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The link between metabolic abnormalities and endothelial dysfunction in type 2 diabetes: an update

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Abstract

Despite abundant clinical evidence linking metabolic abnormalities to diabetic vasculopathy, the molecular basis of individual susceptibility to diabetic vascular complications is still largely undetermined. Endothelial dysfunction in diabetes-associated vascular complications is considered an early stage of vasculopathy and has attracted considerable research interests. Type 2 diabetes is characterized by metabolic abnormalities, such as hyperglycemia, excess liberation of free fatty acids (FFA), insulin resistance and hyperinsulinemia. These abnormalities exert pathological impact on endothelial function by attenuating endothelium-mediated vasomotor function, enhancing endothelial apoptosis, stimulating endothelium activation/endothelium–monocyte adhesion, promoting an atherogenic response and suppressing barrier function. There are multiple signaling pathways contributing to the adverse effects of glucotoxicity on endothelial function. Insulin maintains the normal balance for release of several factors with vasoactive properties. Abnormal insulin signaling in the endothelium does not affect the whole-body glucose metabolism, but impairs endothelial response to insulin and accelerates atherosclerosis. Excessive level of FFA is implicated in the pathogenesis of insulin resistance. FFA induces endothelial oxidative stress, apoptosis and inflammatory response, and inhibits insulin signaling. Although hyperglycemia, insulin resistance, hyperinsulinemia and dyslipidemia independently contribute to endothelial dysfunction via various distinct mechanisms, the mutual interactions may synergistically accelerate their adverse effects. Oxidative stress and inflammation are predicted to be among the first alterations which may trigger other downstream mediators in diabetes associated with endothelial dysfunction. These mechanisms may provide insights into potential therapeutic targets that can delay or reverse diabetic vasculopathy.

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Keywords

Endothelial function; Dyslipidemia; Hyperglycemia; Insulin resistance; Inflammation; Oxidative stress

Introduction

The increased prevalence of obesity is closely associated with the rising incidence of cardiovascular diseases and type 2 diabetes [30, 100]. Diabetes creates an environment adverse to vascular function through a wide variety of metabolic assaults [65], and is linked to macro- and microvasculopathy [35]. Macrovascular complications include coronary artery disease, stroke and peripheral vascular disease. Microvascular consequences include retinopathy and nephropathy, which are regarded as major causes of blindness and end-stage renal failure [51, 60]. Obesity-related insulin resistance, which when severe is Type 2 diabetes, is associated with progression of endothelial impairment [7]. Endothelial dysfunction is a key event in the pathogenesis of diabetic micro- and macrovasculopathy and has gained increasing attention in the study of diabetes-associated cardiovascular complications.

The contributing factors underlying impaired endothelial function in diabetes are varied and commonly include metabolic abnormalities such as hyperglycemia, excess liberation of free fatty acids (FFA) and insulin resistance (see Ref. [71] for review). This review will focus on the current knowledge regarding mechanisms of metabolic abnormalities in type 2 diabetes that drive endothelial dysfunction.

Endothelium and vasomotor function in diabetes

The endothelium releases various contracting and relaxing factors that are responsible for control of blood vessel tone and balance between vasodilation and vasoconstriction (see Ref. [79] for review).

Endothelium-dependent vasoconstriction is exacerbated in diabetes [80]. Endothelin-1 (ET-1), a potent vasoconstricting peptide released from endothelial cells, plays critical roles in diabetes-associated vascular complication (see Ref. [19] for review). ET-1 expression is increased in microvascular endothelial cells isolated from subcutaneous adipose tissue of type 2 diabetic subjects, accompanied by increased basal mitogen-activated protein kinase (MAPK) activity [28]. In cultured endothelial cells, activation of extracellular signal-regulated kinase 5 (ERK5) [89] or inhibition of the janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway [42] suppresses high glucose-induced ET-1 expression. The endothelium also produces cyclooxygenase (COX)-dependent vasoactive factors [20, 88], including the vasoconstrictors, prostaglandin H_2 (PGH_2) and thromboxane A_2 (TXA_2), and the vasodilator, prostacyclin (PGI2). Indomethacin, a nonselective inhibitor of COX, abolished hypoxia-induced dilation of skeletal muscle resistance arterioles in obese Zucker rats, while blockade of PGH_2/TXA_2 receptors and the inhibition of thromboxane synthase increased hypoxia-induced dilation. Moreover, the TXA_2 level was higher in the arterioles of obese rats. Together, these data suggest that

impaired hypoxia-induced dilation in obese rats may be due in part to an increased vascular production of TXA_2 which competes against the vasodilator influences of PGI_2 [29]. In intramyocardial arteries of obese Zucker rats, COX-1 inhibition enhanced arachidonic acid (AA)-induced vasorelaxation and inhibited serotonin-induced vasoconstriction, but COX-2 inhibition reduced AA-induced vasorelaxation without modifying serotonin-induced response [64]. These results suggest that COX-2-mediated vasorelaxation in coronary arteries from insulin-resistant obese Zucker rats is enhanced, which may represent a compensatory mechanism.

Factors contributing to vasodilation include nitric oxide(NO), PGI_2 and endothelium-derived hyperpolarizing factors (EDHF). Among all the factors, NO is the major factor in regulating endothelium-dependent relaxation. *S*-Nitrosylation of soluble guanylyl cyclase (sGC) by endothelial NO was recently identified as a mechanism that may compensate for moderate reduction of vascular NO bio-availability [54]. NO-mediated endothelium-dependent vasodilation is impaired in type 2 diabetic mice (db/db), which is attributed to reduced expression and/or phosphorylation (Ser1177) of endothelial nitric oxide synthase (eNOS) [56, 102], enhanced eNOS uncoupling [55] and increased inactivation of NO by reactive oxygen species (ROS) [11]. Superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and peroxynitrate ($ONOO^-$) are significant ROS in vasculopathy. There are multiple cellular sources of $O_2^{\cdot-}$, including NAD(P)H oxidase, xanthine oxidase, the mitochondrial respiratory chain, the AA cascade (including lipoxygenase and COX) and uncoupled eNOS [66]. NAD(P)H oxidase is a known key source of $O_2^{\cdot-}$ in the vasculature (see Ref. [15] for review). One of the NAD(P)H oxidase isoforms, Nox2, is especially abundant in the endothelium. Endothelium-specific overexpression of Nox2 exacerbated angiotensin II-induced oxidative stress and attenuated endothelium-dependent vasorelaxation [50]. Increased intracellular production of $O_2^{\cdot-}$ derived from NADPH oxidase does not inhibit eNOS activity directly, but instead prevents the extracellular actions of NO by producing $ONOO^-$ [104] leading to protein tyrosine nitration and the generation of nitrotyrosine. NAD(P)H oxidase activity, $O_2^{\cdot-}$ production and nitrotyrosine levels are increased in coronary microvessels and aortae of db/db mice, accompanied by impaired endothelium-dependent vasodilation [23, 102].

In addition to NO, EDHF is also an important mediator of vascular tone and reactivity in diabetes, especially in small resistance vessels (see Ref. [21, 24] for review). A recent study suggests that both NO and EDHF-mediated vasodilation is impaired in mesenteric arteries of Otsuka Long-Evans Tokushima fatty (OLETF) type 2 diabetic rats [45]. Our work shows in coronary arterioles of db/db mice, NO-mediated vasodilation is significantly reduced, but a preserved EDHF function contributes to endothelium-dependent vasodilation [56]. Soluble epoxide hydrolase (s-EH) rapidly hydrolyzes certain epoxylipids (e.g., EET) to less bioactive diols (DHET), thereby attenuating the evoked vasodilator effects. In db/db mice, oral administration of s-EH inhibitors prevented endothelial dysfunction, and the effects were not affected by incubating mesenteric arteries with L-NAME and indomethacin [103].

Thus, diabetes-associated vasodilatory dysfunction is associated with increased production or sensitivity to vasoconctrictors, as well as decreased production or increased degradation of endogenous vasodilators. In addition, in diabetes the relative importance of the

endogenous vasodilatory mechanisms are altered and exhibit compensatory dilatory pathways.

Role of hyperglycemia in diabetes-associated endothelial dysfunction

In diabetes, the progression of vasculopathy is highly dependent upon the degree of hyperglycemia [4]. Prior work proposed various biochemical mechanisms which address how hyperglycemia leads to diabetic endothelial dysfunction [65]. This section will primarily focus on the newly identified signaling pathways by which hyperglycemia-induced metabolites exert adverse effects on endothelial function (Fig. 1).

The increased production of diacylglycerol (DAG) through glycolysis increases activation of protein kinase C (PKC), which is associated with vascular abnormalities in permeability, contractility, extracellular matrix synthesis, cell growth, apoptosis, angiogenesis, leukocyte adhesion, and cytokine activation and inhibition (see Ref. [27] for review). In cultured human microvascular endothelial cells, hyperglycemia-induced increase in PKC activity can be reversed by activation of transcription factor NF-E2-related factor-2 (nrf2), which regulates antioxidant defense responses [90]. The distinctive role of different PKC isoforms and the therapeutic implications require further investigation. In high glucose-treated primary human umbilical vein endothelial cells (HUVEC), the expression of endothelin converting enzyme-1 (ECE-1) increased as was ET-1 production, which was abolished by inhibiting PKC-delta, but not PKC-alpha, and PKC-beta [36]. In a rat model of type 2 diabetes and hypertension, the PKC-beta inhibitor, ruboxistaurin, restored endothelium-dependent vascular relaxation and suppressed vascular contraction [41]. In addition to the direct effects on endothelial cells, hyperglycemia affects ‘cross talk’ of vascular endothelial cells and pericytes through activating PKC-delta, which increases both expression of Src homology-2 domain-containing phosphatase-1 (SHP-1) and pericyte apoptosis, critical factors in development of diabetic retinopathy [26].

Another area of great interest focused on glucose-induced formation of non-enzymatic advanced glycation end products (AGE) [65]. AGE signaling is mediated through the receptor of AGE (RAGE) or other targets such as the toll-like receptor 4 (TLR4) and CD36. Deleterious vascular effects by AGE can occur by receptor-independent or dependent pathways [32]. In HUVEC, glycated albumin, a precursor of AGE, up-regulates NADPH oxidase and enhances oxidative stress [63]. In human aortic endothelial cells (HAEC), high glucose increased the expression of RAGE. High glucose-induced RAGE expression was normalized by overexpression of either uncoupling protein 1 (UCP1), superoxide dismutase 2 (SOD2) or glyoxalase 1(GLO1) [93]. In retinal endothelial cells, RAGE activation by hyperglycemia induces the expression of thioredoxin-interacting protein (TXNIP, an endogenous inhibitor of the antioxidant thioredoxin) and inflammatory genes such as COX-2, vascular endothelial growth factor-A (VEGF-A) and intercellular adhesion molecule-1 (ICAM-1) [58]. In isolated rat mesenteric arteries, methylglyoxal, an AGE precursor, impaired endothelial function and increased nitrotyrosine expression [9]. In isolated rat retina, AGE also caused increased capillary permeability since pretreatment with anti-RAGE antibodies prevented the abnormalities [85]. Lastly, administration of soluble form of RAGE (sRAGE) partially restored coronary endothelial function in db/db mice [25].

These studies highlight the critical importance of AGE in the pathogenesis of vascular dysfunction in diabetes.

Sorbitol, another toxic compound produced by abnormal metabolic pathways in diabetes, results from increased activity of the polyol pathway. In isolated, pressurized rat gracilis muscle arterioles, the aldose reductase (AR) inhibitor, zopolrestat, attenuated hyperglycemia-induced impairment of flow-mediated vasodilation [76]. Increasing doses of sorbitol elicited dose-dependent constrictions, which were abolished by endothelium removal, SQ-29548 or superoxide dismutase (SOD) plus catalase [76]. The sorbitol pathway serves as an important mechanism for diabetic retinopathy [40]. AR levels are lower in endothelial cells compared to pericytes. Hyperglycemia induces significant polyol accumulation in pericytes, which can be inhibited by AR inhibitors, but little or no accumulation in endothelial cells [34].

Increased ROS serves as a final common pathway of hyperglycemia-induced vascular dysfunction through a multitude of mechanisms. In addition to the inactivation of NO, hyperglycemia-induced ROS production may directly promote vascular apoptosis and remodeling. Hyperglycemia-induced endothelial apoptosis of HAEC was decreased by C-peptide, which reduces RAC-1 translocation to the membrane and NAD(P)H oxidase activation [13]. High glucose increases lectin-like oxLDL receptor-1 (LOX-1) expression and reduces eNOS expression in HUVEC, which is reversed by NAD(P)H oxidase inhibition [73]. Hyperglycemia-stimulated vascular matrix metalloproteinase (MMP) activation in bovine aortic endothelial cells can be reduced by treatment with an antioxidant, but not an inhibitor to PKC [77]. Mesentery artery remodeling and expression of MMP-9, MMP-12 and tissue inhibitors of matrix metalloproteinase (TIMP)-1 and TIMP-2 are increased in db/db arteries [67]. In BAEC, normalizing levels of mitochondrial ROS by manganese SOD (MnSOD) and an inhibitor of electron transport chain complex II prevent glucose-induced activation of PKC, formation of AGE, sorbitol accumulation and nuclear factor-kappa B (NFκB) activation [53]. Thus, hyperglycemia-induced biochemical sequelae lead to enhanced oxidative stress. Interventions that reduce oxidative stress also block the production and action of the adverse biochemical sequelae in hyperglycemia.

It is also noteworthy that glycocalyx, a layer of proteoglycans covering the endothelium, is involved in constituting the vascular barrier together with endothelial cells [6]. Acute hyperglycemia reduced glycocalyx volume and induced endothelial dysfunction in healthy human subjects, indicating a potential role for glycocalyx perturbation in mediating vascular dysfunction during hyperglycemia [52].

Therefore, hyperglycemia may induce chronic vascular complications via formation of toxic metabolites such as ROS, AGE, increased sorbitol and persistent activation of PKC. The interactions among various metabolites may further perpetuate the adverse effects of hyperglycemia. Intensive glycemic control, as well as inhibiting the downstream signaling by various metabolites, may serve as potential therapeutic targets for diabetes-induced vascular dysfunction.

Role of insulin resistance in diabetes-associated endothelial dysfunction

The onset of hyperglycemia and diabetes is often preceded by insulin resistance from many years to decades. The role of insulin resistance and subsequent hyperinsulinemia at the level of endothelial cells in vasculopathy has been extensively studied (Fig. 2). In vitro experiments using cultured endothelial cells suggest that insulin can induce the concurrent release of ET-1 and NO, two substances with opposing vasoactive properties. Insulin stimulates ET-1 gene expression and secretion in endothelial cells via a phosphoinositide-3 kinase (PI3K)-dependent inactivation of glycogen synthase kinase-3beta (GSK-3beta) and Ras (an abbreviation of RAt Sarcoma)-MAPK activation [92, 95]. Insulin induces NO production via activation of an insulin receptor tyrosine kinase that phosphorylates insulin receptor substrate-1 (IRS-1), leading to binding and activation of PI3K, phophoinositide-dependent protein kinase-1 (PDK-1) and protein kinase B (Akt)/eNOS pathway [47, 48, 96]. The multidomain adaptor protein, APPL1, modulates the dual vascular effects of insulin. APPL1 potentiates insulin-stimulated Akt activation by competing with the Akt inhibitor Tribble-3 and suppressing ERK1/2 signaling by altering the phosphorylation status of its upstream kinase Raf-1 (RAF proto-oncogene serine/threonine-protein kinase) in HUVEC [84]. In microvascular endothelial cells isolated from type 2 diabetic subjects, IRS-1/Akt phosphorylation was reduced while ERK1/2 activation was increased, suggesting the presence of endothelial cell insulin resistance [28]. Further evidence suggests that insulin is a double-edged sword in the treatment of diabetics. Physiological concentrations of insulin (10^{-10} M) preserve telomere length, reduce p53 and vascular cell adhesion molecule-1 (VCAM-1) expression, and delays endothelial senescence under high glucose conditions through an NO-dependent mechanism. However, supra-physiological concentrations of insulin (10^{-7}–10^{-6} M) in the presence of high glucose promote cellular senescence in an eNOS-independent manner [44].

Animal studies suggest that endothelium-specific insulin resistance does not cause changes in whole-body glucose tolerance, circulating insulin concentrations or insulin sensitivity [17, 81]. Endothelium-dependent vasorelaxation was not examined in endothelium-specific insulin receptor knockout mice; but in transgenic mice with a mutant insulin receptor targeted to endothelium, aortic endothelial function was impaired. Furthermore, in ApoE KO mice with a specific endothelial cell knockout of insulin receptors, atherosclerotic lesion formation is accelerated along with impaired endothelium-dependent vasodilation of carotid arteries, and enhanced VCAM-1 expression and mononuclear cell adhesion [61]. In mice with a genetic deletion of the insulin receptor in all vascular tissues, basal vascular eNOS phosphorylation, endothelial function and blood pressure are normal, despite absent insulin-mediated eNOS phosphorylation [70]. Additionally, knockout of insulin receptors in cardiomyocytes attenuates coronary arterial dysfunction induced by pressure overload, implicating a compensatory mechanism [69]. These studies suggest that the concept of selective insulin resistance is more complex and variable than previously thought [22].

Although in vitro experiments strongly suggest that insulin regulates NO release by endothelial cells, endothelium-intact isolated arteries (mouse aortae and mesenteric arteries) do not relax following the administration of insulin (unpublished work). There is also controversy as to whether insulin-induced relaxation of resistance vessels and increase in

blood flow to skeletal muscles occur at physiological exposure time and concentrations of insulin [5]. A clinical study shows that although troglitazone increased whole-body and forearm glucose uptake, and improved insulin sensitivity, it had no effects on insulin-induced vasodilatory function in obese subjects [72].

Thus, mechanisms underlying the association between insulin resistance and endothelial dysfunction, and therapeutic implications of improving insulin sensitivity in the vasculature warrant further investigations.

Role of FFA in diabetes-associated endothelial dysfunction

Free fatty acids in excess is implicated in the pathogenesis of insulin resistance [33]. As is seen with hyperglycemia-induced glucotoxicity, lipotoxicity from FFA may promote endothelial dysfunction by a number of related mechanisms (Fig. 3).

Endothelial damage by FFA occurs due to a decrease in Bcl-2/Bax ratio, which augments endothelial apoptosis [59]. FFA's apoptotic effects are associated with reduced Akt/eNOS phosphorylation and enhanced caspase-9 activation in HUVEC, which can be prevented by insulin (10^{-8} M) treatment [59]. FFA-induced apoptosis also involves p38 MAPK signaling [10], NFκB activation [68] and GSK-3beta/Wnt/beta-catenin signaling [107]. FFA inhibits insulin-mediated tyrosine phosphorylation of IRS-1, serine phosphorylation of Akt and eNOS, and NO production, while it increases IKKβ (IκB kinase-β) activity and phosphatase and tensin homolog (PTEN) expression [37, 83]. Exposure to FFA enhances the expression of NAD(P)H oxidase subunit, stimulating ROS production [12] and reducing mitochondrial membrane potential [106]. Elevated concentrations of non-esterified fatty acids (NEFA) increase monocyte expression of CD11b, intracellular ROS formation and adhesion to endothelial cells, which can be inhibited by antioxidants, NAD(P)H oxidase inhibitors and PKC inhibitors [105]. FFA increase A disintegrin and metalloproteinase (ADAM)-mediated substrate cleavage resulting in functional effects on cell proliferation, cell migration and endothelial permeability [62]. Moreover, saturated versus unsaturated FFA-induced endothelial apoptosis may be mediated via different mechanisms, and the impact of FFA on endothelial cells depends on vascular origin and growth/proliferation status of the vascular cellular elements. Therefore, it is important to examine the effects of FFA on target tissues that are known to be affected in diabetes, such as human aortic and retinal endothelial cells [2].

Studies on animal models also support the detrimental vascular effects of FFA. In the rabbit, in vitro incubation with FFA impaired endothelial function of isolated aortic rings, which was accompanied by reduced NO levels and enhanced oxidative stress [18]. In Sprague–Dawley rats, FFA infusion increases blood pressure, reduces eNOS and PGI_2 synthase activity and impairs aortic endothelial function [16, 82]. In obese Zucker rats and high fat diet-induced obese mice, inhibiting FFA release from adipose and inhibiting rate-limiting enzyme for fatty acid oxidation in mitochondria reduced aortic ROS production and prevented eNOS and PGI_2 synthase inactivation [16].

In addition to animal models, the adverse effects of FFA on endothelial function are demonstrated in healthy humans and diabetic patients. Infusion of FFA impairs endothelial function, which can be reversed by an inhibitor of the renin–angiotensin system (RAS) [86] or in the presence of rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist [46]. Lipid infusion blocked insulin-mediated increases in microvascular blood velocity and microvascular blood flow in both cardiac and skeletal muscle of healthy young adults [39]. A 48-h physiological increase in plasma FFA to levels of obesity and diabetes in a group of healthy subjects enhanced leukocyte activation and the angiotensin II-forming activity in human mononuclear and polymorpho-nuclear cells [3]. Elevated FFA also increases plasma markers of endothelial activation, such as ICAM-1, VCAM-1 and soluble E-selectin (sE-selectin), and increases plasma levels of myeloperoxidase (MPO) and tissue-type plasminogen activator inhibitor-1 (tPAI-1, an indicator of a prothrombotic state) [43]. In obese subjects with type 2 diabetes, a lipid infusion results in a rapid and sustained elevation in blood pressure, impaired flow-mediated dilatation and increases in C-reactive protein (CRP), but does not change plasma renin and aldosterone levels [78].

In type 2 diabetic subjects, postprandial lipidemia is exaggerated and prolonged. Prolonged postprandial lipidemia is associated with prolonged endothelial dysfunction likely through the effects described above from FFA. This underscores the importance of dietary compliance with low-fat meals for type 2 diabetic patients [1].

Perspectives

Many studies suggest that intensive control of blood glucose delays the onset and retards the progression of diabetic vascular complications. However, to date, the effectiveness of intensive glucose control on the prevention of major cardiovascular events is still inconclusive [14].

The molecular mechanisms by which hyperglycemia, insulin resistance, hyperinsulinemia and dyslipidemia result in endothelial dysfunction overlap and make it difficult to tease out the specific molecular mechanisms. Among the various pathogenic features induced by metabolic abnormalities in diabetes, oxidative stress and inflammatory responses appear to be the first abnormalities which trigger several other mechanisms in diabetes-associated endothelial dysfunction [8]. Although the role of oxidative stress as a contributing mechanism to diabetes-induced endothelial dysfunction is supported by a large body of experimental and clinical studies, antioxidant supplementation (mostly with vitamin E) has not been shown to improve the pathological consequence. In contrast, substances such as statins, activators of peroxisome proliferator-activated receptors and inhibitors of renin–angiotensin–aldosterone system, which possess indirect antioxidant properties, show improved endothelial function in preclinical and clinical studies as well as reducing the incidence of cardiovascular events in diabetic patients [38]. Factors that may contribute to the apparent discrepancy in these studies include patient selection with diseases that differ in extent of oxidative stress as well as the administered dose and type of antioxidant therapy used. Therefore, individualized assessment of the level of oxidative stress and the potential underlying mechanism of oxidative stress before treatment may provide insight into the appropriate therapeutic approach, which may improve the individual’s condition and resolve

this antioxidant paradox. The development of novel, potent antioxidant strategies and early intervention in the process of vascular dysfunction and disease development may also produce benefits in clinical outcomes [49, 71].

In addition to oxidative stress, metabolic abnormalities are correlated directly with markers of inflammation [74, 87]. Chronic low-grade inflammation can be both a cause and consequence of endothelial dysfunction, and the two appear to be tightly linked [65]. Since type 2 diabetes is highly associated with obesity, the metabolic role of adipose tissue potentiates the adverse effects on the vasculature [31, 98, 99]. Adipose tissue secretes a range of proinflammatory molecules, which lead to systemic inflammation and participate in the cross talk between adipose stores and the vascular wall (see Ref. 100 and 101 for review). Local inflammation in the vasculature is attributed to effects by the inflammatory cytokines/chemokines and leukocyte adhesion molecules expressed and released by the endothelium [97, 100]. Anti-inflammatory treatment by neutralizing antibodies to TNFα, MCP-1 and IFNγ effectively attenuated endothelial dysfunction in db/db mice without significantly affecting body weight and glucose metabolism [23, 91, 98]. This suggests that vasoprotection by anti-inflammatory therapies can be independent of their metabolic effects. Thus, newer anti-diabetic agents should not only achieve superior glycemic control, but also improve cardiovascular outcomes [94]. Therapies that combine salutary effects on vascular inflammation and oxidative stress potentially delay or reverse diabetic vasculopathy [57, 99].

Conclusion

Endothelial dysfunction is characterized by a number of functional alterations in the vascular endothelium, which include changes in vasomotor function, enhanced generation of ROS and inflammation resulting in a proatherogenic response, apoptosis, remodeling, and altered barrier function. Impaired endothelial function is a key event associated with subsequent progression of cardiovascular complications in diabetes. Although normal insulin signaling provides protection from glucotoxicity in endothelial cells, hyperinsulinemia further exacerbates hyperglycemia-induced endothelial injury. Insulin resistance leads to enhanced FFA production, which inhibits insulin signaling and accelerates vascular insulin resistance. Thus, glucotoxicity, lipotoxicity, insulin resistance and a mutual interaction between these factors occur to promote the development and progression of endothelial dysfunction in type 2 diabetes. Conventional therapies to reduce hyperglycemia, dyslipidemia and insulin resistance represent important clinical options to improve endothelial function and delay the progression of vascular complications. Therapeutic approaches targeting intracellular mechanisms underlying metabolic alterations, such as inhibiting AGE formation and signaling, suppressing PKC activation, inhibiting the cannabinoid receptor CB(1)-R [75], preventing or decreasing inflammatory responses and restoring the redox balance of the endothelium, are thought to be promising strategies to prevent endothelial dysfunction in the diabetic state. In animal models, to date, these insights are partially established with evidence of favorable effects. Since therapy addressing a single metabolic abnormality has not been beneficial (e.g., vitamin E), to reduce cardiovascular complications in type 2 diabetes may require simultaneous interventions within multiple metabolic and signaling pathways. It may take a multi-component approach such as reducing hyperglycemia,

oxidative stress, inflammation and insulin resistance to ameliorate the adverse effects that progress to diabetic vasculopathy.

Therefore, clinical trials targeting multiple therapeutic targets are urgently needed to validate their effectiveness in ameliorating diabetic vascular complications. Combination therapy that simultaneously targets multiple pathways in the pathogenesis of endothelial dysfunction is an attractive emerging concept for slowing progression of diabetic vascular complications.

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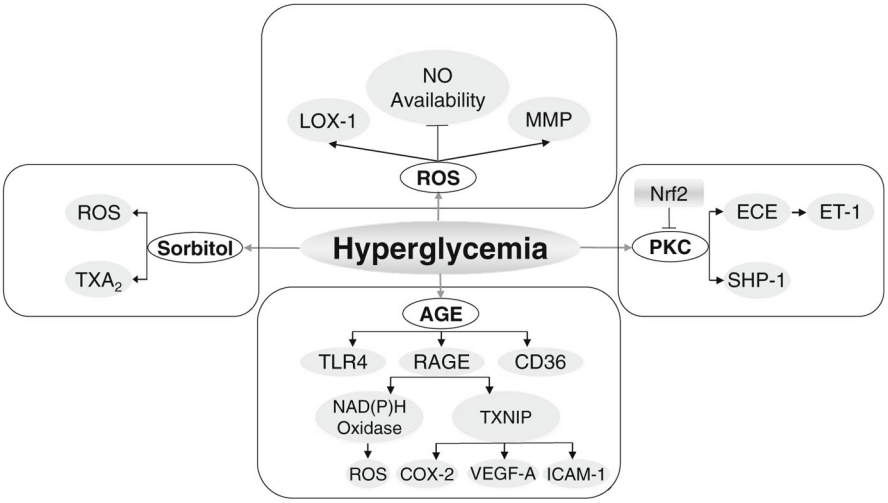

Fig. 1.

The impact of hyperglycemia on endothelial dysfunction. Hyperglycemia causes an increase in toxic metabolites resulting in increased production of ROS, advanced glycation end products (AGE), production of sorbitol and stimulation of protein kinase C (PKC). Activation of these pathways promotes increased vascular oxidative stress, inflammation, apoptosis, atherogenesis and impaired endothelial function. See text for details. *AGE* advanced glycation end products, *COX-2* cyclooxygenase-2, *ECE* endothelin converting enzyme, *ET-1* endothelin-1, *LOX-1* lectin-like oxLDL receptor-1, *MMP* matrix metalloproteinase, *NO* nitric oxide, *Nrf2* transcription factor NF-E2-related factor-2, *PKC* protein kinase C, *RAGE* receptor of AGE, *ROS* reactive oxygen species, *SHP-1* Src homology-2 domain-containing phosphatase-1, *TLR4* toll-like receptor 4, TXA_2 thromboxane A_2, *TXNIP* thioredoxin-interacting protein

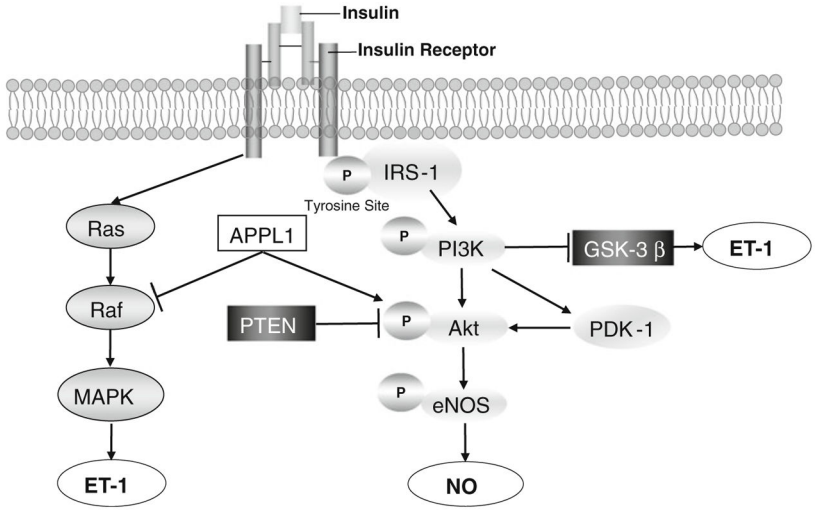

Fig. 2.

Role of insulin resistance in endothelial dysfunction. Insulin regulates endothelial function through both Ras-MAPK and PI3K-Akt-eNOS signaling pathways to maintain the balance between production of vasodilator mechanisms and vasoconstrictor mechanisms. *Akt* protein kinase B, *eNOS* endothelial nitric oxide synthase, *GSK3β* glycogen synthase kinase-3beta, *IRS-1* insulin receptor substrate-1, *MAPK* mitogen-activated protein kinase, *PDK-1* phophoinositide-dependent protein kinase-1, *PTEN* phosphatase and tensin homolog, *Ras* rat sarcoma

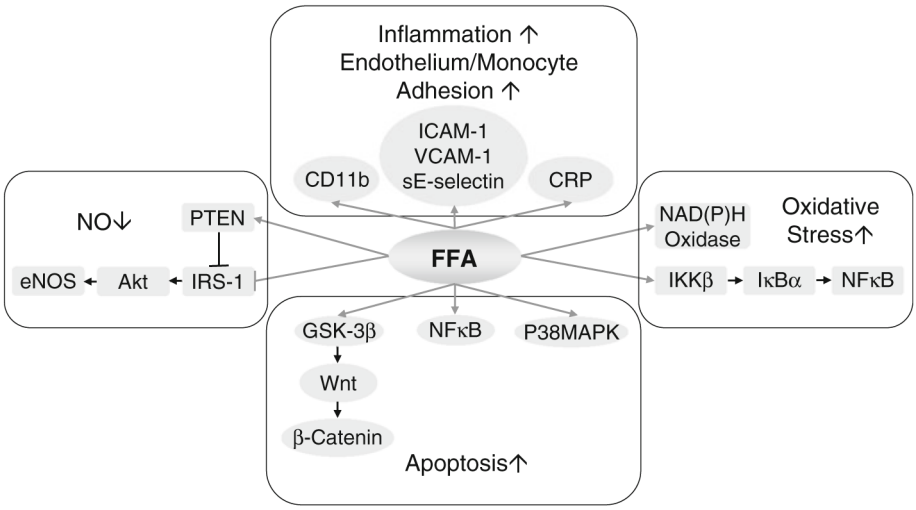

Fig. 3.

Role of free fatty acids in endothelial dysfunction. Free fatty acids (FFA) stimulate endothelial apoptosis, augment vascular oxidative stress, reduce NO availability, enhance endothelial and monocyte activation and increase inflammatory responses. *CRP* C-reactive protein, *ICAM-1* intercellular adhesion molecule-1, IκBα inhibitory subunit of NFκB, *IKK*β IκB kinase-β, NFκB nuclear factor-kappa B, *sE-selectin* soluble E-selectin, *VCAM-1* vascular cell adhesion molecule-1