JOURNAL OF SMOOTH MUSCLE RESEARCH

J. Smooth Muscle Res. 2021; 57: 94–107
Published online: January 29, 2022; doi: 10.1540/jsmr.57.94

Invited Review

Relationships between advanced glycation end products (AGEs), vasoactive substances, and vascular function

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Submitted November 13, 2021; accepted in final form December 19, 2021

Abstract

Vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) are major cell types that control vascular function, and hence dysfunction of these cells plays a key role in the development and progression of vasculopathies. Abnormal vascular responsiveness to vasoactive substances including vasoconstrictors and vasodilators has been observed in various arteries in diseases including diabetes, hypertension, chronic kidney diseases, and atherosclerosis. Several substances derived from ECs tightly control vascular function, such as endothelium-derived relaxing and contracting factors, and it is known that abnormal vascular signaling of these endothelium-derived substances is often observed in various diseases. Derangement of signaling in VSMCs and altered function influence vascular reactivity to vasoactive substances and tone, which are important determinants of vascular resistance and blood pressure. However, understanding the molecular mechanisms underlying abnormalities of vascular functions in pathological states is difficult because multiple substances interact in the development of these processes. Advanced glycation end products (AGEs), a heterogeneous group of bioactive compounds, are thought to contribute to vascular dysfunction, which in turn cause the development of several diseases including diabetes, hypertension, stroke, and atherosclerosis. A growing body of evidence suggests that AGEs could affect these cells and modulate vascular function. This study is focused on the link between AGEs and functions of ECs and VSMCs, particularly the modulative effects of AGEs on vascular reactivities to vasoactive substances.

Key words: advanced glycation end products, contraction, endothelium, relaxation, vascular smooth muscle, vasoactive substance

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Introduction

Vascular tone is tightly controlled by neural, physical, hormonal, and endothelial stimuli that lead to relaxation and contraction responses in vascular smooth muscle cells (VSMCs) (1). In the vascular system, not only endothelial cell (ECs) but also VSMC dysfunctions play pivotal roles in the remodeling processes during the initiation and development of vascular diseases (1, 2). Therefore, identifying the causative factors and the molecular mechanisms which underlie various abnormal phenomena including migration, proliferation, senescence, apoptosis, inflammation, calcification, and dysregulation of functional abilities to several vasoactive substances in both ECs and VSMCs is important to comprehensively understand the pathogenesis and management of vascular dysfunction.

Advanced glycation end products (AGEs) are a heterogeneous group of complex compounds that are formed irreversibly in the circulating blood and tissues through a chain of nonenzymatic chemical reactions (3–9). Endogenous formation of AGEs has been described by three different pathways *in vivo* including the non-enzymatic Maillard reaction, the polyol pathway, and lipid peroxidation (4–9). In all three pathways, formation of AGEs occurs via formation of reactive carbonyl compounds, including glyoxal, methylglyoxal (MGO) and 3-deoxyglucoson. If detoxification is impaired, they can react further with the formation of irreversible AGEs. Given these different pathways, it is not surprising that AGEs are diverse in their chemical structure. Among the most widely investigated AGEs are N(epsilon)-carboxymethyl-lysine (CML), pentosidine, and pyrraline, and, together with an alpha-oxoaldehyde MGO, they have been used as biomarkers for *in vivo* formation of AGEs (4–9). AGEs play an important role in the development of diabetes, especially diabetic vasculopathies, which has been underscored (5); moreover, the levels of AGEs are correlated with the severity of diabetic vascular complications (10–15). Elevated circulating AGEs and the accumulation of tissue AGEs promote apoptosis, calcification, senescence, hyperpermeability, and increase oxidative stress (10, 11, 16–22) (Fig. 1). Therefore, AGEs are now known to be one of the important causative factors in vascular dysfunction development.

This study focuses on the effects of AGEs on vascular tone and its putative role on vascular function (Fig. 1 and Table 1). The endothelium plays a vital role in controlling vascular tone through two main pathways: (a) the generation and release of vasoactive substances, including nitric oxide (NO), prostacyclin (PGI_2), and endothelium-derived contracting factors (EDCFs) (2, 23), and (b) the hyperpolarization of both ECs and VSMCs, referred to as endothelium-derived hyperpolarization [EDH, previously associated with the notion of endothelium-derived hyperpolarizing factors (EDHFs)] (24). Firstly, the relationship between AGEs and endothelium-derived factors are reviewed. Secondly, the relationship between AGEs and some vasoconstrictors are also summarized in (Table 1).

AGEs and NO

Nitric oxide is synthesized as a soluble gas from the amino acid L-arginine in ECs by endothelial NO synthase (eNOS), which has been characterized as a constitutively expressed calcium- and calmodulin-dependent enzyme (25–28). Nitric oxide has diverse biological properties that help maintain vascular homeostasis, including local cell growth control, and vascular tone modulation (i.e. a vasorelaxant effect), playing in this way an important role in normal endothelial function (25, 28). After the release of NO from ECs, NO then stimulates soluble guanylyl cyclase (sGC) to generate a second messenger cyclic guanosine 3′,5′-monophosphate (cGMP) in VSMCs (25, 28). L-Arginine is also a substrate for arginase enzymes that metabolize it to

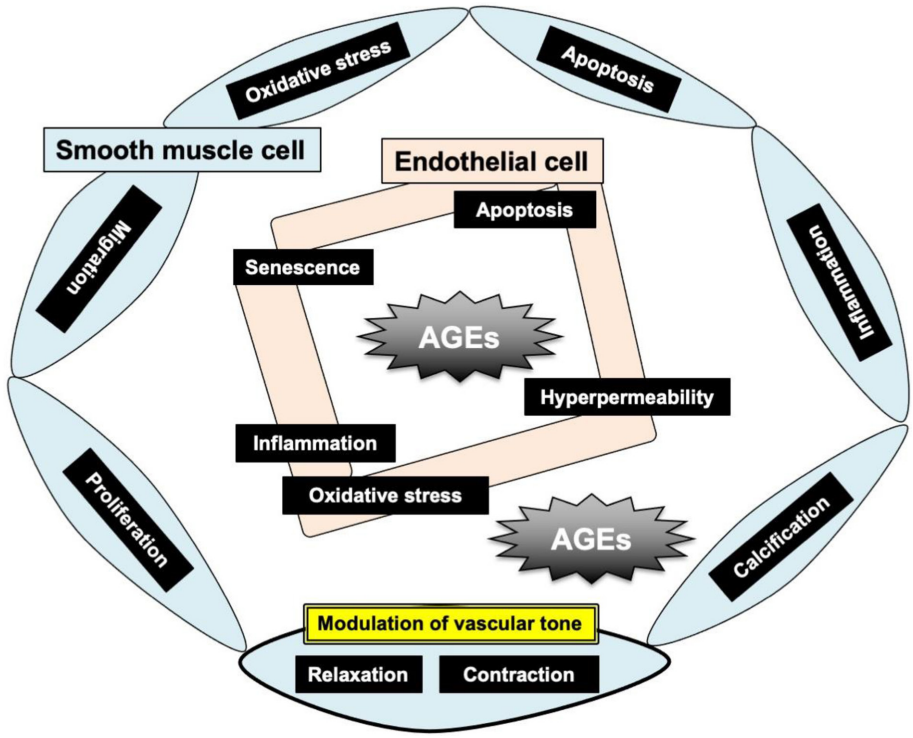

Fig. 1. Advanced glycation end products (AGEs) and relevant events in the endothelial and vascular smooth muscle cells. This study focuses on the relationship between AGEs and vascular tone.

urea and ornithine. Thus, increased arginase activity reduces L-arginine tissue availability and is associated with the inhibition of NO generation by eNOS (29–31). NO bioavailability reduction is often a causative event to the initiation and development of endothelial dysfunction (28, 32–34). AGEs can quench NO (35–37). One of the causative events for impaired NO bioavailability is eNOS down-regulation (28). Exposure of bovine aortic EC to AGE-bovine serum albumin (AGE-BSA) results in marked decreases in the expression of eNOS activity, protein, and transcript levels but does not affect the transcriptional rate of the *eNOS* gene (38). In the rat aorta, AGEs impaired endothelium-dependent relaxation induced by acetylcholine (ACh) while enhancing the endothelium-independent relaxation induced by a NO donor NONOate (31). AGEs could induce *Arg2* mRNA expression but down-regulate *eNOS* mRNA expression (31). Additionally, AGE-induced impairment of ACh-induced relaxation has been prevented by arginase inhibition (by L-ornithine), a superoxide scavenger (tempol), or by NADPH oxidase inhibition (by apocynin), suggesting that the impaired endothelium-dependent relaxation is due to arginase overexpression and NADPH oxidase stimulation (31). In human coronary artery EC, AGEs decrease eNOS expression and NO generation via oxidative stress, p38 mitogen-activated protein kinase (MAPK) activation, and extracellular signal-regulated kinase 1/2 (ERK1/2) activation (39). Yin and Xiong (40) have observed that in isolated Sprague–Dawley rat aorta after AGE-BSA exposure for 1 h, endothelium-dependent relaxation was impaired and was accompanied by decreased nitrite/nitrate contents, elevated malondialdehyde levels, and decreased dimethylarginine dimethylaminohydrolase activity, which is an enzyme that degrades endogenous NOS inhibitor asymmetric dimethylarginine (41). Because AGEs impair NO bioavailability via multiple events as described above, not only the reduction of AGEs but also the manipulation of these signaling molecules are important approaches in maintaining NO homeostasis.

Table 1. Modulative effects of AGEs on vascular responses mediated by vasoactive substances

AGEs	Animal/tissue	Molecular target	Impact on vascular function	References
AGE-BSA	Rat/aorta	↓ NO bioavailability ↑ Arginase ↑ NADPH oxidase	↓ ACh-induced relaxation	El-Bassossy et al., 2018 (31)
AGE-BSA	Rat/aorta	↓ NO bioavailability ↓ DDAH	↓ ACh-induced relaxation	Yin and Xiong, 2005 (40)
MGO	Rat/superior mesenteric artery	↓ NO bioavailability ↓ eNOS ↑ NADPH oxidase	↓ ACh-induced relaxation	Mukohda et al., 2013 (91)
MGO	Rat/aorta	↓ NO bioavailability ↓ eNOS phosphorylation (Ser1177) ↓ AMPKα phosphorylation (Thr172)	↓ ACh-induced relaxation	Turkseven et al., 2014 (92)
AGE-BSA	Rat/mesenteric arteries	↓ SK_{Ca}, IK_{Ca}	↓ EDHF-mediated relaxation	Zhao et al., 2014 (93)
CML	Rat/perfused coronary arteries		↑ ACh-induced contraction	Kamata et al., 2009 (94)
MGO	Rat/superior mesenteric artery, aorta	↑ BK_{Ca}	↓ NAd-induced contraction	Mukohda et al., 2009 (66)
MGO	Rat superior mesenteric artery	↑ Superoxide (by NADPH oxidase)	↓ NAd-induced contraction	Mukohda et al., 2012 (67)
AGE-BSA	Rat/carotid artery	↑ H_2O_2, BK_{Ca}, OCT3	↓ NAd-induced contraction	Matsumoto et al., 2020 (68)
MGO	Rat/carotid artery	↑ ROS (endothelium derived)	↑ Ang II-induced contraction	Mukohda et al., 2010 (74)
MGO	Rat/aorta Rat/perfused kidney	↑ Voltage-activated Ca^{2+} influx ↑ NOX ↑ PKC	↑ PE-, Ang II-, vasopressin-, and KCl-induced contractions	Eid et al., 2018 (95)
CML	Rat/perfused coronary arteries		↑ big ET-1- and ET-1-induced contractions	Matsumoto et al., 2010 (84)
AGE-BSA	Rat/carotid artery	↑ COX/TxS/TP receptor	↑ UDP-induced contraction	Matsumoto et al., 2019 (86)
MGO	Rat/carotid artery	↑ p38 MAPK, PKC, oxidative stress	↑ UDP-induced contraction	Matsumoto et al., 2021 (87)

ACh: acetylcholine; AGEs: advanced glycation end products; AGE-BSA: advanced glycation end products-bovine serum albumin; AMPK: AMP-activated protein kinase; Ang II: angiotensin II; Ca^{2+}: calcium; CML: N^{ε}-carboxymethyl-lysine; COX: cyclooxygenase; DDAH: dimethylarginine dimethylaminohydrolase; EDHF: endothelium-derived hyperpolarizing factor; eNOS: endothelial nitric oxide synthase; IK_{Ca}: intermediate-conductance calcium-activated potassium channels; MAPK: mitogen-activated protein kinase; MGO: methylglyoxal; NAd: noradrenaline; NO: nitric oxide; NOX: NADPH oxidase; OCT3: organic cation transporter 3; PE: phenylephrine; PKC: protein kinase C; ROS: reactive oxygen species; SK_{Ca}: small-conductance calcium-activated potassium channels; TP: thromboxane-prostanoid; TxS: thromboxane synthase; UDP: uridine diphosphate.

AGEs, EDH, and K^+ Channel Activity

EDH is characterized by inducing endothelium-dependent relaxation through NO- and PGI_2-independent mechanisms (2, 42). Moreover, it is known that the contribution of EDH to relaxation increases as the vessel size decreases, which is a predominant EDH activity in the resistance vessels (43). Indeed, impaired EDH-mediated response has been observed in various arteries of diseases associated with increased AGEs including diabetes (24, 44–46). Although the nature of EDH is not completely understood yet, the evidence from arteries of various species including humans suggest that endothelial small-conductance (SK_{Ca}) and intermediate-conductance (IK_{Ca}) Ca^{2+}-activated potassium channels play a key role in mediating the effects of EDH in many

arteries (42, 47). Zhao et al. (48) have demonstrated that AGE-BSA treatment (0.2 mg/ml for 3 h) impairs ACh-induced EDH-type relaxation in small mesenteric arteries of normal rats, and such treatment also impairs NS309, an activator of both SK_{Ca} and IK_{Ca}-induced relaxations in small mesenteric arteries of normal rats. Moreover, they also found that AGEs increased reactive oxygen species (ROS) levels and reduced protein expression of SK_{Ca}/IK_{Ca} in human umbilical vein ECs (HUVECs) (48). Because these dysfunction and abnormal protein expressions are normalized by an antioxidant (alpha-lipoic acid) and H_2O_2 could mimic the effect of AGEs on these protein expressions in cultured HUVECs, AGEs impaired SK_{Ca}/IK_{Ca}-mediated relaxation in rat mesenteric arteries through the down-regulation of both SK_{Ca} and IK_{Ca}, in which the increased oxidative stress was involved (48).

EDH initiated in ECs spreads to adjacent VSMCs through myoendothelial gap junctions in various arteries (24, 47). A gap junction channel is composed of two hemichannels called connexons, and each connexon is composed of six subunit proteins called connexins (Cx) (24, 49, 50). In human and rodent blood vessels, four proteins (Cx37, Cx40, Cx43, and Cx45) are known to be expressed in the gap junctions (49). Vascular ECs express Cx37, Cx40, and Cx43, and VSMCs express Cx43 and Cx45 (49). In human aortic ECs, AGE-BSA down-regulated Cx43 expression in a concentration-dependent manner, and this is mainly the result of reduced Cx43 transcription, involving a process of ERK1/2 and p38 MAPK activation (51). Because gap junction channels formed by different Cx isoforms have different biophysical properties (49), alterations in the number or function of Cx, or both, induced by AGEs, may contribute to an altered EDH-mediated response. Further investigations will be required to evaluate the relationship of AGEs, Cx, gap junctions, and EDH-mediated responses.

K^+ channels in VSMCs play an important role in maintaining the resting membrane potential and in controlling smooth muscle tone (52). Among K^+ channels, voltage-gated potassium channels (Kv) represent key substrates underlying vascular smooth muscle excitability in response to not only pressure-mediated depolarization (e.g., vascular tone) but also vasoactive substances, and their activity and regulation were impaired in the arteries of various diseases including hypertension and diabetes (53, 54). High glucose-induced reduction of Kv channel activity in rat coronary VSMCs was prevented by aminoguanidine, an inhibitor of AGE formation, and anti-receptor for AGE (RAGE) IgG treatments (55), suggesting that high glucose-impaired Kv channel activity in rat coronary VSMCs is mainly mediated by AGEs/RAGE (55). Moreover, they confirmed that AGE-BSA could directly impair Kv current and expression (i.e., Kv1.5 and Kv1.2) by interacting with RAGE (55). They also found that treatment with aminoguanidine partly improved the reduction of Kv-mediated coronary dilation in streptozotocin-induced diabetic rats (55). The same group further observed that AGE-BSA reduced Kv channel expressions (i.e., Kv1.2 and Kv1.5) in time- and concentration-dependent manners in the coronary artery smooth muscle cells (CSMCs) (56) and the expression and current of Kv channels by interacting with RAGE; then, they activate the nuclear factor-kappa B (NF-κB) signaling pathway, subsequently activating inflammation and oxidative stress in CSMCs (56); moreover, *in vivo* studies have observed that breaking and inhibiting the formation of AGEs by aminoguanidine or alagebrium (an AGE breaker) and inhibiting the NF-κB signaling pathway could normalize the Kv channel-mediated endothelium-independent relaxation of coronary arteries in type 2 diabetic Zucker fatty rats (56). Although the contribution of Kv activity to vasorelaxation differs between vessel types (57), these results suggest that blocking AGE formation or blocking AGEs interacting with RAGE, or both, may be a potential therapeutic target against Kv-mediated coronary dysfunction in patients with diabetes.

AGEs and Cyclooxygenase (COX)-derived Prostanoids

COX-derived prostanoids play a pivotal role in vascular tone regulation during various pathophysiological states including diabetes and hypertension (23, 58). COX has two major isoforms including COX-1 and COX-2 (58). COX-1 is constitutively expressed in various tissue and cell types, whereas COX-2 is not expressed in most tissues under physiological states, but its expression can be rapidly and markedly induced (23, 58). Prostacyclin (PGI_2) is the major COX-derived metabolite of arachidonic acid through PGI_2 synthase (PGIS) in ECs and has vasorelaxant and antithrombogenic properties through the IP receptor (2). AGE-BSA treatment for 24 h reduces PGI_2 production in human microvascular ECs (59).

In rat aortic smooth muscle cells, AGE treatment induces COX-2 expression, ROS production, and NF-κB activation and increases ERK and p38 MAPK phosphorylation, and these alterations were suppressed by a statin (60). Although the mechanisms underlying reduction of PGI_2 or COX-2 induction, or both, remains unclear, AGE-derived ROS may be a causative factor because ROS could induce COX-2 (23, 58) and peroxynitrite, which is generated when superoxide reacts with NO, could inhibit PGIS activity (61, 62). Further investigations will be required to examine the relationship among AGEs, regulation of prostanoid production, and modulation of vascular tone.

AGEs and Vasoconstrictors

Noradrenaline (norepinephrine) released by the sympathetic nervous system is one of the major vasoconstrictors (63). Alterations of responsiveness to noradrenaline have been observed in various arteries of diseases associated with elevated AGE levels including diabetes (64, 65). Acute incubation with the major AGE precursor MGO led to the suppression of noradrenaline-induced contraction in the endothelium-denuded superior mesenteric artery and aortae of rats, and this was partly due to the activation of large conductance of Ca^{2+}-activated K^+ (BK_{Ca}) channel (66). Additionally, direct prolonged MGO treatment of the rat superior mesenteric artery using organ culture method led to the suppression of noradrenaline-induced contraction, and this was due to the increased NOX1-derived superoxide generation and subsequent apoptosis (67).

When the rat carotid artery was treated with AGE-BSA for approximately 1 day, noradrenaline-induced contraction was decreased, and this was reversed by treatment with iberiotoxin, an inhibitor of BK_{Ca} (68). Moreover, H_2O_2 inhibited noradrenaline-induced contraction in the control artery but not in the AGE-BSA-treated one; conversely, catalase (a scavenger of H_2O_2) could reverse AGE-BSA-induced reduction of noradrenaline-induced contraction (68). Because iberiotoxin could reverse the suppression of noradrenaline-induced contraction, the suppressive effect of AGE-BSA on noradrenaline-induced contraction in the rat carotid artery is partly due to H_2O_2 generation and ensuing activation of BK_{Ca} channels (68). Increased noradrenaline uptake into VSMCs may also involve in the reduction of noradrenaline-induced contraction in the rat carotid artery since the suppressive effect of AGE-BSA on noradrenaline-induced contraction was prevented by co-treatment with an organic cation transporter 3 (OCT3) inhibitor without changing OCT3 protein expression (68). However, which molecules, including H_2O_2, BK_{Ca} channels, and OCT3, play major roles in rat carotid arteries with prolonged treatment with AGE-BSA remain unclear. Hence, further investigations will be required.

Angiotensin II

The renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in the regulation of body fluid volume, electrolyte balance, arterial tone, and arterial pressure (69–72). Dysregulation of RAAS plays a key

role in the initiation, development, and progression of cardiovascular diseases. Angiotensin II (Ang II) is a multifunctional peptide that influences the function of cardiovascular cells via a complex series of intracellular signaling events initiated by the interaction of Ang II with AT_1 and AT_2 receptors (72, 73). Although only excess Ang II itself contributes to the development of vascular dysfunction (69–73), crosstalk between Ang II and AGEs may produce a vicious cycle of pathogenesis in vascular dysfunction. Acute incubation with MGO enhanced Ang II-induced contraction in rat carotid arteries, and such augmentation was due to endothelium-derived ROS (74). In the mesenteric arteries of spontaneously hypertensive rats (SHR), Mukohda et al. (67) have observed that aminoguanidine reversed increased accumulation of MGO-derived AGEs, improved increased Ang II-induced contraction and reduced ACh-induced relaxation, and increased expression of NOX1 and AT_2 receptors in SHR mesenteric arteries, and that acute treatment with an AT_2 receptor blocker normalized the increased Ang II-mediated contraction in the mesenteric arteries of SHR. These results suggest that either the accumulation of MGO or MGO-derived AGEs, or both, in the mesenteric arteries amplify Ang II-induced contraction via AT_2 receptor activation. Although precise interaction between AGEs and Ang II signaling has yet to be fully clarified, manipulations of this signaling could be a viable target for therapies developed to treat vasculopathies.

Endothelin-1

Endothelin-1 (ET-1) is one of the EDCFs with an important role in the pathogenesis of hypertension, atherosclerosis, and diabetes (75–77). Regarding ET-1 levels in the blood, a strong and positive association of ET-1 with AGEs in polycystic ovary syndrome has been observed (78). A positive correlation was also observed between pentosidine and ET-1 in chronic renal failure (79). ET-1 transcription is regulated by the AGE-inducible redox-sensitive transcription factor NF-κB in ECs (80). In human aortic ECs, AGE-BSA led to increased mRNA expressions of ET-1 and lysyl oxidase (LOX) in a concentration- and time-dependent manner, and AGE-BSA also increased phosphorylation of ERK1/2 and c-Jun-N-terminal kinase (81). Moreover, AGE treatment could increase NF-κB and activator protein 1 (AP-1) binding activity to both ET-1 and LOX cognate promoter regions. Thus, AGEs trigger NF-κB- and AP-1-mediated up-regulation of ET-1 and LOX through the AGE/RAGE/MAPK signaling cascade in human ECs, and contributing to distorted endothelial homeostasis by impairing endothelial barrier function, altering extracellular matrix (ECM) biomechanical properties, and cell proliferation (81). Nemoto et al. have evaluated the relationship between AGEs and ET-1-mediated contraction (82). They have observed that in the type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rat group, the ET-1-induced aortic contraction was enhanced compared with that in the control Long-Evans Tokushima Otsuka (LETO) group. Aminoguanidine treatment reduced the ET-1-induced aortic contraction, whereas both the phenylephrine- and PGE_2-induced contractions were not altered by aminoguanidine treatment in either group. The aortae of aminoguanidine-treated OLETF rats exhibited suppressed ET-1-stimulated ERK phosphorylation, accompanied by down-regulation of ET_A receptor, increased modification of ET_A receptor by Jun activation domain-binding protein (Jab) 1, which is a protein that binds to ET receptor regulating the degradation rate of ET receptors via ubiquitination of these receptors (83), and decreased *O*-GlcNAcylated ET_A receptor levels. Such aminoguanidine-treated rats exhibited normalized plasma ET-1 and CML-AGE levels, and their aortae exhibited reduced hypoxia inducible factor 1α/endothelin-converting enzyme expression (82). Therefore, aminoguanidine improves ET-1-mediated aortic contraction by suppressing ET_A receptor/ERK activities or by ameliorating the imbalance between Jab1 and *O*-GlcNAc, or both, in type 2 diabetes.

In the rat perfused heart, CML enhanced big ET-1-induced and ET-1-induced vasoconstrictions in the nondiabetic control rats but not in the streptozotocin-induced diabetic rats, which have higher concentration

of CML in the plasma (84). Moreover, the release of ET-1 in big ET-1-treated coronary arteries was increased by CML in both the control and diabetic groups. CML may increase the big ET-1-induced coronary vasoconstriction mainly through actions on various contraction-related components coupled with ET-1 signaling (i.e., Ca^{2+} channels or oxidative stress). CML may also increase the vasoconstriction by enhancing conversion of big ET-1 to ET-1 by endothelin-converting enzyme. They may also suggest that in perfused hearts isolated from streptozotocin-induced diabetic rats at the chronic stage of diabetes, the enhancing effect of CML on big ET-1-induced coronary vasoconstriction may be desensitized as a consequence of a prolonged constitutive attack on the vasculature by the increased levels of CML present in these animals (84).

Further studies of crosstalk between ET-1 and AGEs are required for the prevention and management of AGE-related health problems.

Extracellular nucleotides

Extracellular nucleotides and dinucleotides including adenosine triphosphate, adenosine diphosphate, uridine triphosphate, uridine diphosphate (UDP) and uridine adenosine tetraphosphate play important pathophysiological roles including controlling vascular tone (23, 85). Among them, UDP causes not only vasorelaxation but also vasocontraction, depending on the vessel and species. Recently, our group has shown that 1) in the rat aorta, UDP induces the relaxation and this relaxation was not affected by AGE-BSA (0.1 mg/ml for 1 h); 2) in the rat carotid artery, UDP induces the contraction and this was augmented by AGE-BSA; and 3) ACh- and sodium nitroprusside-induced relaxations were not affected by AGE-BSA in either the rat aorta or carotid artery (86). The differences in UDP-induced carotid arterial contraction between the control and AGE-BSA-treated groups was not abolished by an inhibitor of NOS, whereas it was abolished by inhibitors of COX/thromboxane synthase /thromboxane prostanoid (TP) receptor pathway, and TP receptor agonist-induced carotid arterial contraction was greater in the AGE-BSA-treated group than in the control group, whereas AGE-BSA did not modulate prostanoid releases in rat carotid artery (86). These results suggest that the increase in UDP-mediated contraction by acute treatment with AGE-BSA was attributable to the alterations in a pathway(s) downstream of the TP receptor in VSMCs rather than to the alterations in TXA_2 generation.

Acute MGO exposure to the rat carotid artery led to augmentation of UDP-induced contractions, whereas such MGO incubation did not affect serotonin and high K^+-induced contractions (87). Moreover, UDP-induced contraction in the rat carotid artery was suppressed by the p38 MAPK inhibitor in both the control and MGO-treated groups, whereas the difference between UDP-induced contraction in the control and MGO-treated groups was abolished by the p38 MAPK inhibitor (87). Actually, the carotid arterial p38 MAPK activity was increased by MGO treatment (87). Furthermore, protein kinase C (PKC) inhibitor could suppress the UDP-induced contraction of the carotid artery in the MGO-treated group but not in the control group, and MGO-induced enhancement of UDP-induced contraction was prevented by N-acetyl-L-cysteine (87). Collectively, MGO positively regulates UDP-induced contraction in the rat carotid artery through the activation of p38 MAPK, and PKC, and increased oxidative stress (87).

Because UDP plays an important role in controlling vascular tone, the regulation of crosstalk between AGEs and UDP may represent a useful target for the prevention or treatment, or both, of vasculopathies associated with AGE accumulation. The interaction between other nucleotides/dinucleotides and AGEs in the vasculature had not been fully characterized.

Conclusions

Emerging evidence implicates a role for AGEs in vascular dysfunction including modulative effects on vasorelaxant and vasocontractile responses. Abnormal vascular responsiveness to vasoactive substances has been observed in various arteries of diseases including diabetes, hypertension, chronic kidney diseases, and atherosclerosis. There are many compounds, biomolecules and phytochemicals isolated from legumes, fruits, vegetables, or flavonoids, acting as AGE formation blockers, preformed AGE breakers, AGE-RAGE axis blockers, or glyoxalase stimulators. A growing body of evidence suggests that suppression of AGEs-related signaling improves vascular function in various animal studies (55, 56, 88–90). Therefore, further investigations will be required for determination of relationships among these compounds, AGEs-related signaling and vascular function for clinical investigation. In conclusion, the manipulation of AGE signaling within the vascular system is believed to have a considerable potential as a new form of therapy for vascular disorders.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Acknowledgment

The authors thank Enago (www.enago.jp) for the English language review.

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