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REVIEW ARTICLE

Muscle characterization of reactive oxygen species in oral diseases

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Abstract

Importance and objective. Reactive Oxygen Species (ROS) are oxygen-derived molecules that are unstable and highly reactive. They are important signaling mediators of biological processes. In contrast, excessive ROS generation, defective oxidant scavenging or both have been implicated in the pathogenesis of several conditions. This biological paradox of ROS function contributes to the integrity of cells and tissues. So, the aim of this review was examined for published literature related to 'reactive oxygen species and dentistry and muscle'. ***Materials and methods.*** A PubMed search was performed by using the following key words: 'reactive oxygen species and dentistry and muscle'. ***Results.*** Involvement of ROS in pathologic conditions can be highlighted in oral diseases like periodontitis, orofacial pain, temporomandibular disorders and oral cancer. Also, several studies have correlated the increase in ROS production with the initiation of the muscle fatigue process and the process of muscle injury. However, studies evaluating the relation of ROS and orofacial muscles, which can prove very important to understand the fatigue muscle in this region during oral movements, have not yet been conducted. ***Conclusions.*** It is concluded that the data on skeletal muscles, especially those of mastication, are not commonly published in this data source; therefore, further studies in this field are strongly recommended.

Key Words: *muscular diseases, oral pathology, oxidative stress*

Introduction

Oxygen-derived molecules that are unstable and highly reactive, including superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^-), are generically known as reactive oxygen species (ROS) and are the most common free radicals identified in biological systems [1]. ROS production is an integral part of metabolism, which is observed under various physiological conditions. These species serve various biological functions, including phagocytosis, where molecular species are produced to eliminate the offending agent. However, if their production is exacerbated, the body has an efficient antioxidant system that can control and restore the balance [2].

ROS are important signaling mediators of various biological processes. Signal transduction mediated by ROS, known as 'Redox signaling', usually involves reversible and oxidation/reduction-based modifications of components in signaling pathways [3]. ROS are produced in response to various stimuli, including growth factors, cytokines, chemotactic factors, hypoxia and shear stress. Moreover, many vital biological pathways or signaling cascades are regulated by ROS, such as GPCR, Notch [4] and Wnt-β-catenin [5], MAPK, JAK-STAT, NF-κB and PI3K/AKT. Transcription factors such as HIF1-α, AP-1 and NF-κB can themselves be directly modified in a redox-sensitive manner, thereby leading to an altered transcriptional profile of gene products. Furthermore, redox signaling is spatially regulated and confined in specific subcellular regions. The compartmentalization of redox signaling ensures its specificity in gene regulation and cellular functions and that ROS can participate in more dynamic cell behaviors that need co-ordination between different parts of the cell, such as cell migration.

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To cope with the physiological ROS production, mitochondria have evolved a multi-leveled defense network consisting of detoxifying enzymes and non-enzymatic antioxidants. Within the mitochondrial matrix, manganese-dependent superoxide dismutase (MnSOD or SOD_2) converts O_2^- to hydrogen peroxide (H_2O_2), which is further detoxified into O_2 and H_2O by glutathione peroxidase 1 (Gpx-1) and peroxiredoxine III. Alternatively, O_2^- can be released in the intermembrane space (IMS) where it is converted to H_2O_2 by copper–zinc-dependent SOD (SOD1). In addition, O_2^- leaked into IMS can be scavenged by cytochrome c [6]. If mitochondrial antioxidant defenses are fully functioning and electron leakage occurs within the physiological range, oxidative damage is almost completely prevented [7].

In contrast, excessive ROS generation, defective oxidant scavenging or both have been implicated in the aging process and in the pathogenesis of several conditions [8,9]. Thus, ROS are often associated with damage to cellular functions and the type of damage depends on the nature of ROS; furthermore, damages induced by oxidative stress have cumulative effects resulting in various diseases. ROS contributes to a number of human pathologies, so whether exercise-induced oxidative stress contributes to the development of these pathologies is unclear.

This biological paradox of ROS function, being toxic but also functioning as signaling molecules, contributes to the integrity of cells and tissues [10]. Specifically, ROS chemically react with atoms of target proteins leading to covalent protein modifications. Thus, ROS are recognized at the atomic and not at the macromolecular level [11].

The involvement of ROS in pathologic conditions can be highlighted in oral diseases. Several dysfunctions related to the orofacial region present ROS as the causal or perpetuating factor. These include periodontitis, orofacial pain, temporomandibular disorders and oral cancer [12].

Methodology

A search was performed in PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) by using the following key words (separately or combined): 'reactive oxygen species', 'dentistry' and 'muscle'. Selected papers, including reviews, were chosen on the basis of their content (quality and novelty). The main focus was on reactive oxygen species in oral diseases, mainly those related with muscular dysfunctions. Papers that had no relation to the three keywords proposals were excluded from the study. In particular, in order to better understand the knowledge and elucidation of the proposed theme, all review papers of the last 5 years were selected for this study.

Results and discussion

Given the results found after a search made through the PUBMED data bank, in order to be raised all literature reviews linked to the words 'reactive oxygen species and dentistry and muscle' in the last 5 years, it was possible to know the current works related to the proposed topic. Eight literature reviews were found with these filters in the last 5 years. The studies were distributed between the years 2012 (n = 4), 2011 (n = 2) and 2010 (n = 2), suggesting an increase of interest in publications in this area.

Reactive oxygen species (ROSs)

A free radical is an atom with unpaired valence electrons and, thus, is highly reactive and may react with other free radicals via dimerization, to form a molecule with all paired electrons. Free radicals involving oxygen are named reactive oxygen species (ROS), such as superoxide anion, hydroxyl radical and singlet oxygen, and non-radicals such as hydrogen peroxide (H_2O_2), ozone (O_3) and hypochlorous acid (HOCl) [13]. ROS are a class of molecules derived from the metabolism of oxygen (O_2) and are characterized by a high chemical reactivity. ROS are constantly generated within cells by several enzymatic reactions, including those catalyzed by cyclooxygenases, NAD(P)H oxidase and xanthine oxidase; however, the bulk of ROS production (~90%) occurs as a by-product of mitochondrial oxidative phosphorylation (OXPHOS) [7]. Until the 1980s, ROS were seen primarily as toxic agents capable of producing irreversible oxidative modifications altering the biochemical balance of the cell. However, in recent years, ROS are gaining a new role in biological systems since several studies have shown that ROS can act as chemical mediators in intercellular communication.

ROS are more often associated with oxidative damage than the modulation of biological phenomena. The reversible oxidative modifications and oxidative damage differ only in the intensity of the phenomena triggered by ROS; thus, oxidative damage occurs when there are oxidative modifications with a great intensity and over extended periods of time. This situation overcomes the antioxidant capacity, leading to functional and structural changes in the cell that are uncontrolled and sometimes lethal. This condition, characterized by poisoning by free radicals, is commonly known as oxidative stress [14].

Traditionally viewed as toxic byproducts of metabolism, ROS cause damage to lipids, membranes, proteins and DNA through a free-radical mediated chain reaction [3]. Over decades, numerous studies showed that increased oxidative stress plays a central role in the pathogenesis of vascular disease [15,16], including hypertension, atherosclerosis and restenosis [17]. However, recent evidence clearly demonstrates

that moderate ROS concentrations act as intracellular signaling molecules, thereby mediating diverse developmental and physiological processes [7].

Therefore, ROS are not only produced as a cellular response to exogenous stress signals, but also are products of the normal aerobic metabolism in mammalian cells [10]. Superoxide anions and H_2O_2, which is primarily a product of the dismutation of O_2^-, are incipiently generated ROS in cells. In the course of their decomposition, other radicals are immediately or prevalently formed, either enzymatically in reactions that utilize electron transfer during the mitochondrial electron-transport chain, by NADPH oxidases, xanthine oxidase or cytochrome P450s [18–21].

ROS and oral diseases

ROS are considered causal and perpetuating factors of certain pathological conditions [22]. Diseases associated with the orofacial region are not exceptions to this potential interference of ROS, since various orofacial tissue alterations result from the extracellular matrix destruction of the supporting tissue [23]. Thus, temporomandibular dysfunction caused by an inflammatory process is directly related with oxidative stress. Researchers have shown abnormal production of ROS by chondrocytes derived from cartilage formed on the temporomandibular joint (TMJ) of rats in response to inflammatory mediators [24–26]. In addition, Ueno et al. [27] tested the potential of N-acetyl cysteine (NAC), an antioxidant amino-acid derivative, in alleviating oxidative stress-related damage in TMJ chondrocytes [27], obtaining good results. ROS has also been identified in the synovial fluid of the IL-1α-induced TMJ arthritis [22].

ROS play an important role in most local or systemic factors that may delay wound healing. These factors can be bacteremia or sepsis, trauma, poor oxygenation, hypoxia, chronic systemic disorders and various drugs [28]. Thus, the inhibition of ROS production may be considered to be an essential stage of the normal wound healing process. In this context, a profile of scavenging activity of ROS during periodontal mucoperiosteal healing, including different phases of wound repair, has been observed [29].

Some experimental and clinical studies have focused on the impact of ROS on the relationship between periodontal diseases and diabetes mellitus, which are chronic pathologies with a major impact on the health and well-being of millions of individuals [30–33]. Gene expression of antioxidant enzymes (Prx I and II GPx I, catalase and SOD I and SOD II) in the gingival tissue of poorly and well-controlled type 2 diabetic subjects with chronic periodontitis was examined [34]. In this context, other analyses on ROS, such as the biochemical data relating to ROS degradation of extracellular matrix components *in vitro*, together with analytical studies investigating connective tissue degradation products arising from inflammatory periodontal destruction, may be important to define a significant role for ROS in the pathological events occurring during periodontal diseases [23].

Another pathological condition of orofacial origin, presenting ROS as one of the causal factors, is the multi-step process of development of oral cancer [19]. A complex series of cellular and molecular changes participating in cancer development are mediated by a diversity of endogenous and exogenous stimuli and important among them is the generation of ROS. ROS can produce oxidative damage to the tissues and are known as oxidants in biological systems. Many researchers have documented the role of ROS in both initiation and promotion of multi-step carcinogenesis [35,36]. Elevated levels of ROS and reactive nitrogen species (RNS) and lowered antioxidants are found in oral pre-cancer and cancer; however, various antioxidants can render protection against the deleterious action of these free radicals, so treatment with antioxidants has the potential to prevent, inhibit and reverse the multiple steps involved in oral carcinogenesis [37]. In this context, it is known that there is an antioxidant defense against accentuated oxidative stress determined in oral squamous cell carcinoma [38].

In terms of orofacial pain, recent studies indicate that significant analgesic effects in both neuropathic pain [39–41] and inflammatory pain [42,43] are produced by the removal of excess ROS by free radical scavengers. It was observed that the systemic or intrathecal injection scavengers of ROS caused a reduction in mechanical allodynia and hyperalgesia in models of acute inflammation and neuropathic pain, respectively. Dealing specifically with orofacial pain of intra- or extra-oral origin, recent studies also reveal the involvement of ROS, present in the trigeminal ganglion (TG), in the development of orofacial hyperalgesia [44]. To date, the exact cellular localization of ROS production in the TG remains unknown. Thus, Sato et al. [44] showed that trigeminal neurons are equipped with the most potent antioxidant systems compared with satellite glial cells, implying that therapeutic measures for antioxidative stress should be taken to prevent damage to the trigeminal primary sensory neurons in inflammatory pain disorders. In this sense, the localization of ROS-scavenging enzymes in TG is strategically important in protecting TG neurons from ROS-mediated cellular injury under the oral pathological conditions.

Several studies have correlated the increase in ROS production with the initiation of the muscle fatigue process [45,46] and the process of muscle injury [47]. However, studies evaluating the relation of ROS and orofacial muscles, which can prove very important to

understand the fatigue muscle in this region during oral movements, have not yet been conducted.

ROS and muscle activity

Oxidative stress can be a part of some morphological alterations in the masticatory muscles because these areas experience various traumas and inflammatory processes. The synthesis of antioxidants has been demonstrated to prevent muscle degeneration [48]; thus, ROS production may be altered during orofacial muscle disorders. Despite the lack of recent studies on this relationship, it is important to understand how ROS are involved in pathologies that include any muscle changes.

In this context, Abdellatif [49] identified the silencer information regulator (SIR), a family of proteins responsible for homeostasis in mammals. Sir1-4 proteins were discovered in yeast with nicotinamide dinucleotide [NAD (+)] – and adenine acetylases, dependent on the effect of silencing the gene that promotes longevity. An interesting aspect of SIR functionality involves its ability to regulate the circadian rhythm, with effects on the cycle regulating the NAD+ system, which are linked to metabolism [49]. In this review, the relation between SIR and NAD metabolism, mechanism of function and its role in metabolism and mitochondrial functions were discussed as well as the effects on the central nervous and cardiovascular systems. In particular, the effects of Sirt1 extend beyond the metabolism in several organs and cell types. For example, it protects the heart against ischemia by reperfusion, preventing apoptosis mediated by the p53 gene, although a beneficial metabolic effect was not disposed. During cardiac hypertrophy and failure, SIRT1 regulates transcription of contractile proteins as well as transcriptional regulators of the metabolism. Because SIR activity is closely linked to the metabolic state of the body and is related to the availability of NAD, the function of this family of NAD-dependent deacetylase is the focus of metabolism studies.

Thus, the increased production of NADH and flow in the respiratory chain occurs via the primary mechanism by which calcium enhances the capacity of energy, going through the calcium-dependent stimulation of mitochondrial oxidative metabolism. The calcium signaling co-ordinates the response of the target cell with the activation of the production of metabolic energy. This occurs in many tissues, including skeletal and cardiac muscle, where contractile activity and the ATP production are regulated by hepatocytes and endocrine and exocrine cells. These cells use calcium in the secretory process and generate catabolic and anabolic processes [50].

However, with respect to heart problems, Sugden et al. [51] published a review that addresses the metabolic abnormalities in white adipose tissue. This review discusses the etiology of cardiac lipotoxicity and oxidative stress. The concentrations of lipids in plasma can be increased in the presence of high doses of glucose, which facilitates the progressive deterioration in insulin sensitivity or cell malfunction and death of cardiomyocytes [51]. Suleiman et al. [52] stated that these changes pre-dispose the heart to reperfusion injury because of high amounts of reactive oxygen species and intracellular calcium. In addition, the lung damage is associated with an inflammatory response that can lead to systemic oxidative stress, causing further damage to the heart [52].

Chronic diseases such as hypertension, atherosclerosis and diabetes are associated with vascular functional and structural changes, including endothelial dysfunction, altered contractility and vascular remodeling. The underlying cellular events involve changes in the smooth muscle of the vessel, cell migration, inflammation and fibrosis. Many of these stimuli influence cellular changes, particularly angiotensin II. The angiotensin II mediates many vascular effects through species of NAD (P) H oxidase, also derived from ROS. Hypertension is associated with increased ROS production, resulting in oxidative damage because these species act as second messengers, modulating many signaling molecules such as tyrosine phosphatases and transcription factors [53].

Other mediators are described in the literature as potentiating the role of angiotensin II in cell damage, including NADPH (NOx). Maejima et al. [17] discussed the role of NOx in mediating oxidative stress and physiological and pathological functions. NADPH (Nox) are transposed to the membrane protein oxidases, dedicated to the production of ROS, including superoxide and hydrogen peroxide, by transferring electrons from NAD (P) H to molecular oxygen. The Nox2 and Nox4, for example, are expressed in the heart and play an important role in mediating oxidative stress, including under stress. The involvement of Nox2 in the mediation of cardiac hypertrophy induced by angiotensin II and the influence of Nox4 in both hypertrophy and cardiac insufficiency are described as cellular responses to pressure overload. On the other hand, Nox also influence physiological functions such as erythropoiesis and angiogenesis [17].

Satoh et al. [54] show that cyclophilin (CypA), defined as a multi-functional protein, is found in a variety of inflammatory conditions such as rheumatoid arthritis and cancer. CypA, a 20-kDa protein secreted by the vascular smooth muscle cells in response to ROS, acts by stimulating the proliferation and migration of inflammatory cells *in vitro* and *in vivo* and is associated with inflammation and atherosclerosis, promoting apoptosis [54]. Furthermore, CypA has a variety of functions, including intracellular signaling, promoting protein trafficking and regulating the activity of other proteins.

In addition to their intracellular functions, CypA is a secreted molecule with physiological and pathological functions, becoming a potential biomarker and mediator in cardiovascular diseases such as atherosclerosis and vascular stenosis [55].

Although there is still a lack of data on the oxidative status in masticatory muscles, Spassov et al. [56] reported that increased oxidative stress plays an important role in the pathogenesis of Duchenne muscular dystrophy [56]. The study has shown that the oxidative stress is present in masticatory muscles of a mouse with this dystrophy. With respect to specifically masseter muscle, it is known that rats subjected to 3 or 5 weeks of psychological stress present oxidative damage in this tissue [57].

Also, with regard to masseter muscle, evidence about patients with painful symptoms by temporomandibular disorder (TMD) show reduced levels of oxidative stress in samples of masseter compared with patients free of pain. Furthermore, oxidative stress has been associated with intensity of muscle and joint pain, suggesting that oxidative stress contributes to pain in symptomatic patients with TMD [58].

Conclusion

Based on literature reviews, it is possible to state that excessive oxidative stress generated by reactive oxygen species (ROS) may promote diseases and, in particular, oral diseases. With regard to muscle tissue, current studies show significant results in cardiac muscle and vascular endothelium, although the association of these cellular mediators of dental practice is scarce in the literature. Furthermore, we conclude that the data on skeletal muscles, especially those of mastication, are not frequently published in this data source; therefore, we strongly recommend further studies in this field.

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