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Review Article

Oxidative stress and diabetes: What can we learn about insulin resistance from antioxidant mutant mouse models?

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ABSTRACT

The development of metabolic dysfunctions like diabetes and insulin resistance in mammals is regulated by a myriad of factors. Oxidative stress seems to play a central role in this process as recent evidence shows a general increase in oxidative damage and a decrease in oxidative defense associated with several metabolic diseases. These changes in oxidative stress can be directly correlated with increased fat accumulation, obesity, and consumption of high-calorie/high-fat diets. Modulation of oxidant protection through either genetic mutation or treatment with antioxidants can significantly alter oxidative stress resistance and accumulation of oxidative damage in laboratory rodents. Antioxidant mutant mice have previously been utilized to examine the role of oxidative stress in other disease models, but have been relatively unexplored as models to study the regulation of glucose metabolism. In this review, we will discuss the evidence for oxidative stress as a primary mechanism linking obesity and metabolic disorders and whether alteration of antioxidant status in laboratory rodents can significantly alter the development of insulin resistance or diabetes.

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Introduction

The prevalence of metabolic disorders is experiencing a rate of growth that is rapidly placing these diseases among the most significant that affect the world's population. In particular, type 2 diabetes mellitus (T2DM), the most common form of metabolic dysfunction, currently affects more than 20 million people in the United States alone, with almost 60 million more diagnosed with prediabetes conditions [1].

Abbreviations: 4HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxyguanosine; AGE, advanced glucation end-product; Akt/PKB, protein kinase B; Cat, catalase, CuZnSod; Sod1, copper/zinc superoxide dismutase, ECSod; Sod3, extracellular superoxide dismutase; ETC, electron transport chain; GLUT4, glucose transporter; GPx, glutathione peroxidase; IL-6, interleukin-6; IR, insulin receptor; IRS-1, insulin receptor substrate 1; JNK, c-jun N terminal kinase; MAPK, mitogen-activated protein kinases; mCAT, mitochondria-targeted catalase overexpression; MCP-1, monocyte chemotactic protein-1; MDA, malondialdehyde; MnSod;Sod2, manganese superoxide dismutase; Msr, methionine sulfoxide reductase; NADPH, nicotinamide adenine dinucleotide phosphate; NFκB, nuclear factor κ B; PI-3K, phosphatidylinositol 3-kinase; Prdx, peroxiredoxin; PTEN, phosphatase and tensin homolog; PTP, protein-tyrosine phosphatase; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; TBAR, thiobarbituric acid reactive substances; Trx, thioredoxin; TG, transgenic; TNFα, tumor necrosis factor α.

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Complications from diabetes include cardiovascular disease, blindness, nerve damage, and nephropathy. Thus, the increasing incidence of diabetes is a significant health concern beyond the disease itself [2]. The prevalence of T2DM is age dependent, as more than 20% of people older than 60 years of age have diabetes compared to only about 8% of the population as a whole. Importantly, the strongest predictor of the development of T2DM is obesity or increasing fat accumulation. The global population is becoming older because of advances in medicine and at the same time becoming more obese due to an increasingly sedentary lifestyle and changes in diet toward excessive caloric intake. These two factors suggest that the growth of metabolic disorders worldwide is unlikely to slow. Understanding how factors like obesity lead to diabetes and insulin resistance has the potential to expand therapeutic options for future treatment of these diseases. Many inflammatory, endocrine, and intracellular pathways have been found to be dysregulated with obesity. However, the exact mechanism by which obesity causes metabolic diseases like T2DM is still unknown.

One of the earliest factors in the etiology of T2DM is the development of peripheral insulin resistance, or decrease in insulin sensitivity in the insulin-responsive tissues. Insulin resistance *in vivo* is caused either by inadequate insulin production (as defined by metabolic demands) or by abnormalities within the insulin signaling pathway [2]. This pathway is activated by binding of free insulin to the cell membrane-bound insulin receptor (IR). Subsequent activation of the intrinsic tyrosine kinase of IR then phosphorylates the β-subunit of IR which stimulates activation of the insulin signaling cascade through insulin receptor substrate protein-1 (IRS-1), phosphatidylinositol 3-kinase (PI-3K), and protein kinase B (PKB; Akt), ultimately leading to translocation of the glucose transporter (GLUT4) to the cell membrane of skeletal muscle and adipose cells and uptake of glucose [3]. Insulin resistance can be explicitly defined by abnormalities within this pathway. For example, muscle from subjects with T2DM, or from rodent models of diabetes, commonly show reduced insulin-stimulated insulin receptor and IRS-1 phosphorylation and PI-3K activity [4]. Obesity is known to drive the development of insulin resistance. However, not all obese subjects develop T2DM or insulin resistance, suggesting that the mechanism linking obesity with insulin resistance must be capable of being controlled under different circumstances.

It has been recently proposed that oxidative stress may be a primary factor in the etiology of obesity-induced insulin resistance and T2DM. It has long been known that the progression of several diseases and pathologies is greatly dependent on modulation of oxidative stress in mammalian systems [5,6]. As will be discussed in this review, it is becoming increasingly clear that consumption of adipogenic diets and the accumulation of adipose tissue can significantly increase levels of oxidative stress in mammalian systems. As a result, obesity is correlated with a drastic rise in oxidative damage to all cellular macromolecules ubiquitously among mammalian tissues [7–11]. Recent evidence also suggests that oxidative stress can have a significant inhibitory effect on insulin signaling in both *in vitro* and cell culture systems [12–14]. T2DM and insulin resistance are also strongly correlated with a prooxidant environment in both rodent and human studies, which suggests that oxidative stress may significantly alter both the pathogenesis and the progression of these diseases *in vivo*[15,16].

A greater understanding of the role oxidative stress has in the development of T2DM and insulin resistance is important because oxidative stress can be modulated by both intrinsic and extrinsic factors, thus providing a plausible means for prevention of metabolic disorders. The focus of this review is to clarify the role of oxidative stress in the regulation of glucose metabolism and to explore whether modulation of the expression of antioxidant enzymes has a significant effect on this process. As a first step, we must first define what oxidative stress is, what effect oxidative stress has on the cell, and how eukaryotic cells defend themselves from oxidative stress.

Oxidative stress and the antioxidant defense system

Oxidative stress can be defined as a state of imbalance toward the factors that generate reactive oxygen radicals (e.g., superoxide or hydroxyl radicals) and away from the factors that protect cellular macromolecules from these reactants including antioxidants like superoxide dismutases, catalase, and glutathione peroxidases. The factors that generate reactive oxygen species (ROS) exist as products of normal cellular physiology as well as from various exogenous sources. Mitochondria are thought to be the source of most cellular ROS, specifically superoxide radicals. The reactions that generate ATP in the mitochondria require electrons from reduced substrates to be passed along the complexes of the electron transport chain. In the presence of molecular oxygen, electrons that leak from this process react and form the free radical superoxide. Superoxide anions are significant mediators in numerous oxidative chain reactions and are also a precursor to many other ROS [17]. Other significant intracellular sources of ROS include NADPH oxidases (which generate superoxide), nitric oxide synthases (nitric oxide), and lipoxygenases (fatty acid hydroperoxides) [17]. In addition, certain cell types within tissue systems may promote localized environments with elevated oxidative stress. For example, macrophages can produce localized oxidative stress as part of the inflammatory response [18]. Thus, low levels of ROS are typical within both the cell and the higher order tissue and organ systems and some ROS (in particular superoxide and hydrogen peroxide) are required to support natural cellular function and regulate intracellular signaling [19]. However, excess ROS production (or reduced ROS regulation) can severely impair the cell and lead to macromolecular damage, dysfunction, and death.

Under conditions of oxidative stress, free radicals that are not reduced or removed from the cellular environment can cause damage to all cellular macromolecules including nucleic acids, lipids, and proteins [20]. DNA, both nuclear and mitochondrial, are susceptible to oxidation which results in mutations and single-strand breaks along with the formation of 8-hydroxyguanosine (8-OHdG) [21]. 8-OHdG is a relatively stable oxidation product and can be measured both in tissues and in excreted urine which accurately represent the amount of DNA oxidation/ repair rate as a measure of DNA damage within the body as a whole [22,23]. Oxidation of DNA has been strongly implicated in cellular senescence, apoptosis, and the development of cancerous cell phenotypes. On the other hand, oxidation of lipids can cause changes in structure and fluidity of cellular and organelle membranes that are detrimental to cellular processes and functions [24]. This ultimately affects cellular functions, further increasing cellular ROS concentrations [25]. In addition, oxidation of lipids may form lipid radical species that damage other cellular macromolecules. For example, lipid peroxides like malondialdehyde (MDA) and 4-hydroxynonenal (4HNE) can react with both DNA and proteins [26]. Proteins in particular are susceptible to attack by numerous forms of free radicals and ROS which can lead to many different forms of oxidative modification [5,27]. Increases in the accumulation of these forms of protein oxidative damage can lead to functional changes of proteins (generally detrimental) that can alter many cellular physiological processes [28,29]. Once oxidized, proteins must be either repaired or, if repair is not possible, degraded or cleared from the cell to minimize the potential negative effects of these damaged proteins. Almost all amino acids are susceptible to oxidative modification by one or more types of ROS. The sulfur-containing amino acids (cysteine and methionine) are unique in that there are specific enzymes to repair their oxidative damage (cysteine disulfides, methionine sulfoxides) [27,30,31]. However, oxidation to other amino acids, or unresolved damage to cysteine and methionine, can result in oxidation moieties that cannot be repaired. In cases where repair is not possible, oxidized proteins are generally labeled for degradation by the proteasome system or removed through autophagy processes. Despite the efficiency of clearance of oxidized protein, certain damaged proteins can remain and accumulate and promote cellular dysfunction [5,27].