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Relationship Between Oxidative Stress and Cellular Adenosine Triphosphate Levels

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ABSTRACT

Oxidative stress (OS) refers to the deterioration of the balance between oxidants and antioxidants in favor of oxidants, and this may lead to disruptions in redox signaling and control and/or damage at the molecular level. The presence of low levels of reactive oxygen species (ROS) plays a physiological role in intracellular signaling pathways. However, damage may occur in cells and tissues as a result of excessive increase in ROS production. Because ROS have the potential to damage almost all structures in the cell, including lipid, protein, deoxyribo nucleicacid (DNA). The main source of free radicals in the cell is mitochondria. ROS formation is a natural consequence of oxidative phosphorylation resulting in adenosine triphosphate (ATP) production in mitochondria. The attack of these radicals results in damage to the mitochondria, a decrease in the activity of oxidative phosphorylation enzymes and consequently a decrease in ATP synthesis. On the other hand, ATP is needed for antioxidant synthesis, which is necessary for cell defence against increasing ROS. Therefore, a decrease in ATP levels makes tissues vulnerable to OS. In this case, it is likely that tissues exposed to OS will also have problems in ATP production and the decrease in ATP synthesis will further increase oxidative damage.

Keywords: Reactive oxygen species, Adenosine triphosphate, Mitochondria, Antioxidant defense systems

Introduction

Under physiological conditions, tissues and organs have a tightly regulated and highly dynamic redox balance to maintain the balance between oxidants and antioxidants. However, the capacity of the endogenous antioxidant system is exceeded when the formation of reactive oxygen species (ROS) increases for a variety of reasons (Sthijns et al., 2018). This is known as oxidative stress (OS), which leads to impaired redox signalling and control and/or molecular damage (Sthijns et al., 2018). The concept of OS was first officially articulated by Sies in 1985. It continues to be the centre of attention since that day (Sies, 2018).

The presence of low levels of ROS plays a physiological role in intracellular signaling pathways (Kowalczyk et al., 2021). However, in the presence of OS, ROS targets almost all structures in the cell including lipids, proteins, and deoxyribo nucleicacid (DNA). Lipids are the most sensitive structures against ROS oxidation. The reaction of polyunsaturated fatty acids, especially arachidonic acid and docosahexaenoic acids with ROS causes oxidative degradation (Pisoschi and Pop, 2015). As a result of this degradation, by-products such as malondialdehyde (MDA), which is often used to determine the presence of OS as a lipid peroxidation by-product covalently bound to cellular proteins are produced (De Cristóbal et al., 2002; Schütt et al., 2012). ROS, which also targets proteins, causes oxidation of both the backbone and side chains of proteins. Nucleic acids are also targeted by ROS attacks, which can result in DNA-protein cross-linking, strand breaks, and DNA mutations (Pisoschi and Pop, 2015). These attacks result in the formation of modified bases such as 8-hydroxydeoxyguanosine (8OHdG), which is also used as an OS parameter (Schütt et al., 2012).

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The oxidative attack of ROS has been the main subject of numerous studies from the past to the present, and as a result, OS has been observed to play a role in the pathogenesis of many diseases (Ghezzi et al., 2017). For example, oxidative DNA damage has been shown to lead to oncogene activation and thus to tumour formation and/or carcinogenesis (Pramanya & Alı, 2019). In the literature, OS has also been implicated in the etiology of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Gandhi and Abhramov reported an increase in lipid peroxidation products, protein carbonylation, and hydroxylated guanine in both diseases and drew attention to the role of mitochondrial dysfunction in the development of neurodegenerative diseases (Gandhi and Abramov, 2012). It has been suggested that ROS leads to atherosclerotic lesions and lipid accumulation through oxidative changes in low-density lipoproteins (Pramanya & Alı, 2019). It has also been reported that inflammation is triggered by ROS-induced nuclear factor-kappa B activation and is responsible for developing inflammatory diseases such as rheumatoid arthritis (Pramanya & Alı, 2019).

ROS, which are involved in both physiological and pathological processes, are produced as by-products of aerobic respiration and various catabolic and anabolic processes (Liang et al., 2007; Pisoschi and Pop, 2015; Kowalczyk et al., 2021).. The main source of free radicals in the cell is mitochondria. The formation of ROS is mainly a natural consequence of oxidative phosphorylation resulting in the production of adenosine triphosphate (ATP). In this process, approximately 1-2% of the molecular oxygen normally used by cells is converted into ROS. Mitochondria, the source of both ATP synthesis and ROS production, have a double membrane, outer (separating them from the cytosol) and inner. Oxidative phosphorylation occurs in the inner mitochondrial membrane, which contains four large enzyme complexes. The energy released in the reactions in the electron transport chain in this membrane is used for ATP synthesis (Kowalczyk et al., 2021). ATP is a nucleoside triphosphate composed of a nitrogenous base (adenine), a ribose sugar and three phosphate groups (Dunn and Grider, 2020). In the ATP production process, electrons from the electron transport chain escape directly to oxygen, leading to the production of free radicals such as superoxide anion, hydroperoxides, hydroxyl radicals and others (Cui et al., 2012; Martín et al., 2002; Schütt et al., 2012).

These radicals formed during the ATP production process can disrupt the activity of oxidative phosphorylation enzymes, leading to impaired ATP synthesis. (Martín et al., 2002). Disruption in ATP synthesis also adversely affects GSH production. This is because GSH synthesis occurs through a two-step enzymatic process requiring ATP (Lu, 2013). Decreased ATP levels in the oxidative process reduce the effectiveness of antioxidant defense systems that are essential for cellular protection. Unpreventable oxidative attack can further reduce ATP levels and cause a vicious cycle (Lu, 2013).

Mitochondria are considered to be a major target of oxidative attack as well as a source of ROS (López et al., 2009). A large body of literature indicates that mitochondrial functions can be altered by OS (Liang et al., 2007). In a study, it was reported that OS inhibits respiratory chain enzyme complexes and reduces ATP production (Liang et al., 2007). On the other hand, the mitochondrial inner membrane, where ATP production takes place, is rich in polyunsaturated fatty acids, making it susceptible to oxidation (Liang et al., 2007). For example, cardiolipin, an important lipid component of the inner mitochondrial membrane, plays a critical role in the function of mitochondrial proteins such as cytochrome oxidase and its oxidation disrupts mitochondrial activities (Van Remmen and Richardson, 2001).

In the literature, the decrease in ATP levels in OS has been attributed to the increase in its consumption as well as the decrease in its production. Because, repair mechanisms that increase as a result of oxidative damage also require ATP (Wang et al., 2003).

Overall, ATP is essential for the functioning of the cell because it provides the energy for many cellular reactions. For example, ATP provides energy for mechanisms that maintain the correct concentrations of charged particles (i.e. ions such as sodium, potassium, or calcium) in the cell (Nanji & Hiller-Sturmhöfel, 1997). As a result of cellular ATP deficiency, the release of calcium ions from intracellular stores can result in apoptosis. The process of apoptosis is a form of controlled cell death that requires a small amount of ATP (Prauchner, 2017). When ATP levels are further reduced or depleted, apoptosis is replaced by necrosis, which is uncontrolled cell death (Prauchner, 2017). In the literature, it has been reported that both apoptosis and necrosis caused by ATP deficiency are mainly caused by OS and increase in mitochondrial permeability (Prauchner, 2017).

Several studies have been conducted in the past to demonstrate the relationship between OS and cellular ATP levels (Schütt et al., 2012; Agalakova & Gusev, 2012; De Cristóbal et al., 2002). In an *in vitro* study in retinal pigment epithelial cells, Schütt et al. examined the relationship

between decreased ATP synthesis and oxidative damage to intracellular GSH levels, cellular proteins and DNA and concluded that moderately decreased intracellular ATP levels may contribute to oxidative stress damage and dysfunction (Schütt et al., 2012).

Agalakova et al., evaluated ROS accumulation and changes in glutathione and ATP contents in rat erythrocytes in oxidative stress induced by inorganic fluoride. They revealed that ATP concentration showed a dose- and time-dependent decrease in the oxidative process. They pointed out that GSH synthesis and GSH/oxidized glutathione membrane transport are ATP-dependent processes and therefore ATP depletion may be a cause of impaired GSH regeneration in rat erythrocytes (Agalakova & Gusev, 2012).

In another study, it was shown that acute immobilisation stress was accompanied by an increase in lipid peroxidation and a decrease in reduced GSH in the rat brain and a decrease in brain ATP levels (De Cristóbal et al., 2002).

Some researchers have also examined how OS responds to exogenous ATP treatment (Aldemir et al., 2020; Dagel et al., 2024). Aldemir et al. reported that ATP administration blocked the oxidative toxicity of sunitinib in sunitinib-induced cardiotoxicity (Aldemir et al., 2020). In another recent study, it was reported that ATP treatment prevented the increase in oxidant levels and decrease in antioxidants due to 5-fluorouracil treatment and protected renal tissue from oxidative damage (Dagel et al., 2024).

Although the literature is rich in studies on ATP, the use of ATP therapy in OS is very limited and mostly includes preclinical studies (Schütt et al. 2012; De Cristóbal et al., 2002). The results of preclinical studies are encouraging for the trial of ATP application for clinical studies (Aldemir et al., 2020; Dagel et al., 2024).

Conclusion

OS refers to the deterioration of the balance between oxidants and antioxidants in favor of oxidants, and this may lead to disruptions in redox signaling and control and/or damage at the molecular level. The main source of ROS, which is the source of oxidative stress, is mitochondria and at the same time mitochondria is one of the main organelles targeted against oxidative attack. Therefore, damage to mitochondria leads to disruption of oxidative phosphorylation and ATP synthesis. On the other hand, the necessity of ATP synthesis for antioxidant defence makes tissues vulnerable in case of deficiency. In this case, it is likely that tissues exposed to OS also have problems in ATP production and the decrease in ATP synthesis further increases oxidative damage. In order to protect against OS, which has been found to play a role in the pathogenesis of many diseases, new treatment strategies to maintain ATP levels and exogenous ATP therapy may be an important field of research.

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