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Review Article

Reactive metabolites and antioxidant gene polymorphisms in Type 2 diabetes mellitus ☆

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ABSTRACT

Type 2 diabetes mellitus (T2DM), by definition is a heterogeneous, multifactorial, polygenic syndrome which results from insulin receptor dysfunction. It is an outcome of oxidative stress caused by interactions of reactive metabolites (RMs) interactions with lipids, proteins and other mechanisms of human body. Production of RMs mainly superoxide ($O_2^{\bullet -}$) has been found in a variety of predominating cellular enzyme systems including NAD(P)H oxidase, xanthine oxidase (XO), cyclooxygenase (COX), uncoupled endothelial nitric oxide synthase (eNOS) and myeloperoxidase (MPO). The four main RM related molecular mechanisms are: increased polyol pathway flux; increased advanced glycation end-product (AGE) formation; activation of protein kinase C (PKC) isoforms and increased hexosamine pathway flux which have been implicated in glucose-mediated vascular damage. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST), nitric oxide synthase (NOS) are antioxidant enzymes involved in scavenging RMs in normal individuals. Functional polymorphisms of these antioxidant enzymes have been reported to be involved in pathogenesis of T2DM individuals. The low levels of antioxidant enzymes or their non-functionality results in excessive RMs which initiate stress related pathways thereby leading to insulin resistance and T2DM. An attempt has been made to review the role of RMs and antioxidant enzymes in oxidative stress resulting in T2DM.
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Introduction

Diabetes Mellitus (DM) is a chronic disorder characterized by impaired metabolism of glucose and lipids due to defect in insulin secretion (beta cell dysfunction) or action (insulin resistance). The characteristic properties of diabetes mellitus are chronic hyperglycemia, microvascular (eg. retina, renal glomerulus and peripheral nerve) as well as macrovascular (eg. atherosclerosis, coronary artery disease (CAD), stroke) pathologies with more than 17.5 million deaths worldwide attributable to cardiovascular complications [1]. According to International Diabetes Federation (IDF) Diabetes Atlas 5th Edition-2012 update, 371 million people have been reported with DM and the number is expected to rise to >552 million by 2030. The 2012 Indian statistics showed 63.0 million diabetic cases and a prevalence of 8.37% in adult population [2] while a 4.0% prevalence of type 2 diabetes mellitus (T2DM) was reported in North Indian population [3]. The currently favored hypothesis is oxidative stress leading to insulin resistance (IR), β-cell dysfunction, impaired glucose tolerance (IGT) and ultimately T2DM. Furthermore, oxidative stress has been implicated as the underlying cause of both macrovascular and microvascular complications associated with T2DM. It is believed that therapies aimed at reducing oxidative stress would benefit patients with T2DM and also those at risk. The accumulation of glucose and fatty acids within muscles, adipose tissue and pancreatic cells combined with sedentary lifestyle lead to the generation of excess reactive metabolites (RMs). Oxidative stress and RMs are interrelated terms defined in general as excess formation and/or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive thiyl species (RTR). This review aims to explain the role of such RMs and association of antioxidant gene polymorphisms with T2DM.

Types of reactive metabolites (RMs)

ROS: oxygen derived free radicals (ODFR) and oxygen derived non radicals (ODNR)

Oxygen derived free radical and non-radical reactive species are generated in metabolic pathways of biological systems. ODFR include superoxide ($O_2^{\bullet -}$), hydroxyl ($^{\bullet}OH$), peroxyl ($^{\bullet}RO_2$), hydroperoxyl ($^{\bullet}HRO_2^-$) while ODNR include hydrogen peroxide (H_2O_2) and hydrochlorous acid (HOCl). These metabolites are responsible for lipid and protein modifications in case of oxidative stress [4]. Basal oxidative cellular metabolism generates a number of oxygen-derived free radical species through the activation of enzymes that produce superoxide anions and/or byproducts of mitochondrial respiration [5].

Reactive nitrogen species (RNS): nitrogen derived free radicals (NDFR) and nitrogen derived non radicals (NDNR)

Like ROS, RNS can be classified into radical and non-radical species. NDFR include nitric oxide ($^{\bullet}NO$), nitrogen dioxide ($^{\bullet}NO_2^-$) while NDNR include alkyl peroxynitrates ($RONOO^-$), nitrous oxide (HNO_2) and peroxynitrite ($ONOO^-$). $O_2^{\bullet -}$, $^{\bullet}NO$ and $ONOO^-$ are the most widely studied species and play important roles in cardiovascular complications [5]. Nitric oxide ($^{\bullet}NO$) is responsible for formation of many end-products involved in oxidative stress directly or indirectly after reaction with oxygen. $^{\bullet}NO$-derived RNS react with aromatic amino acids, lipids and thiols resulting in lipid and protein modifications [4]. Leukocyte peroxidases are involved in the formation of $^{\bullet}NO_2$ after utilization of H_2O_2 and NO_2^- as substrates. $^{\bullet}NO_2$, $^{\bullet}OH$ and ONOOH are responsible for damages related to oxidative stress eg. oxidation, nitrosation and nitration reactions [5,6].

Reactive thiyl and tyrosyl radicals (RTR)

RMs play a major role in generation of thiyl radicals ($RS^{\bullet}$) and their derivatives, sulfinyl ($RSO^{\bullet}$) and disulfide anion radical ($RSSR^{\bullet -}$) [7]. ROS and RNS induce protein S-glutathionylation either by protein thiol oxidative/nitrosative modification or by presence of protein thiyl radical ($R–S^{\bullet}$), sulfenic acid (R–SOH) and S-nitrosothiol (R–SNO) [7]. Thiyl radicals (TR) may be formed by $^{\bullet}OH$, $ONOO^-$ and/or Fe^{3+} mediated oxidation of thiols. TR may also be derived from sulfur containing moieties including disulfide, thioester or thioether functionalities under conditions of oxidative stress. Once formed, TR not only reacts with themselves and oxygen but also oxidize biological electron donors including ascorbic acid, NADH and ferricytochrome C. Myeloperoxidase uses H_2O_2 generated by the cells to oxidize L-tyrosine to tyrosyl radical. RTR radical initiates lipid peroxidation which may be of pivotal importance in transforming low density lipoprotein (LDL) into atherogenic particles [8]. Glutathione (GSH) is a tripeptide, γ-glutamyl-L-cysteinylglycine detected in all mammalian tissues and is present in disulfide form of glutathione (GSSG) [9]. Thiol status/redox balance determined by redox pair 2GSH/GSSG is an indicator of redox homeostasis or oxidative stress inside the cell. S-glutathionylation has been proposed as a posttranslational modification which is able to protect proteins from over-oxidizing environments in a wide range of diseases including diabetes mellitus [9].

Production of reactive metabolites (RMs)

Production of RMs mainly superoxides ($O_2^{\bullet -}$) have been found in a variety of predominating cellular enzyme systems including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase (XO), cyclooxygenase (COX), uncoupled endothelial nitric oxide synthase (eNOS) and myeloperoxidase (MPO) [10] (Table 1). The various sources of ROS and action of antioxidant enzymes have been represented in Fig. 1. NADPH oxidase uses NADPH as a substrate and is considered as an important source of ROS generation in vascular cells [4]. The lipoxygenase (LPO) and COX generate ROS indirectly by promoting formation of inflammatory mediators. RM production may result from action of arachidonic acid metabolizing enzymes including cytochrome P-450, LPO, COX and those in the mitochondrial respiratory chain [11]. Arachidonic acid (AA) is cleaved from the membrane by phospholipase A2 (PLA2) and is then metabolized by 5-LPO in the presence of its accessory protein 5-lipoxygenase activating protein (FLAP) to form leukotrienes (LTs) [12]. AA is also metabolized by COX to form members of another family of inflammatory mediators, the prostaglandins (PGs) [12]. Mitochondria also generate superoxides as electrons are transferred from complexes I to IV during normal cellular respiration. XO, which converts hypoxanthine and xanthine to uric acid, is an additional source of ROS [12]. Finally, eNOS uncouples to generate superoxide in preference to NO [13].

Reactive metabolites and Type 2 diabetes mellitus

There are four main molecular mechanisms implicated in glucose-mediated vascular damage *viz.* increased polyol pathway flux; increased production of advanced glycation end-product (AGE); activation of protein kinase C (PKC) isoforms, sorbitol, cytokines and prostanoids along with increased hexosamine

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