Adrenomedullin: A vasoactive agent for sporadic and hereditary vascular cognitive impairment

Masafumi Ihara*, Kazuo Washida, Takeshi Yoshimoto, Satoshi Saito

Department of Neurology, National Cerebral and Cardiovascular Center, 6-1 Kishibe Shimmachi, Suita, Osaka 564-8565 Japan

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ABSTRACT

Adrenomedullin (AM) is an endogenous peptide mainly secreted from endothelial cells, which has multiple physiological actions such as anti-inflammation, vasodilation, vascular permeability regulation and angiogenesis. Blood AM levels are upregulated in a variety of pathological states including sepsis, severe COVID-19, acute ischemic stroke and vascular cognitive impairment with white matter changes, likely serving as a compensatory biological defense response against infection and ischemia. AM is currently being tested in clinical trials for ulcerative colitis, Crohn's disease, severe COVID-19 for its anti-inflammatory properties and in ischemic stroke for its additional angiogenic action. AM has been proposed as a therapeutic option for vascular cognitive impairment as its arteriogenic and angiogenic properties are thought to contribute to a slowing of cognitive decline in mice after chronic cerebral hypoperfusion. As AM promotes differentiation of oligodendrocyte precursor cells into mature oligodendrocytes under hypoxic conditions, AM could also be used in the treatment of CADASIL, where reduced oxygen delivery is thought to lead to the death of hypoxia-prone oligodendrocytes. AM therefore holds potential as an innovative therapeutic drug, which may regenerate blood vessels, while controlling inflammation in cerebrovascular diseases.

Introduction

Advances in acute stroke therapies, such as intravenous tissue plasminogen activator and endovascular treatment, have resulted in improved vessel recanalization rate of 70–80%, benefitting many patients after ischemic stroke. However, according to recent global burden of disease data on stroke, in 2013 there were 25.7 million stroke survivors, 6.5 million deaths from stroke, 113 million DALYs due to stroke, and 10.3 million new strokes. Stroke is also the main cause of becoming bedridden, dementia and death [1]. The treatment of acute stroke poses two major issues; firstly, how to resolve tissue damage resulting from acute stroke and, secondly, how to alleviate long-term stroke-associated effects such as vascular cognitive impairment. Despite considerable enthusiasm and investment from the pharmaceutical industry, clinical trials of many drugs for many cardiovascular diseases, including stroke, have been unsuccessful [2]. Nevertheless, several natural endogenously-occurring peptides or peptidomimetics, synthesized by the human body in the evolutionary process, have been approved and used in clinics, as components of ‘pre-built’ drugs [3]. These include tissue plasminogen activator for ischemic stroke and anti-natriuretic peptide for chronic heart failure. In addition to the model pre-built drug, insulin, glucagon-like peptide-1 has recently been used in the treatment of diabetes mellitus, one of the most important risk factors of stroke [4]. In this review, adrenomedullin (AM), which has shown promising pleiotropic properties and has been suggested as a future possible treatment for a variety of diseases, including ischemic stroke and vascular cognitive impairment, will be examined.

Biochemical features of adrenomedullin

AM is a 52-amino acid vasoactive peptide containing a disulfide bond discovered in human pheochromocytoma tissue and coded by a gene on human chromosome 11 [5,6]. Expression of the AM gene is regulated by hypoxia, inflammatory stimuli and shear stress (Fig. 1) and has consensus sequences for binding sites of transcription factors, which include hypoxia-inducible factor-1, nuclear factor for interleukin-6 expression and shear stress responsive element in its promoter region [6]. AM is widely biosynthesized and secreted, not only in the adrenal medulla, but also the cardiovascular system, including cerebral endothelial cells [7].

AM exerts bioactivity by binding to a heterodimer receptor composed of the calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein type 2 (RAMP2) or 3 (RAMP3), named AM1 and AM2 receptors, respectively [8]. Upregulation of AM by hypoxia or shear stress has various physiologically-active effects such as vasodilation, vascular permeability regulation, suppression of vascular endothelium...
AM as a biomarker of cerebrovascular diseases

Blood concentration of AM is proportional to the severity of cerebrovascular lesions [17]. Indeed, overexpression of the AM gene has been detected in stroke patients and is associated with stroke severity [18]. Because of the short (22-minute) half-life of AM [19], midregional pro-adrenomedullin (MR-proAM), a non-functional precursor of AM, has also been used as an indicator of AM production [20]. Plasma MR-proAM levels were significantly higher in patients with unfavorable, compared to favorable, outcomes after ischemic stroke [21]. MR-proAM levels were significantly increased in patients with acute penetrating artery territory infarction, where symptoms were worsening [22], suggesting AM serves as an indicator of microcirculatory failure. Accordingly, Kuriyama et al. found MR-proAM levels to be associated with progression of deep white matter lesions [23]. The odds ratio for high MR-proAM levels was 3.08 (95% confidence interval: 1.49–5.17) in groups with Fazekas grade 3 on brain MRI, suggesting high MR-proAM levels are an independent risk factor for deep white matter lesions. Moreover, a significant inverse correlation was observed between MR-proAM levels and cognitive test scores, suggesting MR-proAM could act as a serum biomarker for vascular cognitive impairment. Interestingly, the same group reported five SNPs of AM receptor genes, consisting of 1 SNP of RAMP2 and 4 SNPs of CLR, are associated with stroke [24].

AM for treatment of cerebrovascular diseases

The efficacy of AM administration as a therapeutic agent has been demonstrated in various animal models of cerebrovascular disorders. AM overexpression or administration has been shown to reduce infarct size in a middle cerebral artery (MCA) occlusion model, which recapitulates acute cerebral ischemia [25]. Furthermore, Miyamoto et al. reported a decrease in ischemic tolerance in heterozygous AM knockout (AM +/−) mice [26]. Consistent with these findings, heterozygous RAMP2 knockout mice showed greater reductions in neurons than wild-
type mice, together with slower recovery of cerebral blood flow in acute ischemia induced by MCA occlusion [27]. These findings suggest AM is an important endogenous peptide that promotes the biological defense response against cerebral ischemia through the AM-RAMP2 system. In addition, AM suppressed neuronal loss and reactive oxygen species levels in a rat model of transient bilateral common carotid artery occlusion and reperfusion [28]. Brain levels of malondialdehyde, a marker of oxidative stress, were lower, while superoxide dismutase and glutathione peroxidase antioxidant enzyme activity was higher in rats receiving AM, compared to those not. Nevertheless, when AM was conditionally knocked out from endothelial cells, mice exhibited less ischemia-induced brain damage. One plausible mechanism behind this phenomenon is the decreased expression of adhesion molecules, such as Mcam and the proinflammatory mediator Lcn2, in conditional knockout mice [29]. In this context, AM may therefore have a harmful effect in the endothelium but a neuroprotective effect when administered systemically [29]. In addition, intracerebroventricular injection of AM results in an increase in ischemic injury [30]. The effects of AM may thus be context- and/or cell type-dependent.

Importantly, AM has been shown to be effective in chronic cerebral hypoperfusion. AM exerts a tissue-protective effect, through angiogenesis and suppression of microglial activation, in mice with chronic cerebral hypoperfusion induced by bilateral common carotid artery stenosis [31]. In this study, AM was shown to upregulate brain vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) expression, specifically in the hypoperfused, but not normoperfused, brain. Accordingly, increased AM has been shown to trigger a feedback system downregulating RAMP2, in the normoperfused, but not hypoperfused, brain [31,32]. The context-specific properties of AM may thus be useful when applied to cerebrovascular diseases as its signaling operates in hypoperfused tissue only. In addition, heterozygous RAMP2 knockout mice have demonstrated enhanced neuronal loss, along with less compensatory capillary growth, after chronic cerebral hypoperfusion [27]. Taken together, these results suggest AM regulates two key growth factors involved in angiogenesis, VEGF and bFGF, in the AM-RAMP2 signaling pathway, making AM an important peptide in facilitating the biological defense response against cerebral oligemia and ischemia.

Effects of AM in cultured cells

AM promotes capillary tube formation of cultured endothelium in vitro, whereas VEGF neutralization abolishes these effects. The upregulation of VEGF and bFGF by AM is thought to be mediated through the AM receptor and PI3K pathway [32]. PI3K phosphorylates Akt, which then activates endothelial nitric oxide synthase in endothelial cells, subsequently leading to activation of an endothelium-dependent cyclic GMP-dependent kinase pathway in vascular smooth vascular cells (VSMCs) [33]. Alternatively, AM can bind directly to AM receptors on VSMCs and activate the CAMP/protein kinase A or PI3K/Akt pathway, causing vasorelaxation via the endothelium-independent pathway [33]. Activation of such endothelial-dependent and endothelial-independent pathways synergistically improve blood perfusion in ischemic tissue [10].

AM exerts its role in cells other than endothelial and VSMCs, promoting differentiation of oligodendrocyte precursor cells (OPC) into myelin-basic-protein-expressing oligodendrocytes under pathological conditions in vitro. AM treatment increases Akt phosphorylation in OPC cultures and PI3K/Akt inhibitor blocked AM-induced OPC differentiation [34], suggesting that AM preserves white matter integrity through the PI3K/Akt signaling pathway.

Clinical application of AM into cardiovascular diseases

AM safety may become an issue for clinical application in cardiovascular diseases. Blood pressure fluctuations associated with vasodilation in the acute phase of cerebral infarction may lead to worsening of cerebral infarction and complications associated with angiogenesis. However, a Phase 1 clinical trial has demonstrated AM to be safe and clinically-tolerable when administered intravenously [35]. All 24 subjects in the single-dose test with continuous 12-h infusion (placebo, 3 ng/kg/min AM, 9 ng/kg/min AM, or 15 ng/kg/min AM; n = 6 each) completed the study. Of 12 subjects in the 8 h per day for 7 days (placebo or 15 ng/Kg/min) multiple-dosing test, one from the AM group withdrew due to headache. However, no serious AEs were reported. Hemodynamic parameters, such as blood pressure and pulse rate, were well maintained in all subjects.

Since AM is an endogenous substance, its antigenicity is low and its safety guaranteed. In addition, AM has already been administered in clinical trials in inflammatory bowel disease [14], congestive heart failure [9], acute myocardial infarction [36] and old cerebral infarction (personal communications with Prof. Kitamura), with no major adverse events recorded. Based on this evidence, an investigator-initiated, double-blind, placebo-controlled, randomized clinical trial, the AMFIS trial (JRCT ID: jRCT2051190092) for acute cerebral infarction, has commenced at a dose of 9 ng/kg/min AM [37]. AM is expected to be an innovative therapeutic drug in the regeneration blood vessels, while controlling inflammation, in the acute phase of cerebral infarction.

Clinical application of AM into vascular cognitive impairment

The effects of AM may also be felt in an important stroke-related comorbidity, vascular cognitive impairment (VCI). Neuronal atrophy resulting from vascular damage in both the temporal and frontal lobes may underlie VCI [38]; therefore, a strategy cerebrovascular blood flow to such regions may hold promise. AM could prove an ideal drug for VCI as it promotes arteriogenesis through arterial dilatation and angiogenesis through capillary outgrowth [31]. In addition, AM may inhibit microglial activation and inflammation observed in VCI [39], as inflammation underlies blood brain barrier disruption and white matter damage in VCI [40]. Such pleiotropic actions of AM may warrant further examination in clinical trials in VCI.

Another target disease of AM could be a hereditary type of VCI caused by NOTCH3 mutations, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Sporadic VCI and CADASIL share underlying mechanisms such as blood-brain barrier disruption and white matter changes [41]. In addition, genetic and clinical studies have shown that CADASIL may be undiagnosed in patients with mild clinical or radiological phenotypes [42,43]. In CADASIL, increased NOTCH3 activity mediates pathological changes in the structure of cerebral arteries, leading to a reduction in maximal dilator capacity of cerebral arteries and cerebral blood flow [44]. Since NOTCH3 is specifically expressed in mural cells among mature somatic cells, impaired cerebral autoregulation in CADASIL is thought to arise from dysfunctional mural cells (e.g. vascular smooth muscle cells and pericytes). However, a recent study has shown pericyte coverage loss and blood brain barrier leakage is not a consistent feature of white matter lesions in CADASIL [45]. Instead, this study suggests reduced oxygen delivery in CADASIL may lead to the death of hypoxia-sensitive oligodendrocytes. Consistent with this notion, NOTCH3 has been shown to be essential for oligodendrocyte development in zebrafish, and NOTCH3 mutants with abnormal myelination show transient reduction in OPCs [46]. In other words, impaired oligodendrogenesis and myelination may be a primary and direct effect of the NOTCH3 mutation in CADASIL. Given AM promotes in vitro differentiation of OPCs, even under hypoxic conditions [34], it may compensate for the death of oligodendrocytes through its direct effect on OPCs and resultant increase in the phosphorylated Akt cell survival signal [34] (Fig. 1). Thus, AM may have at least triple sites of action on components of the neuro-glial-vascular unit consisting of vessels, microglia and oligodendrocytes [47,48] or, more specifically, on the white matter oligovascular unit [49] (Fig. 2).

Disruptions in cell-cell interactions in the oligovascular unit may lead to vascular cognitive impairment [50]. One example is an abnormal
interactions between pericytes and endothelial cells in CASASIL [51]. Direct effects of AM on endothelial and mural cells, the two major components of the oligovascular unit, may lead to hemodynamic stability through facilitated angiogenesis and vasodilation (Fig. 1). OPCs and endothelium contribute to the oligovascular unit, where an exchange of soluble signals plays an important role in sustaining oligodendrocyte homeostasis and WM integrity. Microglial processes are closely associated with the brain endothelium in a fraction of cerebral microvessels and patrol vasculature in the central nervous system.

Conclusions

Based on its angiogenic and anti-inflammatory properties, clinical trials of AM are now taking place in patients with inflammatory bowel disease, COVID-19 and acute ischemic stroke, with more in VCI planned. Furthermore, the oligodendrogenetic properties of AM may offer additional benefits in CASASIL, which features inherent impairments in oligo-vascular unit function.

Declaration of Competing Interest

Dr. Ihara reports personal fees from Daiichi Sankyo, personal fees from Eisai and Bayer, grants from Panasonic, Bristol-Myers Squibb and Otsuka Pharmaceutical, outside the submitted work; Dr. Washida has nothing to disclose; Dr. Yoshimoto reports other from Takeda Pharmaceutical Company Limited, outside the submitted work; Dr. Saito has nothing to disclose.

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Fig. 2. Schematic diagram of the interactions between major cellular components within the brain white matter (WM). WM microvessels are associated with astrocytes, oligodendrocyte precursor cells (OPCs), microglia/macrophages and pericytes. The glial vascular unit of the WM is formed by astrocyte end feet juxtaposed to the WM endothelium. Gial and endothelial cells functionally interact with each other in a paracrine manner. Together with astrocytes, pericytes are important players within the glial vascular unit and modulate vessel diameter. The oligovascular niche is formed by OPCs and the endothelium, where an exchange of soluble signals (e.g. trophic factors such as adrenomedullin (AM) or chemical messengers) plays an important role in sustaining oligodendrocyte homeostasis and WM integrity. Microglial processes are closely associated with the brain endothelium in a fraction of cerebral microvessels and patrol vasculature in the central nervous system.
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