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Review

Molecular pathways associated with oxidative stress in diabetes mellitus

Osasenaga Macdonald Ighodaro

Department of Biochemistry, Lead City University, Ibadan, Nigeria

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ABSTRACT

The role of oxidative stress in the occurrence and development of diabetes mellitus is both critical and pivotal. Several molecular event cascade in different metabolic pathways such as glycolytic, hexosamine, protein kinase C, polyol and advanced glycation end-product (AGE) pathways have been identified as pro-oxidative processes and are usually up-regulated in the diabetics. Inhibition of glyceraldehyde-3-P dehydrogenase by poly-ADP-ribose polymerase 1 and subsequent accumulation of the enzyme substrate (glyceraldehyde-3-P) appears to be central to diabetes-associated oxidative stress. Increased level of glyceraldehyde-3-P activates two major pro-oxidative pathways in diabetes: (i) It activates the AGE pathway, precisely the synthesis of *methylglyoxal* from non-enzymatic dephosphorylation of the triose phosphates (ii) It activates protein kinase C (PKC) pathway by promoting the synthesis of diacylglycerol. In addition, it causes the accumulation of glycolytic metabolites upstream, and this leads to excessive stimulation of other pro-oxidative pathways such as hexosamine and polyol pathways. This review tends to highlight the main oxidative processes associated with diabetes mellitus.

1. Introduction

Diabetes mellitus (DM) is a chronic endocrine and metabolic disorder which is underlined by insulin deficiency or insulin insensitivity or both, and characterized by hyperglycemia and vascular complications (micro and macro).

Similar to several other health conditions such as cancer and neurodegenerative disorders, oxidative stress has been widely linked with the incidence of diabetes mellitus [1–4]. Several studies have shown that oxidative stress is a key element in the development and progression of diabetes and its associated complications [5–8]. In line with this view, Brownlee [9] had earlier proposed oxidative stress as a major participant in the pathophysiology of diabetes and its complications.

Oxidative stress occurs when there is a distortion in the redox balance of the cell, causing damage to membranes and vital biomolecules such as DNA, proteins and lipids [10–12]. Oxidative stress has been shown to compromise the two major mechanisms failing during diabetes which are ***insulin secretion*** and ***insulin action*** [3,13–18]. The role of oxidative stress in diabetes is arguably like the two sides of a coin. The process does not only promote the onset of diabetes but also exacerbates the disease condition and its associated complications. Experimental evidence implicates the role of reactive oxygen species (ROS) in impaired beta-cell function caused by autoimmune reactions, cytokines and inflammatory proteins in type 1 diabetes [7]. Also, hyperglycemia has been noted to promote oxidative stress through *de novo* free radical generation and suppression of the antioxidant defense systems [3]. In chronic hyperglycaemic conditions, production of ROS is perpetuated and hence, the antioxidant enzymes and non enzymatic antioxidants are severely suppressed in various tissues, which further exacerbate oxidative stress [8,19,20]. This explains why diabetic persons tend to have more oxidative cell and organism environments than healthy individuals [8,21,22]. Several molecular pathways which are involved in the induction of oxidative stress are up regulated in diabetes and are the focus of this review.

2. Molecular pathways associated with oxidative stress in diabetes mellitus

The molecular pathways which have been noted to contribute to oxidative stress in diabetes are either involved with glucose metabolism or lipid metabolism. These cellular pathways are discussed below.

2.1. Glucose oxidation pathway (Glycolysis)

It is highly essential for glucose to be oxidized in body cells. The initial process by which this occurs is termed glycolysis. It is a ten-step enzyme catalyzed pathway, the first among other reaction pathways (Kreb cycle and electron transport chain) collectively involved in ATP (energy) generation from glucose. The glycolytic pathway begins with the phosphorylation of glucose by hexokinase or glucokinase to glucose-6-phosphate (G-6-P) and then fructose-6-phophate (F-6-P) through the action of phosphoglucoisomerase [23]. G-6-P can be channeled into

E-mail addresses: Ighodaro.macdonald@lcu.edu.ng, macigho@gmail.com.

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the pentose phosphate pathway to generate NADPH from $NADP^+$ for cellular synthetic reactions [24]. Alternatively, it continues in the glycolytic pathway to yield Glyceraldehyde-3-Phosphate (GAP) which is phosphorylated by glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and the resultant product is further broken down through several reaction steps to produce the glycolytic end product, pyruvate, which when decarboxylated combines with co enzyme A to begin the Kreb cycle in the mitochondrial matrix. The intermediates of this second pathway (Kreb cycle), mainly reduced nicotinamide adenine dinucleotide (NADH) and reduced flavan adenine dinucleotide (FADH2) are subsequently oxidized to generate a proton concentration gradient for ATP synthesis in the inner membrane of the mitochondrion through a process known as electron transport chain [25,26].

Under normal physiological conditions cellular processes (including glucose oxidation) result in mitochondrial production of superoxide anion radical ($O_2^{\cdot}$), howbeit at the level the body antioxidant defense grid can cope with [27]. However, in hyperglycemic conditions (excess blood glucose), there is excessive production of superoxide anion radical ($O_2^{\cdot}$), which suppresses the body antioxidant systems to induce oxidative stress and inflicts damage to nuclear DNA as well as other biomolecules [28–31]. As a result of DNA damage, a DNA repair enzyme, poly-ADP-ribose polymerase-1 (PARP-1) is activated. This enzyme (PARP-1) inhibits GAPDH [3,32,33], resulting in increased levels of GAP and other glycolytic intermediates such as F-6-P and G-6-P as well as glucose (Fig. 1). Accumulation of these molecules in the cell stimulates other pro-oxidative pathways like AGE and PKC pathways due to increased level of GAP; hexosamine and polyol pathways due to increased levels of F-6-P and glucose respectively (Fig. 1) [29,34]. Besides, accumulation of GAP can cause autooxidation of the molecule, leading to production of hydrogen peroxide (H_2O_2) which further promotes oxidative stress [35]. Similarly, autooxidation of glucose can stem from glucose accumulation in cells. This usually results in formation of glyoxal which is a precursor for advanced glycation end products (AGEs) and invariably contributes to cellular oxidative stress (Fig. 1) [36].

2.2. Advanced glycation end-products (AGEs) pathway

Advanced glycation end-products (AGEs), particularly modified proteins occur both in the intracellular compartments and extracellular matrix [37–39]. Both intracellular and extracellular proteins are negatively modified into AGEs with altered functions when their amino acid constituent groups interact with AGE precursors (reducing carbohydrates) such as glyoxal, methylglyoxal and deoxyglucosone [40,41] (Fig. 2). Once formed, AGEs can bind to different AGE receptors (AGE-R1, AGE-R 2, AGE-R 3 and RAGE) or interact abnormally with components of the extracellular matrix to promote ROS generation and invariably favours oxidative stress [42]. Besides proteins, lipids, nucleic acids, carbohydrates and some components of the extracellular matrix can be modified into AGEs. Formation of AGE precursors has been primarily adduced to hyperglycemia [43]. For instance, as earlier stated, accumulation of glucose due to hyperglycemia can lead to its autooxidation, resulting in the formation of glyoxal. In the same vein, non-enzymatic dephosphorylation of the triose phosphates

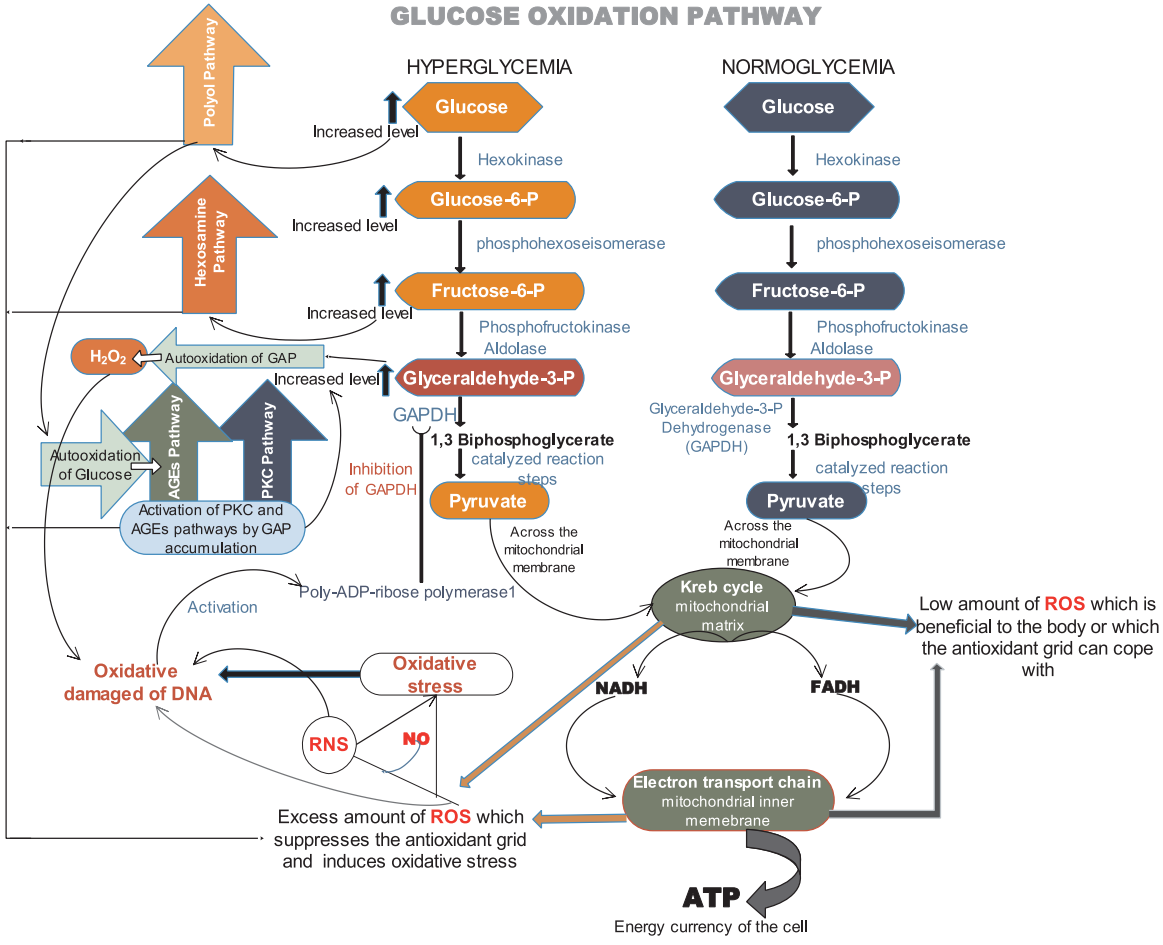

Fig. 1. Glucose oxidation and induced-oxidative stress in hyperglycemic conditions.
In hyperglycemic conditions, there is exccess production of free radicals leading to DNA damage and subsequent activation of Poly ADP ribose polymerase 1, a DNA repairing enzyme. This enzyme inhibits the ctivity of glyceraldehyde-3-phosphate dehydrogenase, resulting in the accumulation of glyceraldehyde-3-phosphate. GAP \accumulation activates a number of pro-oxidative processes including hexosamine, polyol, protein kinase and advanced glycation end product pathways.