Free Radical Biology & Medicine 50 (2011) 567–575

Contents lists available at ScienceDirect

Free Radical Biology & Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Reviews

Oxidative stress, insulin signaling, and diabetes

Justin L. Rains, Sushil K. Jain *

Department of Pediatrics and Department of Biochemistry & Molecular Biology, Louisiana State University Health Sciences Center, Shreveport, LA 71130, USA

ARTICLE INFO

Article history:
Received 24 August 2010
Revised 29 November 2010
Accepted 4 December 2010
Available online 13 December 2010

Keywords:
Oxidative stress
Ketosis
Obesity
Diabetes
Free radicals

ABSTRACT

Oxidative stress has been implicated as a contributor to both the onset and the progression of diabetes and its associated complications. Some of the consequences of an oxidative environment are the development of insulin resistance, β-cell dysfunction, impaired glucose tolerance, and mitochondrial dysfunction, which can lead ultimately to the diabetic disease state. Experimental and clinical data suggest an inverse association between insulin sensitivity and ROS levels. Oxidative stress can arise from a number of different sources, whether disease state or lifestyle, including episodes of ketosis, sleep restriction, and excessive nutrient intake. Oxidative stress activates a series of stress pathways involving a family of serine/threonine kinases, which in turn have a negative effect on insulin signaling. More experimental evidence is needed to pinpoint the mechanisms contributing to insulin resistance in both type 1 diabetics and nondiabetic individuals. Oxidative stress can be reduced by controlling hyperglycemia and calorie intake. Overall, this review outlines various mechanisms that lead to the development of oxidative stress. Intervention and therapy that alter or disrupt these mechanisms may serve to reduce the risk of insulin resistance and the development of diabetes.
Published by Elsevier Inc.

Contents

Abbreviations: AGE, advanced glycated end product; CAP, c-Cbl-associated protein; DAG, diacylglycerol; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ETC, electron transport chain; GH, growth hormone; GLUT4, glucose transporter type 4; GRB-2, growth factor receptor-bound protein 2; GSH, glutathione; GSK-3, glycogen synthesis kinase 3; IKK, IκB kinase; IL-6, interleukin 6; IR, insulin receptor; IRS, insulin receptor substrate; JNK, jun N-terminal kinase; LDM, low-density microsome; MAPK, mitogen-activated protein kinase; mtDNA, mitochondrial DNA; NF-κB, nuclear factor κB; PDK-1, phosphoinositide-dependent kinase 1; PGC-1α, peroxisome proliferator-activated receptor α; PH, pleckstrin homology domain; PI3K, phosphatidylinositol 3′-kinase; PKB/C, protein kinase B/C; PTEN, phosphatase and tension homolog; RAGE, receptor for advanced glycated end product; RNI, reactive nitrogen intermediates; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; SH-2, Src homology 2; SHP-2, Src homology 2-containing tyrosine phosphatase; SIRT1, sirtuin 1; SoHo, sorbin-homology domain; T2D, type 2 diabetes; TCA, tricarboxylic acid; TNF-α, tumor necrosis factor-α; UCP2, uncoupling protein 2; VEGF, vascular endothelial growth factor.

* Corresponding author. Fax: +1 318 675 6059.
E-mail address: sjain@lsuhsc.edu (S.K. Jain).

0891-5849/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.freeradbiomed.2010.12.006

Introduction

Diabetes is a complex metabolic disorder characterized by defects in the body's ability to control glucose and insulin homeostasis. Diabetes has become an epidemic and remains a major public health issue. In 2007, it was estimated that 23.6 million American people (7.8% of the U.S. population) had diabetes [1] and that diabetes would affect 210 million people worldwide by 2010 [2]. These numbers are expected to increase by 50% over the next 20 years, posing a tremendous economic burden on individuals and health care systems worldwide [2]. The total annual economic cost of diabetes in the United States in 2007 was estimated to be $174 billion [1]. With the rising cost and escalating incidence of diabetes, it is increasingly important to understand the mechanisms that lead to the disease. Diabetes is divided into two main types, type 1 and type 2. Type 1 diabetes occurs when the body stops making or makes only a tiny amount of insulin, whereas type 2 diabetes occurs when the body does not make enough or has trouble using the insulin. Type 1 diabetes has been linked mostly to genetics and the production of autoantibodies that destroy pancreatic β-cells [3]. Type 2 diabetes results primarily from insulin resistance and has been linked to factors such as obesity and age. Type 2 diabetes accounts for more than 90% of individuals diagnosed with diabetes [4].

Oxidative stress is thought to be a major risk factor in the onset and progression of diabetes. Many of the common risk factors, such as obesity, increased age, and unhealthy eating habits, all contribute to an oxidative environment that may alter insulin sensitivity either by increasing insulin resistance or impairing glucose tolerance. The mechanisms by which this occurs are often multifactorial and quite complex, involving many cell signaling pathways. A common result of both types of diabetes is hyperglycemia, which in turn contributes to the progression and maintenance of an overall oxidative environment. Macro- and microvascular complications are the leading cause of morbidity and mortality in diabetic patients, but the complications are tissue specific and result from similar mechanisms [5], with many being linked to oxidative stress. There is a large body of clinical evidence correlating diabetic complications with hyperglycemic levels and length of exposure to hyperglycemia [6]. This review discusses the current understanding of insulin signaling and the role of oxidative stress in the insulin signaling process. It also focuses on the many risk factors that alter insulin sensitivity through mechanisms linked to oxidative stress and potentially lead to insulin resistance and diabetes.

Insulin and normal insulin signaling

Insulin is a key hormone with an important role in the growth and development of tissues and the control of glucose homeostasis [7]. Insulin is secreted by pancreatic β-cells as an inactive single-chain precursor, preproinsulin, with a signal sequence that directs its passage into secretory vesicles. Proteolytic removal of this signal sequence results in the formation of proinsulin. In response to an increase in blood glucose or amino acid concentration, proinsulin is secreted and converted into active insulin by special proteases. The active insulin molecule is a small protein that consists of A and B chains held together by two disulfide bonds [8]. The primary role of insulin is to control glucose homeostasis by stimulating glucose transport into muscle and adipose cells, while reducing hepatic glucose production via gluconeogenesis and glycogenolysis. Insulin regulates lipid metabolism by increasing lipid synthesis in liver and fat cells while inhibiting lipolysis. Insulin is also necessary for the uptake of amino acids and protein synthesis [9]. The pleiotropic actions of insulin are all crucial for maintenance of normal cell homeostasis and allow cellular proliferation and differentiation.

Normal insulin signaling occurs through activation of a specific insulin receptor, which belongs to a subfamily of receptor tyrosine kinases [10]. The insulin molecule binds to the α subunit of the receptor, releasing the inhibition of tyrosine autophosphorylation by the β subunit [11,12]. The receptor is autophosphorylated at distinct tyrosine residues. In contrast to most tyrosine kinase receptors, the activated insulin receptor directly phosphorylates insulin receptor substrates (IRS-1 to -4) on multiple tyrosine residues. There are currently four members of the IRS family known to be involved in insulin signaling, with IRS-1/2 being the most important for glucose transport [12,13]. The subcellular distribution of these proteins between the cytoplasm and low-density membrane compartments of the cell has been shown to play a vital role in transmitting the proper insulin response [13,14]. Tyrosine-phosphorylated IRS proteins then act as a binding site for signaling molecules containing SH-2 (Src-homology-2) domains such as phosphatidylinositol 3′-kinase (PI3K), GRB-2/mSOS, and SHP-2. These molecules bind the phosphorylated tyrosine residues of IRS proteins, forming a signaling complex to mediate downstream signaling. PI3K is the main signal mediator of the metabolic and mitogenic actions of insulin. It is composed of a p85 regulatory subunit, which binds to IRS proteins, and a p110 catalytic subunit. After the association of p85 with IRS-1/2, the p110 subunit has increased catalytic activity. This allows phosphorylation of its substrate, PtdIns(4,5)P_2, on the 3′ position of the inositol ring to generate PtdIns(3,4,5)P_3 [11]. The second messenger, PtdIns(3,4,5)P_3, recruits the serine kinases PDK-1, PKB/Akt, and PKC to the plasma membrane via their PH domains. The activation of these kinases results in several of insulin's responses, such as GLUT4 translocation to the membrane, glycogen synthesis by phosphorylation of GSK-3, and lipogenesis by up-regulating synthesis of the fatty acid synthase gene.

In addition to insulin signaling via PI3K, insulin can activate the mitogen-activated protein kinase (MAPK) ERK, which leads to the gene expression of various cellular proliferation or differentiation components. After phosphorylation of IRS-1/2, the adaptor proteins GRB-2 and SOS are recruited and work together with a stimulated tyrosine phosphatase, SHP-2, to activate membrane-bound Ras. Activated Ras leads to a kinase cascade, allowing ERK to translocate to the nucleus for gene expression [12].

Insulin's main action of glucose uptake also requires activation of another signaling pathway involving tyrosine phosphorylation of the Cbl proto-oncogene. Cbl is associated with the adaptor protein CAP, which contains three SH3 domains and a sorbin homology (SoHo) domain. The SoHo domain of the phosphorylated Cbl–CAP complex allows translocation to lipid rafts and association with the protein flotillin. A signaling complex is formed at the site of the lipid raft, resulting in the activation of a small G protein, TC10. TC10 is thought to act as a second signal in recruitment of the GLUT4 protein to the membrane [7,12].

Reactive oxygen species and redox state

Reactive oxygen species (ROS) and the cellular redox state are increasingly thought to be responsible for affecting different biological signaling pathways. ROS are formed from the reduction of molecular oxygen or by oxidation of water to yield products such as superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$). In a biological system, the mitochondria and NAD(PH) oxidase are the major sources of ROS production [15]. In moderate amounts, ROS are involved in a number of physiological processes that produce desired cellular responses. However, large quantities of ROS in a biological system can lead to cellular damage of lipids, membranes, proteins, and DNA. Nitric oxide ($NO^{\bullet}$) is another contributor to ROS concentration and the formation of reactive nitrogen intermediates (RNIs). $NO^{\bullet}$ is generated by specific nitric oxide synthases that also contribute to a large number of physiological processes. $NO^{\bullet}$ can react with superoxide to form a potent oxidizing agent, peroxynitrite ($ONOO^-$), which contributes to cellular damage and oxidative stress [15]. Oxidative stress results from overproduction of ROS and/or decreased