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Neuromodulatory Control of Oxidative Stress Pathways in Diabetic Vascular and Haematological Complications

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease characterized by persistent hyperglycaemia, insulin resistance, mitochondrial dysfunction, endothelial injury, immune dysregulation, and oxidative stress. Oxidative stress is a central mechanism driving both vascular and haematological complications of diabetes, including endothelial dysfunction, atherosclerosis, nephropathy, retinopathy, neuropathy, platelet hyperreactivity, red blood cell damage, impaired erythropoiesis, and anaemia. However, oxidative stress in diabetes is not controlled only by glucose metabolism; it is also shaped by neuromodulatory systems. The autonomic nervous system, hypothalamic-pituitary-adrenal axis, vagus nerve, sympathetic-adrenal-medullary system, neuroimmune reflexes, and neurotransmitter signalling regulate vascular tone, inflammatory cytokines, mitochondrial activity, immune-cell function, coagulation, and redox balance. In diabetes, autonomic imbalance is common, with sympathetic overactivity, reduced parasympathetic tone, impaired baroreflex function, and cardiovascular autonomic neuropathy. This dysregulation enhances reactive oxygen species production, reduces nitric oxide bioavailability, promotes endothelial inflammation, increases platelet activation, impairs microvascular perfusion, and weakens neuroimmune control of inflammation. At the haematological level, neuromodulatory dysfunction contributes to oxidative red blood cell injury, abnormal platelet activation, impaired erythropoietin regulation, iron dysregulation, and inflammatory anaemia. This review discusses the neuromodulatory control of oxidative stress pathways in diabetic vascular and haematological complications, highlighting autonomic, neuroendocrine, inflammatory, mitochondrial, and therapeutic mechanisms.

Keywords: Diabetes mellitus; neuromodulation; oxidative stress; vascular complications; haematological complications

INTRODUCTION

Diabetes mellitus is a systemic metabolic disorder associated with chronic hyperglycaemia and progressive tissue injury. Its complications are traditionally grouped into microvascular complications, such as retinopathy, nephropathy, and neuropathy, and macrovascular complications, such as coronary artery disease, stroke, and peripheral arterial disease. In addition, diabetes produces important haematological abnormalities, including platelet hyperreactivity, endothelial-platelet activation, red blood cell membrane damage, reduced erythrocyte deformability, inflammation-related iron restriction, impaired erythropoiesis, and anaemia. These vascular and blood-related complications are closely linked by oxidative stress [1-5]. Oxidative stress occurs when reactive oxygen species exceed antioxidant capacity. In diabetes, hyperglycaemia, insulin resistance, free fatty acid excess, advanced glycation end-products, mitochondrial overload, protein kinase C activation, and chronic inflammation all increase reactive oxygen species production. Recent reviews of diabetic vascular complications identify

oxidative stress as a key mechanism initiating endothelial dysfunction, inflammation, microvascular disease, macrovascular disease, and atherosclerosis [2,6-8]. However, oxidative stress in diabetes is not controlled by metabolism alone. Neural and neuroendocrine systems strongly influence oxidative pathways through autonomic regulation of vascular tone, immune activity, hormone release, mitochondrial function, and haematopoiesis. The autonomic nervous system regulates sympathetic and parasympathetic outflow to the heart, vessels, kidney, spleen, liver, adipose tissue, and bone marrow. The hypothalamic-pituitary-adrenal axis controls cortisol secretion, while the sympathetic-adrenal-medullary system regulates adrenaline and noradrenaline release. The vagus nerve modulates inflammation through the cholinergic anti-inflammatory pathway, an important neuroimmune reflex involving acetylcholine, nicotinic acetylcholine receptors, the spleen, and inflammatory cytokine control [9-12]. In diabetes, these neuromodulatory systems become disrupted. Cardiovascular autonomic neuropathy is an under-recognized but common complication of diabetes and may occur even in prediabetes, indicating early autonomic involvement in metabolic disease [4,13-16]. This review examines how neuromodulatory dysfunction controls oxidative stress pathways and contributes to diabetic vascular and haematological complications.

Oxidative Stress Pathways in Diabetes

Oxidative stress in diabetes begins with metabolic overload. High intracellular glucose increases electron flux through the mitochondrial respiratory chain, leading to electron leakage and superoxide formation [17-20]. Hyperglycaemia also activates the polyol pathway, increases advanced glycation end-products, stimulates protein kinase C, and enhances hexosamine pathway activity. These pathways increase reactive oxygen species and reduce antioxidant defence. Mitochondrial dysfunction is central to this process. When glucose and fatty acid supply exceeds cellular energy demand, mitochondria become overloaded. This causes impaired oxidative phosphorylation, mitochondrial DNA damage, reduced ATP production, abnormal mitochondrial fission and fusion, and defective mitophagy [21-26]. Damaged mitochondria produce more reactive oxygen species and may release mitochondrial danger signals that activate inflammatory pathways.

Endothelial cells are especially vulnerable. Oxidative stress reduces nitric oxide bioavailability by reacting with nitric oxide to form peroxynitrite. Reduced nitric oxide causes vasoconstriction, platelet adhesion, leukocyte recruitment, and impaired vascular relaxation [27-30]. Oxidative stress also activates nuclear factor-kappa B, inflammasomes, adhesion molecules, and inflammatory cytokines. These changes promote endothelial dysfunction, capillary injury, thrombosis, and atherosclerosis [31-34].

Autonomic Nervous System and Redox Regulation

The autonomic nervous system regulates involuntary physiological functions, including heart rate, vascular tone, renal perfusion, gastrointestinal activity, sweating, endocrine secretion, and immune signalling. Its two major branches, the sympathetic and parasympathetic nervous systems, have complementary effects. Sympathetic activation prepares the body for stress by increasing heart rate, vascular tone, glucose mobilization, lipolysis, and catecholamine release. Parasympathetic activity, especially through the vagus nerve, supports metabolic recovery, anti-inflammatory signalling, and homeostatic regulation. In healthy physiology, autonomic balance helps maintain redox stability [9,35-38]. Sympathetic activation can transiently increase metabolic activity and reactive oxygen species production, while parasympathetic activity restrains excessive inflammation and oxidative injury.

In diabetes, this balance is disturbed. Poor glycaemic control, insulin resistance, obesity, inflammation, and nerve ischemia can damage autonomic fibres [39-41]. The result may be sympathetic predominance, reduced vagal tone, impaired heart-rate variability, abnormal blood pressure regulation, and cardiovascular autonomic neuropathy. Sympathetic overactivity promotes oxidative stress through several mechanisms. It increases catecholamine signalling, vascular smooth muscle contraction, renin-angiotensin-aldosterone system activation, blood pressure, and metabolic substrate release [42-46]. Angiotensin II and catecholamines stimulate NADPH oxidase activity, an important source of vascular reactive oxygen species. Sympathetic activation also increases lipolysis, raising free fatty acids that worsen mitochondrial oxidative stress and insulin resistance [47-50].

Sympathetic-Adrenal-Medullary Activation and Vascular Injury

The sympathetic-adrenal-medullary system releases adrenaline and noradrenaline during stress. These catecholamines increase heart rate, cardiac contractility, vascular tone, glucose production, and lipid mobilization [13,51-54]. In diabetes, chronic sympathetic activation contributes to hypertension, endothelial dysfunction, arterial stiffness, and vascular inflammation. Catecholamines can increase oxidative stress by activating adrenergic receptors on vascular cells and immune cells. This stimulates NADPH oxidase, mitochondrial reactive oxygen species production, and inflammatory signalling [55-60]. Increased vascular tone also reduces microvascular perfusion, creating local hypoxia and further mitochondrial stress. In the presence of hyperglycaemia, catecholamine-driven haemodynamic stress accelerates endothelial injury. Sympathetic activation also affects the kidney. It increases renin release, sodium retention, vasoconstriction, and glomerular pressure [61-63]. These

effects worsen diabetic nephropathy. Oxidative stress in renal endothelial cells, podocytes, mesangial cells, and tubular cells promotes albuminuria, inflammation, fibrosis, and reduced erythropoietin production. In the retina and peripheral nerves, sympathetic dysregulation may impair microvascular blood flow [64-67]. Reduced perfusion increases tissue hypoxia, oxidative stress, and inflammatory injury. This contributes to retinopathy, neuropathy, and diabetic foot disease. Thus, sympathetic overactivity provides a neuromodulatory pathway through which stress biology amplifies diabetic vascular complications [17,68].

Vagus Nerve and Cholinergic Anti-Inflammatory Control

The vagus nerve is a major parasympathetic pathway that connects the brain, heart, lungs, gut, liver, spleen, and immune system. One of its most important roles is regulation of inflammation through the cholinergic anti-inflammatory pathway. This pathway involves vagal signalling, splenic nerve activity, acetylcholine release, nicotinic acetylcholine receptors, and inhibition of excessive cytokine production [18]. Recent reviews describe this pathway as a neuroimmune axis that regulates crosstalk between the nervous system and immune responses [19]. In diabetes, reduced vagal tone is common, especially in cardiovascular autonomic neuropathy. Loss of vagal control may increase inflammatory cytokine production and oxidative stress [20]. This is important because inflammation and oxidative stress reinforce one another.

Cytokines stimulate reactive oxygen species production, while reactive oxygen species activate inflammatory transcription factors and inflammasomes. Vagal dysfunction may also affect metabolism. The vagus nerve participates in pancreatic insulin secretion, hepatic glucose production, gut motility, satiety signalling, and inflammatory regulation [21]. Reduced vagal activity may therefore worsen glycaemic variability, postprandial glucose control, and inflammatory tone. These changes can intensify vascular oxidative stress [22].

HPA Axis, Cortisol, and Oxidative Stress

The hypothalamic-pituitary-adrenal axis is another important neuromodulatory system. It regulates cortisol secretion during stress. Cortisol increases hepatic gluconeogenesis, promotes protein breakdown, increases lipolysis, and opposes insulin action. These effects are adaptive during acute stress but harmful when persistent [23]. In diabetes, chronic cortisol exposure can worsen hyperglycaemia and insulin resistance. Elevated glucose and free fatty acids increase mitochondrial overload and reactive oxygen species production. Cortisol may also contribute to visceral adiposity, hypertension, endothelial dysfunction, and immune imbalance [24]. Through these pathways, HPA-axis dysregulation indirectly promotes oxidative vascular injury.

Cortisol's immune effects are complex. Acute cortisol release limits excessive inflammation, but chronic stress may cause immune dysregulation or glucocorticoid resistance, where inflammatory pathways remain active despite elevated cortisol [25]. Persistent inflammation increases oxidative stress, hepcidin production, endothelial activation, and bone marrow suppression [26]. The HPA axis may also influence haematological complications. Cortisol can affect erythropoiesis, immune-cell function, iron metabolism, and red blood cell turnover indirectly through inflammation and metabolic stress. In diabetes, HPA-axis activation may therefore contribute to anaemia by increasing oxidative stress, worsening renal injury, and promoting inflammatory iron restriction [27].

Neuromodulation of Endothelial Dysfunction

Endothelial dysfunction is a major early event in diabetic vascular disease. Healthy endothelium regulates vascular relaxation, coagulation, leukocyte adhesion, permeability, and tissue perfusion. In diabetes, oxidative stress reduces nitric oxide, increases endothelin-1, enhances adhesion molecules, and promotes endothelial cell death [28]. Neuromodulatory systems regulate endothelial function in several ways. Sympathetic nerves control vascular tone through noradrenaline-mediated vasoconstriction. Excess sympathetic activity increases shear stress, blood pressure, and reactive oxygen species. Parasympathetic and vagal pathways can indirectly protect endothelium by reducing inflammation and improving metabolic homeostasis [29].

Autonomic neuropathy worsens endothelial dysfunction because vascular responses become poorly regulated. Impaired vasodilation reduces tissue oxygen delivery, while excessive vasoconstriction worsens ischemia. In the kidney, retina, heart, and peripheral limbs, this contributes to diabetic microvascular injury [30]. Reviews of endothelial dysfunction in diabetic vascular complications emphasize oxidative stress, inflammation, endothelial-to-mesenchymal transition, and cell death as central mechanisms. Neuromodulatory imbalance can amplify each of these mechanisms.

Platelet Hyperreactivity and Neurovascular Redox Signalling

Platelets are not only haemostatic cells; they are inflammatory and immune-active cells. In diabetes, platelets become hyperreactive due to hyperglycaemia, insulin resistance, oxidative stress, advanced glycation end-products, endothelial dysfunction, and inflammatory mediators [31]. Diabetic platelets show enhanced activation, aggregation, thromboxane production, adhesion, and interaction with leukocytes. These changes contribute to cardiovascular disease, stroke, peripheral arterial disease, and microvascular obstruction [32]. Neuromodulatory

systems affect platelet function through vascular tone, catecholamine exposure, endothelial nitric oxide availability, and inflammatory signalling. Sympathetic activation and catecholamines can increase platelet reactivity, particularly in the context of endothelial dysfunction [33]. Reduced nitric oxide and prostacyclin remove natural platelet-inhibitory signals. Oxidative stress further enhances platelet activation. Inflammatory macrophage dysregulation, including impaired iron-recycling macrophage function, adds a further haematological dimension to neuromodulatory platelet and red cell abnormalities in diabetes [34]. Chronic inflammatory suppression of erythropoiesis compounds this haematological burden, with cytokine-driven marrow suppression limiting erythroid recovery even when erythropoietin is present [35]. Hepcidin-mediated iron restriction, stimulated by inflammatory signalling, further reduces iron availability for erythropoiesis and compounds the anaemia of chronic metabolic disease [36]. Neuromodulatory impairment of erythropoietin regulation through autonomic-renal and HPA-renal pathways may therefore contribute to the anaemic burden in diabetic patients [37]. Chronic physiological and neuroendocrine stress can also directly activate haematopoietic stem cells in a maladaptive manner, shifting haematopoiesis away from erythroid lineages and contributing to anaemia [38].

CONCLUSION

Neuromodulatory systems play a major role in controlling oxidative stress pathways in diabetic vascular and haematological complications. In diabetes, autonomic imbalance, sympathetic overactivity, reduced vagal tone, HPA-axis dysregulation, and cardiovascular autonomic neuropathy interact with hyperglycaemia, insulin resistance, inflammation, mitochondrial dysfunction, and endothelial injury. Sympathetic activation increases vascular tone, catecholamine signalling, NADPH oxidase activity, oxidative stress, platelet reactivity, and renal injury. Reduced vagal tone weakens cholinergic anti-inflammatory control, allowing cytokine-driven oxidative injury and hepcidin-mediated iron restriction. HPA-axis activation worsens hyperglycaemia, lipolysis, oxidative stress, and immune imbalance. These mechanisms contribute to endothelial dysfunction, atherosclerosis, nephropathy, retinopathy, neuropathy, platelet hyperreactivity, red blood cell damage, impaired erythropoiesis, and anaemia. A comprehensive approach to diabetic complications should therefore address not only glucose, blood pressure, and lipids, but also autonomic health, inflammation, oxidative stress, renal function, platelet activity, and haematological status.

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