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Review Article

Oxidative Stress and Antioxidant Level during Diabetes Mellitus

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Abstract

Hyperglycemia (or) Diabetes mellitus is due to insufficiency of insulin secretion or action of endogenous insulin (or) both. Although the etiology of this disease is not well defined, viral infection, autoimmune disease, and environmental factors have been implicated. In diabetes, free radicals are formed by glucose oxidation, the subsequent oxidative degradation of glycated proteins and non-enzymatic glycation of proteins. Insulin resistance can be developed due to unusually high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes, increased lipid peroxidation. Because of this oxidative stress and low level of antioxidant level can promote the development of diabetes and their complications. This problem will be overcome by endogenous antioxidant defense mechanisms including both enzymatic and non-enzymatic pathways. The main function of this antioxidant defense mechanism in human body is to counterbalance the toxic reactive oxygen species (ROS). Commonly presenting non-enzymic antioxidants like vitamins A, C, E and Beta carotene and the enzymic antioxidants like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GRx) play a important role in human body. This review will elaborate the importance of endogenous antioxidant defense mechanisms, their relationship to several pathophysiological conditions and their possible therapeutic implications.

Keywords

Antioxidants
Diabetic mellitus
Free radicals
Oxidative stress
Reactive oxygen species

Introduction

Type 2 diabetes (non-insulin-dependent diabetes) is a multi-causal disease which develops slowly and in a stepwise order (Stumvoli et al., 2005; Waeber and Vollenweider, 2007; Buguslaw, 2001). Initially it commences with insulin resistance, which progress gradually with time until the body fails to maintain glucose haemostasis resulting in glucose intolerance.

Systemically these perturbations are accompanied with changes in a variety of biochemical processes such as obesity, an altered lipid profile and lipid peroxidation (Maharjan et al., 2008). Oxidative damage to unsaturated lipids is a well-established general mechanism for oxidative stress-mediated cellular injury (Yagi, 1994) in addition to increased lipid peroxidation (Syryawansh et al., 2006).

The occurrence of free-radical-induced lipid peroxidation causes considerable changes in the cell membrane (Agrawal et al., 1985). Peroxidation of the lipid membrane has been related to the pathogenesis of many degenerative diseases, such as atherosclerosis, aging, carcinogenesis and diabetes mellitus (Nair et al., 2007). Evidence suggests that oxidative stress is increased in diabetes, because of excessive production of ROS and an impaired antioxidant defense mechanism (West, 2000; Antoine et al., 2002). It has been suggested that ROS induce membrane lipid peroxidation and that the toxicity of the generated fatty acids peroxides are important causes of cell malfunction (Sanocka and Kurpisz, 2004).

The most widely used assay for lipid peroxidation involves the measurement of MDA due to its simplicity. Thus, the lipid peroxide in the blood provides useful information for the prognosis of diabetes in which secondary disorders are often fatal (Tappel, 1973). Antioxidants can be defined as substances whose presence in relatively high concentration significantly inhibits the rate of oxidation of lipids, proteins, carbohydrates and DNA. Antioxidants such as uric acid (UA), SOD and GSH act as potent electron donors; they donate hydrogen atoms to pair up with unpaired electrons on free radicals. Thus, they convert reactive free radicals into inactive substances (Bagchi and Puri, 1998).

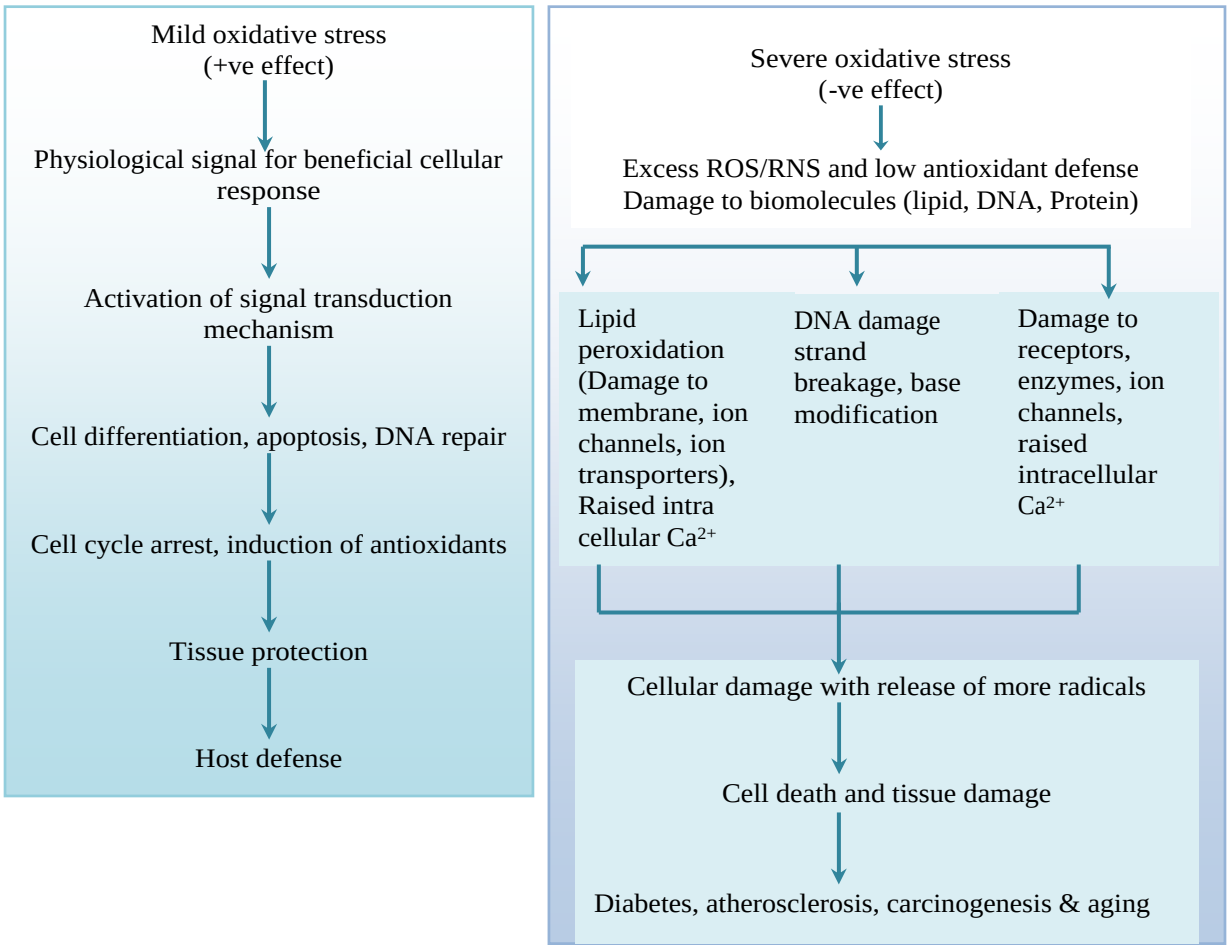
Free radicals and oxidative stress

Free radicals are defined as atoms or molecules that contain one or more unpaired electrons, making them unstable and highly reactive. The most important ROS are the superoxide anion radicals, hydrogen peroxide (H_2O_2), alkoxyl ($RO^{\bullet}$), peroxyl ($ROO^{\bullet}$) and hydroxyl radicals ($^{\bullet}OH$)(Frei, 1994) and hypochlorous acid (HOCl), other non-oxygen species existing as reactive nitrogen species (RNS) such as nitric oxide (NO) and peroxy nitrite (ONOO) have also important bioactivity(Evans, 1999).

Oxidative stress plays a pivotal role in cellular injury from hyperglycemia. High glucose level can stimulate free radical production. Weak defense system of the body becomes unable to counteract the enhanced ROS generation and as a result condition of imbalance between ROS and their protection occurs which leads to domination of the condition of oxidative stress (Halliwell and Gutteridge, 2007; Pandey et al., 2010). A certain amount of oxidative stress/ROS is necessary for the normal metabolic processes since ROS plays various regulatory roles in cells (Gomes et al., 2012). ROS are produced by neutrophils and macrophages during the process of respiratory burst in order to eliminate antigens (Freitas et al., 2010). They also serve as stimulating signals of several genes which encode transcription factors, differentiation, and development as well as stimulating cell-cell adhesion, cell signaling, involvement in vasoregulation, fibroblast proliferation, and increased expression of antioxidant enzymes (Thannickal and Fanburg, 2000; Sen, 2001). However over- and/or uncontrolled production of ROS are deleterious.

Due to oxidative stress the metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels, as well as in the myocardium (Giacco and Brownlee, 2010). Oxidative stress acts as mediator of insulin resistance and its progression to glucose intolerance and installation of diabetes mellitus, subsequently favouring the appearance of atherosclerotic complications, and contributes to rise in many micro- and macrovascular complications (Negre-Salvayre et al., 2009). The responses and signals during oxidative stress are shown below in Fig. 1.

Fig. 1: Responses and signals during oxidative stress (Irshad and Chaudhuri, 2002).



Antioxidants

In health, balance between pro-oxidants and antioxidant is critical for the survival and functioning of aerobic organism (Sies, 1985). Antioxidant has been defined as "any substance that delays or inhibits oxidative damage to a target molecule" (Gutteridge and Halliwell, 1990). In generally all the antioxidants influence the redox status, thereby protecting cells against ROS under certain circumstances, while promoting ROS generation in others. Antioxidants are of two types namely enzymic antioxidant such as SOD (Offer, 2000) CAT, GPx (Ramanathan et al.,1999) and non-enzymic antioxidants such as GSH (Kinalski et al., 2000), ascorbic acid, α-tocopherol (Halliwell and Aruoma, 1991), vitamins, estrogen, β-carotene and flavonoids (Chen et al., 2002).

Enzymic antioxidants

Superoxide dismutase

SOD is the antioxidant enzyme that catalyses the dismutation of superoxide anion into hydrogen peroxide and molecular oxygen. SOD plays important protective roles against cellular and histological damages that are produced by ROS. It facilitates the conversion of superoxide radicals into hydrogen peroxide, and in the presence of other enzymes it converted into oxygen and water. They are found virtually in all aerobic organisms. There are four main families of SOD: like Cu-SOD, Cu-Zn-SOD, Mn-SOD and Fe-SOD. The Cu-Zn-SOD enzyme mainly present in human body. It is considered to be a stress protein, which is synthesized in response to oxidative stress and it will inhibit the $^{\bullet}OH$ production (Ray and Hussain, 2002).

Glutathione peroxidase

GPx are selenoenzymes. Due to this selenium deficiency the GPx activity is being reduced and it will be associated with a high risk of cardiovascular disease (Mannisto et al., 2000).

GPx catalyse the reduction of hydroperoxides at the expense of GSH.

$$ROOH + 2\ GSH \longrightarrow ROH + H_2O + GSSG$$

GPx is present in the cytosol and mitochondrial matrix. The function of this enzyme include, protecting hemoglobin from oxidative destruction by H_2O_2; as a contraction factor of mitochondria; catalase reduction of H_2O_2 and organic peroxides including those derived from unsaturated lipids to alcohol; protects biomembranes from oxidative attack and prevents lipid peroxidation by scavenging H_2O_2 and slowing down dependent free radical attack on the lipids (Rana et al., 2002).

Catalase

CAT is an antioxidative enzyme present nearly in all living organisms. It plays an important role against oxidative stress-generated complications such as diabetes and cardiovascular diseases. CAT acts as main regulator of hydrogen peroxide metabolism. Hydrogen peroxide is a highly reactive small molecule formed as natural by-product of energy metabolism. Excessive concentration of hydrogen peroxide may cause significant damages to proteins, DNA, RNA, and lipids. CAT enzymatically processes hydrogen peroxide into oxygen and water and thus neutralizes it. Increased risk of diabetes has been documented in patients with catalase deficiency.

The deficiency of this enzyme leads, in the β-cell, to an increase in oxidative stress and ultimately to a failure of this cell type. β-cells are rich in mitochondria, and thus this organelle might be a source of ROS (Takemoto et al., 2009). CAT protects pancreatic β-cells from damage by hydrogen peroxide. Low CAT activities, which have been reported in patients with schizophrenia and atherosclerosis , are consistent with the hypothesis that long-term oxidative stress may contribute to the development of a variety of late-onset disorders, such as type 2 diabetes (Góth., 2000).

Non-enzymic antioxidants

Vitamin C

Vitamin C is actively taken up in high concentration by secretary cells of the islets of Langerhans where it is believed to play a role in antioxidant defense mechanism (Bailey and Flatt, 1986). In diabetes mellitus, vitamin C metabolism is abnormal and subjects have been shown to have low vitamin C and high dehydro-2-ascorbic acid concentration in plasma. Vitamin C is a potent inhibitor of protein glycation, which has the particular advantage of low inherent toxicity in humans even in mega doses (Davie et al., 1992).

Vitamin E (α-tocopherol)

It performs its functions as antioxidant in the glutathione peroxidase pathway, and it protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. This would remove the free radical intermediates and prevent the oxidation reaction from continuing. The oxidized α-tocopheroxyl radicals produced in this process may be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol or ubiquinol. However, the importance of the antioxidant properties of this molecule at the concentrations present in the body are not clear and the reason vitamin E is required in the diet is possibly unrelated to its ability to act as an antioxidant (Packer et al., 1994).

Conclusion

Diabetes mellitus has reached epidemic proportions in the last decade, becoming one of the most important diseases worldwide. Several studies indicate oxidative stress is present in the dysfunction of insulin action and secretion that occur during diabetes, as well as in the development of diabetic complications. Nevertheless, oxidative stress is not the primary causes of diabetes, but rather a consequence of nutrient excess, given that oxidative stress is a natural response to stress, in this case, to glucose and/or lipid overload. Vitamins such as E, C and A with antioxidant properties constitute the physiological non- enzymatic defense against oxidative stress. However, the evidence in favor of the use of Vitamin supplementation as antioxidant therapy remains uncertain. Although some beneficial effects have been

proven in observational studies, the results of interventional trials are still ineffective. Mostly dietary vitamin intake which has shown an association with ameliorating the diabetic state, and that oxidative stress is a response to excess of nutrients; it seems that attending the cause of excessive ROS production represents the best therapeutic option. Thus, adequate dietary interventions that reduce hyperglycemia, and increases in oxygen consumption (i.e. improve mitochondrial function) by exercise remain the primary choices for diabetes treatment and prevention of its complications.

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