Chapter 2
Cerebrovascular Disease in Type 1 Diabetes: Role of Oxidative Stress

Denise M. Arrick and William G. Mayhan

2.1 Introduction

Diabetes mellitus is a group of metabolic diseases that produces an increase in blood glucose as a result of inadequate production/release of insulin by the beta cells of the pancreas (type 1 diabetes mellitus, insulin-dependent diabetes, juvenile-onset diabetes) or as a result of inadequate responses of cells to insulin that is produced/released by the pancreas (type 2 diabetes mellitus, non-insulin-dependent diabetes, adult-onset diabetes). Estimates suggest that there are about 26 million children and adults (over 8 % of the population) that have been diagnosed with diabetes, about 7 million individuals that have diabetes but have not been diagnosed, and about 79 million people that are prediabetic. The cost of diabetes has been estimated to be over $180 billion per year (disability, work loss, and premature mortality). The complications from diabetes include, but are not limited to, hypertension, neuropathy, nephropathy, blindness, peripheral vascular disease, inflammation, heart disease, and stroke. Thus, diabetes contributes to an increase in morbidity and mortality in children, adolescents, adults, and the elderly. It remains critical to define mechanisms by which diabetes contributes to dysfunction of many organ systems in order to provide new therapeutic approaches for the prevention of diabetes-induced disease states. In this chapter, we will focus on mechanisms by which type 1 diabetes (T1D) may contribute to an increase in oxidative stress in the brain and how this increase in oxidative stress may contribute to cerebrovascular dysfunction, brain injury, cognitive dysfunction, and perhaps stroke.

D.M. Arrick • W.G. Mayhan (✉)
Department of Cellular Biology and Anatomy, Louisiana State University Health Sciences Center-Shreveport, School of Medicine in Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932, USA
e-mail: wmayha@lsuhsc.edu

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2.2 Oxidant Pathways in Diabetes

T1D impairs nitric oxide synthase (NOS)-dependent responses of large and small peripheral and cerebral blood vessels. Mechanisms responsible for T1D-induced impairment in vascular function appear to be related to the generation of reactive oxygen species (ROS) through a variety of cellular pathways. This increase in oxidative stress during T1D can occur from many cell types (endothelium, vascular smooth muscle, neurons, glia, astrocytes) and represents an imbalance between the production of ROS by oxidizing enzymes and the scavenging of these ROS by antioxidant defense enzymes, which serve to interfere with the downstream signaling events triggered by these ROS. In T1D, the activity of ROS-producing enzymes is increased, while antioxidant defense enzymes appear to be unaltered or decreased, shifting the balance in favor of ROS production. There are several oxidant-producing and antioxidant-protecting pathways that are altered by T1D in peripheral and cerebral blood vessels. In the following sections, we will outline some of the key aspects of these pathways.

2.2.1 Cyclooxygenase Pathway

The cyclooxygenase pathway has been implicated in synthesis of ROS for many years and has been thought to be a contributor to the formation of ROS during diabetes [30, 154, 156]. Early studies by Kontos and colleagues [88, 90, 91, 173] found that application of arachidonate to the cerebral microcirculation could produce dilation of large and small cerebral arterioles. This dilation could be inhibited by a combination of superoxide dismutase (SOD) and catalase, thus implicating a role for superoxide anion, hydrogen peroxide, and hydroxyl radical [90, 173]. It is now becoming apparent that hydrogen peroxide may be acting as an endothelium-derived hyperpolarizing factor in the brain and other vascular organs [89, 92, 104, 167]. Support for the production of ROS by the cyclooxygenase pathway during diabetes can be found in early studies by Pieper et al. [127, 129] and Tesfamariam et al. [155]. Pieper et al. [127] found that oxygen radicals, generated via xanthine plus xanthine oxidase, could impair relaxation of the thoracic aorta in nondiabetic and diabetic rats and that catalase and SOD could enhance relaxation of the thoracic aorta in diabetic rats [129]. Tesfamariam et al. [155] found that indomethacin could restore impaired relaxation of the thoracic aorta in diabetic rats to that observed in nondiabetic rats. Thus, it appeared that ROS generated via the activation of the cyclooxygenase pathway could contribute to impaired vascular function of peripheral blood vessels during T1D. With regard to cerebral vessels, we [108] found that treatment with indomethacin or the thromboxane A2/prostaglandin H2 receptor (SQ 29548) improved impaired endothelial NOS (eNOS)-dependent responses of cerebral arterioles in diabetic rats. In addition, others [79] have reported that indomethacin can restore impaired cerebrovascular reactivity to insulin in

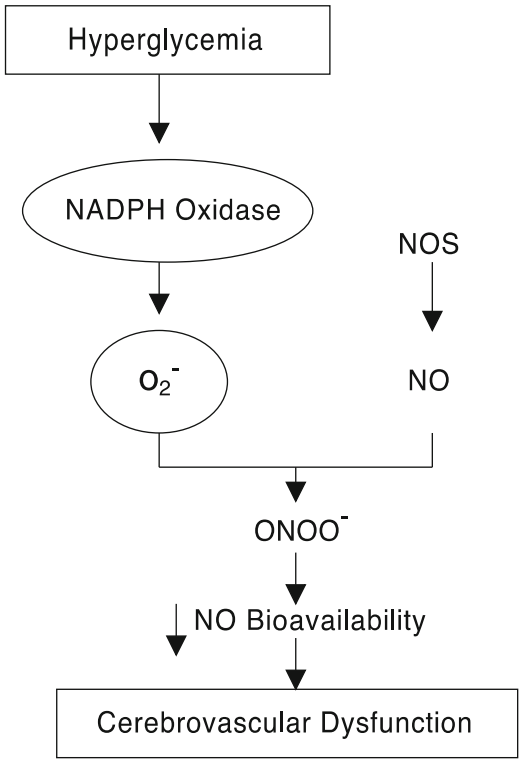

Fig. 2.1 Hyperglycemia-induced activation of NADPH oxidase. Activation of NADPH oxidase isoforms via an increase in cellular levels of glucose (hyperglycemia) can increase the formation of superoxide (O_2^-) from numerous cellular sources. Superoxide can then combine with nitric oxide (NO), forming peroxynitrite ($ONOO^-$), which can then reduce NO bioavailability, leading to cerebrovascular dysfunction

insulin-resistant obese rats. Taken together, these findings suggest that the production of a cyclooxygenase constrictor substance and/or the production of ROS via the cyclooxygenase pathway may contribute to impaired eNOS-dependent responses of cerebral arterioles during T1D.

2.2.2 NADPH Oxidase

NADPH oxidases are a primary source of ROS in the vascular system and are active in all cell types within the walls of blood vessels [66, 162]. NADPH oxidases are comprised of two membrane bound subunits (Nox and p22phox), up to three cytoplasmic subunits (p67phox, p47phox, and p40phox), and a G protein (Rac1/Rac2). Several NADPH oxidases have been identified (Nox1, Nox2, Nox4, and Nox5), and these are a primary source of ROS in the vasculature [13, 17, 30, 156]. Since the formation of ROS (presumably via an increase in cellular levels of glucose) appears to be of primary importance in vascular dysfunction during T1D, compounds that inhibit Nox activity may offer therapeutic benefits in T1D-induced cerebrovascular dysfunction (Fig. 2.1). In fact, investigators have shown that inhibition of Nox with

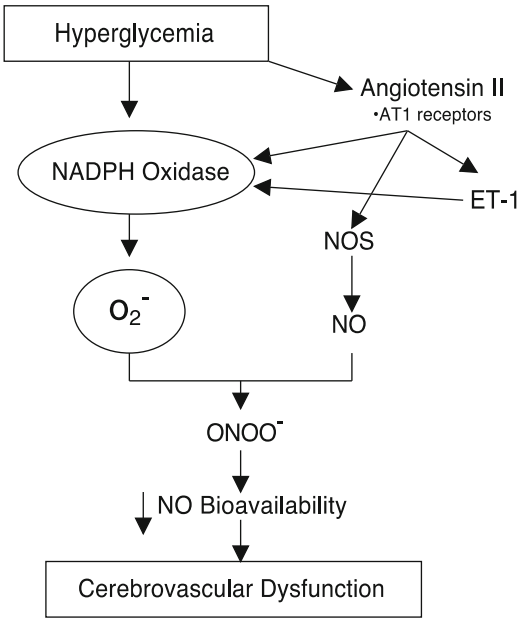

Fig. 2.2 Role for angiotensin II in mediating hyperglycemia-induced activation of NADPH oxidase. Angiotensin, acting via AT-1 receptors, can activate NADPH oxidase, lead to a decrease in NOS activity (and subsequent formation of NO), and/or increase the synthesis/release of endothelin-1 (ET-1). These actions can lead to a decrease in NO bioavailability and cerebrovascular dysfunction

apocynin reversed upregulation of Nox enzymes, improved nitric oxide function, and reduced vascular dysfunction of peripheral blood vessels in diabetic animals [8, 15, 56, 124]. While studies have shown that apocynin can influence the pathogenesis of stroke [153] and can improve impaired cerebrovascular function during hyperhomocysteinemia [33], few studies have examined the role of Nox enzymes in impaired responses of cerebral blood vessels during T1D. In a previous study, we found that T1D increased superoxide levels in brain tissue and increased the protein expression of various subunits of Nox in brain tissue and cerebral blood vessels [105]. Further, we found that chronic treatment of diabetic rats with apocynin could reverse the increase in superoxide levels in brain tissue and also could reverse impaired eNOS-dependent responses of cerebral arterioles [105]. Although studies have shown that Nox may be of benefit during diabetes, some have questioned the specificity, potency, and toxicity of this type of treatment and how it may translate to treatment of humans with diabetes or, in fact, with other disease states [73, 161]. Thus, while there may be a significant role for Nox enzymes in the generation of ROS, there may not be enough definitive evidence to determine which isoform of Nox may be most important in cerebral vessels during T1D.

The precise cellular pathway underlying increased Nox expression/activity in T1D remains unclear. One possibility is that angiotensin II plays a critical role (Fig. 2.2). Stimulation of vascular smooth muscle cells with angiotensin II, thrombin, lipopolysaccharide, and cytokines increases the activity of NADPH oxidase, vascular p47phox expression, and production of ROS [1, 21, 54, 65, 66, 93]. Since tissue and plasma levels of angiotensin-converting enzyme, and thus angiotensin II, are elevated in diabetics [42, 97, 138] and since angiotensin II has been shown to

activate NADPH oxidase (presumably Nox2) via stimulation of AT-1 receptors [65, 132, 177], it seems reasonable to suggest that the formation of superoxide during T1D may be related to angiotensin II-induced stimulation of Nox. Support for this concept can be found in studies that report treatment of diabetic subjects with angiotensin-converting enzyme inhibitors improves impaired NOS-dependent responses of large peripheral blood vessels [24, 116]. Given that angiotensin II can influence the brain via the circulation and via local production, it is not surprising that the cerebral circulation is also quite sensitive to angiotensin II. Investigators have shown that angiotensin II can produce endothelial dysfunction, impair neurovascular coupling, and alter the transport properties of the blood–brain barrier [6, 35, 48, 62, 67, 81, 112, 137]. With regard to T1D, we have reported that treatment of diabetic rats with enalapril [163] or losartan [6] can alleviate impaired eNOS-dependent responses of cerebral arterioles [163]. Although most studies have suggested that angiotensin II promotes endothelial dysfunction largely due to activation of NADPH oxidase and the subsequent formation of superoxide, additional mechanisms may also account for angiotensin II-induced vascular dysfunction. For example, angiotensin II can limit the production of nitric oxide [61, 100], can lead to the formation of an endothelium-derived contracting factor [38, 102, 172], and can lead to an increase in the synthesis/release of endothelin-1 [130, 179]. Impaired responses of cerebral arterioles during T1D have also been implicated to be related to alterations in nitric oxide production [79, 84], the production of a cyclooxygenase constrictor substance [79, 108], and/or the increased synthesis of endothelin-1 [4]. Thus, future studies will be required to determine the mechanism underlying the role for angiotensin II in cerebrovascular dysfunction during T1D.

2.2.3 Mitochondria

The mitochondria are a key source of ROS in cells as a result of an imbalance in the electron transport chain. Since oxidative stress is now widely accepted to play a key role in vascular dysfunction in a variety of disease states, including T1D, it has become apparent that the mitochondria might be a major contributor to this increase in oxidative stress (Fig. 2.3). The production of ROS by the mitochondria is a very complex process that involves oxidative phosphorylation across the electron transport chain; for review see [135]. Although mitochondrial complexes I and III may be mainly responsible for the generation of ROS, complexes II and IV may also result in the production of ROS [25, 115]. The mechanism by which hyperglycemia can lead to an increase in the synthesis/release of ROS by mitochondria is not entirely clear, but appears to involve an increase in electron donors (NADH and FADH2) through the electron transport chain. The role of mitochondria in impaired vascular function during T1D has not been extensively examined, but investigators have shown that inhibition of the electron transport chain can reduce oxidative stress in the heart [25, 98]. In addition, rotenone, an inhibitor of complex I, has been shown to decrease the levels of hydrogen peroxide in the posterior cerebral artery of

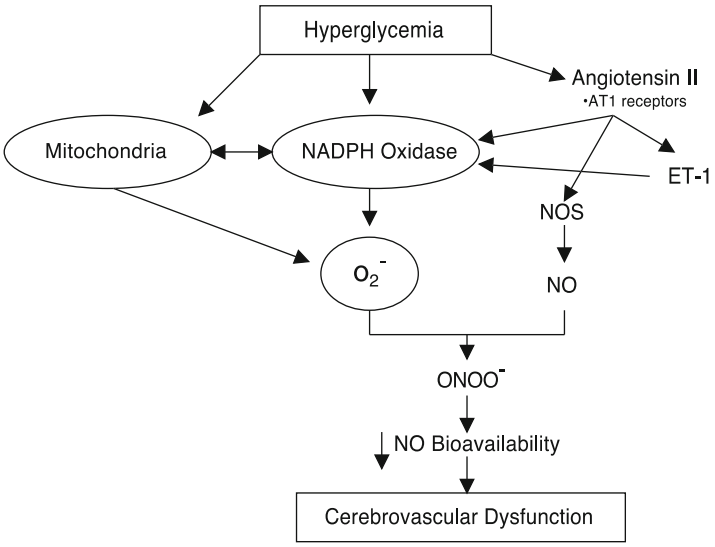

Fig. 2.3 The role of the mitochondria. Increases in cellular levels of glucose can stimulate the mitochondria to release ROS via activation of NADPH oxidase and through the electron transport chain. Once formed, ROS can then produce a decrease in NO bioavailability and cerebrovascular dysfunction

diabetic mice and partially reverse decreased calcium currents in smooth muscle cells during T1D [40]. Thus, we speculate that inhibition of the electron transport chain may have important implications for cerebrovascular dysfunction in T1D. Support for this concept may come from studies of type 2 diabetic patients. One of the more common treatments of type 2 diabetes is metformin. One mechanism of metformin is the ability to inhibit complex I of the electron transport chain [20]. Therefore, it is conceivable that inhibition of the mitochondrial electron transport chain also may have important clinical applications to T1D.

2.2.4 Endothelial NOS

eNOS is modulated by many mechanisms including enzyme phosphorylation, interactions with various proteins, several transcription factors, levels of substrate, and the availability of critical cofactors. In addition, there are various downstream regulators of cellular signaling pathways that are able to modulate eNOS function including Rho kinase (RhoA) [140]. With regard to cofactors for eNOS, tetrahydrobiopterin (BH_4) has been shown to be a critical component of eNOS regulation [2, 23, 64]. In order for eNOS to remain active, it must remain in a dimeric form and BH_4 contributes to the ability of eNOS to remain in this state [16, 32, 168]. There are many studies that have shown that hyperglycemia/diabetes can produce

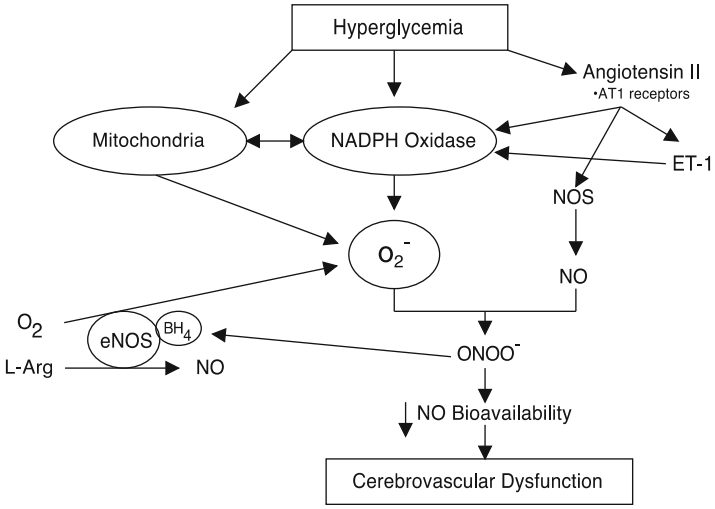

Fig. 2.4 eNOS uncoupling. The formation of $ONOO^-$ by an increase in cellular levels of glucose can contribute to cerebrovascular dysfunction by oxidizing tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2). This deficiency in the availability of BH_4 would force eNOS from its dimeric form to its monomeric form (an uncoupled state). Once in this uncoupled state, electrons flowing from the eNOS reductase domain to the oxygenase domain are diverted to molecular oxygen rather than to L-arginine, resulting in the production of superoxide (O_2^-) rather than nitric oxide (NO). Once formed, superoxide can inactivate NO and produce cerebrovascular dysfunction

reductions in the cellular levels of BH_4, leading to an "uncoupling" of eNOS to its monomeric form, thereby increasing the formation of eNOS-derived superoxide [3, 49, 69, 86, 120]. Thus, it is conceivable that eNOS uncoupling is a viable mechanism by which T1D can produce cerebrovascular dysfunction (Fig. 2.4). Support for this concept can be derived from studies that have shown that treatment of type 2 diabetic patients or patients following a glucose challenge with BH_4 can improve eNOS-dependent dilation [71, 76]. In addition, treatment with sepiapterin, a precursor of BH_4, or supplementation with BH_4 produced an improvement in eNOS-dependent responses of peripheral arteries in diabetic rats [11, 120, 121]. Only a limited number of studies have examined the influence of BH_4 on cerebral blood vessels. Early studies have shown that application of BH_4 to cerebral blood vessels could produce dilation or constriction dependent upon the size of the cerebral artery and/or species [82–84, 136]. A more recent study [79] reports that supplementation with sepiapterin in insulin-resistant obese rats improved dilation of cerebral arterioles in response to insulin suggesting eNOS uncoupling in this model. Unfortunately, there are no studies that we are aware of that have examined the influence of chronic treatment with BH_4 or sepiapterin on responses of cerebral arteries or arterioles during T1D. We have, however, shown that supplementation with BH_4 improves impaired responses of cerebral arterioles during other disease states [44, 145, 146], and thus it is conceivable that eNOS uncoupling may play a critical role in impaired vascular function during T1D.

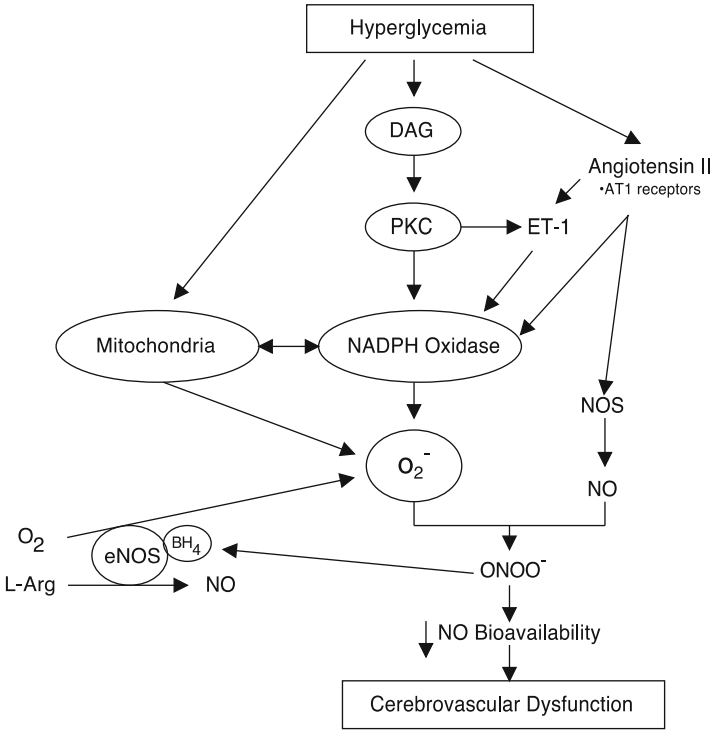

Fig. 2.5 Influence of PKC on cerebrovascular dysfunction. Hyperglycemia can increase the synthesis of diacylglycerol (DAG) which will activate the classical isoforms of protein kinase C (PKC). Once PKC is activated, a variety of events can occur within the cell, including an increase in the expression of endothelin-1 (ET-1) and the activation of NADPH oxidase. These events will lead to cascade of actions to decrease NO bioavailability and cerebrovascular dysfunction

2.2.5 Protein Kinase C

The protein kinase C (PKC) family comprises at least fifteen isoforms. This family of protein kinase enzymes is involved in managing the function of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues on these specific proteins. PKC enzymes are activated by signals such as increases in the concentration of diacylglycerol (DAG) or calcium ions (Ca^{2+}). Hence, PKC enzymes play important roles in several signal transduction cascades. Increases in cellular levels of glucose can increase the synthesis of DAG which, in turn, will activate the classical isoforms of PKC [60, 72, 77]. Once PKC is activated, a variety of events can occur within the cell, which may result in alterations in vascular permeability and/or vascular function (Fig. 2.5). For example, activation of PKC can lead to a decrease in eNOS, an increase in the expression of endothelin-1, and an increase in oxidative stress via NADPH oxidase [9, 18, 31, 77, 122, 131, 133, 169, 180]. In addition, activation of PKC can induce the activation of

several proinflammatory agents such as tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), and nuclear factor-κB (NF-κB) [47, 50, 101, 142, 158, 166].

Many investigators have reported a role for PKC in impaired endothelial function of peripheral blood vessels during T1D [46, 70, 114, 115, 178]. In addition, a few studies have implicated a role for activation of PKC in impaired responses of cerebral blood vessels during T1D. Studies by Pelligrino et al. [123] have shown that treatment of diabetic rats with staurosporine could restore impaired responses of pial arterioles in diabetic rats. In subsequent studies, Pelligrino and colleagues [170] found that PKCδ activity was increased in the glio-pial tissue of diabetic rats, suggesting that this isoform of PKC may ultimately lead to impaired neurovascular coupling during T1D. Others also have reported impairment in neurovascular coupling in diabetic rats was related to an increase in the activity of PKC [171]. This increase in the activity of PKC appeared to be responsible for a decrease in large conductance (BK) calcium channel and inward rectifier (Kir) calcium channel activity [171]. In addition, we have shown that acute hyperglycemia could impair NOS-dependent responses of pial arterioles in rats and this impairment could be reversed by treatment with a PKC inhibitor [106]. Thus, it appears that activation of PKC, through the stimulation of various downstream events, can influence cerebrovascular function during T1D.

2.2.6 Poly(ADP-Ribose) Polymerase

Poly(ADP-ribose) polymerases (PARPs) are an important set of nuclear enzymes that appear to be involved in the response of the cell to DNA injury/DNA strand breaks [27, 59, 126]. These enzymes, of which PARP-1 is most abundant, normally function in DNA repair, but extensive activation of PARP can promote cellular dysfunction and/or cell death via mechanisms involving depletion of NAD+ and ATP within the cell [27, 59, 126]. Activation of PARP has been implicated in the pathogenesis of several disease states including stroke [29, 43, 109, 126], inflammation [63, 80, 151, 181], myocardial dysfunction [28, 119, 164, 180], autoimmune diseases [125, 126], and cognitive impairment following hypoglycemic cell death [144]. Since oxidative stress can induce the activation of PARP [57, 59] and since oxidative stress is increased in T1D, it is conceivable that PARP activation may contribute to vascular dysfunction during T1D (Fig. 2.6).

Several studies have suggested that PARP activation is increased in T1D and this increase may contribute to cardiovascular and endothelial dysfunction. Pacher et al. [119] have reported an increase in the activation of PARP in the heart of diabetic rats and mice, cardiac dysfunction, and a decrease in NOS-dependent reactivity of the thoracic aorta. In addition, these alterations in cardiac/vascular function observed in diabetic rats and mice could be restored to that observed in nondiabetic animals by treatment with PJ-34 [119]. Studies by others [57, 58] also report that T1D activates PARP and induces endothelial dysfunction of the thoracic aorta. In addition,

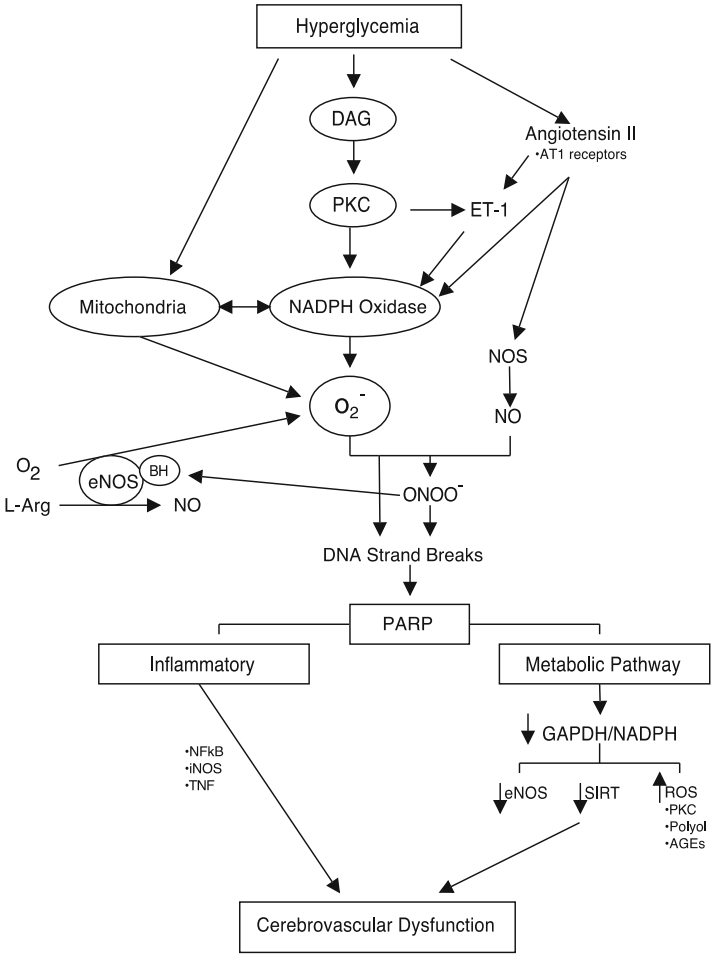

Fig. 2.6 The contribution of PARP. Hyperglycemia during T1D can stimulate increased levels of angiotensin II (AII) and activate PKC. AII and PKC can increase the production of superoxide anion (O_2^-) via activation of NADPH oxidase. Once formed, O_2^- can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), to induce DNA strand breaks thereby activating poly(ADP-ribose) polymerase (PARP). PARP activation can trigger a proinflammatory pathway and the generation of inflammatory mediators (TNFα, iNOS and/or NF-κB) that may lead to cerebrovascular dysfunction. Activation of PARP may, via a metabolic pathway, produce a decrease in NADPH and GAPDH leading to a decrease in cellular energy status (ATP), a decrease in production of eNOS, and a further increase in ROS through activation of several pathways. This decrease in cellular energy status and increase in oxidative stress can lead to cerebrovascular dysfunction

treatment of vascular rings from PARP-deficient mice with glucose (30 mM for 16 h) did not produce endothelial dysfunction, and acute treatment of vascular rings from wild-type mice with PJ-34 prevented endothelial dysfunction induced by an acute episode of hyperglycemia [57]. In studies using T1D rats, we found that acute

treatment of pial arterioles with an inhibitor of PARP (PJ-34) could restore impaired NOS-dependent reactivity [5]. We suggested that the influence of PJ-34 on vascular function was related to its effect on superoxide levels in brain tissue since PJ-34 prevented an increase in superoxide levels found in diabetic rats.

In addition to studies that have examined the role of PARP activation in cerebrovascular dysfunction during T1D, others have suggested that PARP plays an important role in protection of the brain following cerebral ischemia/reperfusion [14, 26, 68, 140]. These investigators have shown that treatment with inhibitors of PARP decreased brain injury and disruption of the blood–brain barrier following ischemia/reperfusion by a mechanism that appeared to be related to preventing an increase in the synthesis/release of inflammatory mediators (TNFα, IL-6, E-selectin, and ICAM-1) [68], thereby preserving endothelial tight junction integrity [96]. Although no studies to our knowledge have examined the influence of PARP inhibition on brain injury following ischemia/reperfusion during T1D, given the results from previous studies, we suggest that future studies should examine the role of this important pathway in the pathogenesis of cerebral ischemia-/reperfusion-induced brain injury and disruption of the blood–brain barrier during T1D. We speculate that the results from these types of studies might have important implications regarding mechanisms for the increased incidence of stroke and cognitive dysfunction observed in diabetic subjects.

Given that PARP activation is a very complex process, it would appear difficult to determine mechanisms that PARP activation produces vascular dysfunction, including cerebrovascular dysfunction, during T1D. Two pathways have been proposed to account for the role of PARP activation in T1D: the proinflammatory and metabolic pathways. The proinflammatory pathway [59, 147, 149] suggests that PARP activates multiple pathways of damage, including NF-κB, PKC, and/or generation of advanced glycosylation end products (AGEs). Activation of these pathways can stimulate the synthesis/release of inflammatory mediators (E-selectin, IL-6, TNFα, ICAM-1, and iNOS) that have been implicated in endothelial dysfunction and brain injury observed in T1D and can generate ROS from additional pathways [68, 94, 103, 117, 128, 134, 181]. Thus, it is possible that PARP activation during T1D can increase the formation of inflammatory mediators that, in turn, produce endothelial dysfunction directly and/or via the production of ROS. The metabolic pathway [57] suggests that hyperglycemia during T1D stimulates the production of oxidants. Although the pathway for the formation of these oxidants in T1D is not entirely clear, it may involve the activation of NADPH oxidase via increased levels of angiotensin II [42, 54, 65, 97, 132, 138]. Evidence suggests that angiotensin II can activate PARP in cultured endothelial cells and can induce DNA strand breaks [150]. In addition, angiotensin II-induced endothelial dysfunction can be prevented by inhibition of NADPH oxidase and PARP [150]. In addition to a possible role for angiotensin II, elevated levels of glucose also have been shown to activate PKC and produce oxidative stress [55, 95, 176]. Further, it has been suggested that oxidative stress may further stimulate the activity of PKC via activation of PARP [41]. It is also conceivable that oxidative stress-induced stimulation of PARP, in turn, activates endothelin-1 to produce vascular dysfunction [110].

Finally, PARP activation can increase ROS formed via an increase in AGEs and the polyol pathway, both of which have been implicated as an important source of ROS during T1D [19, 141, 175]. Regardless of the precise cellular mechanism, once ROS are formed they can induce DNA strand breaks to activate PARP, producing a cellular energy crisis. Without sufficient energy, the endothelium could presumably produce additional levels of ROS and/or have less potential to produce nitric oxide. This metabolic pathway is supported by data obtained from studies that have shown that exposure of endothelium to oxidants can produce depletion of NAD+ in cells that can be prevented by inhibition of PARP, endothelial dysfunction in T1D can be prevented by inhibition of PARP, glucose-induced endothelial dysfunction is prevented in PARP-deficient mice, and altering the energy status within endothelial cells can influence vascular function [22, 58, 59, 119].

2.3 Antioxidant Pathways

Excess production of ROS in the vascular system, the peripheral organ systems, and/or the brain by T1D can be regulated through the expression of a variety of endogenous antioxidant enzymes. These antioxidant enzymes serve to protect the vasculature and/or organ systems, including the brain, by scavenging ROS and interfering with or preventing the activation of downstream signaling events triggered by these ROS. Unfortunately, in T1D where there is a dramatic increase in the levels of ROS, these antioxidant enzyme systems may not be able to adequately regulate these excess levels of ROS and/or may be adversely affected by T1D. This consequence would tip the balance in favor of a prooxidant environment to detrimentally affect vascular function during T1D.

2.3.1 Superoxide Dismutases

The bioactivity of nitric oxide depends, in part, on its ability to interact with ROS, especially superoxide [12]. Early findings suggested that superoxide inactivates nitric oxide [174] and studies since have shown that inactivation of nitric oxide by superoxide contributes to impaired vascular function [36, 37, 107]. While there is considerable attention paid to examining the role of superoxide during disease states, little information is available regarding the functional significance of alterations in the activity/expression of antioxidant pathways during disease states. SODs exist in three isoforms localized within specific cellular compartments. Copper-zinc SOD (SOD-1, CuZnSOD) is located predominately within the cytosol, as well as in the nucleus, and is expressed in all mammalian cells. Manganese SOD (SOD-2, MnSOD) is localized to the mitochondrial matrix, and it is considered to be the primary SOD isoform in relation to oxidative stress in the mitochondria. SOD-2 is needed to protect cellular constituents from superoxide derived

from the electron transport chain. Extracellular SOD (SOD-3, EC-SOD) is also a copper-zinc-containing SOD and is secreted extracellularly. SOD-3 is found bound to heparin sulfate proteoglycans on the surface of cells. It appears that the predominant form of SOD in blood vessels is SOD-1, followed by SOD-2 and the least involving SOD-3 [51–53, 143]. During T1D, superoxide levels are increased in brain tissue [7], but levels of SODs in the brain during T1D are not as clear. Some studies have reported an increase in SOD-2 in brain tissue of diabetic rats [75], but others showing decreases in total SOD activity in the brain [87, 118], and a decrease in SOD-2 and SOD-1 activity and mRNA in the aorta of diabetic rats [78, 85]. In addition, we have reported that SOD-1 and SOD-2 proteins are similar in brain tissue and cerebral microvessels from nondiabetic and diabetic rats, even though levels of superoxide are increased in brain tissue from T1D rats [7].

2.3.2 Glutathione Peroxidases

In addition to SODs, other antioxidant systems tightly regulate cellular redox balance. Cellular protection against ROS and their related by-products involves the activities of endogenous enzymes that belong to the oxidoreductase superfamily [139]. Glutathione peroxidases (Gpx) are a family of antioxidant enzymes that participate in the neutralization of hydrogen peroxide to water utilizing glutathione (GSH) as its substrate. A previous study has shown that Gpx1 plays a functional role in reactivity of cerebral blood vessels in mice [111]. In addition, previous studies have suggested that T1D can reduce Gpx mRNA in patients with T1D [74] and can reduce glutathione levels in the aorta [152] and brain [118] of rats, that the glutathione pathway is susceptible to oxidative stress [39], and that glutathione can protect diabetic rats from neuropathy [165]. However, the role of this endogenous enzyme pathway in protection of cerebral vessels during T1D remains unclear.

Taken together, these findings seem to indicate that antioxidant enzymes (SODs and Gpx) may not be able to compensate for increases in superoxide levels in the brain during T1D and thus may not be able to protect the vasculature from the damaging effects of ROS during T1D.

2.4 A Common Link?

On a cellular/molecular level, there are several major pathways that have been implicated in T1D-induced increases in oxidative stress to account for dysfunction of blood vessels of peripheral organ systems and the brain. Those discussed in this chapter include the cyclooxygenase pathway, NADPH oxidase, eNOS uncoupling, the mitochondria, PKC, and PARP. In addition to these oxidant-producing pathways, it appears that T1D can influence oxidant-protecting pathways (SODs and Gpx) to further alter the balance to favor the damaging effects of ROS. Although not

entirely clear for cerebral blood vessels, based upon findings from previous studies (see [19, 115]), it appears unlikely that oxidant-producing pathways act independently. A unifying hypothesis that has been presented by others [18, 19, 34, 115, 175] suggests that as glucose enters the cell, it stimulates the mitochondria to release superoxide, which in turn activates a number of downstream pathways (PKC, cyclooxygenase, inflammatory cytokines, PARP). These downstream pathways can produce a further increase in the generation of ROS and/or excite other pathways that could contribute to vascular dysfunction. However, this type of unifying hypothesis may not adequately account for the complexity of vascular dysfunction during T1D since inhibition of one of these pathways could not discount the formation of ROS from other distinct pathways, unless there was a linear relationship between the pathways. Faraci [45] has suggested that angiotensin II, acting via AT-1 receptors, can stimulate an increase in the synthesis of ROS from the mitochondria as well as promote inflammation and thus account for cardiovascular-related impairment in vascular function. Others [147, 148] have suggested that increases in cellular levels of glucose can stimulate the production of ROS from a variety of sources, which then activates PARP. Once activated, PARP would stimulate a number of downstream pathways (polyol pathway, PKC, AGEs, inflammatory mediators) that could then lead to the production of more ROS to produce vascular dysfunction. However, one might assume that inhibition of a singular pathway might not restore impaired vascular function given that other oxidant-producing pathways would remain intact. However, studies as outlined in this chapter have shown that inhibition of presumably singular cellular pathways can improve impaired responses of peripheral and cerebral blood vessels during T1D. Thus, although the basic principle that ROS are critical for impaired cerebrovascular function during T1D is certain, what remains uncertain is(are) the cellular pathway(s), indeed networks, that may be activated by ROS during T1D. We suggest that additional studies need to be completed before we can fully address the complexity of the interactions between the various cellular pathways that ultimately contribute to the generation of ROS during T1D.

2.5 Therapeutic Interventions

Based upon the experimental evidence presented in this chapter, one might speculate that inhibition of ROS during T1D would be an attractive therapeutic approach for addressing cerebrovascular dysfunction and its consequences, i.e., cognitive impairment and/or ischemic stroke. The vast majority of studies, several of which are presented in this chapter, have shown that short- and long-term treatment using scavengers of ROS improves vascular function in animal models of T1D. In addition, there are limited data to suggest that treatment of humans with scavengers of ROS improves endothelial function during T1D [159, 160] and brain injury following subarachnoid hemorrhage [10]. However, others have failed to demonstrate a dramatic effect of antioxidant therapy in human subjects with diabetes and/or other cardiovascular-related diseases [99, 113]. There may be several potential key

aspects as to why there are differences with regard to the beneficial effects of inhibition of ROS on vascular function in human subjects. First, the duration of exposure to antioxidant therapy may be important. A recent study reports that reversal of endothelial dysfunction in type 2 diabetic humans was only observed with 5 years of treatment with a combination of agents that lowered blood pressure, blood lipids, and ROS [157]. Second, it is possible that the duration of exposure to ROS during disease states in humans may create a condition whereby the endothelium is less able to respond to antioxidant therapy. Third, it would be rare for a human population not to have multiple risk factors for cardiovascular and cerebrovascular dysfunction. Therefore, the population being studied may not be an appropriate choice due to these multiple risk factors. Fourth, it is difficult to adequately control human subjects during a drug trial and there may be confounding influences in studying this type of population. Fifth, it is certainly possible that mechanisms contributing to vascular dysfunction during disease states, including T1D, are much more complex in humans than in animal models and different modes of therapy need to be examined in more long-term studies before conclusions can be drawn regarding the role of ROS in the pathogenesis of disease states. It may be premature to suggest a single therapeutic approach to limit the production of ROS during cardiovascular-related diseases, including T1D.

2.6 Closing Statement

The production of ROS appears to be the critical component of cerebrovascular dysfunction during T1D. Once ROS are formed, they can damage the endothelium directly and/or activate downstream networks that can lead to the generation of inflammatory mediators and/or produce an additional increase in the levels of ROS. We suggest that these processes not only contribute to impairment of dilator and constrictor responses of cerebral arteries and arterioles but also contribute to impaired neurovascular coupling, leading to an increase in the susceptibility of the brain to injury following ischemia/reperfusion, cognitive dysfunction, and an increase in prospect for ischemic stroke in diabetic humans.

References

1. Alexander JS, Elrod JW (2002) Extracellular matrix, junctional integrity and matrix metalloproteinase interactions in endothelial permeability regulation. J Anat 200:561–574
2. Alp NJ, Channon KM (2004) Regulation of endothelial nitric oxide synthase by tetrahydrobiopterin in vascular disease. Arterioscler Thromb Vasc Biol 24:413–420
3. Alp NJ, Mussa S, Khoo J, Cai S, Guzik T, Jefferson A, Goh N, Rockett KA, Channon KM (2003) Tetrahydrobiopterin-dependent preservation of nitric oxide-mediated endothelial function in diabetes by targeted transgenic GTP-cyclohydrolase I overexpression. J Clin Invest 112:725–735

4. Arrick DM, Mayhan WG (2010) Inhibition of endothelin-1 receptors improves impaired nitric oxide synthase-dependent dilation of cerebral arterioles in type-1 diabetic rats. Microcirculation 17:439–446
5. Arrick DM, Sharpe GM, Sun H, Mayhan WG (2007) Diabetes-induced cerebrovascular dysfunction: role of poly(ADP-ribose) polymerase. Microvasc Res 73:1–6
6. Arrick DM, Sharpe GM, Sun H, Mayhan WG (2008) Losartan improves impaired nitric oxide synthase-dependent dilatation of cerebral arterioles in type 1 diabetic rats. Brain Res 1209:128–135
7. Arrick DM, Sun H, Patel KP, Mayhan WG (2011) Chronic resveratrol treatment restores vascular responsiveness of cerebral arterioles in type 1 diabetic rats. Am J Physiol Heart Circ Physiol 301:H696–H703
8. Asaba K, Tojo A, Onozato ML, Goto A, Quinn MT, Fujita T, Wilcox CS (2005) Effects of NADPH oxidase inhibitor in diabetic nephropathy. Kidney Int 67:1890–1898
9. Awazu M, Parker RE, Harvie BR, Ichikawa I, Kon V (1991) Down-regulation of endothelin-1 receptors by protein kinase C in streptozotocin diabetic rats. J Cardiovasc Pharmacol 17:S500–S502
10. Ayer RE, Zhang JH (2008) Oxidative stress in subarachnoid haemorrhage: significance in acute brain injury and vasospasm. Acta Neurochir Suppl 104:33–41
11. Bagi Z, Koller A (2003) Lack of nitric oxide mediation of flow-dependent arteriolar dilation in type 1 diabetes is restored by sepiapterin. J Vasc Res 40:47–57
12. Beckman JS, Koppenol WH (1996) Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and the ugly. Am J Physiol 271:C1424–C1437
13. Bedard K, Krause KH (2007) The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev 87:245–313
14. Besson VC, Zsengeller Z, Plotkine M, Szabo C, Marchand-Verrecchia C (2005) Beneficial effects of PJ34 and INO-1001, two novel water-soluble poly(ADP-ribose) polymerase inhibitors, on the consequences of traumatic brain injury in rat. Brain Res 1041:149–156
15. Bitar MS, Wahid S, Mustafa S, Al-Saleh E, Dhaunsi GS, Al-Mulla F (2005) Nitric oxide dynamics and endothelial dysfunction in type II model of genetic diabetes. Eur J Pharmacol 511:53–64
16. Bouloumie A, Bauersachs J, Linz W, Scholkens BA, Wiemer G, Fleming I, Busse R (1997) Endothelial dysfunction coincides with an enhanced nitric oxide synthase expression and superoxide anion production. Hypertension 30:934–941
17. Brandes RP, Kreuzer J (2005) Vascular NADPH oxidases: molecular mechanisms of activation. Cardiovasc Res 65:16–27
18. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414:813–820
19. Brownlee M (2005) The pathobiology of diabetic complications: a unifying mechanism. Diabetes 54:1615–1625
20. Brunmair B, Staniek K, Gras F, Scharf N, Althaym A, Clara R, Roden M, Gnaiger E, Nohl H, Waldhausl W, Furnsinn C (2004) Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions? Diabetes 53:1052–1059
21. Burkey JL, Campanale KM, O'Bannon DD, Cramer JW, Farid NA (2002) Disposition of LY333531, a selective protein kinase C beta inhibitor, in the Fischer 344 rat and beagle dog. Xenobiotica 32:1045–1052
22. Cappelli-Bigazzi M, Battaglia C, Pannain S, Chiariello M, Ambrosio G (1997) Role of oxidative metabolism on endothelium-dependent vascular relaxation of isolated vessels. J Mol Cell Cardiol 29:871–879
23. Channon KM (2004) Tetrahydrobiopterin: regulator of endothelial nitric oxide synthase in vascular disease. Trends Cardiovasc Med 14:323–327
24. Cheetham C, Collis J, O'Driscoll G, Stanton K, Taylor R, Green D (2000) Losartan, an angiotensin type 1 receptor antagonist, improves endothelial function in non-insulin-dependent diabetes. J Am Coll Cardiol 36:1461–1466

25. Chen Q, Vazquez EJ, Moghaddas S, Hoppel CL, Lesnefsky EJ (2003) Production of reactive oxygen species by mitochondria: central role of complex III. J Biol Chem 278: 36027–36031
26. Chiarugi A (2005) Poly(ADP-ribosyl)ation and stroke. Pharmacol Res 52:15–24
27. Chiarugi A (2002) Poly(ADP-ribose) polymerase: killer or conspirator? The 'suicide hypothesis' revisited. Trends Pharmacol Sci 23:122–129
28. Chiu J, Xu BY, Chen S, Feng B, Chakrabarti S (2008) Oxidative stress-induced, poly(ADP-ribose) polymerase-dependent upregulation of ET-1 expression in chronic diabetic complications. Can J Physiol Pharmacol 86:365–372
29. Chrissobolis S, Miller AA, Drummond GR, Kemp-Harper BK, Sobey CG (2011) Oxidative stress and endothelial dysfunction in cerebrovascular disease. Front Biosci 16:1733–1745
30. Chrissobolis S, Faraci FM (2008) The role of oxidative stress and NADPH oxidase in cerebrovascular disease. Cell 14:495–502
31. Cosentino F, Eto M, De Paolis P, van der Loo B, Bachschmid M, Ullrich V, Kouroedov A, Delli Gatti C, Joch H, Volpe M, Luscher TF (2003) High glucose causes upregulation of cyclooxygenase-2 and alters prostanoid profile in human endothelial cells: role of protein kinase C and reactive oxygen species. Circulation 107:1017–1023
32. Cosentino F, Hishikawa K, Katusic ZS, Luscher TF (1997) High glucose increases nitric oxide synthase expression and superoxide generation in human aortic endothelial cells. Circulation 96:25–28
33. Dayal S, Arning E, Bottiglieri T, Boger RH, Sigmund CD, Faraci FM, Lentz SR (2004) Cerebral vascular dysfunction mediated by superoxide in hyperhomocysteinemic mice. Stroke 35:1957–1962
34. Dhar A, Dhar I, Desai KM, Wu L (2010) Methylglyoxal scavengers attenuate endothelial dysfunction induced by methylglyoxal and high concentrations of glucose. Br J Pharmacol 16:1843–1856
35. Didion SP, Faraci FM (2003) Angiotensin II produces superoxide-mediated impairment of endothelial function in cerebral arterioles. Stroke 34:2038–2042
36. Didion SP, Ryan MJ, Baumbach GL, Sigmund CD, Faraci FM (2002) Superoxide contributes to vascular dysfunction in mice that express human renin and angiotensinogen. Am J Physiol Heart Circ Physiol 283:H1569–H1576
37. Didion SP, Hathaway CA, Faraci FM (2001) Superoxide levels and function of cerebral blood vessels after inhibition of CuZn-SOD. Am J Physiol 281:H1697–H1703
38. Didion SP, Sigmund CD, Faraci FM (2000) Impaired endothelial function in transgenic mice expressing both human renin and human angiotensinogen. Stroke 31:760–765
39. Dincer Y, Akcay T, Alademir Z, Ilkova H (2002) Effect of oxidative stress on glutathione pathway in red blood cells from patients with insulin-dependent diabetes mellitus. Metabolism 51:1360–1362
40. Dong L, Xie MJ, Zhang P, Ji LL, Liu WC, Dong MQ, Gao F (2009) Rotenone partially reverses decreased BK Ca currents in cerebral artery smooth muscle cells from streptozotocin-induced diabetic mice. Clin Exp Pharmacol Physiol 36:e57–e64
41. Du X, Matsumura T, Edelstein D, Rossetti L, Zsengeller Z, Szabo C, Brownlee M (2003) Inhibition of GAPDH activity by poly(ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. J Clin Invest 112:1049–1057
42. Duntas L, Keck FS, Haug C, Hetzel W, Wolf CF, Rosenthal J, Pfeiffer EF (1992) Serum angiotensin-converting enzyme activity and active renin plasma concentrations in insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 16:203–208
43. Eliasson MJ, Sampei K, Mandir AS, Hurn PD, Traystman RJ, Bao J, Pieper A, Wang ZQ, Dawson TM, Snyder SH, Dawson VL (1997) Poly(ADP-ribose) polymerase gene disruption renders mice resistant to cerebral ischemia. Nat Med 3:1089–1095
44. Fang Q, Sun H, Mayhan WG (2003) Impairment of nitric oxide synthase-dependent dilatation of cerebral arterioles during infusion of nicotine. Am J Physiol Heart Circ Physiol 284: H528–H534

45. Faraci FM (2011) Protecting against vascular disease in brain. Am J Physiol Heart Circ Physiol 300:H1566–H1582
46. Fatehi-Hassanabad Z, Imen-Shahidi M, Fatehi M, Farrokhfall K, Parsaeei H (2006) The beneficial in vitro effects of lovastatin and chelerythrine on relaxatory response to acetylcholine in the perfused mesentric bed isolated from diabetic rats. Eur J Pharmacol 535:228–233
47. Ferro T, Neumann P, Gertzberg N, Clements R, Johnson A (2000) Protein kinase C-a mediates endothelial barrier dysfunction induced by TNF-a. Am J Physiol 278:L1107–L1117
48. Fleegal-DeMotta MA, Doghu S, Banks WA (2009) Angiotensin II modulates BBB permeability via activation of the AT(1) receptor in brain endothelial cells. J Cereb Blood Flow Metab 29:640–647
49. Forstermann U, Munzel T (2006) Endothelial nitric oxide synthase in vascular disease: from marvel to menace. Circulation 113:1708–1714
50. Frey RS, Rahman A, Kefer JC, Minshall RD, Malik AB (2002) PKCzeta regulates TNF-alpha-induced activation of NADPH oxidase in endothelial cells. Circ Res 90:1012–1019
51. Fukai T, Galis ZS, Meng XP, Parthasarathy S, Harrison DG (1998) Vascular expression of extracellular superoxide dismutase in atherosclerosis. J Clin Invest 101:2101–2111
52. Fukai T, Siegfried MR, Ushio-Fukai M, Cheng Y, Kojda G, Harrison DG (2000) Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. J Clin Invest 105:1631–1639
53. Fukai T, Siegfried MR, Ushio-Fukai M, Griendling KK, Harrison DG (1999) Modulation of extracellular superoxide dismutase expression by angiotensin II and hypertension. Circ Res 85:23–28
54. Fukui T, Ishizaka N, Rajagopalan S, Laursen JB, Capers Q, Taylor WR, Harrison DG, de Leon H, Wilcox JN, Griendling KK (1997) p22phox mRNA expression and NADPH oxidase activity are increased in aortas from hypertensive rats. Circ Res 80:45–51
55. Ganz MB, Seftel A (2000) Glucose-induced changes in protein kinase C and nitric oxide are prevented by vitamin E. Am J Physiol 278:E146–E152
56. Gao X, Belmadani S, Picchi A, Xu X, Potter BJ, Tewar-Singh N, Capobianco S, Chilian WM, Zhang C (2007) Tumor necrosis factor-alpha induces endothelial dysfunction in Lepr(db) mice. Circulation 115:245–254
57. Garcia Soriano F, Virag L, Jagtap P, Szabo E, Mabley JG, Liaudet L, Marton A, Hoyt DG, Murthy KG, Salzman AL, Southan GJ, Szabo C (2001) Diabetic endothelial dysfunction: the role of poly(ADP-ribose) polymerase activation. Nat Med 7(1):108–113
58. Garcia Soriano F, Pacher P, Mabley J, Liaudet L, Szabo C (2001) Rapid reversal of the diabetic endothelial dysfunction by pharmacological inhibition of poly (ADP-ribose) polymerase. Circ Res 89:684–691
59. Garcia Soriano F, Virag L, Szabo C (2001) Diabetic endothelial dysfunction: role of reactive oxygen and nitrogen species production and poly(ADP-ribose) polymerase activation. J Mol Med 79:437–448
60. Geraldes P, King GL (2010) Activation of protein kinase C isoforms and its impact on diabetic complications. Circ Res 106:1319–1331
61. Gerzanich V, Ivanova S, Zhou H, Simard JM (2003) Mislocalization of eNOS and upregulation of cerebral vascular Ca^{2+} channel activity in angiotensin-hypertension. Hypertension 41:1124–1130
62. Girouard H, Park L, Anrather J, Zhou P, Iadecola C (2006) Angiotensin II attenuates endothelium-dependent responses in the cerebral microcirculation through nox-2-derived radicals. Arterioscler Thromb Vasc Biol 26:826–832
63. Goldfarb RD, Marton A, Szabo E, Virag L, Salzman AL, Glock D, Akhter I, McCarthy R, Parrillo JE, Szabo C (2002) Protective effect of a novel, potent inhibitor of poly(adenosine 5′-diphosphate-ribose) synthetase in a porcine model of severe bacterial sepsis. Crit Care Med 30:974–980
64. Govers R, Rabelink TJ (2001) Cellular regulation of endothelial nitric oxide synthase. Am J Physiol 280:F193–F206

65. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW (1994) Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 74:1141–1148
66. Griendling KK, Sorescu D, Ushio-Fukai M (2000) NAD(P)H oxidase. Role in cardiovascular biology and disease. Circ Res 86:494–501
67. Guillot FL, Audus KL (1991) Angiotensin peptide regulation of bovine brain microvessel endothelial cell monolayer permeability. J Cardiovasc Pharmacol 18:212–218
68. Haddad M, Rhinn H, Bloquel C, Coqueran B, Szabo C, Plotkine M, Scherman D, Margaill I (2006) Anti-inflammatory effects of PJ34, a poly(ADP-ribose) polymerase inhibitor, in transient focal cerebral ischemia in mice. Br J Pharmacol 149:23–30
69. Hamon CG, Cutler P, Blair JA (1989) Tetrahydrobiopterin metabolism in the streptozotocin induced diabetic state in rats. Clin Chim Acta 181:249–254
70. He Z, King GL (2004) Protein kinase Cbeta isoform inhibitors: a new treatment for diabetic cardiovascular diseases. Circulation 110:7–9
71. Heitzer T, Krohn K, Albers S, Meinertz T (2000) Tetrahydrobiopterin improves endothelium-dependent vasodilation by increasing nitric oxide activity in patients with Type II diabetes mellitus. Diabetologia 43:143–1438
72. Hempel A, Maasch C, Heintze U, Lindschau C, Dietz R, Luft FC, Haller H (1997) High glucose concentrations increase endothelial cell permeability via activation of protein kinase C alpha. Circ Res 81:363–371
73. Heumuller S, Wind S, Barbosa-Sicard E, Schmidt HH, Busse R, Schroder K, Brandes RP (2008) Apocynin is not an inhibitor of vascular NADPH oxidases but an antioxidant. Hypertension 51:211–217
74. Hodgkinson AD, Bartlett T, Oates PJ, Millward BA, Demaine AG (2003) The response of antioxidant genes to hyperglycemia is abnormal in patients with type 1 diabetes and diabetic nephropathy. Diabetes 52:846–851
75. Huang WC, Juang SW, Liu IM, Chi TC, Cheng JT (1999) Changes of superoxide dismutase gene expression and activity in the brain of streptozotocin-induced diabetic rats. Neurosci Lett 275:25–28
76. Ihlemann N, Rask-Madsen C, Perner A, Dominguez H, Hermann T, Kober L, Torp-Pedersen C (2003) Tetrahydrobiopterin restores endothelial dysfunction induced by an oral glucose challenge in healthy subjects. Am J Physiol Heart Circ Physiol 285:H875–H882
77. Inoguchi T, Sonta T, Tsubouchi H, Etoh T, Kakimoto M, Sonoda N, Sato N, Sekiguchi N, Kobayashi K, Sumimoto H, Utsumi H, Nawata H (2003) Protein kinase C-dependent increase in reactive oxygen species (ROS) production in vascular tissues of diabetes: role of vascular NAD(P)H oxidase. J Am Soc Nephrol 14:S227–S232
78. Kamata K, Kobayashi T (1996) Changes in superoxide dismutase mRNA expression by streptozotocin-induced diabetes. Br J Pharmacol 119:583–589
79. Katakam PV, Snipes JA, Steed MM, Busija DW (2012) Insulin-induced generation of reactive oxygen species and uncoupling of nitric oxide synthase underlie the cerebrovascular insulin resistance in obese rats. J Cereb Blood Flow Metab 32:792–804
80. Kauppinen TM, Suh SW, Berman AE, Hamby AM, Swanson RA (2009) Inhibition of poly(ADP-ribose) polymerase suppresses inflammation and promotes recovery after ischemic injury. J Cereb Blood Flow Metab 29:820–829
81. Kazama K, Anrather J, Zhou P, Girouard H, Frys K, Milner TA, Iadecola C (2004) Angiotensin II impairs neurovascular coupling in neocortex through NADPH oxidase-derived radicals. Circ Res 95:1019–1026
82. Kinoshita H, Katusic ZS (1996) Exogenous tetrahydrobiopterin causes endothelium-dependent contractions in isolated canine basilar artery. Am J Physiol 271:H738–H743
83. Kinoshita H, Milstien S, Wambi C, Katusic ZS (1997) Inhibition of tetrahydrobiopterin biosynthesis impairs endothelium-dependent relaxations in canine basilar artery. Am J Physiol 273:H718–H724
84. Kinoshita H, Tsutsui M, Milstien S, Katusic ZS (1997) Tetrahydrobiopterin, nitric oxide and regulation of cerebral arterial tone. Prog Neurobiol 52:295–302

85. Kobayashi T, Kamata K (1999) Relationship among cholesterol, superoxide anion and endothelium-dependent relaxation in diabetic rats. Eur J Pharmacol 367:213–222
86. Kohli R, Meininger CJ, Haynes TE, Yan W, Self JT, Wu G (2004) Dietary L-arginine supplementation enhances endothelial nitric oxide synthesis in streptozotocin-induced diabetic rats. J Nutr 134:600–608
87. Kokoglu E, Belce A, Gumustas K, Altug T (1994) A possible relationship between superoxide dismutase and chronic complications of diabetes mellitus in the brain. Med Sci Res 22:781–782
88. Kontos HA, Wei EP, Ellis EF, Jenkins LW, Povlishock JT, Rowe GT, Hess ML (1985) Appearance of superoxide anion radical in cerebral extracellular space during increased prostaglandin synthesis in cats. Circ Res 57:142–151
89. Kontos HA, Wei EP, Kukreja RC, Ellis EF, Hess ML (1990) Differences in endothelium-dependent cerebral dilation by bradykinin and acetylcholine. Am J Physiol 258:H1261–H1266
90. Kontos HA, Wei EP, Povlishock JT, Christman CW (1984) Oxygen radicals mediate the cerebral arteriolar dilation from arachidonate and bradykinin in cats. Circ Res 55:295–303
91. Kontos HA, Wei EP, Povlishock JT, Kukreja RC, Hess ML (1989) Inhibition by arachidonate of cerebral arteriolar dilation from acetylcholine. Am J Physiol 256:H665–H671
92. Lacza Z, Puskar M, Kis B, Perciaccante JV, Miller AW, Busija DW (2002) Hydrogen peroxide acts as an EDHF in the piglet pial vasculature in response to bradykinin. Am J Physiol Heart Circ Physiol 283:H406–H411
93. Landmesser U, Cai H, Dikalov S, McCann L, Hwang J, Jo H, Holland SM, Harrison DG (2002) Role of p47(phox) in vascular oxidative stress and hypertension caused by angiotensin II. Hypertension 40:511–515
94. Le Page C, Sanceau J, Drapier JC, Wietzerbin J (1998) Inhibitors of ADP-ribosylation impair inducible nitric oxide synthase gene transcription through inhibition of NF kappa B activation. Biochem Biophys Res Commun 243:451–457
95. Lee TS, Saltsman KA, Ohashi H, King GL (1989) Activation of protein kinase C by elevation of glucose concentration: proposal for a mechanism in the development of diabetic vascular complications. Proc Natl Acad Sci 86:5141–5145
96. Lenzser G, Kis B, Snipes JA, Gaspar T, Sandor P, Komjati K, Szabo C, Busija DW (2007) Contribution of poly(ADP-ribose) polymerase to postischemic blood-brain barrier damage in rats. J Cereb Blood Flow Metab 27:1318–1326
97. Lieberman J, Sastre A (1980) Serum angiotensin-converting enzyme: elevations in diabetes mellitus. Ann Intern Med 93:825–826
98. Liu Y, Zhao H, Li H, Kalyanaraman B, Nicolosi AC, Gutterman DD (2003) Mitochondrial sources of H_2O_2 generation play a key role in flow-mediated dilation in human coronary resistance arteries. Circ Res 93:573–580
99. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, Ross C, Arnold A, Sleight P, Probstfield J, Dagenais GR (2005) Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 293:1338–1347
100. Loot AE, Schreiber JG, Fisslthaler B, Fleming I (2009) Angiotensin II impairs endothelial function via tyrosine phosphorylation of the endothelial nitric oxide synthase. J Exp Med 206:2889–2896
101. Magnuson DK, Maier RV, Pohlman TH (1989) Protein kinase C: a potential pathway of endothelial cell activation by endotoxin, tumor necrosis factor, and interleukin-1. Surgery 106:216–223
102. Manabe K, Shirahase H, Usui H, Kurahashi K, Fujiwara M (1989) Endothelium-dependent contractions induced by angiotensin I and angiotensin II in canine cerebral artery. J Pharmacol Exp Ther 251:317–320
103. Martin S (1997) Soluble adhesion molecules in type 1 diabetes mellitus. Horm Metab Res 29:639–642
104. Matoba T, Shimokawa H, Nakashima M, Hirakawa Y, Mukai Y, Hirano K, Kanaide H, Takeshita A (2000) Hydrogen peroxide is an endothelium-derived hyperpolarizing factor in mice. J Clin Invest 106:1521–1530

105. Mayhan WG, Arrick DM, Sharpe GM, Patel KP, Sun H (2006) Inhibition of NAD(P)H oxidase alleviates impaired NOS-dependent responses of pial arterioles in type 1 diabetes mellitus. Microcirculation 13:567–575
106. Mayhan WG, Patel KP (1995) Acute effects of glucose on reactivity of the cerebral microcirculation: role of activation of protein kinase C. Am J Physiol 269:H1297–H1302
107. Mayhan WG, Sharpe GM (2001) Generation of superoxide anion impairs histamine-induced increases in macromolecular efflux. Microvasc Res 61:275–281
108. Mayhan WG, Simmons LK, Sharpe GM (1991) Mechanism of impaired responses of cerebral arterioles during diabetes mellitus. Am J Physiol 260:H319–H326
109. McCullough LD, Zeng Z, Blizzard KK, Debchoudhury I, Hurn PD (2005) Ischemic nitric oxide and poly (ADP-ribose) polymerase-1 in cerebral ischemia: male toxicity, female protection. J Cereb Blood Flow Metab 25:502–512
110. Minchenko AG, Stevens MJ, White L, Abatan OI, Komjati K, Pacher P, Szabo C, Obrosova IG (2003) Diabetes-induced overexpression of endothelin-1 and endothelin receptors in the rat renal cortex is mediated via poly(ADP-ribose) polymerase activation. FASEB J 17: 1514–1516
111. Modrick ML, Didion SP, Lynch CM, Dayal S, Lentz SR, Faraci FM (2009) Role of hydrogen peroxide and the impact of glutathione peroxidase-1 in regulation of cerebral vascular tone. J Cereb Blood Flow Metab 29:1130–1137
112. Modrick ML, Didion SP, Sigmund CD, Faraci FM (2009) Role of oxidative stress and AT1 receptors in cerebral vascular dysfunction with aging. Am J Physiol Heart Circ Physiol 296:H1914–H1919
113. Munzel T, Gori T, Bruno RM, Taddei S (2010) Is oxidative stress a therapeutic target in cardiovascular disease? Eur Heart J 31:2741–2748
114. Nangle MR, Cotter MA, Cameron NE (2003) Protein kinase Cbeta inhibition and aorta and corpus cavernosum function in streptozotocin-diabetic mice. Eur J Pharmacol 475:99–106
115. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I, Brownlee M (2000) Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 404:787–790
116. O'Driscoll G, Green D, Rankin J, Stanton K, Taylor R (1997) Improvement in endothelial function by angiotensin converting enzyme inhibition to insulin-dependent diabetes mellitus. J Clin Invest 100:678–684
117. Okada S, Shikata K, Matsuda M, Ogawa D, Usui H, Kido Y, Nagase R, Wada J, Shikata Y, Makino H (2003) Intercellular adhesion molecule-1-deficient mice are resistant against renal injury after induction of diabetes. Diabetes 52:2586–2593
118. Ozkaya YG, Agar A, Yargicoglu P, Hacioglu G, Bilmen-Sarikcioglu S, Ozen I, Aliciguzel Y (2002) The effect of exercise on brain antioxidant status of diabetic rats. Diabetes Metab 28:377–384
119. Pacher P, Liaudet L, Garcia Soriano F, Mabley JG, Szabo E, Szabo C (2002) The role of poly(ADP-ribose) polymerase activation in the development of myocardial and endothelial dysfunction in diabetes. Diabetes 51:514–521
120. Pannirselvam M, Simon V, Verma S, Anderson T, Triggle CR (2003) Chronic oral supplementation with sepiapterin prevents endothelial dysfunction and oxidative stress in small mesenteric arteries from diabetic (db/db) mice. Br J Pharmacol 140:701–706
121. Pannirselvam M, Verma S, Anderson TJ, Triggle CR (2002) Cellular basis of endothelial dysfunction in small mesenteric arteries from spontaneously diabetic (db/db –/–) mice: role of decreased tetrahydrobiopterin bioavailability. Br J Pharmacol 136:255–263
122. Park JY, Takahara N, Gabriele A, Chou E, Naruse K, Suzuma K, Yamauchi T, Ha SW, Meier M, Rhodes CJ, King GL (2000) Induction of endothelin-1 expression by glucose: an effect of protein kinase C activation. Diabetes 49:1239–1248
123. Pelligrino DA, Koenig HM, Wang Q, Albrecht RF (1994) Protein kinase C suppresses receptor-mediated pial arteriolar relaxation in the diabetic rat. Neuroreport 5:417–420
124. Picchi A, Gao X, Belmadani S, Potter BJ, Focardi M, Chilian WM, Zhang C (2006) Tumor necrosis factor-alpha induces endothelial dysfunction in the prediabetic metabolic syndrome. Circ Res 99:69–77

125. Pieper AA, Brat DJ, Krug DK, Watkins CC, Gupta A, Blackshaw S, Verma A, Wang ZQ, Snyder SH (1999) Poly(ADP-ribose) polymerase-deficient mice are protected from streptozotocin-induced diabetes. Proc Natl Acad Sci USA 96:3059–3064
126. Pieper AA, Verma A, Zhang J, Snyder SH (1999) Poly (ADP-ribose) polymerase, nitric oxide and cell death. Trends Pharmacol Sci 20:171–181
127. Pieper GM, Gross GJ (1988) Oxygen free radicals abolish endothelium dependent relaxation in diabetic rat aorta. Am J Physiol 255:H825–H833
128. Pieper GM, Haq RU (1997) Activation of nuclear factor-κB in cultured endothelial cells by increased glucose concentration: prevention by calphostin C. J Cardiovasc Pharmacol 30:528–532
129. Pieper GM, Langenstroer P, Siebeneich W (1997) Diabetic-induced endothelial dysfunction in rat aorta: role of hydroxyl radicals. Cardiovasc Res 34:145–156
130. Pollock DM (2005) Endothelin, angiotensin, and oxidative stress in hypertension. Hypertension 45:477–480
131. Potenza MA, Gagliardi S, Nacci C, Carratu' MR, Montagnani M (2009) Endothelial dysfunction in diabetes: from mechanisms to therapeutic targets. Curr Med Chem 16:94–112
132. Rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman BA, Griendling KK, Harrison DG (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: contribution to alterations in vascular tone. J Clin Invest 97:1916–1923
133. Reeves EP, Dekker LV, Forbes LV, Wientjes FB, Grogan A, Pappin DJ, Segal AW (1999) Direct interaction between p47phox and protein kinase C: evidence for targeting of protein kinase C by p47phox in neutrophils. Biochem J 344:859–866
134. Ribau JCO, Hadcock SJ, Teoh K, DeReske M, Richardson M (1999) Endothelial adhesion molecule expression is enhanced in the aorta and internal mammary artery of diabetic patients. J Surg Res 85:225–233
135. Rolo AP, Palmeira CM (2006) Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. Toxicol Appl Pharmacol 212:167–178
136. Rosenblum WI (1997) Tetrahydrobiopterin, a cofactor for nitric oxide synthase, produces endothelium-dependent dilation of mouse pial arterioles. Stroke 28:186–189
137. Ryan MJ, Didion SP, Mathur S, Faraci FM, Sigmund CD (2004) Angiotensin II-induced vascular dysfunction is mediated by the AT1A receptor in mice. Hypertension 43: 1074–1079
138. Schernthaner G, Schwarzer C, Kuzmits R, Muller MM, Klemen U, Freyler H (1984) Increased angiotensin-converting enzyme activities in diabetes mellitus: analysis of diabetes type, state of metabolic control and occurrence of diabetes vascular disease. J Clin Pathol 37:307–312
139. Schulze PC, Yoshioka J, Takahashi T, He Z, King GL, Lee RT (2004) Hyperglycemia promotes oxidative stress through inhibition of thioredoxin function by thioredoxin-interacting protein. J Biol Chem 279:30369–30374
140. Sharma A, Bernatchez PN, de Haan JB (2012) Targeting endothelial dysfunction in vascular complications associated with diabetes. Int J Vasc Med 2012:750126
141. Sheetz MJ, King GL (2002) Molecular understanding of hyperglycemia's adverse effects for diabetic complications. JAMA 288:2579–2588
142. Siflinger-Birnboim A, Johnson A (2003) Protein kinase C modulates pulmonary endothelial permeability: a paradigm for acute lung injury. Am J Physiol Lung Cell Mol Physiol 284: L435–L451
143. Stralin P, Karlsson K, Johansson BO, Marklund SL (1995) The interstitium of the human arterial wall contains very large amounts of extracellular superoxide dismutase. Arterioscler Thromb Vasc Biol 15:2032–2036
144. Suh SW, Aoyama K, Chen Y, Garnier P, Matsumori Y, Gum E, Liu J, Swanson RA (2003) Hypoglycemic neuronal death and cognitive impairment are prevented by poly(ADP-ribose) polymerase inhibitors administered after hypoglycemia. J Neurosci 23:10681–10690

145. Sun H, Mayhan WG (2005) Sex difference in nitric oxide synthase-dependent dilatation of cerebral arterioles during long-term alcohol consumption. Alcohol Clin Exp Res 29: 430–436
146. Sun H, Patel KP, Mayhan WG (2001) Tetrahydrobiopterin, a cofactor for NOS, improves endothelial dysfunction during chronic alcohol consumption. Am J Physiol Heart Circ Physiol 281:H1863–H1869
147. Szabo C (2005) Cardioprotective effects of poly(ADP-ribose) polymerase inhibition. Pharmacol Res 52:34–43
148. Szabo C (2005) Roles of poly(ADP-ribose) polymerase activation in the pathogenesis of diabetes mellitus and its complications. Pharmacol Res 52:60–71
149. Szabo C (2009) Role of nitrosative stress in the pathogenesis of diabetic vascular dysfunction. Br J Pharmacol 156:713–727
150. Szabo C, Pacher P, Zsengeller Z, Vaslin A, Komjati K, Benko R, Chen M, Mabley JG, Kollai M (2004) Angiotensin II-mediated endothelial dysfunction: role of poly(ADP-ribose) polymerase activation. Mol Med 10:28–35
151. Szabo C, Dawson VL (1998) Role of poly(ADP-ribose) synthetase in inflammation and ischaemia-reperfusion. Trends Pharmacol Sci 19:287–298
152. Tachi Y, Okuda Y, Bannai C, Bannai S, Shinohara M, Shimpuku H, Yamashita K, Ohura K (2001) Hyperglycemia in diabetic rats reduces the glutathione content in the aortic tissue. Life Sci 69:1039–1047
153. Tang XN, Cairns B, Cairns N, Yenari MA (2008) Apocynin improves outcome in experimental stroke with a narrow dose range. Neuroscience 154:556–562
154. Tesfamariam B (1994) Free radicals in diabetic endothelial cell dysfunction. Free Radic Biol Med 16:383–391
155. Tesfamariam B, Jakubowski JA, Cohen RA (1989) Contraction of diabetic rabbit aorta caused by endothelium-derived p GH2–TxA2. Am J Physiol 257:H1327–H1333
156. Thomas SR, Witting PK, Drummond GR (2008) Redox control of endothelial function and dysfunction: molecular mechanisms and therapeutic opportunities. Antioxid Redox Signal 10:1713–1765
157. Tian J, Wen Y, Yan L, Cheng H, Yang H, Wang J, Kozman H, Villarreal D, Liu K (2011) Vascular endothelial dysfunction in patients with newly diagnosed type 2 diabetes and effects of 2-year and 5-year multifactorial intervention. Echocardiography 28:1133–1140
158. Tilton RG (2002) Diabetic vascular dysfunction: links to glucose-induced reductive stress and VEGF. Microsc Res Tech 57:390–407
159. Timimi FK, Ting HH, Haley EA, Roddy MA, Ganz P, Creager MA (1998) Vitamin C improves endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. J Am Coll Cardiol 31:552–557
160. Ting HH, Timimi FK, Boles KS, Creager SJ, Ganz P, Creager MA (1996) Vitamin C improves endothelium-dependent vasodilation in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 97:22–28
161. Touyz RM (2008) Apocynin, NADPH oxidase, and vascular cells: a complex matter. Hypertension 51:172–174
162. Touyz RM, Chen X, Tabet F, Yao G, He G, Quinn MT, Pagano PJ, Schiffrin EL (2002) Expression of a functionally active gp91phox-containing neutrophil-type NAD(P)H oxidase in smooth muscle cells from human resistance arteries: regulation by angiotensin II. Circ Res 90:1205–1213
163. Trauernicht AK, Sun H, Patel KP, Mayhan WG (2003) Enalapril prevents impaired nitric oxide synthase-dependent dilatation of cerebral arterioles in diabetic rats. Stroke 34: 2698–2703
164. Tsutsui H, Kinugawa S, Matsushima S (2011) Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol 301:H2181–H2190
165. Ueno Y, Kizaki M, Nakagiri R, Kamiya T, Sumi H, Osawa T (2002) Dietary glutathione protects rats from diabetic nephropathy and neuropathy. J Nutr 132:897–900

166. Vancurova I, Miskolci V, Davidson D (2001) NF-kappa B activation in tumor necrosis factor alpha-stimulated neutrophils is mediated by protein kinase Cdelta. Correlation to nuclear Ikappa Balpha. J Biol Chem 276:19746–19752
167. Vanhoutte PM (2001) Endothelium-derived free radicals: for worse and for better. J Clin Invest 107:23–25
168. Vasquiz-Vivar J, Martasek P, Whitsett J, Joseph J, Kalyanaraman B (2002) The ratio between tetrahydrobiopterin and oxidized tetrahydrobiopterin analogues controls superoxide release from endothelial nitric oxide synthase: an EPR spin trapping study. Biochem J 362:733–739
169. Venugopal SK, Devaraj S, Yang T, Jialal I (2002) Alpha-tocopherol decreases superoxide anion release in human monocytes under hyperglycemic conditions via inhibition of protein kinase C-alpha. Diabetes 51:3049–3054
170. Vetri F, Chavez R, Xu HL, Paisansathan C, Pelligrino DA (2013) Complex modulation of the expression of PKC isoforms in the rat brain during chronic type 1 diabetes mellitus. Brain Res 1490:202–209
171. Vetri F, Xu H, Paisansathan C, Pelligrino DA (2012) Impairment of neurovascular coupling in type 1 diabetes mellitus in rats is linked to PKC modulation of BK(Ca) and Kir channels. Am J Physiol Heart Circ Physiol 302:H1274–H1284
172. Virdis A, Ghiadoni L, Taddei S (2010) Human endothelial dysfunction: EDCFs. Pflugers Arch 459:1015–1023
173. Wei EP, Ellison MD, Kontos HA, Povlishock JT (1986) O_2 radicals in arachidonate induced increased blood-brain barrier permeability to proteins. Am J Physiol 251:H693–H699
174. Wei EP, Kontos HA, Christman CW, DeWitt DS, Povlishock JT (1985) Superoxide generation and reversal of acetylcholine induced cerebral arteriolar dilation after acute hypertension. Circ Res 57:781–787
175. Wolf G (2004) New insights into the pathophysiology of diabetic nephropathy: from haemodynamics to molecular pathology. Eur J Clin Invest 34:785–796
176. Wolf BA, Williamson JR, Easom RA, Chang K, Sherman WR, Turk J (1991) Diacylglycerol accumulation and microvascular abnormalities induced by elevated glucose levels. J Clin Invest 87:31–38
177. Wong WT, Tian XY, Xu A, Ng CF, Lee HK, Chen ZY, Au CL, Yao X, Huang Y (2010) Angiotensin II type 1 receptor-dependent oxidative stress mediates endothelial dysfunction in type 2 diabetic mice. Antioxid Redox Signal 13:757–768
178. Yakubu MA, Sofola OA, Igbo I, Oyekan AO (2004) Link between free radicals and protein kinase C in glucose-induced alteration of vascular dilation. Life Sci 75:2921–2932
179. Yoshida K, Yasujima M, Kohzuki M, Kanazawa M, Yoshinaga K, Abe K (1992) Endothelin-1 augments pressor response to angiotensin II infusion in rats. Hypertension 20:292–297
180. Zhang L, Zalewski A, Liu Y, Mazurek T, Cowan S, Martin JL, Hofmann SM, Vlassara H, Shi Y (2003) Diabetes-induced oxidative stress and low-grade inflammation in porcine coronary arteries. Circulation 108:472–478
181. Zingarelli B, Salzman AL, Szabo C (1998) Genetic disruption of poly (ADP-ribose) synthetase inhibits the expression of P-selectin and intercellular adhesion molecule-1 in myocardial ischemia/reperfusion injury. Circ Res 83:85–94

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