Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

Potential Role of Oxidative Stress on the Pathophysiology of Neuropathic Pain in the Inflammatory Diseases

Ahmad Ghasemi[1], Bahman Jalali Kondori[2], Maedeh Ghasemi[3], Zahra Bahari[1*]

1. *Dept. of Physiology and Medical Physics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran*
2. *Dept. of Anatomical Sciences, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran*
3. *Dept. of Physiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*

Article Info

10.30699/jambs.31.149.514

Received: 2023/07/17;
Accepted: 2023/09/27;
Published Online: 29 Jan 2024;

Use your device to scan and read the article online

Corresponding Information:
Zahra Bahari,
Dept. of Physiology and Medical Physics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

E-Mail: bahari_441@yahoo.com & bahari.zahra.441@gmail.com

ABSTRACT

Neuropathic pain (NP) is the outcome of lesion or disease of the nervous system, and it substantially influences the quality of life. Various inflammatory diseases such as rheumatoid arthritis (RA) and even cancer, may cause NP. Today, treatment of NP is the biggest pharmacological hurdles. Targeting inflammation is a broad task, since many mediators are involved in onset of particular disease. Among these many mediators, the reactive oxygen and nitrogen species generated by macrophages and neutrophils are of great interest because of their major contribution in development of inflammation and NP. This review will concentrate on the pathogenesis of inflammation based on involvement of reactive oxygen and nitrogen species and the activation of signalling cascades in response to oxidative stress. A systematic, and comprehensive search was conducted in the database. Based on the inclusion criteria, more than 300 peer-reviewed publications and 200 articles were chosen. In this review, data on oxidative stress and inflammation is compiled and discussed in the context of chronic neuropathic pain. It is suggested that oxidative stress can activate a variety of pro-inflammatory factors involved in chronic diseases. Animal and clinical evidence suggests that oxidative stress and inflammation linked to overproduction of ROS are highly likely to represent a critical factor for the development of NP in inflammatory diseases.

Keywords: Neuropathic Pain, Oxidative Stress, Inflammation, ROS, Inflammatory Disease

Introduction

NP is a chronic disorder, which carectrised by unpleasant sensory symptoms such as allodynia (pain in response to a non-noxious stimulus) and hyperalgesia (an increased response to a noxious stimulus) (1). According to the International Association for the Study of Pain (IASP), NP is "pain begun or produced by a lesion or malfunction in the somatosensory nerve system, either in the peripheral nervous system (PNS) or in the central nervous system (CNS). About 18% of patients with chronic pain suffer from NP (2). Various of the clinical diseases have been linked to NP including; diabetes mellitus, leprosy, cancer, AIDS-related neuropathy, phantom limb pain, postherpetic neuralgia, cervical disc protrusion, and multiple sclerosis (MS) (3). It is reported that oxidative stress are one of the important and common mechanism in all of the mentioned diseases (Figure 1). The peripheral nerve axoplasm is rich in phospholipids and mitochondria. If their antioxidant system is weakened, they are therefore more sensitive to oxidative stress (such as reducing the enzymes SOD and catalase) (4). Furthermore, unlike the blood-brain barrier in the CNS, the blood vessels of peripheral neurons are permeable to neurotoxins such as reactive oxygen species (ROS). There is some evidence that all of above diseases disrupts the electron transport chain and ROS generation and promotes mitochondrial damage and inflammation (4, 5). Additionally, increased production of ROS can increase activity of different enzymes and ion channels (4). Therefore, metabolic dysfunction and ATP deficiency also caused by acting of ROS on the activity of enzymes in the mitochondria. (5). Generally, increased ROS generation in various diseases can increase nociceptor sensitivity, microtubule depolymerization, and nerve degeneration. All of these events lead to release of inflammatory mediators in response to ROS accumulation. (4). Here, we will report some pathogenesis of inflammation based on involvement of reactive oxygen and nitrogen species and the activation of

signalling cascades in response to oxidative stress (Figure 1).

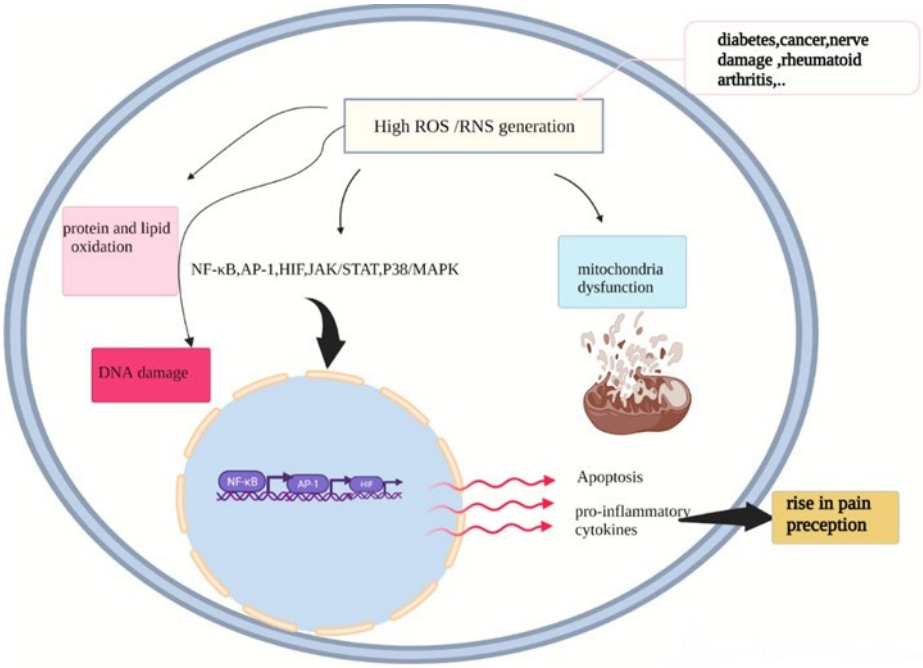

Figure 1. An illustration of oxidative stress-induced NP. Generation of ROS is increased in the various diseases such as diabetes mellitus, leprosy, MS, and RA. Due to high lipid content, neural cells in the PNS and CNS are susceptible to high content of ROS and subsequent lipid peroxidation. High content of ROS can activate several transcriptional factors such as nauclear factor kappa B (NFKB). Over activation of NFKB leads to increased generation of inflammatory markers and also apoptosis. Additionally, high content of ROS can induce DNA damage Oxidative stress and inflammation are mutually exclusive processes. During inflammatory illnesses, mitochondrial dysfunction can increase ROS production, and lipids and proteins oxidation. Therefore, increased levels of ROS and subsequently increased levels of inflammatory agents lead to maintenance of NP (4, 5). The figure was created by BioRender scientific illustration software.

Rheumatoid Arthritis (RA) and oxidative stress

RA is a chronic inflammatory disease, which characterized by joint degeneration and systemic symptoms including pain, stiffness, swelling, and joint defects (6). The most typically problem in the rheumatologic disorders is pain. Its prevalence is 0.5-1% of the population (7). Oxidative stress plays a critical role in the initiating of RA (8). It has been reported excess level of ROS at the damaged joints in the RA can induce inflammation and hyperalgesia as well as chronic pain (9-11). The major free radicals wich generated in RA is nitric oxide (NO) and superoxide anion. The NO generates by NO synthase (NOS). There is ample evidence for NO's role in the development of chronic pain in the RA (12). For example, it can induce vasodilation and increase vascular permeability to pain-producing substances such as bradykinin. In addition, cyclooxygenase (COX) over-activation and the high production of prostaglandins by NO may lead to inflammation and chronic pain (12). Therefore, NOS inhibitors could be a therapeutic target for RA patients with chronic pain.

In addition to NO, disruption of the nuclear factor erythroid 2 (NF-E2) / heme oxygenase-1 (HO-1) pathway, an important oxidative stress signaling pathway, leads to the development of chronic pain in RA. Indeed, it is suggested that this signaling pathway can be considered as a novel target for analgesia in the RA (12-15).

In patients with RA, the activity of NF-E2 / HO-1 pathway is decreased and oxidative / antioxidant balance is disrupted. Activating of the NF-E2 linke to the Nrf2 transcription factor.

In the case of oxidative stress in the RA, the HO-1 enzyme catalysis the heme group to carbon monoxide (CO), Fe^{2+}, and biliverdin, which is then converted to bilirubin by the enzyme bilirubin reductase (13). Disruption of HO-1 activity can increase generation and release of free radocals in primary afferent neurons and so amplified pain perception in the CNS. So, the HO-1 enzyme plays an important role in the antioxidant/oxidant balance and pain perception (14).

It is also reported that activating the Nrf2 / HO-1 signalling pathway can reduce pain perception in the patients with the RA (16). Moreover, Nrf2 activators are considered adjunctive therapy by increasing the influence of analgesic drugs (16-18). Therefore, the Nrf2 / HO-1 pathway is also considered a new strategy for regulating gene transcription in oxidative stress.

Leprosy and oxidative stress

Leprosy is one of the most common treatable peripheral neuropathies (19), mainly occurring in tropical and subtropical countries. It usually involves the skin, nerves, nasal mucosa, and eyes. Leprosy is caused by Mycobacterium leprae (*M. leprae*), an intracellular gram-positive alcohol-acid-fast bacillus. NP can occur as a chronic complication of leprosy via various mechanisms, such as peripheral nerve irritation, inflammatory responses, vasculitis, and oxidative stress. Leprosy has tropism to Schwann cells (SCs) and macrophages (20), and causes nerve damage, demyelination, loss of axonal conduction, inflammation, and eventually disability. Leprosy-induced NP reported in 11-22 % of patients; and 85 % of them developed NP after the antimicrobial treatment period (21, 22).

Although, the underlying mechanism (s) of leprosy-induced NP is far from clear, oxidative stress is an important factor in development of pain in leprosy. Free radicals, such as superoxide anion, hydrogen peroxide, and hydroxyl radicals, are produced during phagocytosis by macrophages (host cells of *M. leprae*), the principal defense mechanisms against bacterial infections (21). Although, nonenzymatic and enzyme-based antioxidants (Vitamins A, E, C, and glutathione) can modulate the high generation of free radicals in the body, the imbalance of oxidant/anti-oxidant capacity in leprosy is in favor of excess ROS production. Oxidative stress and high generation of ROS by the *M. leprae* disregulates glucose metabolism in the SCs dururing leprosy. For example; the glucose-6-phosphate dehydrogenase (G6PDH) activity and intracellular glucose metabolism were elevated when SCs was infected with the *M. leprae* (23); then, mitochondrial membrane potential was affected, ROS production increased, and SCs became apoptotic. Additionally, excess level of ROS in the leprosy reduces mitochondrial activity and lactate production in infected SCs by reducing host cell energy sources (24). The Krebs cycle in SCs is critical for myelination, so decreased lactate and mitochondrial membrane potential in the infected cells may lead to early demyelination in leprosy (25, 26). Therefore, the activity of G6PDH enzyme increases in the leprosy.

Leprosy neuropathy is divided into two stages: first, the involvement of SCs with infection initiates intrinsic injury mechanisms and oxidative stress, and second, change of SCs glucose metabolism cause axonal damage, loss of neurons, and NP (27). It has been also reported that *M. leprae* causes neuropathy by lowering SCs differentiation and myelination genes such as MBP, MPZ / P0, and Krox 20 (28-30).

Additinally, NP and axonal damage observed after impaired lactate transfer from glial cells to neurons (28, 29). In line of this, in the one study, Save et al., showed incresed sciatic nerve conduction velocity in the *M. leprae*-infected sciatic nerve (31). These events are related to various factors including; the decreased lactate production in SCs, decreased axonal Krebs cycle activity, loss of mitochondrial function and swelling, decreased axon energy production, decreased axon metabolism, hypophosphorylation neurofilaments, and loss of neural conduction (32). The relationship between oxidative stress and immunological markers in the pathogenesis of leprosy needs further investigation.

Guillain-Barré syndrome (GBS) and oxidative stress

GBS is an acute polyneuropathy that begins with an autoimmune reaction. The leukocytes infiltrate into the PNS, causing neuroinflammation, demyelination, and axonal degeneration. Its prevalence is 1-2 cases per 100,000 populations per year. It is the most common inflammatory demyelinating polyneuropathy (AIDP) in North America and Europe (32-37). In AIDP, the immune system responds to SCs or myelin, which causes demyelination. GBS was triggered by previous infections with various microorganisms in the gut and upper respiratory tract (37). As many as 60% of cases are caused by autoantibodies, including anti-GM1 (anti-GM1) and anti-GD1a, linked to C. jejuni infection. Campylobacter jejuni is the most prevalent infectious agent that causes GBS, followed by cytomegalovirus (CMV) and Epstein–Barr virus (EBV). Microbiota-host nervous system molecular mimicry accounts for much of GBS's pathogenesis (36, 37).

Moderate to severe NP symptoms are among the signs and symptoms of GBS. As many as 55% to 86% of patients report experiencing discomfort in their lower back/sciatica/neck/muscle, joint, and visceral areas. Acute NP is most likely caused by neuroinflammation, whereas chronic NP is most likely caused by sensory fiber neurodegeneration (36). The primary etiology of the illness remains a mystery, despite several hypotheses (33-35). However, it has been established that oxidative stress and free radical toxicity play a significant role in the developing GBS. (34). Therefore, anti-oxidant therapy may help alleviate some symptoms of GBS such as areflexia or hyperreflexia.

In the bacterial-induced GBS, phagocytic cells are activated to defend against bacteria and viruses that produce ROS. The high production of ROS by phagocytosis causes deficiency of NADPH oxidase, which may be associated with autoimmunity. For halide compounds to operate as a substrate, superoxide anion must first be transformed to hydrogen peroxide via NADPH oxidase (MPO)-catalyzed processes (38).

Aditionally, it is reported that increased CSF levels of uric acid (UA) are a sign of elevated oxidative stress in the GBS. One of the most important activities of the UA is to remove peroxynitrite and other ROS from the plasma, which accounts for around 60 percent of its antioxidant activity (39). The UA as an energy biomarker is associated with nucleic acid catabolism, adenosine, and ATP metabolism (39), as well as, has a

neuroprotective effect on the CNS in models of MS, brain ischemia, and spinal cord injury (40). Studies have shown that its serum level changed in some diseases such as MS, neuromyelitis Optica (NMO), Alzheimer and Parkinson's disease (41). Similarly, in one study, Chang et al., demonstrated that UA levels in CSF are greatly raised in patints with GBS and AIDP (42), and a purine or ATP metabolism is also enhanced in GBS. Toxins like oxygen and nitrogen are produced by macrophage activity, inducing nerve inflammation. Peroxynitrite and other free radicals lead to the spread of damage by disrupting the respiratory chain and ATP metabolism (43). Indeed, increased production of pro-inflammatory cytokines due to myelin degeneration involved in the etiology of GBS. Experimental autoimmune neuritis (EAN) is the most prevalent subtype of GBS and is used as an animal model for AIDP (44). The central and peripheral sensitivity to the initiation and maintenance of NP is increased by activation of spinal glial cells (45). The P2X4 receptor (P2X4R) is an ATP-gate ion channel that upregulated spinal microglia, demonstrating an essential role in NP following peripheral nerve injury. When extracellular ATP is bound to its receptors (P2X4R), it exerts an excitatory impact on synapses (46). According to Zhang et al., findings, P2X4R was implicated in developing EAN mechanical allodynia by increasing P2X4R expression in lumbar spinal microglia, particularly those located in the dorsal horns of the spinal column (47). Another cause of GBS and EAN is a protein called macrophage migration inhibitory factor (MIF) (48). Inflammation, cell proliferation, suppression of apoptosis, and regulation of immune cell migration and activation all contribute to the pathophysiology of many forms of inflammation and autoimmune illnesses (49).

Also, down-regulating P53 activity protects macrophages from NO-induced apoptosis (50, 51, 52). GBS patients have higher plasma and CSF MIF concentrations than healthy individuals. When MIF is neutralized, symptoms of EAN in mice may be improved or eliminated (48). Stressful or infectious conditions, such as lipo-oligosaccharide (LOS) of C. jejuni, release significant quantities of MIF into the bloodstream, which increases GBS infection (53). LOS increase in NF-κBp65 translocation, MIF, and TLR-4 expression in monocytes (54). Through the stimulation of cytokine release (TNF- and IL-1), MCP-1, and iNOS (inducible nitric oxide synthase), MIF produces neuronal excitability (55). As a result, MIF activates T cells in GBS and EAN nerve injury by promoting the production of proinflammatory cytokines and other toxic mediators (NO, matrix metalloproteinases MMPs) (56). Extracellular fluids seem to include serum albumin, which has antioxidant properties and may play a role in protecting cells from free radicals. (57). Albumin levels are reduced in GBS patients compared with healthy individuals (58), but the mechanism of this effect is still unclear.

Fibromyalgia (FM) and oxidative stress

Chronic FM is charectrised by widespread pain, fatigue, sleep difficulties, cognitive impairment, and severe depression. FM is a diagnosis given to patients who suffer from widespread chronic pain that cannot be explained by other sources, such as systemic inflammation or injury (59-67). It is demonstrated that patients with converted migraine and headaches have a high prevalence of FM. The headaches associated with FM may be caused by mitochondrial dysfunction and oxidative stress (67). Various factors including genetics, infections, and physical or mental traumas, are likely asscociated with the pathogenesis of FM (59-62). The data indicated an imbalance between oxidants and antioxidants capacity in FM patients (68, 69). Indeed, the alterations of the oxidant and antioxidant indicators may serve as essential biomarkers for diagnosing and treating FM (70). These markers strongly correlate with the FM clinical symptoms, implying that oxidative stress may partially contribute to FM's development. The total antioxidant capacity (TAC), antioxidant enzyme activities, and antioxidant compounds were evaluated in patients with the FM. Compared to healthy controls, FM patients had lower TAC and zinc levels but higher antioxidants copper and ceruloplasmin levels. Several evidence suggested that zinc and copper may play an important role in FM (71, 72).

It is reported that blood mononuclear cells in patients with FM have decreased mitochondrial DNA and coenzyme Q10 (CoQ10) concentration and increased amounts of ROS (63). Oxidative stress is also associated with muscle pain-related factors such as muscle Z band disorganization, abnormal mitochondrial shapes and numbers, and sarcolemma damage, resulting in muscle stiffness and pain (64). Muscle biopsy samples of FM patients also revealed the presence of inflammation markers, an excess of subsarcolemmal mitochondria, aberrant mitochondria, ragged red fibers, and a deficiency of cytochrome-c-oxidase (CcO) (complex IV of oxidative phosphorylation) (65). Additionally, unmyelinated nerve fibres, and inflammatory foci were detected as a pattern of neurogenic inflammation in the FM patients (66).

It was discovered that SOD and catalase activity was lower in FM patients compared to healthy controls (73). The decreased activity of these antioxidant enzymes in FM patients may affect the body's hydrogen peroxide (H2O2) and superoxide levels. Increased H2O2 production has been associated with pain in patients with FM (73).

Oxidative Stress and the role of coenzyme Q10 in the FM patients

It has been identified that several oxidative-related factors found in skin biopsies taken from FM patients including; mitochondrial malfunction, low CoQ10 levels, mitochondrial Genome contents, and enzymatic activities. In FM patients, the activities of respiratory chain enzymes (complex III, complex I + III, and

complex II + III) directly dependent on CoQ10 and mobility of complexes I, II, and IV were dramatically reduced (64). The laser doppler flowmetry technique demonstrated that patients with FM have aberrant microcirculation of the skin over sensitive areas. The results confirm that localized hypoxia and the ensuing drop in high-energy phosphate concentrations cause oxidative stress and membrane LPO. Improper control of capillary blood flow might lead to abnormal microcirculation (64).

CoQ10 deficiency has been associated with various illnesses, including FM symptoms. CoQ10 serves two critical functions in cells: first, as a cofactor for mitochondrial activity, and second, as a highly effective free radical scavenger, protecting cells from oxidative stress-induced lipid peroxidation and DNA damage. Additionally, decreased ATP levels and increased oxidative stress are linked to CoQ10 deficiency. Lipid peroxide (LPO), produced in response to oxidative stress, is known to reflect intracellular ROS generation indirectly (63-65, 74).

Oxidative Stress and the role of inflammation in the FM patients

Endogenously generated oxidants are responsible for mast cell invasion (75), increased production of proinflammatory mediators, and changes in sensory perception of pain caused by microglia activation. Mast cells are adjacent to nerve fibres, enabling them to migrate and control nociception and neural activity (76). Due to their migration and degranulation, proinflammatory, vasoactive, and neurosensitizing mediators are produced. Mast cells are known to help with allergies and immunology, and they have also been linked to FM inflammation. Mast cells and microglia also communicate (77, 78). In pain competitions, microglia in the thalamus are responsible for maintaining the sensation of pain after the initial stimulus has passed (79). Increased Interleukin 8 (IL-8) levels, a strong predictor of central sensitization and hyperalgesia, may be associated with glial cell activation. Excitatory chemicals in the CNS or proinflammatory cytokines secreted by peripheral immune cells stimulate glial cells. This cycle may be exacerbated by stress, explaining why FM symptoms can develop in reaction to stress. The fact that IL-8 levels have increased without IL-1 levels suggests that FM symptoms are controlled by the sympathetic system rather than by prostaglandin-related processes (80). An increase in pro-inflammatory cytokines (IL-1 and TNFa) and growth factors (NGF and VEGF) was seen in both the nerves and the brain, contributing to the persistence of inflammation and pain (81).

Cancer pain and oxidative stress

Current treatment options for cancer pain, a well-known and significant medical problem, are generally ineffective. To improve pain control in patients with cancer, we need to understand the interplay between tumor microenvironment, cancer therapy, and the body's responses to these biochemical changes. Immune system stimulation results in the recruitment of white blood cells (i.e., macrophages, neutrophils, T cells) and produce inflammatory mediators. They impact the external micro-environment surrounding cancer cells (82). Therefore, we can improve pain management and quality of life of these patients significantly by understanding details about the molecular processes that lead to nociception produced during cancer development and therapy. An oxidative environment surrounds cancer cells, intimately linked to immune system activation (82). In this part, we want to focus on oxidative stress generated in the tumor microenvironment and the impact on cancer symptoms.

One of the metabolic waste products of cancer cells' resistance to oxidative stress is the amino acid glutamate (83). Tumors create an oxidative environment in the extracellular space through glutamate release, promoting neuronal transmission and human pain (84). ROS levels rise dramatically in bone tumor micro-environments, resulting in massive glutamic acid synthesis and release (85). Glutamate stimulates afferent neuron excitability by activating NMDA receptors on the peripheral nerve ends, changing synaptic plasticity in the dorsal horn, and enhancing pain sensitivity via central sensitization (86). Cystine is exchanged for glutamate in a 1:1 ratio by the system xC antiporter, Na+-independent, and secretes glutamate from cancer cells. Antioxidant defense mechanisms are crucial for cancer cells since they are constantly exposed to high oxidative stress (87). Cancer biology's two critical features are the cellular dependency on glycolysis for energy supply even in the presence of oxygen and tumor formation and angiogenesis responses to hypoxic and low glucose tumor environments (88). Cancer cells develop chronic glucose intolerance and rely on an increased glucose uptake rate to generate glycolytic ATP. Glycolysis harms cancer cells in an aerobic environment by producing ROS due to respiration (89). Increased expression of xCT and system xC activity has improved cancer cell survival in response to increased oxidative stress (88, 90). This mechanism, xC glutamate/cystine antiporter, enhances the import of cystine by metabolically active cancer cells developing in bone (Traverso, Ricciarelli, et al., 2013). In the bone environment, autocrine and paracrine effects of extracellular glutamate may influence tumor and host cell activity (91). Autocrine and paracrine effects of extracellular glutamate in the bone environment may influence tumor and host cell activity (92). As a result, peripheral nociceptors in the brain may be activated either directly or indirectly.

It is well established that the redox state of the tumor microenvironment affects the pain threshold by changing the peripheral NO levels. In various pain types, NO appears to be a key neurotransmitter modulating spinal nociceptive processing. The isoform iNOS is distinguished by its higher NO production than

the constitutive members (93). It has a role in establishing and maintaining central and peripheral sensitization in inflammatory and NP and is expressed in response to cytokine exposure. Numerous investigations have demonstrated that iNOS level in the tumor microenvironment is importantly associated with nociception (93). In pathologic situations, nitric oxide produced by the iNOS enzyme activates TRPV1 and TRPA1 channels in rats, increasing nociception and sensitizing the CNS to pain (94).

Cancer-induced bone pain (CIBP) and oxidative stress

It has been established that CIBP is an independent kind of pain in the spinal cord and dorsal root ganglia, distinct from inflammatory and NP based on neurochemical and cellular characteristics. Primarily, people with CIBP seek treatment because the condition has progressed (95). Patients who seek therapy for CIBP are typically already in the advanced stages of cancer, and CIBP is frequently the first evident sign (96). This type of bone pain usually results from distant metastasis rather than primary bone cancer. For instance, metastases to the bones can alter the balance between bone deposition and resorption, leading to lesions with abnormally high levels of proinflammatory or analgesic chemicals released into the bone microenvironment.

CIBP is characterized by extensive astrocyte proliferation and hypertrophy in the dorsal horn of the spinal cord (97), as well as a notable lack of change in the expression of the neuropeptide's substance P and calcitonin gene-related peptide, which are both expected features of both inflammatory and NP models (98). The extended activation of several inflammatory cytokines, the acidic tumor-bone micro-environment, increased ROS levels, and central sensitization mediated by brain plasticity all have been related to CIBP (96). Antioxidants maintain a dynamic balance between ROS formation and removal under normal conditions. Cancer-related pain affects 30 to 50 percent of disease patients and 75 to 90 percent of individuals with late-stage metastatic cancer (99). The production of ROS is thought to play a role in the central sensitization of CIBP, and certain cancers can increase ROS levels in the dorsal horn of the spine (100).

Discussion

Due to high lipid content, neural cells are susceptible to excess content of ROS (oxidative stress) and lipid peroxidation. It is well accepted that ROS considered as a signaling molecule (at low concentrations), and also as a mediator of inflammation (at high concentrations). The main sources of ROS are mitochondrial respiratory chain and NADPH oxidase (4, 5). It is reported that excess content of ROS during NP can turn on an inflammatory machine and subsequently increased release of pro-inflammatory cytokines, including; TNF-α, IL-1β, IL-2, and IL-6, and adhesion molecules (4).The high ROS generation in NP can initiate the proinflammatory generation through activation of multiple transcription factors, including human polynucleotide phosphorylase (hPNPaseold-35), nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), specificity protein 1 (Sp1), peroxisome proliferator-activated receptors (PPARs). Therefore, high ROS generation and inflammation are closely related, which are taking part in the pathogenesis of chronic NP. So, oxidative stress and inflammation are mutually exclusive processes and antioxidants maintain a dynamic balance between ROS formation and removal under normal conditions (5).

Different disorders such as diabetes mellitus, RA, leprosy, cancer, AIDS-related neuropathy, postherpetic neuralgia, cervical disc protrusion, and MS are related to NP (3). There is some evidence that oxidative stress in all of mentioned disorders highly related to pathophysiology of NP. The peripheral nerve axoplasm is rich in phospholipids and mitochondria. If their antioxidant system is weakened, they are therefore more sensitive to oxidative stress. There is some evidence that oxidative damage in central and peripheral nervous system may play a role in the pathophysiology of NP, which disrupts the electron transport chain and ROS generation and promotes mitochondrial damage and inflammation. High production of ROS during NP can activate transduction of ion channels, so peripheral nerve function is altered (9). Generally, increased ROS generation in various diseases can increase nociceptor sensitivity, microtubule depolymerization, and nerve degeneration.

Conclusion

The present study relies on previous researchs that suggest inflammation and oxidative stress are mutually exclusive processes. Excess content of ROS during various diseases such as RA, leprosy, GBS, and FM can turn on an inflammatory machine and subsequently increased release of pro-inflammatory cytokines. On the other hand, inflammatory diseases increase ROS generation and oxidative stress exacerbates inflammation. Since, neural cells are vulnerable to excess level of ROS and lipid peroxidation due to their high lipid content. As a result, neuroinflammation has been linked to oxidative stress in NP.

Acknowledgments

Not applicated.

Funding

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contribution

Z. B. contributed in designing the study and supervising and editing the manuscript. A. Gh., B.J. K., and M. Gh. prepared the manuscript. All authors read and confirmed the manuscript.

References

1. Bahari Z, Meftahi GH. Spinal α2 -adrenoceptors and neuropathic pain modulation; therapeutic target. Br J Pharmacol. 2019;176(14):2366-81. [DOI:10.1111/bph.14580] [PMID] [PMCID]
2. Haanpää ML, Gourlay GK, Kent JL, et al. Treatment considerations for patients with NP and other medical comorbidities. Mayo Clin Proceed. 2010:85(3 Suppl):S15-25. [DOI:10.4065/mcp.2009.0645] [PMID] [PMCID]
3. White FA, Jung H, Miller RJ. Chemokines and the pathophysiology of NP. PNAS. 2007;104(51): 20151-8. [DOI:10.1073/pnas.0709250104] [PMID] [PMCID]
4. Mirasheh MH, Zohrehvand MR, Kazemi R, et al. The analgesic and anxiolytic activity of resveratrol mediated by different sub-types of α-adrenoceptors of anterior cingulate cortex following neuropathic pain in male rats. J Adv Med Biomed Res. 2020; 28(129):183-90. [DOI:10.30699/jambs.28.129.183]
5. Zohrehvand MR, Kazemi R, Mirasheh MH, et al. Crocin suppressed cold allodynia and anxiety through α 2-adrenoceptors in the anterior cingulate cortex following chronic constriction injury of sciatic nerve in rats. J Pharm Res. 2020;24(6):833-41. [DOI:10.35333/JRP.2020.242]
6. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: A Synopsis. AJMC. 2014;20(7):128-35.
7. Seegobin SD, Ma MH, Dahanayake C, et al. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. Arthrit Res Ther. 2014;16(1):1-12. [DOI:10.1186/ar4439] [PMID] [PMCID]
8. Carrasco C, Naziroğlu M, Rodríguez AB, Pariente JA. NP: delving into the oxidative origin and the possible implication of transient receptor potential channels. Front Physiol. 2018;9:95. [PMCID] [DOI:10.3389/fphys.2018.00095] [PMID]
9. Filippin LI, Vercelino R, Marroni N, Xavier RM. Redox signalling and the inflammatory response in rheumatoid arthritis. Clin Exp Immunol. 2008; 152(3):415-22. [PMID] [PMCID] [DOI:10.1111/j.1365-2249.2008.03634.x]
10. Stamp LK, Khalilova I, Tarr JM, et al. Myeloperoxidase and oxidative stress in rheumatoid arthritis. Rheumatol. 2012;51(10): 1796-803. [DOI:10.1093/rheumatology/kes193] [PMID]
11. Vaya J. Exogenous markers for the characterization of human diseases associated with oxidative stress. Biochimie. 2013;95(3):578-84. [DOI:10.1016/j.biochi.2012.03.005] [PMID]
12. Roerig S, Wolf R, Grisham MB. Nitric oxide, chronic joint inflammation, and pain. Nitric Oxide. 2000:873-94. [DOI:10.1016/B978-012370420-7/50054-X]
13. Gozzelino R, Jeney V, Soares MP. Mechanisms of cell protection by heme oxygenase-1. Annu Rev Pharmacol Toxicol. 2010;50:323-54. [PMID] [DOI:10.1146/annurev.pharmtox.010909.105600]
14. Barañano DE, Wolosker H, Bae BI, Barrow RK, Snyder SH, Ferris CD. A mammalian iron ATPase induced by iron. J Biol Chem. 2000;275(20):15166-73. [DOI:10.1074/jbc.275.20.15166] [PMID]
15. Alcaraz MJ, Ferrándiz ML. Relevance of Nrf2 and heme oxygenase-1 in articular diseases. Free Radic Biol Med. 2020;157:83-93. [PMID] [DOI:10.1016/j.freeradbiomed.2019.12.007]
16. Staurengo-Ferrari L, Badaro-Garcia S, Hohmann MS, et al. Contribution of Nrf2 modulation to the mechanism of action of analgesic and anti-inflammatory drugs in pre-clinical and clinical stages. Front Pharmacol. 2019:1536. [PMCID] [DOI:10.3389/fphar.2018.01536] [PMID]
17. Kapetanaki SM, Burton MJ, Basran J, et al. A mechanism for CO regulation of ion channels. Nat Commun. 2018;9(1):1-10. [PMID] [PMCID] [DOI:10.1038/s41467-018-03291-z]
18. Abreu TM, Ribeiro NA, Chaves HV, et al. Antinociceptive and anti-inflammatory activities of the lectin from marine red alga Solieria filiformis. Planta Med. 2016;82(07):596-605. [DOI:10.1055/s-0042-101762] [PMID]
19. Said G. Infectious neuropathies. Neurol Clin. 2007; 25(1):115-37. [DOI:10.1016/j.ncl.2006.11.004] [PMID]
20. de Freitas MR, Said G. Leprous neuropathy. Handbook of clinical neurology. 2013;115:499-514. [DOI:10.1016/B978-0-444-52902-2.00028-X] [PMID]
21. Saunderson P, Bizuneh E, Leekassa R. NP in people treated for multibacillary leprosy more than ten years previously. Lepr Rev. 2008;79(3):270-6. [DOI:10.47276/lr.79.3.270] [PMID]
22. Vijayaraghavan R, Suribabu C, Oommen P, Panneerselvam C. Vitamin E reduces reactive oxygen species mediated damage to bio-molecules

in leprosy during multi-drug therapy. Curr Trends Biotechnol Pharm. 2009;3(4):428-39.

23. Borah K, Girardi KdCdV, Mendum TA, et al. Intracellular mycobacterium leprae utilizes host glucose as a carbon source in Schwann cells. MBio. 2019;10(6):02351-19. [PMID] [PMCID] [DOI:10.1128/mBio.02351-19]
24. Medeiros RCA, de Vasconcelos Girardi KdC, Cardoso FKL, et al. Subversion of schwann cell glucose metabolism by mycobacterium leprae. J Biol Chem. 2016;291(41):21375-87. [PMCID] [DOI:10.1074/jbc.M116.725283] [PMID]
25. Batista-Silva R, Sola-Penna M, de Oliveira MF, et al. Subversion of schwann cell glucose metabolism by. JBC. 2016;291(47):24803.[PMID][PMCID] [DOI:10.1074/jbc.A116.725283]
26. Pooya S, Liu X, Kumar V, et al. The tumour suppressor LKB1 regulates myelination through mitochondrial metabolism. Nat Commun. 2014; 5(1):1-16. [DOI:10.1038/ncomms5993] [PMID] [PMCID]
27. Scollard DM, Truman RW, Ebenezer GJ. Mechanisms of nerve injury in leprosy. Clin Dermatol. 2015;33(1):46-54. [DOI:10.1016/j.clindermatol.2014.07.008] [PMID]
28. Lee Y, Morrison BM, Li Y, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487(7408):443-8. [DOI:10.1038/nature11314] [PMID] [PMCID]
29. Tang F, Lane S, Korsak A, et al. Lactate-mediated glia-neuronal signalling in the mammalian brain. Nat Commun. 2014;5(1):1-14. [DOI:10.1038/ncomms4993] [PMID] [PMCID]
30. Domenech-Estévez E, Baloui H, Repond C, et al. Distribution of monocarboxylate transporters in the peripheral nervous system suggests putative roles in lactate shuttling and myelination. J Neuroscience. 2015;35(10):4151-6. [PMID] [PMCID] [DOI:10.1523/JNEUROSCI.3534-14.2015]
31. Save MP, Shetty VP, Shetty KT. Hypophosphorylation of NF-H and NF-M subunits of neurofilaments and the associated decrease in KSPXK kinase activity in the sciatic nerves of Swiss white mice inoculated in the foot pad with Mycobacterium leprae. Lep Rev. 2009;80(4):388-401. [DOI:10.47276/lr.80.4.388]
32. Chiu SY. Matching mitochondria to metabolic needs at nodes of Ranvier. Neurosci. 2011;17(4): 343-50. [DOI:10.1177/1073858410393740] [PMID]
33. Jasti AK, Selmi C, Sarmiento-Monroy JC, Vega DA, Anaya J-M, Gershwin ME. Guillain-Barré syndrome: causes, immunopathogenic mechanisms and treatment. Expert Rev Clin Immunol. 2016; 12(11):1175-89. [DOI:10.1080/1744666X.2016.1193006] [PMID]
34. Ghabaee M, Jabedari B, Al-E-Eshagh N, Ghaffarpour M, Asadi F. Serum and cerebrospinal fluid antioxidant activity and lipid peroxidation in Guillain-Barre syndrome and multiple sclerosis patients. Int J Neurosci. 2010;120(4):301-4. [DOI:10.3109/00207451003695690] [PMID]
35. Yuki N, Hartung H-P. Guillain-barré syndrome. N Engl J Med. 2012;366(24):2294-304. [DOI:10.1056/NEJMra1114525] [PMID]
36. Van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. Lancet Neurol. 2008;7(10):939-50. [DOI:10.1016/S1474-4422(08)70215-1] [PMID]
37. Walling A, Dickson G. Guillain-Barré syndrome. AFP. 2013;87(3):191-7.
38. Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol. 2005;77(5):598-625. [DOI:10.1189/jlb.1204697] [PMID]
39. Amorini AM, Petzold A, Tavazzi B, et al. Increase of uric acid and purine compounds in biological fluids of multiple sclerosis patients. Clin Biochem. 2009;42(10-11):1001-6. [DOI:10.1016/j.clinbiochem.2009.03.020] [PMID]
40. Cutler RG, Camandola S, Feldman NH, et al. Uric acid enhances longevity and endurance and protects the brain against ischemia. Neurobiol Aging. 2019; 75:159-68. [PMID] [PMCID] [DOI:10.1016/j.neurobiolaging.2018.10.031]
41. Min JH, Waters P, Vincent A, et al. Reduced serum uric acid levels in neuromyelitis optica: serum uric acid levels are reduced during relapses in NMO. Acta Neurol Scand. 2012;126(4):287-91. [DOI:10.1111/j.1600-0404.2012.01643.x] [PMID]
42. Chang SH, Tian XB, Wang J, et al. Increased cerebrospinal fluid uric acid levels in Guillain-Barré syndrome. Front Neurol. 2020:1501. [PMID] [DOI:10.3389/fneur.2020.589928] [PMCID]
43. Lassmann H, van Horssen J. Oxidative stress and its impact on neurons and glia in multiple sclerosis lesions. Biochim Biophys Acta Mol Basis Dis. 2016;1862(3):506-10. [DOI:10.1016/j.bbadis.2015.09.018] [PMID]
44. Moalem-Taylor G, Allbutt HN, Iordanova MD, Tracey DJ. Pain hypersensitivity in rats with experimental autoimmune neuritis, an animal model of human inflammatory demyelinating neuropathy. Brain Behav Immun. 2007;21(5):699-710 [DOI:10.1016/j.bbi.2006.07.007] [PMID]
45. McMahon SB, Cafferty WB, Marchand F. Immune and glial cell factors as pain mediators and modulators. Exp Neurol. 2005;192(2):444-62. [DOI:10.1016/j.expneurol.2004.11.001] [PMID]

46. North RA. Molecular physiology of P2X receptors. Physiol Rev. 2002;82(4):1013-67. [DOI:10.1152/physrev.00015.2002] [PMID]

47. Zhang Z, Zhang Z-Y, Fauser U, Schluesener H. Mechanical allodynia and spinal up-regulation of P2X4 receptor in experimental autoimmune neuritis rats. Neurosci. 2008;152(2):495-501. [PMID] [DOI:10.1016/j.neuroscience.2007.12.042]

48. Yamout B, Hourani R, Salti H, et al. Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study. J Neuroimmunol. 2010;227(1-2):185-9. [DOI:10.1016/j.jneuroim.2010.07.013] [PMID]

49. Wang S, Cen X, Liang X, Tang Y. Macrophage migration inhibitory factor: a potential driver and biomarker for head and neck squamous cell carcinoma. Oncotarget. 2017;8(6):10650. [PMID] [DOI:10.18632/oncotarget.12890] [PMCID]

50. Jung H, Seong HA, Ha H. Critical role of cysteine residue 81 of macrophage migration inhibitory factor (MIF) in MIF-induced inhibition of p53 activity. JBC. 2008;283(29):20383-96. [DOI:10.1074/jbc.M800050200] [PMID]

51. Falvey JD, Bentley RW, Merriman TR, et al. Macrophage migration inhibitory factor gene polymorphisms in inflammatory bowel disease: an association study in New Zealand Caucasians and meta-analysis. WJG. 2013;19(39):6656. [PMID] [DOI:10.3748/wjg.v19.i39.6656] [PMCID]

52. Sainaghi PP, Collimedaglia L, Alciato F, et al. The expression pattern of inflammatory mediators in cerebrospinal fluid differentiates Guillain-Barré syndrome from chronic inflammatory demyelinating polyneuropathy. Cytokine. 2010; 51(2):138-43. [DOI:10.1016/j.cyto.2010.05.005] [PMID]

53. Healy ZR, Liu H, Holtzclaw WD, Talalay P. Inactivation of tautomerase activity of macrophage migration inhibitory factor by sulforaphane: a potential biomarker for anti-inflammatory intervention. Cancer Epidemiol Biomarkers Prev. 2011;20(7):1516-23. [PMID] [PMCID] [DOI:10.1158/1055-9965.EPI-11-0279]

54. Wang YZ, Tian FF, Liu H, et al. Macrophage migration inhibitory factor is necessary for the Lipo-oligosaccharide-induced response by modulation of Toll-like receptor 4 in monocytes from GBS patients. J Neuroimmunol. 2013;257(1-2):67-75. [DOI:10.1016/j.jneuroim.2013.01.006] [PMID]

55. Bye CR, Thompson LH, Parish CL. Birth dating of midbrain dopamine neurons identifies A9 enriched tissue for transplantation into parkinsonian mice. Exp Neurol. 2012;236(1):58-68. [DOI:10.1016/j.expneurol.2012.04.002] [PMID]

56. Shen D, Lang Y, Chu F, et al. Roles of macrophage migration inhibitory factor in Guillain-Barré syndrome and experimental autoimmune neuritis: beneficial or harmful? Expert Opin Ther Targets. 2018;22(7):567-77. [DOI:10.1080/14728222.2018.1484109] [PMID]

57. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. FEBS Lett. 2008;582(13):1783-7. [DOI:10.1016/j.febslet.2008.04.057] [PMID]

58. Su Z, Chen Z, Xiang Y, et al. Low serum levels of uric acid and albumin in patients with Guillain-Barre syndrome. Medicine. 2017;96(15). [PMID] [DOI:10.1097/MD.0000000000006618] [PMCID]

59. McGarry T, Biniecka M, Veale DJ, Fearon U. Hypoxia, oxidative stress and inflammation. Free Rad Biol Med. 2018;125:15-24. [PMID] [DOI:10.1016/j.freeradbiomed.2018.03.042]

60. Fais A, Cacace E, Atzori L, Era B, Ruggiero V. Plasma phospholipase, γ-CEHC and antioxidant capacity in fibromyalgia. Int J Rheum Dis. 2017; 20(5):550-4. [DOI:10.1111/1756-185X.12787] [PMID]

61. Alcocer-Gómez E, Garrido-Maraver J, Bullón P, et al. Metformin and caloric restriction induce an AMPK-dependent restoration of mitochondrial dysfunction in fibroblasts from Fibromyalgia patients. Biochim Biophys Acta. 2015;1852(7): 1257-67. [DOI:10.1016/j.bbadis.2015.03.005] [PMID]

62. Zündorf G, Reiser G. Calcium dysregulation and homeostasis of neural calcium in the molecular mechanisms of neurodegenerative diseases provide multiple targets for neuroprotection. ARS. 2011; 14(7):1275-88. [DOI:10.1089/ars.2010.3359] [PMID] [PMCID]

63. Cordero MD, De Miguel M, Moreno Fernández AM, et al. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. Arthritis Res Ther. 2010;12(1):1-11. [DOI:10.1186/ar2918] [PMID] [PMCID]

64. Sánchez-Domínguez B, Bullón P, Román-Malo L, et al. Oxidative stress, mitochondrial dysfunction and, inflammation common events in skin of patients with Fibromyalgia. Mitochondrion. 2015; 21:69-75. [DOI:10.1016/j.mito.2015.01.010] [PMID]

65. Lucas H, Brauch C, Settas L, Theoharides T. Fibromyalgia-new concepts of pathogenesis and treatment. Int J Immunopathol Pharmacol. 2006; 19(1):5-10. [DOI:10.1177/205873920601900102] [PMID]

66. Kim S-H, Kim DH, Oh D-H, Clauw DJ. Characteristic electron microscopic findings in the

skin of patients with fibromyalgia-preliminary study. Clin Rheumatol. 2008;27(3):407-11. [DOI:10.1007/s10067-007-0807-7] [PMID]

67. Cordero MD, Cano-García FJ, Alcocer-Gómez E, De Miguel M, Sánchez-Alcázar JA. Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q10 effect on clinical improvement. PloS One. 2012;7(4):35677. [PMID] [DOI:10.1371/journal.pone.0035677] [PMCID]
68. Chung CP, Titova D, Oeser A, et al. Oxidative stress in fibromyalgia and its relationship to symptoms. Clin Rheumatol. 2009;28(4):435-8. [DOI:10.1007/s10067-008-1072-0] [PMID] [PMCID]
69. Miranda-Díaz AG, Rodríguez-Lara SQ. The role of oxidants/antioxidants, mitochondrial dysfunction, and autophagy in fibromyalgia. InTech; 2018. Available from: [DOI:10.5772/intechopen.70695]
70. La Rubia M, Rus A, Molina F, Del Moral ML. Is fibromyalgia-related oxidative stress implicated in the decline of physical and mental health status. Clin Exp Rheumatol. 2013;31(6 Suppl 79):121-7.
71. Al-Gebori AM, Tarik M, Rajab A, Al-Osami MH, Turki KM. Levels of magnesium, zinc, calcium and copper in serum of patients with fibromyalgia syndrome. Iraq Post Med J. 2011;10(2).
72. Sendur OF, Tastaban E, Turan Y, Ulman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. Rheumatol Int. 2008;28(11):1117-21. [DOI:10.1007/s00296-008-0593-9] [PMID]
73. Altindag O, Celik H. Total antioxidant capacity and the severity of the pain in patients with fibromyalgia. Red Report. 2006;11(3):131-5. [DOI:10.1179/135100006X116628] [PMID]
74. Wang H, Moser M, Schiltenwolf M, Buchner M. Circulating cytokine levels compared to pain in patients with fibromyalgia-a prospective longitudinal study over 6 months. J Rheumatol. 2008;35(7):1366-70.
75. Fusco R, Siracusa R, D'Amico R, et al. Melatonin plus folic acid treatment ameliorates reserpine-induced fibromyalgia: An evaluation of pain, oxidative stress, and inflammation. Antioxidants. 2019;8(12):628. [DOI:10.3390/antiox8120628] [PMID] [PMCID]
76. Aich A, Afrin LB, Gupta K. Mast cell-mediated mechanisms of nociception. Int J Mol Sci. 2015; 16(12):29069-92. [DOI:10.3390/ijms161226151] [PMID] [PMCID]
77. Theoharides TC, Tsilioni I, Bawazeer M. Mast cells, neuroinflammation and pain in fibromyalgia syndrome. Front Cell Neurosci. 2019:353. [PMID] [DOI:10.3389/fncel.2019.00353] [PMCID]
78. D Skaper S, Facci L, Giusti P. Neuroinflammation, microglia and mast cells in the pathophysiology of neurocognitive disorders: a review. CNS Neurol Disord Drug Targets. 2014;13(10):1654-66. [DOI:10.2174/1871527313666141130224206] [PMID]
79. Hansson E. Long-term pain, neuroinflammation and glial activation. Scandin J Pain. 2010;1(2):67-72. [DOI:10.1016/j.sjpain.2010.01.002] [PMID]
80. Kosek E, Altawil R, Kadetoff D, et al. Evidence of different mediators of central inflammation in dysfunctional and inflammatory pain-interleukin-8 in fibromyalgia and interleukin-1 β in rheumatoid arthritis. J Neuroimmunol. 2015;280:49-55. [DOI:10.1016/j.jneuroim.2015.02.002] [PMID] [PMCID]
81. Vincent L, Vang D, Nguyen J, et al. Mast cell activation contributes to sickle cell pathobiology and pain in mice. Am J Hematol. 2013;122(11): 1853-62. [DOI:10.1182/blood-2013-04-498105] [PMID] [PMCID]
82. Bhattacharyya S, Saha J. Tumour, oxidative stress and host T cell response: cementing the dominance. Scand J Immunol. 2015;82(6):477-88. [DOI:10.1111/sji.12350] [PMID]
83. Zhu YF, Linher-Melville K, Wu J, et al. Bone cancer-induced pain is associated with glutamate signalling in peripheral sensory neurons. Mol Pain. 2020;16:1744806920911536. [PMID] [PMCID] [DOI:10.1177/1744806920911536]
84. Yi H, Talmon G, Wang J. Glutamate in cancers: From metabolism to signaling. Biomed Res J. 2020;34(4):260. [DOI:10.7555/JBR.34.20190037] [PMID] [PMCID]
85. Ungard RG, Seidlitz EP, Singh G. Inhibition of breast cancer-cell glutamate release with sulfasalazine limits cancer-induced bone pain. Pain. 2014;155(1):28-36. [DOI:10.1016/j.pain.2013.08.030] [PMID]
86. Dai WL, Yan B, Jiang N, et al. Simultaneous inhibition of NMDA and mGlu1/5 receptors by levo-corydalmine in rat spinal cord attenuates bone cancer pain. IJC. 2017;141(4):805-15. [DOI:10.1002/ijc.30780] [PMID]
87. Bridges RJ, Natale NR, Patel SA. System xc- cystine/glutamate antiporter: an update on molecular pharmacology and roles within the CNS. Br J Pharmacol. 2012;165(1):20-34. [PMCID] [DOI:10.1111/j.1476-5381.2011.01480.x] [PMID]
88. Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia. 2015;3:83. [DOI:10.2147/HP.S93413] [PMID] [PMCID]

89. Ganapathy-Kanniappan S, Geschwind J-FH. Tumor glycolysis as a target for cancer therapy: progress and prospects. Mol Cancer. 2013;12(1):1-11. [DOI:10.1186/1476-4598-12-152] [PMID] [PMCID]

90. Bansal A, Simon MC. Glutathione metabolism in cancer progression and treatment resistance. JCB. 2018;217(7):2291-8. [DOI:10.1083/jcb.201804161] [PMID] [PMCID]

91. Traverso N, Ricciarelli R, Nitti M, et al. Role of glutathione in cancer progression and chemoresistance. Oxid Med Cell Longev. 2013; 2013. [DOI:10.1155/2013/972913] [PMID] [PMCID]

92. Dutta S, Ray S, Nagarajan K. Glutamic acid as anticancer agent: An overview. SPJ. 2013;21(4): 337-43. [DOI:10.1016/j.jsps.2012.12.007] [PMID] [PMCID]

93. Vannini F, Kashfi K, Nath N. The dual role of iNOS in cancer. Redox Biol. 2015;6:334-43. [PMCID] [DOI:10.1016/j.redox.2015.08.009] [PMID]

94. Csekő K, Beckers B, Keszthelyi D, Helyes Z. Role of TRPV1 and TRPA1 ion channels in inflammatory bowel diseases: potential therapeutic targets? Pharmaceuticals. 2019;12(2):48. [DOI:10.3390/ph12020048] [PMID] [PMCID]

95. Zajączkowska R, Kocot-Kępska M, Leppert W, Wordliczek J. Bone pain in cancer patients: mechanisms and current treatment. Int J Mol Sci. 2019;20(23):6047. [DOI:10.3390/ijms20236047] [PMID] [PMCID]

96. Lozano-Ondoua A, Symons-Liguori A, Vanderah TW. Cancer-induced bone pain: mechanisms and models. Neuroscience Lett. 2013;557:52-9. [DOI:10.1016/j.neulet.2013.08.003] [PMID] [PMCID]

97. Ni H, Xu LS, Wang Y, et al. Astrocyte activation in the periaqueductal gray promotes descending facilitation to cancer-induced bone pain through the JNK MAPK signaling pathway. Mol Pain. 2019;15: 1744806919831909. [PMID] [PMCID] [DOI:10.1177/1744806919831909]

98. Zhang Y, Lin C, Wang X, Ji T. Calcitonin gene related peptide: A promising bridge between cancer development and cancer associated pain in oral squamous cell carcinoma. Oncology Lett. 2020; 20(5):253. [DOI:10.3892/ol.2020.12116] [PMID] [PMCID]

99. Falk S, Bannister K, Dickenson AH. Cancer pain physiology. Br J Pain. 2014;8(4):154-62. [PMID] [DOI:10.1177/2049463714545136] [PMCID]

100. Zhou YQ, Liu DQ, Chen SP, et al. Reactive oxygen species scavengers ameliorate mechanical allodynia in a rat model of cancer-induced bone pain. Redox Biol. 2018;14:391-7. [PMCID] [DOI:10.1016/j.redox.2017.10.011] [PMID]

How to Cite This Article:

Ghasemi A, Jalali Kondori B, Ghasemi M, Bahari Z. Potential Role of Oxidative Stress on the Pathophysiology of Neuropathic Pain in the Inflammatory Diseases. J Adv Med Biomed Res. 2023; 31(139):514-24.

Download citation:
BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks

Send citation to:
Mendeley Zotero RefWorks