Adrenomedullin
A Protective Factor for Blood Vessels

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Abstract—Adrenomedullin (AM) is a vasodilator peptide having a wide range of biological actions such as reduction of oxidative stress and inhibition of endothelial cell apoptosis. The AM gene is expressed in vascular walls, and AM was found to be secreted from cultured vascular endothelial cells, smooth muscle cells, and adventitial fibroblasts. Plasma AM levels in patients with arteriosclerotic vascular diseases are elevated in possible association with the severity of the disease. When administered over a relatively short period, AM dilates blood vessels via an endothelium-dependent or independent mechanism. Experiments in vitro have shown that AM exerts multiple actions on cultured vascular cells, which are mostly protective or inhibitory against vascular damage and progression of arteriosclerosis. Either prolonged infusion or overexpression of AM suppressed intimal thickening, fatty streak formation, and perivascular hyperplasia in rodent models for vascular remodeling or atherosclerosis. Intimal thickening induced by periartrial cuff was more severe in AM gene-knockout mice than their littermates, suggesting a protective role for endogenous AM. Moreover, AM has recently been suggested to possess angiogenetic properties. Collectively, a body of evidence suggests that AM participates in the mechanism against progression of vascular damage and remodeling, thereby alleviating the ischemia of tissues and organs. (Arterioscler Thromb Vasc Biol. 2005;25:0-0.)

Key Words: adrenomedullin ■ vasodilatation ■ endothelium ■ smooth muscle cell ■ arteriosclerosis

Cardiovascular diseases secondary to arteriosclerosis of blood vessels are currently among the leading causes of death in developed countries. A number of factors, both humoral and mechanical, have been shown to modulate vascular function in humans as well as in experimental animals.1 Blood vessel dysfunction resulting from an imbalance of those factors accelerates the process of vascular remodeling and atherosclerosis.1 Vasoconstrictors including angiotensin II and endothelins not always but mostly act as proatherogenic factors, whereas vasodilators, either peptides or non-peptides, such as natriuretic peptides, nitric oxide (NO), and prostaglandin (PG) I2, have antiatherogenic properties.1 In 1993, a new vasodilator peptide, adrenomedullin (AM), was isolated from the tissue extract of a human pheochromocytoma by monitoring cAMP levels in rat platelets.2 Substantial levels of the AM peptide and gene expression were detected in the cardiovascular tissues including blood vessels. As listed in the Table, AM was found to exert a wide range of biological actions related to vascular functions in cultured cells, with which observations in vivo have been mostly accordant. Ever since the discovery of AM, efforts have been made to clarify the role of this bioactive peptide in blood vessels and a substantial amount of basic and clinical data has been accumulated. In this review, after summarizing the biochemical and pharmacological features of AM, we discuss its role in blood vessels, which is assumed to be protective, or inhibitory against the progression of vascular damage and remodeling.

Biochemistry of AM

Human AM is a 52-aa peptide with a ring structure formed by a disulfide bond and amidated tyrosine at the C terminus (Figure 1), both essential for binding to receptors and biological activity.2–4 Based on sequence homology, AM is thought to belong to the calcitonin gene–related peptide (CGRP) superfamily.2–4 Cloning of the cDNA encoding AM revealed the AM precursor peptide proproAM to comprise 185 amino acids, with the C terminus followed by a pair of basic amino acids, Arg-Arg, a typical processing signal (Figure 2).5 In addition to AM, proproAM was found to contain another bioactive peptide, proadrenomedullin N-terminal 20 peptide (PAMP), in the N-terminal portion.6 PAMP lowered blood pressure when injected intravenously, but its action is weaker than that of AM and there is currently little information available as to the role of PAMP in the vasculature.3,4 In a sequence analysis of the genomic DNA for human proproAM, AM was found to be encoded in the fourth exon and PAMP in the second and third exons (Figure 2).6 When processed from proproAM, AM-Gly, an intermediate form (iAM), is produced, and then iAM is converted by the amidation enzyme to the mature form of AM (mAM) having an amide structure at the C terminus.7 The mature form of PAMP is thought to be produced by a similar process (Figure 2).
In an effort to isolate unknown bioactive peptides having sequence homology with AM, another member belonging to the CGRP superfamily was recently discovered independently by two groups and named intermedin/AM-2.8,9 Human intermedin/AM-2 consists of 47 amino acid residues with an intramolecular ring structure formed by a disulfide bond and amidated tyrosine at the C terminus, showing structural homology with AM.8,9 Intermedin/AM-2 was shown to shear the receptors with AM by cultured cells,8 and in accord with this, it exerted vasodilator actions similar to AM ex vivo.10 However, data on the biochemical and pharmacological features of this novel peptide are currently very limited, and further characterization, such as the tissue distribution and effects on vascular cells, is necessary to discuss its role in blood vessels.

The biological feature of AM initially characterized was a potent, long-lasting, blood pressure–lowering effect with reduced peripheral resistance after intravenous bolus injection or infusion in a relatively short period of time.2,11,12 The hypotensive effect of AM observed in those studies was shown to be largely secondary to direct vasodilatation,11,12 which was further demonstrated by ex vivo studies with isolated rat aorta and with perfused rat mesenteric artery.13,14 The mechanisms by which AM dilates blood vessels are not completely understood; however, based on the numerous articles published to date, it is clear that AM directly dilates blood vessels of the systemic and pulmonary circulation in an endothelium-dependent or independent manner.14–23

AM has been shown to exert an endothelium-dependent vasodilatation via the NO-cyclic GMP (cGMP) pathway in rat aorta, in renal or hindquarter vascular bed of rats, and in canine kidneys.14–17 In a further analysis of the mechanism, AM dilated rat aorta by activating phosphatidylinositol 3-kinase (PI3K) and Akt via the Ca2+/calmodulin-dependent pathway, which leads to increased production of NO through phosphorylation of endothelial NO synthase.18 On the other hand, endothelium-independent vasodilatation by AM has also been shown ex vivo in experiments with dog arteries or porcine coronary artery.19,20 The mechanisms so far proposed for endothelium-independent vasodilatation are an increase in the intracellular cyclic AMP (cAMP) level, a decrease in the Ca2+ concentration, and the activation of K+ channels in vascular smooth muscle cells (SMCs).21–23

In humans, similarly to animals, intravenous infusion of AM lowered systemic and pulmonary vascular resistance, reducing blood pressure and increasing heart rate.24 AM-induced forearm arterial vasodilatation in healthy human subjects was attenuated by N-nitro-L-arginine (L-NAME).25 In human coronary arterioles, vasodilatation induced by AM ex vivo was found to be dependent on the generation of NO and the activation of K+ channels, but not on guanylate or adenylate cyclase.26 A difference between species was also observed regarding the mechanisms. For example, pulmonary vasodilator responses were reduced by N-nitro-L-arginine methyl ester (L-NAME) in rats, but not in cats.27 Currently, there is little data available on the vasodilator effect on veins, whereas Barder et al reported that vasodilatation of femoral veins in canines was endothelium-dependent, but independent of cAMP and cGMP.28 Thus, the mechanism by which AM achieves direct vasodilatation appears to differ depending on species, the size of blood vessels, or regions where the vessels are isolated.

### Receptors Mediating Vascular Actions of AM

AM has been shown to elevate intracellular cAMP levels in not all but many cells and tissues, including blood vessels,
AM Production in Blood Vessels and Atherosclerotic Lesions

AM was initially isolated from pheochromocytoma tissue, but subsequently the AM gene was found to be expressed in various organs and tissues, including the cardiovascular tissues and cells in humans as well as in rats.3–5,35 Immuno- and immunohistochemical studies revealed that three layers of the vessel wall were positive for AM peptide.35,36 and consistent with this, AM was found to be produced and secreted from 3 types of cultured vascular cells: endothelial cells, SMCs, and adventitial fibroblasts.37–39 According to Marutsuka et al, AM peptide was expressed in the endothelium of rat aortic arch in a site-dependent fashion, ie, intense immunohistochemical staining for AM was observed in the area where branches begin and on the inner side of the curvature.40 In these areas, shear stress is relatively low, and indeed, production of AM has been found to be modulated by shear stress in cultured vascular endothelial cells.41,42 Other factors known to stimulate production of AM in endothelial cells are oxidative stress and hypoxia.43,44

Immunoreactivity for AM was reported to be detected in SMCs of the intima and media of human atherosclerotic lesions.40 Interestingly, its expression in coronary artery plaques obtained by directional atherectomy was augmented in patients with unstable angina in comparison with stable angina.35 This finding is consistent with cell culture studies showing that AM production and secretion from cultured vascular SMCs were increased by factors, presumably proatherogenic, such as angiotensin II, endothelin-1, aldosterone, interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α).38,46,47 In addition, aldosterone was shown to stimulate AM production in cultured adventitial fibroblasts as well as in vascular SMCs.38,39 Macrophages play a pivotal role in the progression of atherosclerotic vascular lesions.1 Production of AM was detected in macrophages not only in a cell culture experiment,38 but also by immunohistochemical analysis where intense positive staining was found in advanced atherosclerotic vascular lesion of humans.40

Circulating AM in the Bloodstream

Radioimmunoassays for AM revealed that AM peptide was circulating in the blood at mean plasma levels ranging from 2.8 to 10 fmol/mL in healthy human subjects.7,49,50 Immuno-reactive AM in plasma or tissues was found to consist of 2 molecular forms, mAM and iAM (Figure 2), with the major molecular type in plasma and tissues being iAM and mAM, respectively.7,49–51 As described in the next section, plasma levels of immunoreactive AM were found to be higher in patients with arteriosclerotic vascular diseases than controls, although there was no notable difference in the ratio of mAM and iAM.52 iAM is thought to have no biological effects by itself, but our ex vivo study showed that iAM dilated rat aorta after its conversion to mAM probably in the aortic wall.53 Meanwhile, very little information is currently available as to the role of iAM, which should be clarified further with experiments in vivo.

To identify the organs or tissues contributing to the plasma AM level, we examined the plasma levels of AM of various sites in blood vessels of patients with ischemic heart disease.54 What we found was a step-up in plasma AM levels between the femoral artery and vein.54 Taking the active secretion of AM from cultured vascular cells into account, it seems likely that the vasculature contributes to the plasma AM level, secreting AM into the bloodstream. On the other hand, there was found to be a step-down between the plasma AM levels of the pulmonary artery and capillary.54 Substantial levels of AM gene expression were detected in the lungs and the presence of AM peptide in the pulmonary vasculature was immunohistochemically proven,3,55 but the lungs appear to be a target organ or a site for the clearance of circulating AM peptide rather than an AM-secreting organ.

Consistent with this notion is the report of abundant expression of AM receptors in the lungs.56

Plasma Level of AM in Arteriosclerosis

As an approach to clarifying the role of AM in arteriosclerosis, AM levels in plasma of patients with various types or degrees of arteriosclerotic vascular disease were measured, and the relationships between the plasma levels and the other clinical parameters were examined.52,57,58 In patients with cerebrovascular disease, a possible association was found between plasma AM levels and endothelial damage by comparing the plasma levels of AM with those of endothelin and thrombomodulin, markers of endothelial damage.57 Similarly in patients with chronic ischemic stroke, increased plasma AM levels were shown to be associated with the degree of carotid atherosclerosis.58 Recently, Suzuki et al reported that plasma AM concentrations were elevated in patients with peripheral arterial occlusive disease in proportion to its severity.52 Moreover, they found close associations between the plasma levels of AM and those of such inflammatory parameters as C-reactive protein and IL-6 in the patients.52 This finding is not only comparable with the increased production of AM in cultured SMCs by inflammatory cytokines,46 but also of interest in view of the involvement of low-grade inflammation in the development and progression of atherosclerotic vascular lesions.59 Because arterial stiffness is an important cardiovascular risk factor, we
measured plasma AM levels in patients with various degrees of atherosclerosis and compared the plasma levels with indirectly measured pulse wave velocity, a parameter used to assess arterial stiffness and sclerosis. As shown in Figure 3, a significant correlation was noted between the plasma AM levels and pulse wave velocity and this relationship was confirmed by multiple regression analysis to be independent of age and blood pressure. These findings are indirect, but indicative of a possible pathophysiological role of AM in arteriosclerotic vascular diseases.

In the latter part of this review, vascular protective effects of AM will be discussed based on the results of cell culture and animal experiments. An important issue we need to mention in this section, therefore, is the significance of the increased plasma AM levels in patients with arteriosclerosis. Because of active production of AM in cultured vascular cells and vessel walls, AM has been assumed to act in a autocrine or paracrine fashion. Indeed, blockade of the actions of endogenous AM by anti-AM antibody or the AM antagonist impaired the vascular protective effects in vitro. Moreover, according to our experiments in vivo, the long-term infusion of AM significantly suppressed neointimal formation and adventitial hyperplasia, raising plasma AM levels by 1 to 2 fmol/mL, an increase within the physiological range. This suggests a possible role for AM, not only as a local modulator, but also as a factor circulating in the blood.

Vascular Protective Effects In Vitro

As discussed in the section Vascular Actions of AM, AM exerts endothelium-dependent vasodilatation, which can be blocked by inhibitors for NO synthase. Consistent with this, in cultured vascular endothelial cells, AM was found to stimulate phospholipase C activation and inositol 1,4,5-triphosphate formation, resulting in an elevation of the intracellular Ca2+ level and activation of NO synthase. Kato et al reported that AM inhibited serum deprivation–induced apoptosis of cultured rat vascular endothelial cells. Blockade of the endogenous AM by anti-AM anti-serum impaired the inhibitory effect of the nonimmune serum on apoptosis, suggesting an autocrine or paracrine role for AM. According to the subsequent study by that group, AM upregulated the expression of Max protein, leading endothelial cells to survive. Meanwhile, other adenylate cyclase activators such as PG I2, and forskolin failed to exert an antiapoptotic effect and a cAMP antagonist was unable to block the effect of AM, therefore a cAMP-independent mechanism seems involved in this action. An antiapoptotic effect of AM was further observed by an independent group. Sata et al found that AM inhibited serum deprivation–induced apoptosis of cultured human umbilical vein endothelial cells. In their experiment, the effect of AM was abrogated by 1-NAME, but not by an inhibitor for soluble guanylate cyclase, suggesting an NO-dependent but cGMP-independent mechanism.

Furthermore, AM was shown to cause vascular regeneration by promoting the proliferation and migration of cultured vascular endothelial cells. AM promoted re-endothelialization of wounded human umbilical vein endothelial cells, and this effect was attenuated by inhibitors for protein kinase A and PI3K, suggesting an action mediated by cAMP and the PI3K–Akt pathway. Stimulation of the proliferation and migration of endothelial cells may be involved in the angiogenic action of AM, which will be discussed later in this review. Although the mechanisms of action are still under investigation, these effects of AM on endothelial cells may be protective against vascular damage and arteriosclerosis.

The proliferation of vascular SMCs in the media and intima of arteries is involved in the progression of vascular remodeling or atherosclerotic lesions. Because AM is produced by SMCs in the media, its effects on the proliferation and migration of this type of cell were tested in vitro; however, there has been some inconsistency regarding the actions of AM. AM was shown to inhibit the proliferation of cultured SMCs via a mechanism mediated by cAMP, whereas Iwasa et al found that AM stimulated proliferation of the cells in a mitogen-activated protein kinase–dependent manner. Horio et al reported an inhibitory effect of AM on the migration of cultured SMCs, which is presumably mediated by intracellular cAMP. Inhibition of the migration of SMCs by AM was confirmed by an independent group, but according to this report, AM inhibited migration via a cAMP-independent mechanism. These discrepancies may have resulted from differences in the experimental conditions or types of cultured cells used, though there has currently been no clear explanation. Meanwhile, as discussed in the next section, recent studies in vivo suggest that AM inhibits intimal hyperplasia induced by periarterial cuff or by intimal balloon injury.

Another vascular protective action of AM recently reported in SMCs was a reduction in the generation of reactive oxygen species (ROS), a group of molecules involved in vascular damage and the progression of arteriosclerosis. The generation of intracellular ROS induced by angiotensin II was inhibited by AM, in a cAMP- and protein kinase A–dependent manner, in cultured vascular SMCs of rats. Moreover, AM weakened redox-sensitive cellular responses such as the activation of c-Jun amino-terminal kinase (JNK) and gene expression for plasminogen activator inhibitor (PAI)-1,
monocyte chemoattractant protein-1, and Nox-1, a component of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.\footnote{71}

Not only the intima and media but also the adventitial layer has been recognized to have a significant role in the process of vascular remodeling. Blood vessels would increase their stiffness if an excessive accumulation of extracellular matrix or proliferation of adventitial fibroblast were to occur. The proliferation of adventitial fibroblasts induced by aldosterone, a factor involved in the fibrosis of cardiovascular tissue, was found to be suppressed by AM, with a concomitant reduction in the activity of extracellular signal-related kinase.\footnote{39} Additionally in that study, autocrine or paracrine inhibition by AM was proposed, based on the production of AM by the adventitial fibroblasts and on augmented proliferation by the AM receptor antagonists.\footnote{39} By synthesizing and degrading matrix proteins, adventitial fibroblasts are known to modulate the formation of the extracellular matrix in the adventitia. Our recent experiments showed that AM upregulated the enzymatic activity and protein expression of matrix metalloproteinase-2 (MMP-2), which degrades collagens and elastin, in cultured adventitial fibroblasts of rat aorta possibly via the cAMP–protein kinase A pathway.\footnote{72} Collectively, these findings suggest a role for AM in modulating adventitial proliferation and extracellular matrix formation.

**Vascular Protective Effects In Vivo**

As discussed above, plasma AM levels are elevated in patients with various arteriosclerotic vascular diseases, and the findings from cell culture studies have implied a role for AM, which is presumably protective of blood vessels. To investigate whether or not AM has protective effects on vascular damage and remodeling in vivo, 3 experimental approaches have so far been taken: long-term administration of AM, virally-mediated overexpression of AM, and genetic manipulation of the AM gene.

Using the first method, we found that prolonged AM infusion for 2 weeks partially inhibited neointimal hyperplasia induced by balloon injury in rat carotid arteries (Figure 4).\footnote{63} Meanwhile, somewhat conflicting findings were obtained by Shimizu et al, who showed that chronic infusion of the AM antagonist CGRP(8–37) inhibited neointimal hyperplasia induced by ballooning in rats.\footnote{73} CGRP(8–37) is a CGRP receptor antagonist, which has been able to block some, but not all, the actions of AM in relatively short-term experiments.\footnote{16,20,30,62} However, it has yet to be clarified whether or not this antagonist can block the action of endogenous AM when infused chronically. It should be noted that in our study mentioned above, the prolonged infusion of AM suppressed not only balloon injury–induced intimal hyperplasia but also the proliferation of fibroblasts and collagen deposition of the adventitia (Figure 4),\footnote{63} a finding consistent with the in vitro inhibitory effect of AM on the proliferation of cultured adventitial fibroblasts.\footnote{30} Inhibition of adventitial hyperplasia by AM was confirmed by our study in vivo, in which perivascular fibrosis of coronary arteries of rats infused chronically with angiotensin II was suppressed by coinfusion of AM.\footnote{64} This effect was accompanied by the suppression of fibroblast activation and transforming growth factor (TGF)-β1 expression, but not by a significant reduction of blood pressure.\footnote{64}

In accord with the effect of prolonged infusion of AM, adenosine-mediated local delivery of the AM gene was shown to inhibit neointimal hyperplasia of carotid arteries after balloon injury in rats.\footnote{74} Interestingly in that study, endothelial regeneration was more pronounced in rats given the AM gene than in the controls,\footnote{74} a result consistent with the cell culture experiments, where AM promoted reendothelialization of a wounded monolayer of endothelial cells.\footnote{65} The inhibition of neointimal hyperplasia by the AM gene delivery was accompanied by an elevation of tissue cGMP levels, suggesting a mechanism involving the NO–cGMP pathway.\footnote{74}

Thirdly, vascular protective effects have been suggested by genetic manipulation of the AM gene in mice. Transgenic mice overexpressing the AM gene (AM-Tg) were found to be resistant to neointimal hyperplasia induced by a periarterial cuff placed on the femoral artery.\footnote{75} This resistance seems also to be mediated by the NO–cGMP pathway because it disappeared on administration of l-NAME.\footnote{75} Moreover, a protective effect of AM was demonstrated by cross-mating apoE knockout (apoE-KO) mice with AM-Tg. The apoE-KO mice overexpressing AM showed a less extensive hypercholesterolemia-induced fatty streak formation with a greater endothelium-dependent vasodilation, compared with the control apoE-KO mice.\footnote{75} In contrast to the mice overexpressing AM, heterozygotes of AM knockout mice given angio-
tensin II and excessive salt showed a more severe perivascular fibrosis and intimal thickening of coronary arteries, compared with their wild-type littermates, despite a similar elevation of blood pressure. Based on increases in the production of ROS and in NADPH oxidase expression in the AM knockout mice, the possibility of augmented oxidative stress was raised as the mechanism responsible for the severe vascular lesions. Periarterial cuff-induced intimal thickening of the femoral artery was also found to be more severe in the knockout mice, compared with the control mice. The enhanced neointimal formation was reversed by delivery of the AM gene and by an NADPH oxidase inhibitor or tempol, a superoxide dismutase mimetic, further suggesting augmented oxidative stress in the AM knockout mice.

Lastly in this section, we should mention the effect of AM on the pulmonary vascular bed as a protective action. In addition to the pulmonary vasodilator effect, prolonged subcutaneous infusion of AM was found to inhibit medial thickening of the pulmonary artery of rats with pulmonary hypertension induced by monocrotaline. However, when infused intravenously, AM lowers not only pulmonary artery pressure but also systemic blood pressure. In an attempt to avoid the effect on the systemic circulation, Nagaya et al administered AM as an aerosol using an ultrasonic nebulizer in rats with pulmonary hypertension. Repeated inhalation effectively inhibited medial thickening of pulmonary arteries, reducing pulmonary artery pressure and total pulmonary resistance, without affecting the systemic arterial pressure or heart rate. Furthermore, the same group reported that in patients with idiopathic pulmonary arterial hypertension, inhalation of AM lowered pulmonary artery pressure and resistance, improving exercise tolerance. Although the long-term effects need to be examined, this novel approach seems promising for using AM in the treatment of primary pulmonary hypertension, for which few effective medical treatments are currently available.

Angiogenic Effect of AM
A novel action of AM only recently discovered is angiogenesis, an effect implied by experiments with cultured vascular endothelial cells. By subcutaneously injecting gel plugs containing AM into mice, AM was found to promote neovascularization in a protein kinase A- and PI3K-dependent manner. Consistent results were obtained by Iimuro et al, who showed that AM increased collateral capillary density in ischemic limbs of mice, augmenting the expression of vascular endothelial growth factor (VEGF) and activating Akt. Conversely, heterozygotes of AM gene knockout mice showed less capillary development and VEGF expression compared with their wild-type littermates, suggesting a role for endogenous AM. In addition to augmented VEGF expression and activations of protein kinase A and Akt, mitogen-activated protein kinase/extracellular signal-regulated kinase1/2 (ERK1/2) and focal adhesion kinase were proposed as the intracellular mediators responsible for AM-induced endothelial proliferation. Hypoxia was reported to increase not only expression of AM but also of CRLR, a component of AM receptor, in cultured endothelial cells. This suggests significance of the AM signaling system in angiogenesis under hypoxic conditions. It would also be of interest to compare the angiogenic effects of AM with the findings from homozygotes of AM gene knockout mice, which died in the uterus because of insufficient development of blood vessels.

Very recently, AM infusion was shown to enhance the angiogenic potency of implanted bone marrow–derived cells by inhibiting apoptosis of the cells. Angiogenesis after transplantation of bone marrow–derived mononuclear cells was augmented by AM in rats with hind limb ischemia. Similarly in a rat model of cerebral infarction, the angiogenic effect of transplanted mesenchymal stem cells was enhanced by AM infusion in ischemic penumbra of the brain, improving neurological deficits. Collectively, it seems likely that AM possesses angiogenic properties, suggesting its potential as a therapeutic tool in the treatment of organ or tissue ischemia.

Conclusion and Perspective
Since the discovery of the novel vasodilator peptide AM, much research, basic and clinical, has been done to clarify the vascular actions of AM and its role in modulating vascular remodeling and atherosclerosis. As discussed in this review, a substantial amount of data accumulated in this field suggests that AM functions as a protective factor for blood vessel, exerting various vascular actions, mostly inhibitory, against vascular damage and remodeling. Research on AM now seems to be entering a new phase, with clinical benefits to be examined and specified. AM itself is orally inactive, but the development of either analogues of AM or drugs inhibiting the degradation of AM would provide us a new therapeutic tool to inhibit the progression of vascular damage and remodeling. They would, in particular, be beneficial for patients with primary pulmonary hypertension, for which therapeutic methods one can choose are currently very limited. Meanwhile, there is no doubt that more basic studies are necessary to resolve issues such as the receptor system and the intracellular mechanisms mediating the vascular actions of AM. Angiogenic properties appear to be another feature that should be characterized further in vitro and in vivo.

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