in the SAH study and clinical trials are shown as the mean \pm SD. All others are shown as the median with the interquartile range. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; AHF, acute heart failure; ACS, acute coronary syndrome; CHF, congestive heart failure; SAH, subarachnoid hemorrhage; H & H, Hunt and Hess grading scale; UC, ulcerative colitis

Fig. 2 Doses of adrenomedullin (AM) used in early studies and recent clinical trials. PA, primary aldosteronism; HT, hypertension; DM, diabetes mellitus; AMI, acute myocardial infarction; CRF, chronic renal failure; EHT, essential hypertension; CHF, congestive heart failure; PH, pulmonary hypertension; UC, ulcerative colitis; CD, Crohn's disease; CI, cerebral infarction; COVID-19, coronavirus disease 2019



community-acquired pneumonia, with values of 0.74 (95% CI: 0.67–0.79) and 0.73 (95% CI: 0.70–0.77), respectively [80]. In addition, MR-pro ADM seems to be a useful prognostic marker for COVID-19 [81–91]. Both BNP and NT-pro-BNP have been established as markers for HF. Interestingly, MR-pro ADM has been reported to demonstrate superior prognostic significance compared to that of natriuretic peptides or related pro-segments in several studies [92–94]. However, other studies failed to detect this superiority of MR-pro ADM [95–97]. Based on all the existing data, MR-pro ADM appears to remain a subsidiary marker of HF. An intermediate prognostic value of MR-pro ADM in myocardial infarction has also been reported [98–100]. Likewise, interesting observations have been reported for MR-pro ADM regarding catheter ablation, infectious endocarditis, and transcatheter aortic valve replacement [101–104]. Wallentin et al. performed a comparative analysis of the importance of biomarkers in chronic coronary heart disease and reported that NT-pro-BNP, troponin-T, and BNP demonstrate high importance, while AM remains less important [105]. Current guidelines

recommend only BNP and/or NT-pro-BNP as markers for HF management [106]. AM is an inhibitor of tissue congestion; thus, AM and MR-pro ADM are attractive and superior biomarkers for tissue congestion, such as edema and pulmonary congestion [41, 76]. However, BNP and/or NT-pro-BNP are more important biomarkers for diagnosis and prognosis estimation for HF; [97] therefore, AM remains an ancillary marker under the present circumstances.

Interventional studies on AM for humans

Figure 2 summarizes the doses of AM used for studies in humans [33–36, 52, 60, 74, 107–111]. Initially, relatively large doses of AM were administered to humans in an effort to alter hemodynamic states and humoral factors. The highest reported dose was 50 ng/kg/min, at which obvious decreases in blood pressure and increases in heart rate occurred, even after short-term administration [35]. An increase in the cardiac index was also observed, probably due to a decrease in systemic vascular resistance [35]. AM

also decreases pulmonary arterial pressure in patients with pulmonary hypertension and lowers systemic blood pressure [36]. AM has also been reported to have diuretic and natriuretic effects in humans [35, 62], but other studies failed to confirm these effects [109]. Therefore, the diuretic and natriuretic effects of AM seem to be limited in humans. AM also induces humoral alterations. For instance, when relatively high doses of AM are used for short-term administration, AM increases plasma renin activity (PRA) and noradrenaline levels but does not change the plasma aldosterone concentration (PAC) [34, 62, 108, 109]. The increases in PRA and noradrenaline levels seem to be responses secondary to the hypotension caused by the vasodilative action of AM. On the other hand, the use of a lower dose of AM for long-term administration causes an obvious decrease in the PAC, while the impact on PRA and noradrenaline is quite limited [60]. Direct suppression of aldosterone release from the adrenal glands and aldosterone-producing adenomas by AM has also been reported [112, 113], indicating that this direct effect is independent of the PRA increase caused by AM.

The indicated doses in Fig. 2 may have some measurement errors due to incompleteness and heterogeneity in the preparation and weighing methods. In contrast, our clinical trial used AM prepared according to good manufacturing practice (GMP), and thus, the doses were exactly measured [37, 74]. For example, we observed clear decreases in blood pressure and the PAC with the infusion of AM at a dose of 15 ng/kg/min in a previous study [60], but blood pressure and the PAC were stable in phase 1 trials even though we used the same amount of AM [74]. Previously, based on our experience, we used a 1.4-fold dose of a bulk AM powder to compensate for internal water contamination in the bulk powder; therefore, the actual dose of the AM formulation might have been higher than the attributed 15 ng/kg/min.

Translational studies on AM for CVDs

We developed an AM formulation for the treatment of IBD [114]. The minimization of the hemodynamic and humoral effects of AM is essential to prevent adverse events in patients with IBD. We confirmed that AM at a dose of 15 ng/kg/min is safe and tolerable for both healthy individuals and patients with IBD. This dose was also effective in patients with steroid-resistant ulcerative colitis [37]. We are currently conducting an investigator-initiated clinical trial using this maximum dose of AM to treat patients with moderate to severe pneumonia caused by COVID-19 (jRCT2071200041, jRCT2071210038). We expect that this dose of AM will be effective, even in patients with severe pneumonia, as indicated in Fig. 1. Furthermore, this dose, based on human equivalent dose conversion, is similar

to that of an effective AM dose used in the treatment of LPS-induced pneumonia in mice [40].

Heart failure

Because AM is a vasodilative peptide, the administration route is limited to continuous venous infusion. Additionally, the half-life of AM in the bloodstream is very short (less than 30 min) [74], suggesting that AM treatment administration may be limited to the acute phase of the disease. While the hemodynamic and humoral effects of AM seem to be attractive for the treatment of CVDs, the regulation of these effects is difficult in general clinical practice. Therefore, we explored the upper limit of safe and effective doses of AM. We determined that AM at a dose of 15 ng/kg/min causes very limited hemodynamic influences, but the C_{max} of this dose overcomes the plasma concentration of AM in HF (Fig. 1). These findings suggest that 15 ng/kg/min AM is probably effective for HF, where it may reduce pulmonary edema by stabilizing endothelial barrier function without having notable hemodynamic or humoral effects. The combination therapy of AM and human ANP (hANP) for decompensated HF was also reported in a pilot study [115]. This approach is interesting, but hANP alone seems to be sufficient for the treatment of ordinary HF. Notably, the combination of AM and hANP may be useful for treating patients with worsening HF due to pneumonia. Because AM countervails severe inflammation and related organ damage through various mechanisms [116], it may contribute to the amelioration of the complicated state of HF with inflammation.

Myocardial infarction

The application of AM for treating patients with acute myocardial infarction has been attempted previously [33], but the development of this application has since stagnated.

Pulmonary hypertension

Venous infusion of AM can dilate pulmonary arteries and decrease pulmonary arterial pressure; however, it also decreases systemic blood pressure [36]. In addition to the difficulty in its handling, AM fails to exceed the performance of existing drugs available for treating pulmonary hypertension, making its current status for this use unsatisfactory.

Imaging of pulmonary circulation

AM receptors are abundantly expressed in the lungs, especially in the endothelium of alveolar capillaries [117, 118], and the lung functions as a primary site for AM

clearance [119, 120]. Additionally, the expression of AM receptors is altered under pathological conditions, such as pulmonary hypertension [121]. An interesting approach for imaging the human pulmonary vascular endothelium is by using AM receptor ligands, such as ^{125}I -rAM (1-50) and $^{99\text{m}}\text{Tc}$ -PulmoBind, for PET and SPECT imaging [122–124]. Compared to existing radiopharmaceuticals for pulmonary vascular imaging, namely, $^{99\text{m}}\text{Tc}$ -albumin macroaggregates, small molecules of AM receptor ligands can be used to visualize pulmonary microcirculation. In addition, AM receptor ligands can be used to detect alterations in the biology of the pulmonary circulation, which are reflected in changes in AM receptor expression [124]. This approach seems to be a promising alternative for the assessment of the pulmonary circulation.

Cerebral infarction

An investigator-initiated clinical trial using AM to treat patients with cerebral infarction was conducted at the National Cerebral and Cardiovascular Center Hospital, Suita, Japan [111]. This trial used our AM formulation at a dose of 9 ng/kg/min along with a 72-h continuous infusion of AM in a second cohort [111]. As AM levels increase during ischemic stroke, AM may be beneficial for tissue protection and for promoting angiogenesis after stroke. Increased AM levels are also associated with later neurological severity and the long-term outcomes of patients who have suffered an ischemic stroke [125, 126]. In a focal ischemic model, the infarct size increased in mice with brain-specific conditional KO of AM [127]. In addition, brain protective effects of AM have been reported, such as decreased apoptosis and the promotion of nerve regeneration and angiogenesis against ischemic injury and hypoxic stress [128–132]. This trial aimed to evaluate the efficacy and safety of AM and tissue plasminogen activator (tPA) combination therapy in acute ischemic stroke. The recanalization of the major cerebral arteries can be achieved by tPA treatment. At the same time, AM may contribute to ameliorating acute brain ischemic damage and facilitating cerebrovascular regeneration. Additionally, AM can preserve cognitive decline after chronic cerebral hypoperfusion [130].

Reinforcement of endogenous AM

Plasma concentrations of AM increase in various diseases, but the increase is not necessarily sufficient to relieve the diseases. Conversely, it should be beneficial to increase endogenous AM concentrations to enhance the benefit of AM in regard to disease improvement. The endopeptidase neprilysin inhibits the degradation of natriuretic peptides

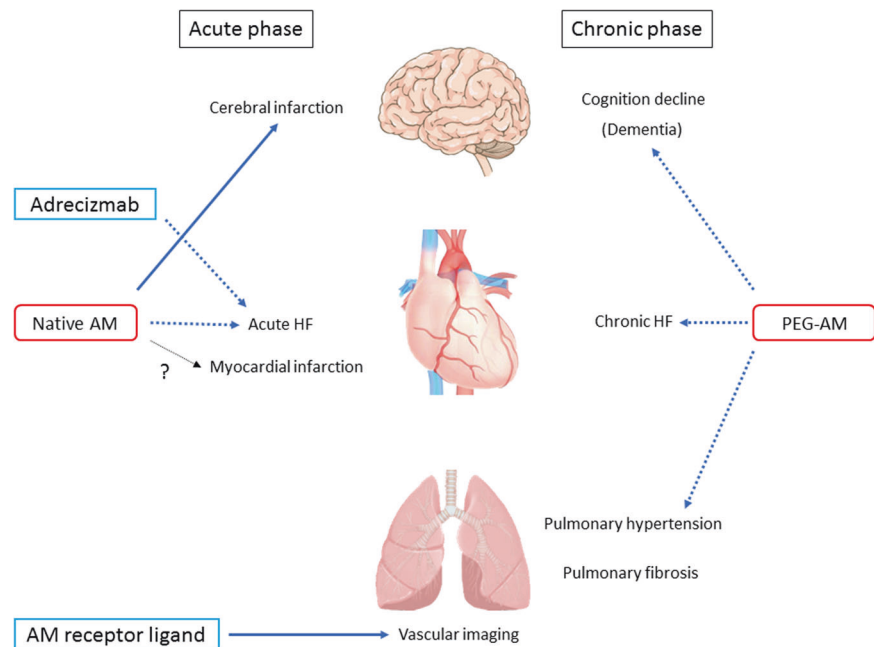
and other peptides, such as bradykinin, substance P, and AM, and contributes to HF improvement [133]. The preservation of natriuretic peptides is thought to be the main effect of ANRIs, but AM may also significantly contribute to HF improvement. Indeed, the proportional increase in levels of bioactive ADM markedly exceeds the increase in BNP levels in HF patients who receive treatment that includes an ANRI [134]. This approach may also be useful for treating other diseases, especially those that exhibit increased plasma levels of AM.

Adrecizumab is a nonneutralizing humanized high-affinity antibody directed against the N-terminus of AM. Adrecizumab binds to AM, forming a large molecule; this modification protects the bound AM from proteolytic enzymes and results in a longer half-life of AM in the bloodstream. The N-terminus of AM is unrelated to its bioactivity. Therefore, adrecizumab can enhance the beneficial effects of endogenous AM in patients with high plasma levels of AM. The effectiveness of adrecizumab was confirmed in a rodent model of sepsis [135], and a phase 1 trial was successfully conducted [136]. More recently, a phase 2 trial for patients with sepsis has been ongoing [137]. Adrecizumab may also be used for the treatment of patients with HF, especially those with higher levels of plasma AM.

AM modifications to extend its half-life in the bloodstream

To overcome some of the limitations of AM, we have developed derivatives that exhibit a long half-life and less vasodilative activity than native AM. As noted above, the N-terminus of AM is unrelated to its bioactivity. Therefore, various structures can be attached at this region of AM with limited influence on its activity. The leading derivative is a 5 kDa polyethylene glycol-modified (PEGylated) AM, which has a longer half-life and less hypotensive effect than nonmodified AM [138]. However, because the practical use of this derivative was reported to be unfeasible, a PEGylated AM derivative with a larger molecular weight of 60 kDa was created [139]. This derivative maintains an effective concentration for ~2 weeks and has less of a hemodynamic effect, allowing it to be administered by subcutaneous injection [139]. Other derivatives have also been developed, such as an IgG Fc region fused-AM and human albumin-modified AM [140, 141]. The 60 kDa PEGylated AM has shown therapeutic usefulness in a rodent model of colitis, similar to that of native AM [139]. Additionally, 60 kDa PEGylated AM was effective in a rat model of vascular dementia [142]. Long-lasting and subcutaneously injectable formulations of AM will be applied as chronic therapy, such as maintenance therapy for treating

Fig. 3 Potential applications of adrenomedullin (AM) and PEGylated AM (PEG-AM) in cardiovascular diseases. HF, heart failure



patients with IBD. A clinical trial on patients with IBD is currently planned using this 60 kDa PEGylated formulation of AM. In addition, this formulation may be applied to treat chronic HF or cerebrovascular diseases. Moreover, AM is expected to be a therapeutic agent for neurodegenerative diseases [143]. Finally, PEGylated AM can also be applied for treating pulmonary hypertension and may delay the progression of pulmonary fibrosis [58].

Conclusion

AM is an important biologically active peptide that helps maintain vascular tone and endothelial barrier function. Initially, the attention of researchers was centered on the vasodilative action of AM, but the regulation of this action in clinical settings was difficult. Thereafter, for IBD therapy, we developed an AM formulation that functions within the range of minimal vasodilative activity to reduce the adverse effects related to the vasodilation characteristics of native AM. Translational studies on AM are currently focused on its pleotropic effects and not only on its vasodilative effects. Under these circumstances, the applications of native AM for treating CVDs, as well as other conditions such as cerebral infarction, are limited. However, AM derivatives that exhibit longer half-lives, such as PEGylated AM, are promising for the general overall area of CVDs. The current attempts and possible application of AM and its derivatives in treating CVDs are summarized in Fig. 3. Unfortunately, the current applications of AM are limited; however, the future potential, especially for AM derivatives, seems to be promising.

Author contributions TK performed the literature review and wrote the paper. KK reviewed the paper.

Compliance with ethical standard

Conflict of interest The authors declare no competing interests.

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