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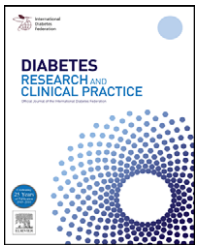

Review

Molecular pathology of oxidative stress in diabetic angiopathy: Role of mitochondrial and cellular pathways

Zhirajr Mokini, M. Loredana Marcovecchio, Francesco Chiarelli*

Department of Paediatrics, University of Chieti, Via Dei Vestini 5, 66100 Chieti, Italy

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ABSTRACT

Diabetes mellitus is characterized by chronic hyperglycaemia and a significant risk of developing micro- and macrovascular complications. Growing evidence suggests that increased oxidative stress, induced by several hyperglycaemia-activated pathways, is a key factor in the pathogenesis of endothelial dysfunction and vascular disease.

Reactive oxidant molecules, which are produced at a high rate in the diabetic milieu, can cause oxidative damage of many cellular components and activate several pathways linked with inflammation and apoptosis. Among the mechanisms involved in oxidative stress generation, mitochondria and uncoupling proteins are of particular interest and there is growing evidence suggesting their pivotal role in the pathogenesis of diabetic complications. Other important cellular sources of oxidants include nicotinamide adenine dinucleotide phosphate oxidases and uncoupling endothelial nitric oxide synthase. In addition, diabetes is associated with reduced antioxidant defences, which generally contrast the deleterious effect of oxidant species. This concept underlines a potential beneficial role of antioxidant therapy for the prevention and treatment of diabetic vascular disease. However, large scale trials with classical antioxidants have failed to show a significant effect on major cardiovascular events, thus underlying the need of further investigations in order to develop therapies to prevent and/or delay the development of micro- and macrovascular complications.

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* *Corresponding author*. Tel.: +39 0871 358015; fax: +39 0871 574831.
E-mail address: m.marcovecchio@unich.it (M.L. Marcovecchio).
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1. Introduction

Diabetes mellitus refers to a number of disorders characterized by chronic hyperglycaemia and alterations of cellular homeostasis, which lead to diffuse vascular damage and multiorgan dysfunction [1].

Individuals with diabetes worldwide are presently about 170 million, corresponding to 5–8% of the total population in western countries and are expected to be 366 million by the year 2030 [2]. The fact that diabetes is a long-lasting disease and that its incidence is increasing both in industrialized and developing countries, underlines its contribution to the general morbidity and mortality, the overall cost for public health and the importance of early implementation of preventive and therapeutic strategies [3].

The evidence of a chronic toxicity due to hyperglycaemia, which is related to activation of polyol pathway, increased production of advanced glycation end products (AGEs), activation of protein kinase C (PKC) and hexosamine biosynthetic pathways, has led to the hypothesis of a common final mediator of these molecular pathways, represented by increased oxidative stress [4]. This condition can, in turn, induce a diffuse endothelial dysfunction and contribute to the progressive development of micro- and macrovascular complications and multiorgan damage [5] (Fig. 1).

Table 1 – Oxidant molecules and antioxidant enzymes.

Oxidative stress molecules
Reactive oxygen species
Free radicals
Hydroxyl (OH)
Superoxide (O_2^-)
Peroxyl (RO_2)
Hydroperoxyl (HRO_2^-)
Non-radicals
Hydrogen peroxide (H_2O_2)
Hypochlorous acid (HOCl)
Reactive nitrogen species
Free radicals
Nitric oxide (NO)
Nitrogen dioxide (NO_2)
Non-radicals
Peroxynitrite (ONOO)
Alkyl peroxynitrates (RONOO)
Reactive chlorine species
Antioxidant defence system
Superoxide dismutase (SOD)
CuZnSOD – cytosol
MnSOD – mitochondria
Glutathione peroxidase (GSH)
Catalase (CAT)
Superoxide reductase (SOR)
Peroxiredoxin (PRX)
Glutathione reductase (GR)
Thioredoxin reductase (TRX/TRXR)

The generation of reactive oxygen species (ROS) is increased in subjects with diabetes, particularly in those with poor glycemic control, whereas antioxidant defenses are generally reduced [5]. Several pathways, distinguished in enzymatic, non-enzymatic and mitochondrial, are involved in the generation of oxidative stress in diabetes, and they appear to be interrelated to the four main pathways activated by hyperglycaemia [4]. Nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, cyclooxygenase, cytochrome P_{450}-dependent oxygenases, uncoupled endothelial nitric oxide synthase (eNOS), mitochondrial electron transport chain (ETC), AGEs, PKC and activation of polyol and hexosamine pathways can all contribute to an overproduction of ROS [4]. In particular, it appears that mitochondrial ROS production plays a key role in the pathogenesis of diabetic complications [4]. The increased mitochondrial ROS production can stimulate several processes, including PKC activity, synthesis of growth factors and cytokines, stimulation of nuclear factor-kappa B (NF-kB) and NADPH oxidase. Consequently, inhibition of mithochondrial oxidant generation might provide a potential approach for the prevention of diabetic vascular complications.

2. What do we know about oxidative stress and defense systems?

Oxidative stress derives from an excessive production and/or insufficient removal of highly reactive molecules, such as ROS, reactive chlorine species (RCS) and reactive nitrogen species (RNS) [6]. In diabetes, increased oxidants and reduced antioxidant systems are present, independently of age, and have multiple negative effects [7]. ROS are generated mainly in the mitochondria, where in normal conditions at least 0.2% of oxygen is converted to radicals, but evidence suggests that other pathways may contribute for up to 25% of the total cellular ROS production [8] (Table 1).

The most important oxidant species are superoxide (O_2^-), nitric oxide (NO), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) [8]. O_2^- results from the reduction of oxygen by oxidases. When O_2^- is produced together with NO, $ONOO^-$ is rapidly formed. Dismutation of O_2^- produces H_2O_2, which may be reduced to water by catalase or glutathione peroxidase. NO is normally produced by eNOS in the vasculature or iNOS, when expressed in special circumstances [8].

Several cellular and mitochondrial enzymes are involved in the detoxification of reactive molecules [20]. Superoxide dismutase (SOD – present in the cytosol as CuZnSOD and in the mitochondria as MnSOD) together with glutathione peroxidase (GPX), in the cytosol, and catalase (CAT), in the peroxysomes, constitute the enzymatic antioxidant defence system [9]. Other antioxidant enzymes are superoxide reductase, peroxiredoxin, glutathione reductase and thioredoxin/thioredoxin reductase [10] (Table 1). Diabetes can reduce levels and activity of these enzymes, thus suppressing defense responses and contributing to increased oxidative stress [7].