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Review article

Mitochondrial mechanisms of endothelial dysfunction

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ABSTRACT

Endothelial cells play an important physiological role in vascular homeostasis. They are also the first barrier that separates blood from deeper layers of blood vessels and extravascular tissues. Thus, they are exposed to various physiological blood components as well as challenged by pathological stimuli, which may exert harmful effects on the vascular system by stimulation of excessive generation of reactive oxygen species (ROS). The major sources of ROS are NADPH oxidase and mitochondrial respiratory chain complexes. Modulation of mitochondrial energy metabolism in endothelial cells is thought to be a promising target for therapy in various cardiovascular diseases. Uncoupling protein 2 (UCP2) is a regulator of mitochondrial ROS generation and can antagonise oxidative stress-induced endothelial dysfunction. Several studies have revealed the important role of UCP2 in hyperglycaemia-induced modifications of mitochondrial function in endothelial cells. Additionally, potassium fluxes through the inner mitochondrial membrane, which are involved in ROS synthesis, affect the mitochondrial volume and change both the mitochondrial membrane potential and the transport of calcium into the mitochondria. In this review, we concentrate on the mitochondrial role in the cytoprotection phenomena of endothelial cells.

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Introduction

In most mammalian cells, mitochondria are primarily considered the major supplier of ATP. However, discoveries during the last three decades have revealed that mitochondria participate in many other cellular processes including apoptosis, calcium signalling and reactive oxygen species (ROS) synthesis [1,2]. Furthermore, in some cells in which anaerobic glycolysis covers the majority of the cytosolic energy demand, these "additional" mitochondrial functions are shifted towards signalling phenomena. Endothelial cells belong to this category, although they are not a homogenous population. Endothelial tissue originating from different organs may differ considerably in terms of its metabolic profile. For example, blood–brain barrier endothelial cells seem to be more metabolically active than those in other blood vessel beds, and their mitochondria represent approximately 10% of the cytoplasmic volume, while in other capillaries, the mitochondria occupy half of that volume [3]. Similarly, the intracellular distribution of mitochondria among various endothelial cells differs and reflects their important signalling role in the regulation of cell-specific processes such as ROS-dependent gene expression or modulation of local Ca^{2+} concentrations and signalling [4]. These mitochondrial functions are indispensable for proper endothelial function. On the other hand, different stimuli that affect endothelial cells may induce a pathological response leading to inflammation, cell death and eventually serious vascular diseases. Although the molecular mechanisms of these processes may be diverse, mitochondrial participation seems to be undoubtable. First, it relies on the excessive formation of ROS, impaired calcium homeostasis and ATP deficiency. Moreover, mitochondrial dynamics and intracellular organisation of the mitochondrial network are of crucial importance for proper endothelial cell function. Thus, impairment of mitochondrial dynamics and pathological changes in metabolic properties leading to unnecessarily high ROS formation must result in diverse abnormalities of the vasculature (for review see [5]).

Mitochondrial ROS are thought to be excessively formed when the rate of reduced NADH oxidation is insufficient, and the [NADH]/[NAD^+] ratio increases. This may happen when the activity of respiratory complex I or III is reduced (experimentally by treatment of cells with rotenone or antimycin, respectively) or due to transient cessation of oxygen supply. Subsequent re-oxygenation may be followed by uni-electron reduction of molecular oxygen and superoxide formation. Interestingly, more recently it has been found that an hypoxic insult may result in the reversed reaction catalysed by succinate dehydrogenase leading to ubichinol-mediated fumarate reduction and succinate accumulation. Moreover, an excessive fumarate delivery may also be due to accelerated aspartate metabolism or purine nucleotide degradation. After re-oxygenation ADP level rises slowly thus electrons delivered by succinate cannot flow through the respiratory chain, but they are reversed to reduce NAD^+ to NADH. The latter is an electron donor directly reducing molecular oxygen leading to ROS generation. This indicates a mechanism of potential metabolic/enzymatic regulation of the mitochondrial ROS formation [6].

An excessively enhanced mitochondrial membrane potential ($\Delta\Psi$) due to insufficient use of it for oxidative phosphorylation flow to oxygen is an important factor increasing ROS generation. It may happen when ADP supply is not effective enough or NADH delivery exceeds capacity of ADP phosphorylation. In such cases, slight mitochondrial uncoupling may substantially reduce ROS formation [7]. Under experimental conditions, this may be performed by the use of protonophores, while in the intact cells, specific proteins of the inner mitochondrial membrane participate in controlled small dissipations of $\Delta\Psi$m. It is assumed that uncoupling proteins (UCPs) and the potassium channels present in mitochondria belong to this category. This review is focused on mitochondrial aspects of endothelial physiology and pathophysiology.

Mitochondria and ROS in endothelial pathology

For many years, ROS have captured the attention of biologists and physicians due to their important function in the regulation of multiple cellular and extracellular processes such as activation of stress-induced mitochondrial biogenesis, inflammation and immunological responses [8]. However, under various pathological conditions or upon action of stimuli that predispose cells to abnormal ROS formation, the physiological response may become uncontrollable and reach an intensity that can lead to cellular damage and serious, eventually life-threatening consequences. Thus, ROS are highly desirable, as long as they are produced within the physiological range of intensity, but harmful if generated excessively. Mammalian cells may produce ROS in many ways; however, mitochondrial respiratory chain complexes and NADPH-oxidase (NOX) catalysed reactions are considered the most common way of ROS production. Interestingly, NOX4, which is one of the isoforms of NOX present in endothelial cells, may at least partially co-localise with mitochondria, thus it may also be considered a mitochondrial source of ROS [9,10]. Increased activity of mitochondrial NOX4 that inhibits complex I leads to a reduction of mitochondrial oxidative capacity and acceleration of respiratory chain-mediated ROS generation [11]. Moreover, ROS may also be produced by the participation of growth factor adaptor protein p66Shc, which catalyses cytochrome *c* oxidation, particularly under pro-apoptotic conditions or when complex IV activity is insufficient to oxidise excessively accumulated reduced cytochrome *c*. This hypothetically might happen during reduced oxygen delivery (hypoxia) or due to inhibition of cytochrome *c* oxidase by Nitric oxide (NO). In addition, an activation of p66Shc in hyperglycaemia also favours increased ROS formation [12,13]. Superoxide formation by the mitochondrial respiratory chain is a physiological process, which occurs under normal conditions and relies on premature electron flow to oxygen catalysed by respiratory complexes I and III. On the basis of data obtained from isolated organelles, it is estimated that ROS generation consumes 0.1–2% of the total oxygen utilised by mitochondria. However, the precise *in vivo* data for endothelial cells are not available [14]. ROS formation by mitochondrial complexes is closely related to oxidative mitochondrial metabolism. The mitochondrial inner membrane potential ($\Delta\Psi$m), which is modulated by numerous metabolic factors, seems to exert a direct influence on the intensity of ROS production. NO, cytosolic Ca^{2+}, fatty acids, respiratory substrates, the oxygen supply and activity of some mitochondrial proteins (such as UCPs) and the permeability of the transition pore (PTP) complex affect the $\Delta\Psi$m, mitochondrial redox state (NADH/NAD^+ ratio) and finally ROS production [14]. Under physiological conditions, an orchestrated action of these elements results in normal ROS formation, which has a desired signalling function in cells (Fig. 1) [15]. It has been found that vasodilatation, hypoxia signalling, autophagy and induction of inflammatory responses are induced by ROS derived from mitochondria. Several *in vivo* studies have shown that pharmacological reduction of the ROS level affects normal flow-mediated vasodilatation. Both endothelial metabolism and exposition of endothelial cells to various physiological and pathological stimuli depend on the type of vascular bed, i.e., localisation of cells in different parts of the vascular system. Thus, the role of ROS in endothelial cell signalling is difficult to generalise, as it strongly depends on the origin of the cells. However, multiple risk factors such as ageing, hyperglycaemia, infection and hypoxia affect mitochondrial metabolism and alter the $\Delta\Psi$m value, triggering

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