Life Sciences 118 (2014) 129–135

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Linking the beneficial effects of current therapeutic approaches in diabetes to the vascular endothelin system

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ARTICLE INFO

Article history:
Received 28 October 2013
Accepted 24 December 2013
Available online 11 January 2014

Keywords:
Diabetes
Endothelial dysfunction
ET-1
Type 2 diabetes
Vascular smooth muscle

ABSTRACT

The rising epidemic of diabetes worldwide is of significant concern. Although the ultimate objective is to prevent the development and find a cure for the disease, prevention and treatment of diabetic complications is very important. Vascular complications in diabetes, or diabetic vasculopathy, include macro- and microvascular dysfunction and represent the principal cause of morbidity and mortality in diabetic patients. Endothelial dysfunction plays a pivotal role in the development and progression of diabetic vasculopathy. Endothelin-1 (ET-1), an endothelial cell-derived peptide, is a potent vasoconstrictor with mitogenic, pro-oxidative and pro-inflammatory properties that are particularly relevant to the pathophysiology of diabetic vasculopathy. Overproduction of ET-1 is reported in patients and animal models of diabetes and the functional effects of ET-1 and its receptors are also greatly altered in diabetic conditions. The current therapeutic approaches in diabetes include glucose lowering, sensitization to insulin, reduction of fatty acids and vasculoprotective therapies. However, whether and how these therapeutic approaches affect the ET-1 system remain poorly understood. Accordingly, in the present review, we will focus on experimental and clinical evidence that indicates a role for ET-1 in diabetic vasculopathy and on the effects of current therapeutic approaches in diabetes on the vascular ET-1 system.

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Introduction

Diabetic vasculopathy, including macro- and micro-vascular disorders, is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM) [type 1 (T1DM) and type 2 (T2DM)]. Endothelial dysfunction, characterized by an imbalance between endothelium-derived relaxing factors (EDRFs) and contracting factors (EDCFs), plays an important role on the development and progression of diabetic vasculopathy (Forbes and Cooper, 2013; Mather, 2013; Muniyappa and Sowers, 2013; Sowers, 2013).

Endothelin-1 (ET-1), an endothelial cell (EC)-derived peptide, is a potent vasoconstrictor with mitogenic, pro-oxidative and pro-inflammatory properties that are particularly relevant to the pathophysiology of diabetic vasculopathy (Callera et al., 2006; Tostes and Muscara, 2005; Kohan et al., 2011b). Not only the expression and functional effects of ET-1 and its receptors are greatly altered in diabetic conditions, but also

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http://dx.doi.org/10.1016/j.lfs.2013.12.216

abnormal ET-1 signaling and responses have been implicated in diabetes-related vasculopathy. For instance, circulating and local levels of ET-1 are increased in diabetic animal models and diabetic patients (Kanie et al., 2003; Matsumoto et al., 2007, 2009; Ergul, 2011; Pernow et al., 2012). Both ET-converting enzyme/ET-1 expression and activation of ET-1-selective mitogen-activated protein kinases (MAPK) are increased in the Otsuka Long-Evans Tokushima fatty (OLETF) rat, a model of T2DM (Jesmin et al., 2006). ET-1-mediated responses are due to the activation of two distinct G protein-coupled receptors, the ET_A and ET_B receptors. ET_A receptors, mainly localized in vascular smooth muscle cells (VSMCs), contribute to the vasoconstrictor and proliferative responses to ET-1. Activation of ET_B receptors, located in VSMCs of certain vascular beds, also induces vasoconstriction (Ergul, 2011; Pernow et al., 2012). On the other hand, ET_B receptors located in ECs lead to vascular relaxation via the release of EDRFs such as nitric oxide (NO) and prostacyclin (PGI_2). Abnormal expression of ET-1 receptors (ET_A and ET_B) is detected in the vasculature of diabetic subjects (Kobayashi et al., 2008; Matsumoto et al., 2009; Nemoto et al., 2012a, 2012b). Thus, the comprehension of signaling mechanisms activated by these receptors in both ECs and VSMCs is important in diabetic vasculopathy. There are seminal recent reviews focusing on ET-1-induced responses, the relative roles of ET_A and ET_B receptors in mediating ET-1 actions, and ET-1-activated signaling pathways in diabetic patients and animal models of diabetes (Kalani, 2008; Ergul, 2011; Pollock and Pollock, 2011; Pernow et al., 2012). Therefore, in this review we will particularly focus on the effects of therapeutic approaches in diabetes on the vascular ET-1 system (Fig. 1).

In the face of the global epidemic of diabetes, it is critical that we update our understanding of the pathogenesis of diabetes and related vascular complications. This may ultimately lead to novel treatment options for prevention and/or delaying the progression of diabetic complications (Forbes and Cooper, 2013). The mechanisms regulating ECs and VSMC function are important therapeutic targets in diabetic vascular complications (Forbes and Cooper, 2013; Porter and Riches, 2013). Accordingly, the regulation of the vasoconstrictor, mitogenic, pro-oxidative and pro-inflammatory properties of ET-1 is undoubtedly important in diabetic complications. Although there are various therapeutic approaches for the treatment of diabetes, including normalization of glucose and fat metabolism, few reviews have focused on how the therapeutic approaches in diabetes impact the ET-1 system. In this review, we summarize some of the experimental and clinical evidence indicating that the beneficial effects of current therapeutic approaches in diabetes include normalization of the ET-1 system. In addition, we briefly discuss the beneficial effects produced by the inhibition of the vascular ET-1 system in diabetic vasculopathy.

ET-1 and therapeutic interventions for diabetes

Anti-diabetic drugs

Metformin is one of the most prescribed therapeutic drugs for prediabetic subjects and patients diagnosed with T2DM. Metformin, a biguanide derivate (1,1-dimethylbiguanide), acutely decreases hepatic glucose production, mostly through a transient inhibition of the mitochondrial respiratory chain complex I and activation of AMPK (AMP-activated protein kinase), a cellular metabolic sensor (Viollet et al., 2012). Sachidanandam et al. (2009) reported that glycemic control with metformin in Goto-Kakizaki (GK) rats, a T2DM model, attenuates increased vascular media-to-lumen ratio, myogenic tone and collagen synthesis. Metformin also normalizes plasma ET-1 levels and mesenteric artery ET_A receptor expression in these animals, indicating that glycemic control not only inhibits vascular remodeling and activation of the ET-1 system, but also has preventive effects on T2DM-associated vasculopathy. Women with polycystic ovary syndrome, who present with hyperinsulinemia, insulin resistance, and hyperandrogenemia, appear to be at higher risk for T2DM and exhibit elevated ET-1 levels (Diamanti-Kandarakis and Dunaif, 2012; Imbar et al., 2012). Treatment with metformin lowers ET-1 in this syndrome (Diamanti-Kandarakis et al., 2001; Orio et al., 2005).

The thiazolidinediones, also known as glitazones, such as rosiglitazone and pioglitazone, are also used in the treatment of T2DM (Ahmadian et al., 2013). Thiazolidinediones activate nuclear factor peroxisome proliferator-activated receptor γ (PPARγ) and affect various physiological responses, including vascular function (Iglarz et al., 2003). In VSMCs, the PPARγ activator rosiglitazone prevents ET-1-stimulated vascular pro-

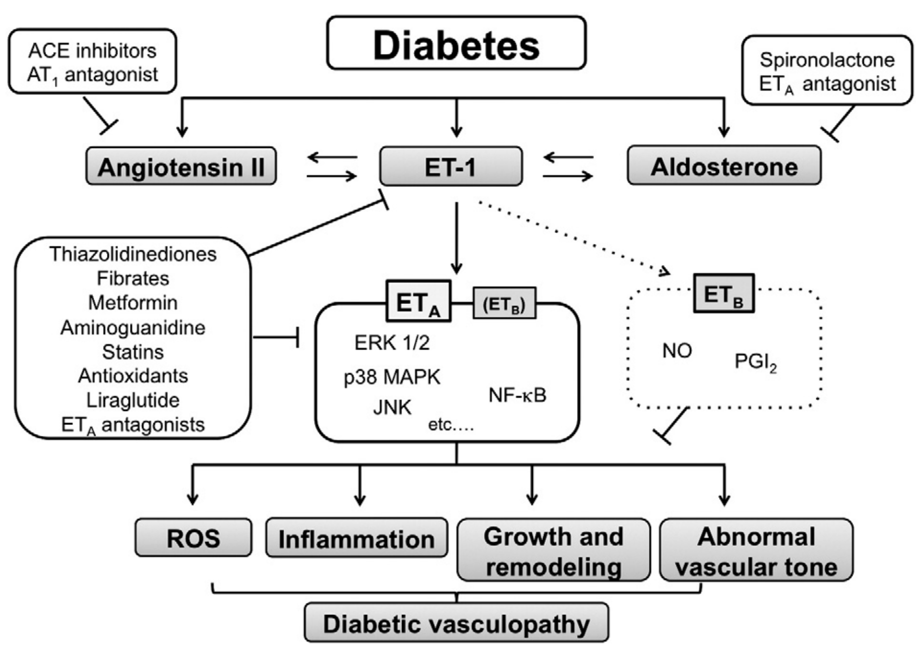

Fig. 1. Mechanisms by which current therapeutic interventions in diabetes modulate the vascular ET-1 system and decrease diabetic vasculopathy. In diabetic states, the vasculoprotective effects of ET_B activation may be impaired in endothelial cells. ET_A (and sometimes ET_B) receptor activation induces oxidative stress, inflammation, growth/remodeling, and abnormal vascular tone; major players in diabetic complications. ACE: angiotensin converting enzyme; AT_1: angiotensin II type 1 receptor; ERK: extracellular signal-regulated kinase; ET-1: endothelin-1; ET_A: ET_A receptor; ET_B: ET_B receptor; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-kappa B; NO: nitric oxide; PGI_2: prostacyclin; ROS: reactive oxygen species.

inflammatory effects such as nuclear factor-kappa B (NF-κB) binding, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule (ICAM), and cyclooxygenase (COX)-2 expression (Montezano et al., 2007). In ECs, rosiglitazone inhibits oxidized low-density lipoprotein-induced ET-1 secretion (Martin-Nizard et al., 2002). We showed that treatment with pioglitazone improves endothelial function by suppressing oxidative stress via increased superoxide dismutase activity and decreased NAD(P)H oxidase activity and that pioglitazone also decreases ET-1 levels, which might be attributable to the inhibition of the transcription factor activator protein-1 (AP-1) signaling (Matsumoto et al., 2007). In T2DM patients, treatment with pioglitazone reduces urinary albumin excretion and urinary ET-1 levels (Nakamura et al., 2000). Potenza et al. (2006) found that treatment of spontaneously hypertensive rats (SHR), which exhibit endothelial dysfunction and insulin resistance, with rosiglitazone reduces blood pressure, insulin resistance, circulating ET-1 and insulin levels and increases adiponectin levels. Considering that the beneficial effects of thiazolidinediones are shadowed by some side effects, such as the risk for fluid retention, bone loss, weight gain, and congestive heart failure (Ahmadian et al., 2013), the development of newer classes of molecules with reduced or no adverse side effects is warranted.

The incretin glucagon like peptide-1 (GLP-1) has a well recognized role on glucose-stimulated insulin release and the regulation of plasma glucose homeostasis (Kim and Egan, 2008). GLP-1 receptor agonists and inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme, which activate the GLP-1 system, are used in the treatment of T2DM (Russell, 2013). Dai et al. (2013) recently found that liraglutide, a GLP-1 agonist, decreases ET-1 expression by inhibiting the phosphorylation of NF-κB in human umbilical vein endothelial cells (HUVECs). The incretin-based therapy may have direct effects on endothelial integrity.

The chemical reaction whereby proteins are glycosylated is spontaneous, proportional, and indiscriminate to glucose concentrations. The in vivo relevance of the Maillard reaction, which results from a chemical reaction between an amino acid and a reducing sugar and the subsequent production and accumulation of advanced glycation end-products (AGEs), was first emphasized in studies with the inhibitor of advanced glycation, aminoguanidine (Brownlee et al., 1986). The breakdown of AGEs has been shown to improve endothelial function (Gao et al., 2008; Farmer and Kennedy, 2009; Win et al., 2012). We recently reported that treatment of T2DM rats with aminoguanidine normalizes ET-1-induced aortic contraction by suppressing ET_A receptor/extracellular signal-regulated kinase (ERK) activities and/or by normalizing the imbalance between c-Jun activation domain-binding protein-1 (Jab1) and glycosylation with *O*-linked N-acetylglucosamine (*O*-GlcNAc) (Nemoto et al., 2012a). Since transcription of ET-1 is regulated by NF-κB in AGE-stimulated ECs (Quehenberger et al., 2000) and positive association of ET-1 with AGEs is seen in polycystic ovary syndrome (Christakou et al., 2011), the breakdown of AGE may produce beneficial effects by suppressing ET-1 expression/activity.

Blockade of the renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system (RAAS) plays a key role on blood pressure control via the actions of angiotensin II (Ang II) and increased RAAS activity leads to hypertension and associated target-organ damage Paul et al., 2006; Ruster and Wolf, 2006. Ang II type 1 receptor (AT_1) antagonists have become an important drug class in the treatment of DM due to its protective effects on diabetic nephropathy (Michel et al., 2013). A crosstalk between Ang II and ET-1 is well established. For example, Ang II increases expression of preproendothelin mRNA and ET-1 in ECs (Emori et al., 1991), VSMCs (Hong et al., 2004), and vascular adventitial fibroblasts (An et al., 2007). Ang II infusion into rats increases the aortic ET-1 content, and this is blocked by the AT_1-receptor antagonist losartan (d'Uscio et al., 1998). In contrast, ET-1 stimulates the conversion of Ang I to Ang II in pulmonary ECs (Kawaguchi et al., 1990) and ET_A receptor antagonism reduces the vasoconstrictor responses to Ang II (Wenzel et al., 2001). Therefore, it is possible that blockade of the RAAS confers renal protection in diabetic conditions by normalizing ET-1 signaling. Indeed, we found that treatment of T2DM GK rats with losartan normalizes ET-1-induced mesenteric artery contraction by suppressing ERK activity and/or normalizing endothelial function (Matsumoto et al., 2010). Similar effects of losartan were found in the aorta from hyperinsulinemic diabetic rats (Kobayashi et al., 2008). Of importance, treatment of diabetic patients with angiotensin converting enzyme (ACE) inhibitors lowers plasma ET-1 levels (Iwase et al., 2000; Schneider et al., 2002).

It has been suggested that concomitant blockade of both ET-1 and Ang II endocrine/paracrine pathways may lead to additional end-organ protection in diabetes. Accordingly, combination of a selective ET_A receptor antagonist and an ACE inhibitor produces impressive benefits, including regression of lesions in diabetic nephropathy (Gagliardini et al., 2009). Mohanan et al. (2011) found that TRC120038, a dual AT_1/ET_A receptor antagonist, reduces hypertension and diabetic end-organ damage in obese Zucker spontaneously hypertensive fatty rats, an animal model of moderate hypertension, diabetes with progressive renal and cardiac dysfunction. The effects of TRC120038 were similar, or even better, than those produced by candesartan (Mohanan et al., 2011). Although this compound is theoretically effective for diabetic complications, further detailed studies on its safety and toxicity are required to shape its use in humans. Goddard et al. (2004) found a synergy, affecting both systemic and renal hemodynamics as well as renal tubular function, between the effects of ET_A receptor antagonism and ACE inhibition in humans. They suggested that these synergic effects are due to ET_B-receptor-mediated NO-dependent mechanisms (Goddard et al., 2004). These findings show that further investigation on selective ET_A receptor blockade, over combined ET_A/ET_B receptor blockade, as a useful adjunct to ACE inhibition in the management of the systemic and renal hemodynamics is needed (Goddard et al., 2004).

Aldosterone exerts important vascular effects by acting in the endothelium, VSMCs, adventitial layer, and also in the perivascular adipose tissue. Aldosterone influences vascular contraction, sensitizes the vasculature to effects of vasoconstrictors, induces growth and remodeling, and has pro-inflammatory and oxidative properties (Struthers, 2004; Schiffrin, 2006). Of importance, aldosterone levels are increased in T1DM (Hollenberg et al., 2004) as well as in T2DM (Fredersdorf et al., 2009). Basic and clinical studies have demonstrated that increased plasma aldosterone levels predict the development of insulin resistance and that aldosterone directly interferes with insulin signaling in the vascular tissue (Bender et al., 2013). In addition, a crosstalk between aldosterone and ET-1 has been documented (Rossi et al., 2001; Briet and Schiffrin, 2013). For instance, in Sprague Dawley (SD) rats, aldosterone increases plasma ET-1 levels and induces vascular remodeling, which is prevented by ET_A receptor blockade (Pu et al., 2003). Maron et al. (2012) observed that the elevated vascular levels of ET-1 in pulmonary hypertension are associated with increased circulating and lung tissue levels of aldosterone. In addition, the antagonism of ET_A receptor attenuates blood pressure elevation and prevents vascular remodeling/hypertrophy of aorta and mesenteric resistance arteries in aldosterone-infused rats (Park and Schiffrin, 2001). Treatment with spironolactone in streptozotocin (STZ)-induced diabetic rats decreases renal collagen deposition and early renal injury (Fujisawa et al., 2004). Whereas increased aldosterone and ET-1 levels in STZ-induced diabetic rats are associated with decreased renal expression of Dot1a, which is a splice variant of Dot1 (disruptor of telomeric silencing) and chromosome 9 (Af9) — negative regulators of ET-1 transcription, spironolactone decreases ET-1 expression and increases Dot1a and Af9 expression in a renal proximal tubular cell line (Zhou et al., 2012). These data reinforce the suggestion that aldosterone receptor antagonism is an effective intervention for diabetic complications such as diabetic nephropathy (Heerspink and de Zeeuw, 2011). Since mineralocorticoid receptor antagonists exhibit side effects related to blockade of androgen receptors, e.g. sexual dysfunction, gynecomastia and feminization (Abuannadi and O'Keefe, 2010; Funder, 2013), the development of newer classes of molecules with reduced or no side effects is warranted.

Other drugs

Regulation of PPARs plays an important role as therapeutic targets against cardiovascular and metabolic diseases (Matsumoto et al., 2008; Millar, 2013; Ferroni et al., 2013; Cheang et al., 2013). Three isotypes of PPARs such as PPARα, PPARβ/δ (PPARβ) and PPARγ are recognized and their role on glucose and lipid metabolism is well known. As mentioned above, there is a crosstalk between PPARγ and ET-1 in diabetes, which also seems the case for PPARα or PPARβ and ET-1 signaling. Fenofibrate, an agonist of PPARα, not only inhibits ET-1 expression in human ECs (Glineur et al., 2013), but also decreases ET-1-induced p38MAPK activation in cardiomyocytes (Irukayama-Tomobe et al., 2004a), and decreases ET-1-induced cardiac hypertrophy through negative regulation of AP-1 binding activity and inhibition of the c-Jun N-terminal kinase (JNK) pathway (Irukayama-Tomobe et al., 2004b). We showed in a previous study that treatment of STZ-induced diabetic rats with bezafibrate improves endothelial function and this is associated with decreased ET-1 production (Kanie et al., 2003). Zarzuelo et al. (2013) found that the activation of PPARβ with GW0742 (a PPARδ/β agonist) in deoxycorticosterone acetate (DOCA)–salt hypertensive rats normalizes endothelial function partly by reducing ET-1-induced superoxide generation. Moreover, Quintela et al. (2012) demonstrated that treatment of rats with T1DM (STZ-induced diabetes) and with GW0742 restores endothelial function via an increase in NO bioavailability as a result of down-regulation of prepro-ET-1 and reduced NAD(P)H oxidase-derived superoxide generation.

The 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) are used to lower low-density lipoprotein levels. Statins are recognized to have pleiotropic effects (other than reducing dyslipidemia), including increasing NO bioavailability as well as reducing oxidative stress and inflammation (Lefer et al., 2001; Abdul Rahman and Chetter, 2010; Chen et al., 2011). Moreover, statins lower ET-1 production and prepro-ET-1 mRNA expression (Hernandez-Perera et al., 1998, 2000; Mueck et al., 1999; Ozaki et al., 2001; Ohkita et al., 2006) in ECs. Statins also suppress basic fibroblast growth factor-induced up-regulation of ET_A and ET_B receptors (Xu et al., 2002). Of importance, statins normalize abnormal ET-1 signaling in diabetes. Lee et al. (2003) found that chronic treatment with atorvastatin prevents coronary atheroma and the enhanced myoplasmic Ca^{2+} level and tyrosine phosphorylation responses to ET-1, but does not decrease plasma cholesterol in diabetic dyslipidemia. Nakamura et al. (2001) reported that treatment of patients with T2DM exhibiting microalbuminuria and dyslipidemia with cerivastatin lowers urinary albumin excretion and circulating ET-1 levels. We found that enhanced ET-1-induced vascular contraction in OLETF rat is caused by an increase in kinase suppressor of Ras 1 (KSR1)/ERK complexes after protein phosphatase 2A (PP2A) activation (Nemoto et al., 2012b) and that treatment of OLETF rats with pravastatin improves ET-1-induced contractions and suppresses ET-1-induced ERK phosphorylation, with the associated phosphorylated KSR1 and phosphorylated PP2A levels being increased toward normal levels. These data suggest that in T2DM rats, pravastatin normalizes ET-1-induced contraction via a suppression of PP2A/KSR1/ERK activities (Nemoto et al., 2012b).

Calcium dobesilate, which is considered an angioprotective drug, has been used in the treatment of diabetic retinopathy and chronic venous insufficiency in various countries during the last few decades (Berthet et al., 1999; Allain et al., 2004). Although its efficacy and detailed molecular mechanisms in the treatment of diabetic retinopathy are still unclear, there are several reports suggesting that this compound has beneficial effects on retinal ECs (Leal et al., 2010). Javadzadeh et al. (2013) found that the administration of this compound in patients with diabetic retinopathy reduces circulating levels of ET-1 and C-reactive protein (CRP), a marker of systemic inflammation. Although future investigations on the molecular mechanisms of calcium dobesilate are required, these results indicate that beneficial effects of calcium dobesilate on diabetic retinopathy may be through a reduction of ET-1.

A number of epidemiologic studies have demonstrated that the consumption of functional foods containing bioactive polyphenols is associated with normalization of metabolic and/or vascular dysfunction (Munir et al., 2013; van Dam et al., 2013). There is a growing body of evidence suggesting that green tea polyphenols, especially the most abundant green tea catechin, epigallocatechin gallate (EGCG), have beneficial effects on cardiovascular and metabolic health (Babu and Liu, 2008). For example, EGCG has anti-inflammatory, anti-angiogenic, and anti-proliferative effects on both ECs and VSMCs (C.J. Wang et al., 2010; Yang et al., 2013). Considering possible effects of EGCG on the ET-1 system, Reiter et al. (2010) observed that EGCG decreases the expression and secretion of ET-1 in ECs partly via Akt- and AMPK-stimulated forkhead box protein O1 (FOXO1) regulation of the ET-1 promoter. C.J. Wang et al. (2010) found that EGCG inhibits ET-1-induced CRP expression by suppressing reactive oxygen species (ROS). Moreover, we recently found that long-term treatment of OLETF rats at the chronic stage of T2DM with EGCG suppresses ET-1-induced contraction in large arteries and normalizes endothelial function (Matsumoto et al., 2013). Resveratrol, a plant-derived stilbene polyphenol found in red wine, has various vasculoprotective effects, such as increased transcription and action of NO synthase (Wallerath et al., 2002), anti-inflammatory effects (Jimenez-Gomez et al., 2013), and induction of potent endothelium-independent relaxation (Novakovic et al., 2006). Resveratrol reduces ET-1 production as well as ET-1 effects (El-Mowafy et al., 2009; Liu et al., 2003; Lopez-Sepulveda et al., 2011; Nicholson et al., 2010). Resveratrol activates SIRT1 [sirtuin (silent mating type information regulation 2 homolog) 1], which is a key regulator of metabolic pathways and stress resistance and has anti-inflammatory, anti-apoptotic, and anti-senescent effects in ECs (Schmitt et al., 2010). Yang et al. (2010) found that resveratrol increases SIRT1 expression and NO production stimulated with insulin in HUVEC under high glucose conditions. Resveratrol also counteracts up-regulation of ET-1 mRNA and E-selectin induced by high glucose via SIRT1-independent and -dependent mechanisms, respectively. The molecular mechanisms by which resveratrol modulates vascular ET-1 expression remain unclear, and further research is required. These results suggest that consumption of functional food such as polyphenols may play an important role to suppress the ET-1 system in diabetic states. It is important to mention that despite the strong evidence on the vasculoprotective effects of polyphenols, no studies to date have confirmed the benefits of polyphenols in diabetic patients. Additional research, focusing on diabetic patients and using a range of doses, is needed to advance the field.

Oxidative stress plays an important role in diabetes-associated vascular complications (Hink et al., 2001). ROS generation induces ET-1 synthesis via transforming growth factor-β (TGF-β) (Kahler et al., 2000; Sugo et al., 2001) and ET-1 enhances ROS generation via NAD(P)H oxidase in ECs (Dong et al., 2005). Apocynin, an inhibitor of NAD(P)H oxidase, abrogates hypoxia-induced increased ET-1 mRNA levels in carotid arteries from male SD rats (Liu et al., 2013) and abolishes ET-1-induced activation of the MAPK in aortic VSMC under high glucose conditions (Banes-Berceli et al., 2005). Bardoxolone, an oral antioxidant and inflammation-modulator, increases renal function in patients with chronic kidney diseases associated with T2DM (Pergola et al., 2011a, 2011b). Considering that a decrease in ROS generation abrogates diabetes-induced vascular damage, the use of antioxidants that modulate ET-1 signaling may be clinically important in the treatment of this disease.

Effects of ET-1 receptor blockade on diabetic vasculopathy

Diabetes, obesity, and insulin resistance are associated with increased ET-1 expression and activity, and ET-1 is an important contributor to the abnormalities in vascular tone, including impaired endothelium-dependent relaxation and insulin resistance in these conditions (Matsumoto et al., 2008; Ergul, 2011; Shemyakin et al., 2011; Pernow et al., 2012; Mather, 2013). Moreover, blockade of ET-1 signaling improves vasodilation in diabetes and obesity, and antagonism of ET-1 actions in the vasculature improves insulin resistance (Kanie and Kamata, 2002; Shemyakin et al., 2006; Ahlborg et al., 2007; Lteif et al., 2007; Ergul, 2011; Pernow et al., 2012; Rafnsson et al., 2012; Mather, 2013). For example, ET_A antagonists have beneficial effects on diabetic vascular dysfunction, including increased blood flow in the retina (Z. Wang et al., 2010), skin microcirculation (Settergren et al., 2008), and increased forearm blood flow (Cardillo et al., 2002), and attenuated diabetes-associated aortic atherosclerosis (Watson et al., 2010). ET_A receptor antagonists as well as combined ET_A/ET_B antagonists in rats with STZ-induced diabetes decreased proteinuria and normalized the renal matrix protein (Hocher et al., 2001) and improved endothelium-dependent relaxation in the aorta (Kanie and Kamata, 2002). On the other hand, ET_B antagonism might produce undesirable effects since, in some cases, ET_B blockade exacerbates ET-1 contraction and decreases vascular relaxation, which might be due to the suppression of EDRFs signaling (Ergul, 2011). Since the activation of ET_B receptor can lead not only to vasorelaxation, but also to vasoconstriction, a detailed understanding of the role of ET_B receptors and the balance between ET_A and ET_B receptors in the systemic vasculature (or in specific vascular beds) is required when ET antagonists are considered in the treatment of diabetic vasculopathy. At present, selective ET_A antagonists have been approved only for restricted clinical uses, including prostate cancer metastasis prevention (atrasentan) and primary pulmonary hypertension (bosentan) due to toxicity concerns. Very recently, macitentan, a new dual ET receptor antagonist that significantly reduces morbidity and mortality in patients with pulmonary arterial hypertension (Pulido et al., 2013), has been approved for the treatment of pulmonary hypertension. A large phase 3 trial (ASCEND — a randomized, double blind, placebo controlled, parallel group study to assess the effect of the endothelin receptor antagonist avosentan on time to doubling of serum creatinine, end stage renal disease or death in patients with type 2 diabetes mellitus and diabetic nephropathy) examined the effects of avosentan, a potent, and non-peptidergic selective ET_A receptor antagonist, on renal disease progression in diabetic nephropathy (Mann et al., 2010; Benz and Amann, 2011; Kohan and Pollock, 2013). Treatment with avosentan decreased proteinuria after 3–6 months treatment (Mann et al., 2010). However, the study was terminated due to increased morbidity and mortality associated with avosentan-induced fluid retention. Phase 2 trials with lower doses of avosentan (than in the ASCEND), atrasentan, and sitaxsentan (the latter two being highly ET_A-selective antagonists) showed reductions in proteinuria on top of the RAAS blockade (Kohan et al., 2011a; Kohan and Pollock, 2013). Infrequent and clinically insignificant fluid retention was observed at the most effective doses. Additional trials using ET_A antagonists are being performed and planned in patients with diabetic nephropathy (Kohan and Pollock, 2013). Moving forward, such studies must be performed with careful selection of patients and attention to dosing in order to minimize adverse side effects.

Conclusions

Although the mechanisms involved in the development and progression of diabetic vasculopathy are still unknown (partially due the number of factors related to these processes), ET-1 undoubtedly plays a key role in the pathogenesis and progression of diabetic vasculopathy. This brief review summarizes the relationship between the ET-1 system and the current therapeutic strategies for diabetes. Several drugs for diabetes directly and/or indirectly affect the vascular ET-1 system. Moreover, a number of experimental studies demonstrate that the blockade of ET-1 signaling has beneficial effects on diabetic vascular dysfunctions. Although it is currently unclear whether the association of ET-1 antagonists and other therapeutic drugs will be beneficial, experimental and clinical evidence indicate that ET-1 blockade is important against diabetic vasculopathy.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.lfs.2013.12.216.

Conflict of interest statement

There are no potential conflicts of interest among the authors regarding the publication of this manuscript.

Acknowledgments

This study was supported in part by the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the Science Research Promotion Fund from the Promotion and Mutual Aid Corporation for Private Schools of Japan, Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq), Brazil.

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