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Review Article

Oxidative Stress-Induced Sensitization: A Feature of Chronic Pain. Implications for the Management of Orofacial Diseases and Disorders: A Literature Review

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Abstract

Pain is a multidimensional unpleasant experience that was found to compromise multiple facets of life. Oxidative stress is the oxidant-antioxidant imbalance that results in cellular damage. A wide spectrum of diseases and disorders including those of the orofacial region was linked to oxidative stress. Chronic pain from orofacial pathologies is correlated to a state of neuronal hypersensitivity known as central sensitization. Increased reactive intermediates from oxidative stress were found to mediate sensitization mechanisms. In this review, the link between chronic pain experience and oxidative stress is discussed. Moreover, the possible implications of such a relation in the context of orofacial diseases and disorders along with the importance of antioxidants as promising modalities that target the pain pathway are also overviewed.

Keywords

Chronic pain, Oxidative stress, Antioxidants, Orofacial pain.

Declaration of Conflicting Interest

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Author Contributions

Aliaa A B Eita contributed to conceptualization of the review idea, data collection, drafting and critically revising the manuscript.

Introduction

Pain is a displeasing occurrence that has been gaining considerable attention through various research aspects.[1] It is defined according to the International Association for the Study of pain (IASP) as "an unpleasant, sensory, and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[2] Several pathways mediate the transmission of pain impulses from peripheral tissues to the central nervous system (CNS). This results in different characters of sensations (sharpness, throbbing, dullness, stinging and soreness) that subsequently bear negative impacts on emotions.[3] Pain has been classified by more than one classification system according to duration, location, transmission mechanisms and other parameters. However, some types can fit to more than one category for which pain is frequently described as acute, chronic, inflammatory, neuropathic and nociceptive.[4]

Recognizing the difference between acute and chronic pain is crucial for appropriate diagnosis and treatment planning. While acute pain is that lasts for less than three months, chronic pain lasts for longer time durations.[5] Most orofacial diseases and disorders especially those affecting the oral

mucosa are characterized by chronicity with periods when signs and symptoms exacerbate and remit.[6] This fluctuating nature could provoke confusion between chronic pain and another term related to long lasting pain as well namely episodic. Episodic pain in the course of a disease is repetitive where a single attack lasts for less than 15 days per month. On the other hand, chronic pain persists for more than three months and on a minimum of 15 days per months.[5]

The persistence of orofacial manifestations over long durations renders pain the major patients' concern regardless of the pathology itself. Moreover, in frequent incidences, cases present with either severe manifestations or resistance to intended therapeutic modalities which add on their burden and complicate the treatment outcomes.[7] Therefore, understanding the essentials of pain physiology, its origin in the orofacial region and the pathways of the possible functional and structural changes in response to its chronic nature is important for pain management and the further development of high efficacy medications that target the patients' main concerns.[8]

Pain: From Protective to Pathological Perspectives

Despite the annoying experience yielded from a particular pain sensation at a time, it is found to be a crucial physiologic phenomenon for survival and tissue protection from damage by intense and noxious stimuli. Also, the resultant persistent pain from the failure to get rid of those stimuli especially in prolonged periods of inflammation and cancers is described as an adaptive warning response from additional damage. However, it is discovered to be pathological.[9] Unfortunately, the chronic pain experience related to various human diseases is characterized by a state of hypersensitivity which in most cases doesn't reflect the actual quality and magnitude of an intended input or stimulus.[10]

Pain hypersensitivity, also known as sensitization is the abnormal functional and structural changes in the components of pain pathway that lead to reduced neuronal threshold, increased membrane excitability and enhanced nociceptive input.[9, 10] This results in either spontaneous pain or exaggerated and prolonged painful sensations from stimuli that basically elicit pain (hyperalgesia) and others that are normally non-painful (allodynia). Sensitization could be peripheral or central according to the location of hypersensitivity. Changes to the peripheral nerves of the injury site are called peripheral sensitization, while hypersensitivity of the CNS is called central sensitization (CS).[10, 11]

The Link Between Reactive Intermediates and Sensitization

Normal cellular signaling processes require the involvement of reactive intermediates. Those are chemically active radical and non radical molecules of mainly oxygen and nitrogen that help maintain body function and homeostasis.[12] They are also called reactive oxygen and nitrogen species (ROS/ RNS respectively). Pollutants, radiation, drug toxicity, smoking, and inflammation raise the concentrations of ROS and RNS far beyond their physiologic limits.[13] At that time, the body loses its ability to neutralize such intermediates. This compromises the cellular components in the form of DNA, lipid and protein damage and the cells are consequently described to be put under a state of oxidative stress. Oxidative stress is known to play significant roles in the pathogenesis of different diseases as Cardiovascular, neurodegenerative and psychiatric diseases as well as cancers and orofacial pain diseases and disorders.[14, 15]

Central sensitization was found to be involved in the course of intracranial pain, neuropathic pain and inflammatory pain.[16-18] As oxidative stress is widely linked to an array of diseases and conditions, efforts have been made by several studies to search the link between reactive intermediates and CS in different pain models. Interestingly, induced inflammatory and neuropathic pain in animals revealed elevated levels of ROS and RNS during CS of the spinal cord which strengthens the role of oxidative stress in the mediation of chronic pain and sensitization.[19] Studies of higher molecular levels have shown that reactive intermediates can stimulate mainly CS. Mechanisms involve downregulation of gamma-aminobutyric acid (GABA) release,[20] activation of glial cells,[21] upregultion of calcium channels transient receptor potential (TRP) superfamily,[22] cytokine biosynthesis and release and others.[23, 24]

Oxidative Stress in the Orofacial Region

The oral cavity is easily subjected to pro-oxidant noxious substances in some foods, smoking, dental materials and certain treatments. This makes oral tissues vulnerable to free radical damage and suggests that oxidative stress in the oral cavity can predispose to various oral and systemic diseases.[25]

There is mounting evidence that oxidative stress contributes to several oral mucosal diseases as oral lichen planus, oral pemphigus vulgaris, recurrent apthous stomatitis and oral cancer, as well as other orofacial pain conditions and disorders as burning mouth syndrome (BMS) and temporomandibular joint disorder (TMJD).[6, 14, 26] Elevated levels of both reactive species and products of the oxidative damage along with lowered levels of markers of the antioxidant defense were noted in different orofacial diseases and disorders.[14, 27, 28]

Orofacial Pain at a Glance

Most recently in 2020, the Orofacial Pain Classification Committee has set a comprehensive and detailed classification for orofacial pain and proposed guidelines for its diagnosis. The major distinct types included pain attributed to disorders of dentoalveolar and anatomically related structures, myofascial orofacial pain, temporomandibular joint pain, orofacial pain attributed to lesions or disease of the cranial nerves, orofacial pain resembling presentations of primary headaches and idiopathic orofacial pain.[5]

There is a variety in the character of felt pain in the orofacial region. Patients most frequently report the dentoalveo*lar and* related structures as the site of their chief complaint. Oral mucosal pain from lesions like erosions or ulcers manifests mainly as burning and soreness. This resultant unpleasant sensation is due to nociceptors activation from either inflammatory tissue damage or thermal and mechanical stimuli. Pain from other origins as damaged neurogenic structures (BMS, post herpetic neuralgia and trigeminal neuropathies) and temporomandibular joint and myofacial diseases and disorders are usually felt as burning, numbness, stinging, a dull ache and headache.[5, 8]

In Orofacial pathologies, research has marked the significance of CS. Different sensitizing mediators were identified; they include noradrenaline, serotonin, prostaglandins, nerve growth factor and nitric oxide. Furthermore, in BMS, structural and functional changes to the CNS were noted.[8] Also, de Siqueira et al. (2013)[29] noted the presence of sensorial alterations as high cold and tactile thresholds in patients with chronic somatic and neuropathic orofacial pain due to sensitization.

Rodríguez de Sotillo *et al.* (2011)[14] revealed a significant association between pain from TMJD and elevated oxidative stress biomarkers 8-hydroxydeoxyguanosine, malondialdehyde and total antioxidant status which indirectly proposes the negative impact of reactive species on the orofacial pain pathway. From all those findings, along with the correlation between oxidative stress and oral diseases and the contribution of ROS and RNS to sensitization, it is highly suggested that reactive intermediates induced oxidative stress is one possible mechanism for CS in orofacial diseases and disorders.

The Relevance of Pain Assessment and Management

As chronic pain is the main subjective concern in oral medicine and orofacial pain clinics, clinicians face major challenges in the assessment of pain and its consequences. By time, persistent pain renders patients fail to accurately explain the site and duration of their existing orofacial pain. However, they present with other significant symptoms like fatigue, low self esteem, depression, decreased productivity, mood and withdrawal disorders.[30, 31]This is because pain doesn't only bear perceptive or discriminative aspects towards a particular harmful event, it is also motivational in nature providing an early perception of danger. This dimension involves the rise of some irrelevant symptoms to a disease nature that could act as a motivational alarm to get rid of certain actions or habits in an attempt to avoid a threat.[32] It was found that CS also predisposes to such symptoms. Furthermore, the amplified pain perception during CS causes tissue hypersensitivity beyond the actual injury site which hinders pain localization (secondary hyperalgesia).[11]

It was found that pain from oral mucosal lesions and other orofacial tissues negatively alter the quality of life and psychological status of patients.[33, 34] On the contrary, those psychosocial parameters were also suggested to contribute to the onset of such diseases.[35] This cause-effect relation raised the attention towards pain assessment in clinical trials as a turning point in comprehensively understanding the essentials of disease management. A methodological study by Yan et al. (2020)[36] suggested setting a core outcome set for oral lichen planus where both the physical and psychosocial pain dimensions are to be assessed. They concluded that paying more attention to patient reported outcome measures avoids the incomplete impression about the pros and cons of a therapeutic modality obtained from objective points of view alone. Moreover, other authors highlighted the mandate of psychological intervention in the context of orofacial pain management for obtaining long term positive results.[37]

Psychological factors play important reliable yet complex roles in the experience of chronic pain due to the domination of its anticipated motivational aspect.[32] However, knowing that CS is a significant feature that complicates chronic pain experience, it is better understood that modulation of its pathways is a promising forward step to pain management from the physical and subsequently the psychosocial aspects.[11] By understanding that oxidative damage is a risk factor for CS, antioxidants are considered reliable safe candidates for pain pathway regulation.[38]

Antioxidants as Pain Killers: Evidence-Based Implications

Antioxidants are promising molecules that play roles in neutralizing the damaging effect of oxidative stress on cells. Various classification systems have identified the types of antioxidants. They can be natural or synthetic, endogenous or dietary, and enzymatic or non enzymatic. The most famous feature of all antioxidants is the ability of scavenging free radicals and reactive molecules.[39]

Antioxidants have been gaining considerable attention by research in health and disease

owing to their broad beneficial properties. They can protect against atherosclerosis, osteoporosis, cardiovascular and neurodegenerative disease as well as some cancers like oral cancer. Also, they were found to reduce stress hormones levels and prevent cell aging by promoting normal tissue growth and renewal. Besides, they have proven anti-inflammatory, antiviral and immunomodulatory efficacies.[39] Studies of different designs noted their clinical therapeutic relevance from their impact on signs and symptoms resolution.[40] Moreover, they were found to reduce a wide range of biomarkers as inflammatory, immune and oxidative stress markers.[41]

The positive outcomes of pain management after using antioxidants have been often attributed to their potency in reversing the signs of a disease (pain relief in oral lichen planus in parallel with resolution of erosions and ulcers).[40]Nonetheless, it has also been proved that free radical scavengers perform their analgesic effect through regulation of the pain pathway. Kim et al. (2004)[42] reported that systemic administration of the ROS scavenger phenyl-N-tert-butylnitrone (PBN) relieved induced mechanical allodynia in rats. Besides, they noted that the repeated injection of reagent caused no tolerance or loss of potency. Another study revealed the inhibitory effect of vitamin E on neuropathic pain behaviors that are caused by CS in experimental models.[38]

In the orofacial region, Chen ***et al.*** (2009)[43] investigated the analgesic effect of vitamin C in patients with post herpetic neuralgia. They reported a significant reduction in spontaneous pain with restoration of vitamin C plasma levels in patients as compared to placebo ($p< 0.001$). Additionally, at baseline, plasma vitamin C concentrations were significantly lower in patients than healthy controls ($p< 0.001$) which suggested that ascorbate levels could contribute to pain modulation in post herpetic neuralgia. Furthermore, some authors noted reduced sensory dysfunction from sensitization after administration of free radical scavengers in induced orofacial pain in mice.[44, 45]

Alpha lipoic acid (ALA) is an endogenous antioxidant and a promising mitochondrial coenzyme. It was found to have optimistic therapeutic effects in BMS. Femiano et al. (2000)[46] noted a significant reduction in BMS symptoms following administration of ALA for one month ($p< 0.0001$). Later in 2015, Palacios-Sánchez ***et al.***[47] revealed significant improvement of burning sensation, dysguesia and xerostomia in 64% of BMS patients treated with ALA as compared to placebo for two months ($p= 0.009$). Moreover, they reported 68.75% stability for one month post treatment cessation.

Apart from their direct radical-scavenging ability, antioxidants were interestingly found to participate in pain modulation through other different mechanisms. ALA was found to support neuronal regeneration by stimulating nerve growth factors.[47] Besides, the carotenoid antioxidant lycopene has proven efficacy in cyclooxygenase-2 inhibition which consequently downregulates prostaglandins. Such actions could act as both therapeutic and prophylactic mechanisms against sensitization of nociceptors.[48] This could be in parallel with Saawarn et al. (2011)[40] who reported a significant reduction in pain scores after lycopene administration for two months in oral lichen planus patients as well as stability after a post-treatment cessation period of eight weeks. In addition, research proved that the stem bark aqueous extract of Mangifera indica (mango) can downregulate the expression of related-genes to the synthesis of pain mediators.[49]

Conclusions

Patients with orofacial diseases and disorders present with chronic pain that affects their quality of life and psychological status. As chronic pain experience is characterized by central sensitization which further complicates diagnosis, pain assessment and management, it is important to pay more attention to both pain and its consequences as an outcome measure in upcoming research. This aids in comprehensive assessment of the subjective manifestations of orofacial pathologies as well as the efficacy of intended treatments. Moreover, oxidative stress was found to be involved in central sensitization mechanisms. Therefore, antioxidants are considered safe and reliable therapeutic options that modulate the pain pathway beside their wide-ranging benefits in human health and disease. The broad investigation of those agents by further studies especially in relation to biomarkers of pain would yield promising outcomes in the context of management of orofacial pain patients.

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