Oxidative stress and diabetes

N Agrawal, S Singh, N Singh, S Kalra, G Srivastava

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Abstract

Type 2 diabetes mellitus is a multifaceted metabolic disorder with varied pathophysiologic and clinical manifestations. This review discusses the pathways by which oxidative and glyco oxidative stress is increased in hyperglycemia or diabetes.

INTRODUCTION

There is ample evidence of an important role of oxidative and glyco oxidative (carbonyl) stress in the pathogenesis of diabetic complications. Some of these pathways are listed in Table 1. (1) The relative importance of these pathways may differ from person to person and from cell type to cell type.

Figure 1

Table 1- Pathways Implicated in Increased ROS or Dicarbonyl Generation in Diabetes

- Increased mitochondrial electron transport activity induced by hyperglycemia and fatty acids.
- Altered activity of endothelial nitric oxide synthase (eNOS).
- Activation of nonphagocytic cell NADH/NADPH oxidase.
- Increased glucose autooxidation.
- Activation of RAGE receptors by AGE.
- Increased cyclooxygenase and/or lipoxygenase activity.
- Increased xanthine oxidase activity.
- Increased cytochrome P-450 activity.

INCREASE IN ELECTRON TRANSPORT IN MITOCHONDRIA

Hyperglycemia in cells in which glucose uptake is not regulated by insulin stimulates a chain of biochemical events. Glucose is metabolized by glycolysis and the tricarboxylic acid (TCA) cycle. This leads to generation of CO_2 reduction of NAD^+ and FADH, and formation of NADH and $FADH_2$. NADH and $FADH_2$ are deoxidized by donating electrons to the electron transport chain in the mitochondria. The activation of this chain generates a proton gradient which leads to production of adenosine triphosphate (ATP), and reduces O_2 to superoxide. (2)

The formation of superoxide in the mitochondria suppresses glyceraldehyde-3-phosphate dehydrogenase (GADPH) and generates diacylglyceride as well as fructose-3-phosphate.

Diacylglycerol activates protein kinase C (PKC) while fructose-3-phosphate increases the activity of hexosamine pathway. Through both these pathways, an increase in various transcription factors such as specificity factor 1 and transforming growth factor (TGF-β_1) which stimulates expansion of mesangial cells.

The increase in mitochondrial superoxide production also increase the formation of advanced glycation endproducts (AGE) and activates the polyol pathway.

In the polyol pathway, NADPH is used as a cofactor to convert glucose to sorbitol, and it may impair cellular antioxidant defence mechanisms. In uncontrolled hyperglycemia, there is an increase in the cytosolic ratio of NADH/NAD^+ , which impairs the activity of GADPH, and increases formation of prooxidative glucose metabolites.

Mitochondrial metabolism is increased not only by hyperglycemia, but also by high fatty acid levels. The increase in electron transport in mitochondria is a major source of oxidative stress in diabetes.

ALTERATION IN ENDOTHELIAL NO SYNTHASE

The availability of NO in diabetes is reduced, and this leads to vasoconstriction, an altered vascular redox state, abnormal growth of vascular smooth muscle cells, and prothrombotic changes in the vessel wall. (3)

eNOS is a major source of superoxide in diabetes, where it preferentially transfers electrons to molecular oxygen, thus 'uncoupling' itself and producing superoxide instead of NO.

eNOS mRNA and protein have been noted to be increased in the aortic wall of animals with diabetes. Increase eNOS activity has also been noted in kidneys of animal models of diabetes.

Uncoupled eNOS is thus a source of oxidative stress in diabetes.

NONPHAGOCYTIC CELL NADH/NADPH OXIDASE

Nonphagocytic cells such as endothelial cells and renal cells contain NADH/NADPH exidases which are functionally different from the oxidase seen in plasma membrane of neutrophils. (4)

Non phagocytic cells can use both NADH and NADPH, while the neutrophil enzyme system prefers NADPH. Non phagocytic cells continuously generate low levels of superoxide intracellularly, while neutrophils produce high levels in bursts, which is released extracellularly. NADPH oxidase subunit is preassembled in the cytosol of nonphagotic cells and associated with intracellular cytoskeleton. In neutrophils, the cytosolic NADPH oxidase translocates to plasma membrane and associated with various catalytic components such as gp 91 phox and p22 phox.

Animal studies show that NADH/NADPH oxidase is the major contributor of superoxide in the kidney, with the mitochondria contributing much less. NADPH oxidase is activated or upregulated by TNF-□ and thrombin in the endothelial cells, and various factors such as Ang II, AGE, hyperglycemia, fatty acids and platelet-derived growth factor in vascular smooth muscle cells.

The superoxide thus formed has been implicated in the pathogenesis of diabetic nephropathy, by suppressing bioavailability of NO, increasing glomerular TGF-□ and matrix protein accumulation, as well as decreasing renal matrix metalloproteinases.

GLUCOSE AUTO OXIDATION

Glycooxidation or auto-oxidative glycosylation is the term given to sequential glycation and oxidation reaction which occur in diabetes and leads to production of advanced glycation endproducts such as pentosidine, pyrraline and NG-(carboxymethyl) lysine (CML).

Metal-catalyzed oxidative processes that generate reactive oxygen species can auto-oxidize glucose and other sugars. The resultant accumulation and increased formation of AGE is a marker of local oxidative stress in diabetic tissue. (5)

ADVANCED GLYCATION ENDPRODUCTS (AGE)

A variety of processes occur in cells once reactive AGE are formed by glucose auto-oxidation or other reactions.

Alteration in both protein structure and function, including inter-molecular cross-linking of collagen take place. Extracellular AGE-modified proteins interact with several cell surface receptor for AGE (RAGE). RAGE is activated to stimulate NADPH oxidase, activate PKC, mitogen-activated protein kinase, TGF-□, nuclear factor (NF)-KB, activator protein 1, and p21, and thereby increase ROS generation. (6)

AGE generation, thus, contributes to oxidative stress in diabetes.

ENDOGENOUS ANTIOXIDANT DEPLETION

Diabetes is associated with lower levels of endogenous antioxidants such as vitamins A,C,E, lycopine and lipoic acid. Total serum antioxidant capacity is reduced, and antioxidant effect of serum albumin and high densely lipoprotein is impaired in people with diabetes. It is uncertain, however, whether depleted levels of these endogenous antioxidants and free radical scavengers are a cause or an effect of oxidative stress. (7)

ALTERATION IN ACTIVITY OF ANTIOXIDANT ENZYMES

Conflicting results are available about the activity of various anti oxidant enzymes. Cystosolic Cu^{2+} /Zn^{2+} SOD (SOD 1) and mitochondrial Mn^{2+} SOD (SOD2) are lower in human diabetic neutrophils. Renal SOD 1 and glutathione peroxidase is found to be increased in diabetic rat kidneys. SOD 2 shows no change.

Glutathione oxidase activity to higher in the renal cortex of diabetic mice than non-diabetic controls.

The exact contribution of antioxidant enzymes to oxidative stress in diabetes is not fully understood. (1) Genetic enhancement of SOD1 actively has been shown to be a renoprotective therapy in diabetes.

CONCLUSION

Oxidative stress is an important pathophysiologic factor in diabetes mellitus. This article has reviewed the various pathways by which oxidative stress occurs in diabetes.

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Author Information

Navneet Agrawal
Dept of Medicine, GR Medical College, Gwalior, India

Sanjeev Kumar Singh
Dept of Biochemistry, GR Medical College, Gwalior, India

Neelima Singh
Dept of Biochemistry, GR Medical College, Gwalior, India

Sanjay Kalra
B.R.I.D.E., Karnal, India

Gautam Srivastava
B.R.I.D.E., Karnal, India