REVIEW ARTICLE

Behavioral and inflammatory changes in the nervous system as a tool for studying monoiodoacetate-induced osteoarthritis

Alterações comportamentais e inflamatórias no sistema nervoso como ferramenta para o estudo da osteoartrite induzida por monoiodoacetato

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Abstract

Objective: This study aims to elucidate the mechanisms underlying neuroinflammation and behavioral changes in the MIA-induced OA model. **Methodology**: PubMed and Science Direct databases were used, employing the descriptors MIA, Osteoarthritis, Neuroinflammation, Rat, Monoiodoacetate-induced Osteoarthritis, and Boolean operators AND and OR, and studies published between 2019 and 2023 were included. Review articles, studies in humans, animal models of joint destabilization, meniscectomy-induced osteoarthritis, fracture-induced osteoarthritis, or intra-articular compression-induced osteoarthritis were excluded from the analysis. **Results**: the 16 articles considered in this study highlight the roles of various inflammatory cytokines acting in the central nervous system (CNS) and peripheral nervous system (PNS) that synergistically facilitate nociception and behavioral disorders correlated with anxiety and depression. The main factors involved in the neuroinflammatory process in OA induced by MIA involve pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, sensitizing nerves in the PNS, in dorsal root ganglia (DRG), and sciatic nerve. Neuroinflammation affects different parts of the CNS, namely: the spinal cord, the hippocampus, and the prefrontal cortex. In the CNS and PNS, inflammatory cytokines facilitate the transmission of the nociceptive signal and increase microglial and astrocytic activity, inducing persistent hypernociception, anxiety, and depressive behaviors. **Conclusion**: in the MIA-induced OA model, neuroinflammation in the PNS and CNS is responsible for persistent nociception, as well as brain changes that generate behavioral conditions related to anxiety and depression.

Keywords: hipernociception; neuroinflammation; rodents.

Resumo

Objetivo: Este estudo visa elucidar os mecanismos subjacentes à neuroinflamação e às alterações comportamentais no modelo de OA induzida por MIA. Metodologia: foram utilizadas as bases de dados PubMed e Science Direct, empregando os descritores MIA, Osteoartrite, Neuroinflamação, Rato, Osteoartrite induzida por monoiodoacetato e os operadores booleanos AND e OR. Foram incluídos estudos publicados entre 2019 e 2023. Artigos de revisão, estudos em humanos, modelos animais de desestabilização articular, osteoartrite induzida por meniscectomia, osteoartrite induzida por fratura ou osteoartrite induzida por compressão intra-articular foram excluídos. Resultados: os 16 artigos considerados neste estudo destacam o papel de diversas citocinas inflamatórias que atuam no sistema nervoso central (SNC) e no sistema nervoso periférico (SNP), facilitando, sinergicamente, a nocicepção e os distúrbios comportamentais correlacionados com ansiedade e depressão. Os principais fatores envolvidos no processo neuroinflamatório na osteoartrite induzida por MIA envolvem citocinas pró-inflamatórias, como TNF-α, IL-1β e IL-6, que sensibilizam os nervos no SNP, nos gânglios da raiz dorsal (GRD) e no nervo ciático. A neuroinflamação afeta diferentes partes do SNC, nomeadamente: medula espinal, hipocampo e córtex pré-frontal. No SNC e no SNP, as citocinas inflamatórias facilitam a transmissão do sinal nociceptivo e aumentam a atividade microglial e astrocítica, induzindo hipernocicepção persistente, ansiedade e comportamentos depressivos. Conclusão: no modelo de OA induzida por MIA, a neuroinflamação no SNP e SNC é responsável por nocicepção persistente e por alterações cerebrais que geram comportamentos relacionadas à ansiedade e à depressão.

Palavras chave: hipernocicepção; neuroinflamação; roedores.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent chronic degenerative joint disease that leads to disability and affects more than 500 million people worldwide[1]. Primarily associated with aging and obesity, OA most commonly affects the knee and hip joints, and secondarily, the hands[2]. With multifactorial pathophysiology, osteoarthritis causes irreversible damage to cartilage and subchondral bone due to an imbalance between degradation and synthesis of the extracellular matrix[3]. It is commonly referred to as a chronic whole-joint disorder, initiated with biochemical and cellular changes in the synovial tissues of the joints, leading to histological changes of the joint and whole-tissue dysfunction[4]. Residual or generalized joint pain is the most relevant symptom, often accompanied by stiffness, joint deformity, and reduced mobility, resulting in restricted

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movement and muscle weakness around the joints affected by arthritis[5]. There is also evidence for ongoing pain in the MIA model[6].

Currently, there is no cure for OA, in part due to an incomplete understanding of the pathological mechanism of driving disease initiation and progression. Therefore, elucidating pathological signaling pathways and the key molecules involved in the pathogenesis of OA is crucial for the design of therapeutic targets and drug development[1]. Systemic or topical pharmacological treatments exhibit palliative characteristics due to the impossibility of altering the natural course of joint degeneration. In these cases, the results are simply the improvement of patients' quality of life, maintenance of satisfactory joint mobility, and reduction of severe joint pain[7,1]. Research into inflammatory arthropathies has invested in animal models that reproduce characteristics of these diseases. Notably, chemical induction by monoiodoacetate mimics the arthropathies presented by humans due to the inflammatory and degenerative characteristics of the articular cartilage[8]. The MIA-induced OA model completely mimics primary OA in humans; the joint histological changes are similar to those observed in humans, namely synovitis and cartilage degeneration. In this model, hypernociception is mainly caused by inflammatory mediators, exposure of the subchondral bone, damage to sensory nerve endings9, and inflammatory changes in the dorsal root ganglion and spinal cord[8]. Therefore, both peripheral and central mechanisms appear to contribute to hypernociception in advanced stages of MIA-induced OA[8].

The changes in the CNS in the OA model are correlated with the main clinical manifestation, such as chronic pain. Damage to sensory nerve endings9 and inflammatory changes in the dorsal root ganglion and spinal cord8 cause neuroinflammation mainly in the spinal cord, but also in the hippocampus and prefrontal cortex, with an increase in ionized calcium-binding adapter molecule 1 (Iba1), a marker of microglial activation, and an increase in pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)[10]. Additionally, in these experimental models, a proportion of neurons in the dorsal root ganglion (DRG) expressed immunoreactivity for ATF-3, a marker of neuronal injury, suggesting the development of neuropathic pain. The increased expression of ATF-3 in the DRG suggests that pain in MIA-induced OA models is not only caused by mechanical stimuli but also by dysfunction in the nerves that transmit pain[11]. Similarly, studies in patients with OA have reported a neuropathic component associated with abnormally excitable pain pathways in both the peripheral and central nervous systems, and patients with chronic OA, nociceptor input from chemokines and pro-inflammatory cytokines can induce both peripheral and central sensitization[12]. Both neural and glial elements of the CNS at such sites as the sensory cortex, hypothalamus, and mid-brain, together with the dorsal horn of the spinal cord, show changes of central sensitization that modulate afferent nociceptive input and contribute to neuropathic pain[13].

Given the complexity of the pathophysiological manifestations in the nervous system in OA, the objective of this review was to identify changes in this system in the MIA-induced OA model, highlighting the main mechanisms that lead to neuroinflammation and the consequences of inflammation on animal symptoms.

METHODOLOGY

A systematic review was conducted through a bibliographic search of the experimental preclinical studies was searched in the PubMed and ScienceDirect databases, which were selected due to their relevance and broad coverage of biomedical and experimental studies, particularly in the fields of inflammation, neuroscience, and musculoskeletal diseases. PubMed was used as one of the primary databases in biomedicine, while ScienceDirect was included to expand the scope of the search and capture experimental studies that may not be indexed in a single database. The search strategy was designed to identify relevant studies while maintaining adequate specificity. The search was conducted in the PubMed/MEDLINE database using controlled descriptors (MeSH) and free terms related to monoiodoacetate-induced osteoarthritis, nervous system, neuroinflammation, inflammation, and behavioral changes, combined using Boolean operators AND and OR."("Osteoarthritis"[Mesh] OR osteoarthritis[tiab]) AND ("monosodium iodoacetate"[tiab] OR monoiodoacetate[tiab] OR "MIA-induced"[tiab])) AND ("Nervous System"[Mesh] OR "Central Nervous System"[Mesh] OR "Peripheral Nervous System"[Mesh] OR nervous system[tiab]) AND ("Neuroglia"[Mesh] OR "Microglia"[Mesh] OR "Astrocytes"[Mesh] OR neuroinflammation[tiab]) AND ("Inflammation"[Mesh] OR "Cytokines"[Mesh]) AND ("Pain"[Mesh] OR "Nociception"[Mesh] OR "Hyperalgesia"[Mesh] OR "Allodynia"[Mesh]).

Studies published between February 2019, and December 2023 were included. Eligible studies consisted of original experimental research conducted in rats or mice using monoiodoacetate-induced osteoarthritis as the experimental model. Exclusion criteria were Review articles, human studies, animal models of joint destabilization, osteoarthritis induced by meniscectomy, and osteoarthritis induced by fracture or intra-articular compression.

RESULTS AND DISCUSSION

Considering the exclusion criteria, title screening, and abstract evaluation, 737 articles were excluded. To compose the final sample, 16 were considered to align with the objectives of this study (Figure 1). The main factors involved in the neuroinflammatory process in MIA-induced OA involve pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, both in the peripheral nervous system (DRG and sciatic nerve) and central nervous system (spinal cord, hippocampus, and prefrontal cortex). In the central and peripheral nervous system, these cytokines facilitate the transmission of the nociceptive signal and increase microglial and astrocytic activity (Figure 2). Furthermore, this neuroinflammation causes changes in the CNS, such as persistent hypernociception, anxiety, and depressive behaviors (Table 1).

Figure 1. Flowchart of the analysis of the articles included in the study

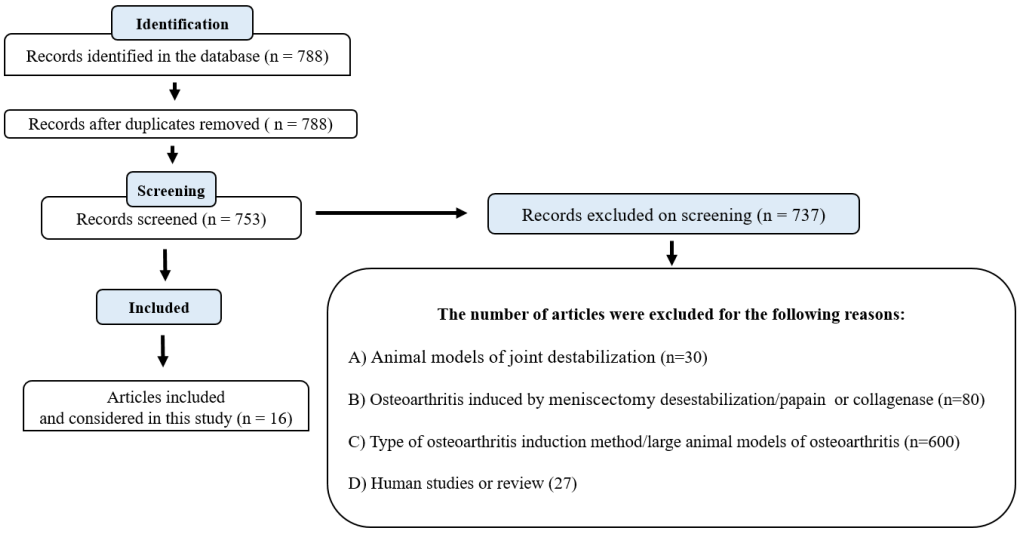

Figure 2. Effect of monosodium iodoacetate (MIA) on cytokines that alter transmission of the nociceptive signal and microglial astrocytic activity in the central and peripheral nervous system. TNF-α - Tumor necrosis factor alpha, IL-8 - Interleukin-8, TRL4 - Toll-like receptor 4, IL-1β - Interleukin-1 Beta, GFAP - Glial Fibrillary Acidic Protein, PK2 - Prokineticin 2 (PK2), IL-6 - Interleukin-6, Iba-1 - Ionized calcium-binding adaptor molecule 1, PKR - Protein kinase R, MMPs - Matrix metalloproteinases.

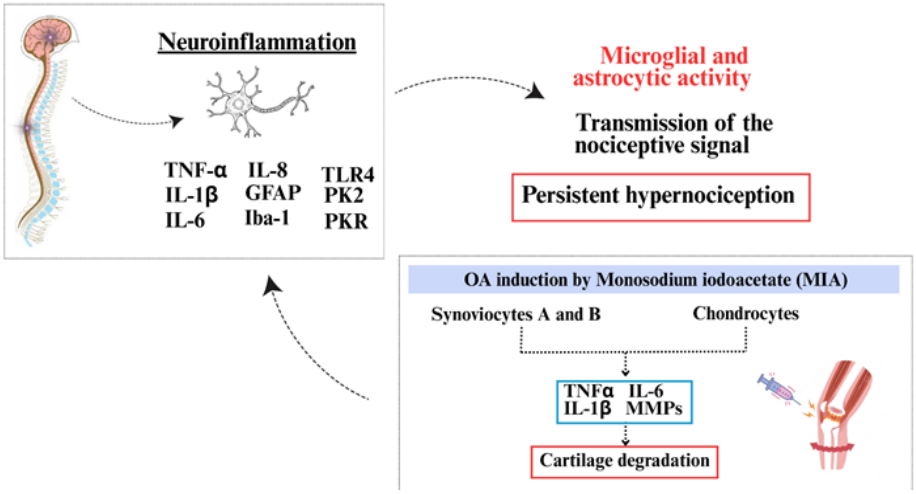

Table 1. Main inflammatory and behavioral changes in the MIA-induced osteoarthritis model

Neuroinflammatory and behavioral alterations observed in the MIA-induced osteoarthritis model	References
Inflammatory changes in the dorsal root ganglion and spinal cord. Peripheral and central mechanisms appear to contribute to hypernociception in advanced stages of MIA-induced OA.	Lockwood et al. (2019)
Inflammatory processes stimulate nociception through the release of inflammatory cytokines IL-1β, TNF-α, and IL-6 in different tissues of the nervous system.	Li et al. (2020)
Expression of CGRP, TRPV1, NGF and Netrin1, c-fos expression intensity.	Zhang et al. (2021)
Overexpression of TLR4 and elevated activity of microglia astrocytes (GFAP).	Garcia et al. (2022).
Mechanical allodynia, anxiety-like behavior, depression and cognitive impairment, elevated neuroinflammatory markers in brain areas. In the hippocampus of mice, IL-6 and TNFα levels were elevated. Significant increase in TNFα and IL-10. Significant increase in TLR4, iba1 and GFAP in HPC. In the prefrontal cortex and hypothalamus there was a significant increase in IL-6, TNFα and IL-10 and a reduction in neurotrophic factor.	Amodeo et al. (2023)

Neuroinflammatory and behavioral alterations observed in the MIA-induced osteoarthritis model	References
Hypersensitivity to pain and thermal hyperalgesia. Brd4 expression. Expression of pro-inflammatory cytokines and chemokines. Production of ROS.	Sun et al. (2023)
Anxiety-like behavior, depression. In the sciatic nerve and spinal cord, the expression of PK2 and PKR1 is increased. Elevation in pro-inflammatory cytokines IL-1β and IL-6 and markers GFAP, CD11b and ATF3. In the hippocampus, mice with OA show increased expression of PK2, PKR2, IL-1β, TNFα and GFAP. In the prefrontal cortex, there is an increase in the levels of IL-1β, TNFα and Iba1.	Galimberti et al. (2023)
Elevated expression of toll like receptor 4 (TLR4) and stimulation of nociceptive signal transmission in the central nervous system.	ZHOU et al., (2019)
Increased AMP/AMPK-activated protein kinase signaling and activation of astrocytes and microglia that produce cytokines (TNF-α, IL-1β, IL-6) in the spinal cord.	Sun et al., (2022)
Central sensitization leads to the development of neuroinflammation in the spinal cord and brain.	Ji et al. (2018)
Upregulation of pro-inflammatory cytokines and activation of astrocytes and microglia in the dorsal root ganglia (DRGs) and spinal cord. Elevated levels of IL-6 and TNFα, toll like receptor (TLR4) and iba-1 (marker of microglial activation) in the hippocampus (HPC), prefrontal cortex (PFC) and hypothalamus (HPT).	Amodeo et al. (2024)
Positive regulation of PK2 and PKR1 in the sciatic nerve and spinal cord, and high levels of IL-1β and IL-6, associated with the activation of Schwann cells and macrophages, due to demyelination, and expression of GFAP, CD11b and ATF3, indicative astrocytosis and neuroinflammation	Muley et al. (2017)
In the hippocampus, there is a marked increase in the expression of PK2 and PKR2 and elevated levels of TNF-α, IL-1β and GFAP. In the prefrontal cortex, there is an increase in the levels of IL-TNFα, IL-1β and Iba. Behavioral changes: anxiety and depression.	Khan et al. (2020)
Behavioral changes: anxiety and depression.	Carcolé et al. (2019a); Carcolé et al. (2019b); Batallé et al., (2019); Batallé et al., (2021).

The MIA-induced osteoarthritis (OA) model reproduces clinically and pathophysiologically relevant features of the disease and is widely used for the study of chronic inflammatory pain. The inflammatory process triggered by MIA leads to exposure of the subchondral bone and damage to nociceptors, resulting in hypernociception12. These peripheral events are associated with increased release of inflammatory mediators, such as TNF-α, IL-1β, and IL-6, activation of type A and type B synoviocytes, and increased expression of matrix metalloproteinases (MMPs), which promote degradation of articular cartilage[10].

Peripheral damage resulting from MIA-induced OA directly impacts the dorsal root ganglion (DRG), leading to neuroinflammation. Indeed, studies have demonstrated increased expression of proteins related to cellular stress and repair, such as Brd4, suggesting DNA damage in both neuronal and non-neuronal DRG cells1,9,10. In addition, activation of glial cells and macrophages has been observed, as indicated by the expression of ATF3, CD11b, and GFAP, reflecting neuronal inflammation and a possible demyelination process, ultimately resulting in amplification of nociceptive signaling to the central nervous system[12,13].

The progression of MIA-induced OA leads to the establishment of neuroinflammation in the spinal cord, characterized by astrocyte and microglial activation, evidenced by increased expression of GFAP and Iba-1; elevated levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6); upregulation of toll-like receptor 4 (TLR4); and activation of pain-related signaling pathways (AMP/AMPK)[14]. Alterations in the expression of neurotransmitters, receptors, and nociceptive mediators (CGRP, TRPV1, NGF, Netrin-1), as well as c-Fos, a marker of neuronal activity, have also been reported[15]. These factors facilitate and sustain nociceptive transmission, characterizing central sensitization.

Beyond the spinal cord, neuroinflammation extends to brain regions involved in pain modulation and emotional behavior. In the hippocampus, increased expression of TNF-α, IL-1β, IL-6, GFAP, and components of the prokineticin system has been observed, with elevated levels of PK2 and its receptors (PKR1/PKR2). In the prefrontal cortex, increased expression of TNF-α, IL-1β, and Iba-1 indicates microglial activation, with similar alterations identified in the hypothalamus14. These changes reinforce the role of central sensitization and widespread neuroinflammation in the impairment of cognitive and emotional functions associated with chronic pain.

Animals with MIA-induced OA exhibit classical behaviors of chronic pain, including thermal hyperalgesia, mechanical allodynia, alterations in weight-bearing distribution between limbs, and postural asymmetry. In addition, anxiety- and depression-like behaviors are observed, particularly in more advanced stages of the disease. These behaviors are closely

associated with neuroinflammation in regions such as the hippocampus and prefrontal cortex, highlighting the interaction between chronic pain, neurogenic inflammation, and emotional states[10].

Taken together, these findings indicate that MIA-induced OA involves interconnected peripheral and central mechanisms, in which joint inflammation triggers peripheral sensitization, glial activation, neuroinflammation, and central sensitization. These processes ultimately contribute to the maintenance of chronic pain, as well as behavioral and emotional alterations.

This is a pioneering study that emphasizes relevant neuroinflammatory and behavioral changes established in an animal model of osteoarthritis. In addition, we sought to correlate behavioral, central, and peripheral inflammatory changes with the clinical and pathophysiological characteristics of osteoarthritis.

Studies have shown a significant relationship between the overexpression of a protein (Sens2) in stress processes in the spinal cord that influences pain behaviors in rats with OA, and this overexpression enhances AMP/AMPK-activated protein kinase signaling and influences the activation of astrocytes and microglia that produce cytokines (TNF-α, IL-1β, IL-6) in the spinal cord in animals with OA pain[14].

The pain induced by the MIA model has been related to the development of anxiety behavior, depressive behavior, and neuroinflammation in mice[10]. In MIA-induced osteoarthritis, there is heightened expression of neurotransmitters and receptors (CGRP, TRPV1, NGF, Netrin1), increased fluorescence intensity and expression of c-fos (marker of neuronal activity), as well as a greater number of visible and activated axons[15]. These changes also contribute to the facilitation and persistence in the transmission of the nociceptive signal from the periphery to the central nervous system. Furthermore, enhanced Iba-1 activity was described (marker of microglial activity), and reactivity of glial fibrillary acidic protein (GFAP), a protein exclusively expressed in astrocytes in the central nervous system (CNS), was identified16. In addition to Iba-1 and GFAP, pro-inflammatory factors have been identified in the spinal cord, such as cytokines (TNF-α, IL-1β, IL-6)[17] and high expression of toll-like receptor 4 (TLR4), which together result in stimulation of nociceptive signal transmission in the central nervous system[18].

Due to the inflammatory process caused by MIA in the hypernociception model caused by inflammatory mediators, exposure of the subchondral bone causes damage to sensory nerve endings[9]. This damage is associated with inflammatory changes in the dorsal root ganglion (DRG) and spinal cord[8] as well as neuroinflammation of the hippocampus and prefrontal cortex. Therefore, both peripheral and central mechanisms appear to contribute to hypernociception in advanced stages of MIA-induced OA[8]. Other studies strengthen this hypothesis, given that previous studies demonstrated that attenuation of inflammatory processes leads to improvement in this inflammatory nociception and pain reduction through the inhibition of inflammatory cytokines (TNF-α, IL-1β, IL-6)17. Furthermore, the inhibition of inflammatory processes in the spinal cord has been shown to decrease hypernociception, improve motor coordination and depressive and anxious behavior, in addition to a reduction in the production of cytokines (TNF-α) and protein kinases (PK2, PKR) in the hippocampus[14,19,18].

In mouse models of OA, pain-related behaviors have been demonstrated, such as thermal hyperalgesia and mechanical allodynia, which manifest especially in the ipsilateral paw. After 4 weeks of OA, these mice display persistent hypernociception and anxiety- and depression-like behaviors19. These responses are accompanied by an upregulation of the secreted bioactive peptide prokineticin 2 (PK2) and its receptor (PKR1), associated with an increase in pro-inflammatory cytokines and metalloproteinases (MMPs), which are critical factors in the degradation of articular cartilage. This increased degradation in cartilage stimulates type A synoviocytes to release inflammatory cytokines (TNFα, IL-1β, IL-6) and MMPs, which accelerate the progression of osteoarthritis[20].

Neuroinflammation and high expression of PK2 and PKR1 have already been demonstrated in the sciatic nerve and spinal cord of animals with OA induced by MIA, alongside high levels of IL-1β and IL-6. This inflammatory condition is associated with the activation of Schwann cells and macrophages, suggesting demyelination, and the expression of markers such as GFAP, CD11b, and ATF3, which indicate astrocytosis and neuronal inflammation[19].

In OA-affected mice, significant neuroinflammation was observed in the hippocampus, with an increase in the expression of PK2 and PKR2 and high levels of TNFα, IL-1β, and GFAP. Considering the crucial role of the hippocampus in mood regulation, this neuroinflammation can influence the emotional and affective aspects of chronic pain, contributing to changes in animal behavior[21,19]. In the prefrontal cortex, increased levels of TNFα, IL-1β, and Iba1 were observed, which contribute to behavioral changes, such as anxiety and depression, frequently associated with OA models[21,19], highlighting the complexity of the interaction between neurogenic inflammation and emotional states.

Central sensitization in chronic pain conditions leads to the development of neuroinflammation in the spinal cord and brain22. A study showed that OA induced the upregulation of pro-inflammatory cytokines and activation of astrocytes and microglia in the dorsal root ganglia (DRGs) and spinal cord of mice. Furthermore, in the same study, elevated levels of IL-6 and TNFα, TLR4, and iba-1 (marker of microglial activation) were found in the hippocampus, prefrontal cortex, and hypothalamus[10].

Research has shown that OA induced by MIA caused an increase in the levels of a protein called Brd4 in the DRG in rats.

Notably, there is increased expression of Brd4 in response to MIA-induced OA with DNA repair function. This increase in Brd4 expression may indicate damage to neuronal and non-neuronal cells present in DRGs, since this protein has repair activity in the genetic material of somatic cells[23].

Microglial activation promotes the expression of pro-inflammatory cytokines and chemokines, which aggravates MIA-induced OA pain. Thus, OA is associated with changes in the perception of nociception, where there is hyperalgesia to thermal and mechanical stimuli. In addition, there is allodynia, changes in weight distribution between the limbs, and asymmetry in body weight support[14].

Furthermore, in MIA-induced OA, there are also behaviors similar to anxiety and depression, data that corroborate preclinical studies in which animals treated with MIA exhibit these behavioral characteristics in parallel with OA[24,25,26,27].

These findings highlight the complexity of the interaction between neurogenic inflammation and the emotional aspects of chronic pain, highlighting the crucial role of these brain regions in modulating the pain response and emotional states associated with osteoarthritis.

Although the evidence reinforces the relevance of neuroinflammation and behavioral alterations in experimental models of osteoarthritis, particularly those induced by monosodium iodoacetate (MIA), several limitations must be considered. The MIA model, although widely used, does not fully reproduce the complexity and slow progression of human osteoarthritis, which restricts the direct extrapolation of findings, especially to the early stages of the disease.

A large proportion of studies relies on inflammatory and glial markers as indirect indicators of neuroinflammation, whose associations with chronic pain and emotional alterations remain predominantly correlational, with a paucity of functional approaches capable of confirming causal relationships. Moreover, behavioral tests used to infer anxiety- and depression-like behaviors in rodents may be influenced by joint pain and motor impairments, making it difficult to distinguish emotional alterations from adaptive responses to pain.

From a conceptual perspective, the literature often assumes a linear relationship between inflammation, central sensitization, and emotional alterations, although this interaction is complex and bidirectional. Mechanisms involving central neural circuits, the hypothalamic–pituitary–adrenal axis, stress, and synaptic plasticity remain insufficiently explored in an integrated manner. In addition, variability across species, sex, and disease duration, as well as the predominance of studies conducted in male animals, limits the understanding of sex-related differences.

Finally, although some emerging proteins have been proposed as potential therapeutic targets, there remains a lack of translational validation in human tissues and clinical evidence supporting their applicability in human osteoarthritis.

CONCLUSIONS

Sodium monoiodoacetate-induced osteoarthritis involves not only peripheral joint degeneration but also significant neuroinflammatory processes in the peripheral nervous system, spinal cord, and key brain regions such as the hippocampus and prefrontal cortex. These processes are associated with behavioral changes, including enhanced pain sensitivity, anxiety, and depressive-like symptoms, demonstrating that osteoarthritis has a substantial central nervous system component. These findings suggest that therapeutic interventions should target not only the joint but also the neuroimmune mechanisms contributing to pain and behavioral comorbidities. Future research should explore the temporal progression of neuroinflammation, identify specific molecular targets, and evaluate strategies capable of modulating both neuroinflammatory processes and behavioral outcomes, with the aim of developing more comprehensive and effective treatments that improve the quality of life of patients with osteoarthritis.

CONCLUDING REMARKS

Several changes in the nervous system were identified in the MIA model of osteoarthritis, such as inflammatory changes in the dorsal root ganglion and spinal cord in the central nervous system, in the hippocampus, and in the prefrontal cortex. It was observed that the reduction in neuroinflammation was responsible for reducing the symptoms of osteoarthritis.

REFERENCES

1. Yao Q, Wu X, Tao C, Gong W, Chen M, Qu M, et al. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. Signal Transduct Target Ther. 2023 Feb; 8(1): 56. doi: 10.1038/s41392-023-01330-w.

2. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014 Jul; 73(7): 1323-30. doi: 10.1136/annrheumdis-2013-204763.

3. Zeng L, Xiao CZ, Deng ZT, Li RH. Chondroprotective Effects and Multitarget Mechanisms of Fu Yuan Capsule in a Rat Osteoarthritis Model. Evid Based Complement Alternat Med. 2017: 8985623. doi: 10.1155/2017/8985623.

4. Molnar V, Matisic V, Kodvanj I, Bjelica R, Jelec Z, Hudetz D, et al. Cytokines and Chemokines Involved in Osteoarthritis Pathogenesis. Int J Mol Sci. 2021 Aug; 22(17): 9208. doi: 10.3390/ijms22179208.

5. Sofat N, Ejindu V, Kiely P. What makes osteoarthritis painful? The evidence for local and central pain processing. Rheumatology 2011 Dec; 50(12): 2157–65. doi: 10.1093/rheumatology/ker283.

6. Liu P, Okun A, Ren J, Guo RC, Ossipov MH, Xie J, King T, et al. Ongoing pain in the MIA model of osteoarthritis. Neurosci Lett 2011 Apr; 493(3): 72–5. doi: 10.1016/j.neulet.2011.01.027.

7. Mcalindon TE, Bannuru RR. Osteoarthritis: Is viscosupplementation really so unsafe for knee OA? Nat Rev Rheumatol. 2012 Nov; 8(11): 635-6. doi: 10.1038/nrrheum.2012.152.

8. Lockwood SM, Lopes DM, MacMahon SB, Dickenson AH. Characterisation of peripheral and central components of the rat monoiodoacetate model of osteoarthritis. Osteoarthritis Cartilage. 2019 Apr; 27(5): 712-22. doi: 10.1016/j.joca.2018.12.017.

9. Aso K, Ikeuchi M, Izumi M, Sugimura N, Kato T, Ushida T, et al. Nociceptive phenotype of dorsal root ganglia neurons innervating the subchondral bone in rat knee joints. Eur J Pain. 2014 Feb; 18(2): 174-81. doi: 10.1002/j.1532-2149.2013.00360.x.

10. Amodeo G, Magni G, Galimberti G, Riboldi B, Franchi S, et al. Neuroinflammation in osteoarthritis: From pain to mood disorders. Biochem Pharmacol. 2024 Oct; 228: 116182. doi: 10.1016/j.bcp.2024.116182.

11. Ivanavicius SP, Ball AD, Heapy CG, Westwood FR, Murray F, Read SJ. Structural pathology in a rodent model of osteoarthritis is associated with neuropathic pain: increased expression of ATF-3 and pharmacological characterisation. Pain 2007 Apr; 128(3): 272–82. doi: 10.1016/j.pain.2006.12.022.

12. Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. Semin Arthritis Rheum. 2014; 44(2):145-54. doi: 10.1016/j.semarthrit.2014.05.011.

13. Gwilym SE, Keltner JR, Warnaby CE, Carr AJ, Chizh B, Chessell I, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum 2009 Sep; 61:1226–34. doi: 10.1002/art.24837.

14. Sun J, Song FH, Wu JY, Zhang L-Q, Li D-Y et al. Sestrin2 overexpression attenuates osteoarthritis pain via induction of AMPK/PGC-1α-mediated mitochondrial biogenesis and suppression of neuroinflammation. Brain Behav Immun. 2022 May; 102: 53-70. doi: 10.1016/j.bbi.2022.02.015.

15. Zhang L, Li M, Li X, Liao T, Ma Z, Zhang L, et al. Characteristics of sensory innervation in synovium of rats within different knee osteoarthritis models and the correlation between synovial fibrosis and hyperalgesia. J Adv Res. 2021 Jun; 35: 141-51. doi: 10.1016/j.jare.2021.06.007.

16. García MM, Molina-Álvarez M, Rodríguez-Rivera C, et al. Antinociceptive and modulatory effect of pathoplastic changes in spinal glia of a TLR4/CD14 blocking molecule in two models of pain in rat. Biomed Pharmacother. 2022 Jun; 150:112986. doi: 10.1016/j.biopha.2022.112986.

17. Li Y, Wu F, Wei J, Lao L, Shen X. Laser Moxibustion Alleviates Knee Osteoarthritis Pain by Inhibiting Spinal Microglial Activation-Mediated Neuroinflammation in Rats. Photobiomodul Photomed Laser Surg. 2020 Apr; 38(4): 237-43. doi: 10.1089/photob.2019.4744.

18. Zhou P, Xiang L, Yang Y, Wu Y, Hu T, et al. N-Acylethanolamineacidamidase (NAAA) inhibitor F215 as a novel therapeutic agent for osteoarthritis. Pharmacol Res. 2019 Jul; 145: 104264. doi: 10.1016/j.phrs.2019.104264.

19. Galimberti G, Amodeo G, Magni G, Riboldi B, Balboni G, Onnis V, Ceruti S, Sacerdote P, Franchi S. Prokineticin System Is a Pharmacological Target to Counteract Pain and Its Comorbid Mood Alterations in an Osteoarthritis Murine Model. Cells. 2023 Sep; 12(18): 2255. doi: 10.3390/cells12182255.

20. Hu Q, Ecker M. Overview of MMP-13 as a Promising Target for the Treatment of Osteoarthritis. Int J Mol Sci. 2021 Feb; 22(4): 1742. doi: 10.3390/ijms22041742.

21. Khan AR, Geiger L, Wiborg O, Czeh B. Stress-Induced Morphological, Cellular and Molecular Changes in the Brain-Lessons Learned from the Chronic Mild Stress Model of Depression. Cells. 2020 Apr; 9(4):1026. doi: 10.3390/cells9041026.

22. Ji R-R, Nackley AG, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. Anesthesiology. 2018 Aug; 129(2): 343-66. doi: 10.1097/ALN.0000000000002130.

23. Sun J, Wang XH, Song FH, Li D-Y, Gao S-J, Zhang L-Q, et al. Inhibition of Brd4 alleviates osteoarthritis pain via suppression of neuroinflammation and activation of Nrf2-mediated antioxidant signalling. Br J Pharmacol. 2023 Dec; 180(24): 3194-214. doi: 10.1111/bph.16195.

24. Carcolé M, Zamanillo D, Merlos M, Fernández-Pastor B, Cabañero D, Maldonado R. Blockade of the Sigma-1 Receptor Relieves Cognitive and Emotional Impairments Associated to Chronic Osteoarthritis Pain. Front Pharmacol. 2019 May; 10: 468. doi: 10.3389/fphar.2019.00468.

25. Carcolé M, Kummer S, Gonçalves L, Zamanillo D, Merlos M, Dickenson A, et al. Sigma-1 receptor modulates neuroinflammation associated with mechanical hypersensitivity and opioid tolerance in a mouse model of osteoarthritis pain. Br J Pharmacol. 2019 Oct; 176(29): 3939-55. doi: 10.1111/bph.14794.

26. Batallé G, Cabarga L, Pol O. The Inhibitory Effects of Slow-Releasing Hydrogen Sulfide Donors in the Mechanical Allodynia, Grip Strength Deficits, and Depressive-Like Behaviors Associated with Chronic Osteoarthritis Pain. Antioxidants. 2019 Dec; 9(1): 31. doi: 10.3390/antiox9010031.

27. Batallé G, Bai X, Pouso-Vázquez E, Roch G, Rodríguez L, Pol O. The Recovery of Cognitive and Affective Deficiencies Linked with Chronic Osteoarthritis Pain and Implicated Pathways by Slow-Releasing Hydrogen Sulfide Treatment. Antioxidants. 2021 Oct; 10(10): 1632. doi: 10.3390/antiox1010163.

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