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REWIEW ARTICLE

Osteoarthritis induced by monosodium iodoacetate model: evolution of inflammatory, nociceptive and histopathological markers

Osteoartrite induzida pelo modelo de monoiodoacetato de sódio: evolução de marcadores inflamatórios, nociceptivos e histopatológicos

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Abstract

Objectives: this study aimed to highlight the evolution of the osteoarthritis (OA) model induced by monosodium iodoacetate (MIA) and its collaboration with the knowledge of the pathophysiology of inflammation, hypernociception and cartilage degeneration. **Methods**: PubMed and Science Direct were used with the descriptors: knee osteoarthritis or osteoarthritis of ankle) and (rat or osteoarthritis induced by monoiodoacetate) and (animal model of osteoarthritis or joint nociception). Studies containing rats, mice, and monoiodoacetate-induced osteoathritis were included. Exclusion criteria were: Animal models of osteoarthritis induced by destabilization; meniscectomy-induced osteoarthritis; non-invasive animal models of osteoarthritis induced by fracture, compression and tibial overload; animal models of osteoarthritis with large animals and models of osteoarthritis by papain or bacterial collagenase. We summarized studies that used MIA to induce knee or ankle OA in rats or mice and the evolution of the inflammatory markers. **Results:** a total of 38 original manuscripts met the inclusion criteria and were considered in the study. The model of OA induced by MIA is well-established and explored with several methodologies and has been widely used in different species. MIA induces cell death, progressive loss of chondrocytes and histological changes that mimics human OA. Studies with this model demonstrated inflammation, neurogenic hyperalgesia, release of cytokines and matrix metalloproteinases. More recently, molecular biology data confirm the activation of nuclear transcription factors, which modulates the expression of citokines in apoptotic chondrocytes. **Conclusion**: the MIA-induced OA has been useful in predicting several characteristics for the elucidation of osteoarthritis pathophysiology.

Keywords: osteoarthritis; inflammation; cartilage; arthralgia; chronic disease.

Resumo

Objetivo: destacar a evolução do modelo de osteoartrite (OA) induzida pelo iodoacetato monossódico (MIA) e sua colaboração com o conhecimento da fisiopatologia da inflamação, hipernocicepção e degeneração da cartilagem. **Métodos**: foram utilizados PubMed e Science Direct com os descritores: osteoartrite do joelho ou osteoartrite do tornozelo) e (rato ou osteoartrite induzida por monoiodoacetato) e (modelo animal de osteoartrite ou nocicepção articular). Foram incluídos estudos contendo ratos, camundongos e osteoartrite induzida por monoiodoacetato. Os critérios de exclusão foram: Modelos animais de osteoartrite induzida por desestabilização; osteoartrite induzida por meniscectomia; modelos animais não invasivos de osteoartrite induzida por fratura, compressão e sobrecarga tibial; modelos animais de osteoartrite com animais de grande porte e modelos de osteoartrite por papaína ou colagenase bacteriana. Resumimos estudos que utilizaram MIA para induzir OA de joelho ou tornozelo em ratos ou camundongos e a evolução dos marcadores inflamatórios. **Resultados**: um total de 38 manuscritos originais atenderam aos critérios de inclusão e foram considerados no estudo. O modelo de OA induzido por MIA está bem estabelecido e explorado com diversas metodologias e tem sido amplamente utilizado em diferentes espécies. O MIA induz morte celular, perda progressiva de condrócitos e alterações histológicas que mimetizam a OA humana. Estudos com este modelo demonstraram inflamação, hiperalgesia neurogênica, liberação de citocinas e metaloproteinases de matriz. Mais recentemente, dados de biologia molecular confirmam a ativação de fatores de transcrição nuclear, que modulam a expressão de citocinas em condrócitos apoptóticos. **Conclusão**: a OA induzida por MIA tem sido útil na predição de diversas características para a elucidação da fisiopatologia da osteoartrite.

Palavras-chave: osteoartrite; inflamação; cartilagem; arthralgia; doença crônica.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent chronic degenerative joint disease leading to disability and affects more than 500 million people worldwide. OA causes irreversible damage to cartilage and subchondral bone due to an imbalance between degradation and synthesis of the extracellular matrix. It is commonly referred to as a chronic disorder affecting the entire joint, which is triggered by biochemical and cellular changes in synovial tissues, leading to histological changes in the joint and dysfunction of the entire tissue. There is currently no cure for OA, in part due to a paucity of understanding of the pathological mechanism of disease onset and progression. Therefore, a better understanding of the signaling pathways and key molecules involved in the pathogenesis of OA is crucial for the development of new therapeutic targets[1].

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Systemic or topical pharmacological treatments for OA exhibit are palliative and are only reflected in improving the patient's quality of life, maintaining satisfactory joint mobility, and reducing severe joint pain. Classical anti-inflammatory drugs (NSAIDs or corticosteroids), topical or systemic, are the first line of analgesic medication, but their use may be limited, given the undesirable effects on the cardiovascular, gastrointestinal, and renal systems. Experimental research into inflammatory arthropathies has invested in animal models that are capable of reproducing the pathological changes observed in humans. We can highlight the chemical induction of osteoarthritis by sodium monoiodoacetate (MIA), which mimics the inflammatory and degenerative characteristics of articular cartilage[2].

MIA-induced OA mimics primary OA in humans, with joint histological changes, synovitis, and cartilage degeneration. In the above-mentioned model, hypernociception is mainly caused by inflammatory mediators, such as TNF-α, IL-1β and IL-6, exposure of the subchondral bone, damage to sensory nerve endings and inflammatory changes in the dorsal root ganglion and spinal cord. Thus, both peripheral and central mechanisms appear to contribute to hypernociception in advanced stages of MIA-induced OA[3].

The field of research into inflammatory arthropathies has increased since its pathophysiology is unclear and therapy is inefficient. Currently, pharmacological treatments that slow the progression of disease in the joint and reduce symptoms known as "DMOADs", demonstrate a slowdown in the clinical signs and symptoms of OA. Some endotypes used in this treatment are cartilage-based, such as ADAMTS-5 inhibitors, fibroblast growth factor (FGF-18), inhibitors of the Wnt/ß-catenin signaling pathway, senolytic agents, and gene therapy.[4]

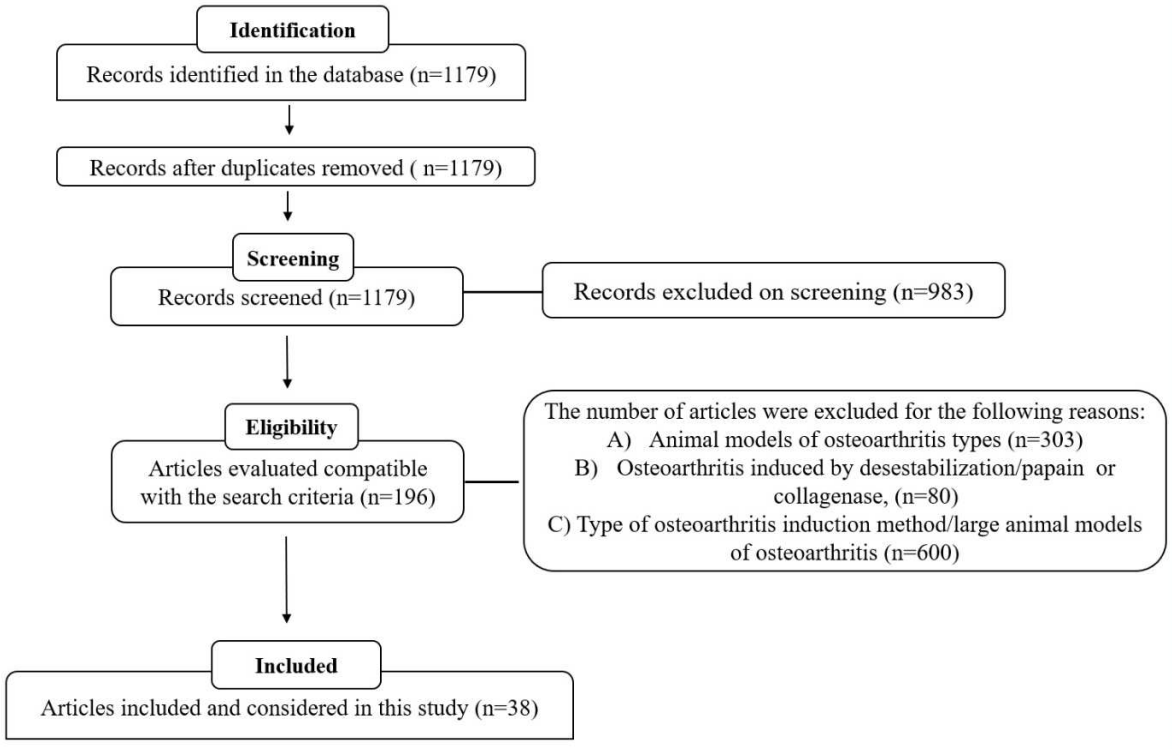
METHODOLOGY

This review focuses on the main effects of monoidoacetate in intra-articular injection. A literature search was performed in electronic databases, including PubMed and Science Direct, using the following descriptors: (Knee Osteoarthritis OR Osteoarthritis of ankle) AND (Rat OR Osteoarthritis induced by Monoiodoacetate) and (Animal model of osteoarthritis or Joint nociception). Only studies containing rats, mice, and monoiodoacetate-induced osteoathritis were included from August to December 2023. Exclusion criteria were: Animal models of osteoarthritis induced joint destabilization; medial lateral partial meniscectomy-induced osteoarthritis models; non-invasive animal models of osteoarthritis induced by intra-articular fracture or compression and tibial overload; in addition, studies with animal models of osteoarthritis with large animals. Furthermore, models of osteoarthritis established by chemical induction, such as papain or bacterial collagenase, were considered exclusionary criteria. We summarized the studies that used intra-articular injection of MIA to induce knee and ankle OA in rats or mice, as well as the evolution and complexity of the inflammatory markers involved in the studies.

RESULTS AND DISCUSSION

The first database searches identified 1179 articles. After screening, considering the titles, and checking the abstracts, 983 articles were excluded, leaving 196. To compose the final sample, the inclusion criteria were applied, and 38 articles were considered to meet the study objectives. (Figure 1).

Figure 1. Diagram of search criteria and selection of studies related to the research topic



Inflammatory markers and hypernociception in osteoarthritis

A series of cytokines are found in the pathophysiology of osteoarthritis, being responsible for several events such as the degradation of collagenases and metalloproteinases (MMP'S), ADAMTS and TIMP, induction of nitric oxide synthase, COX2 and PGE2 synthase, activating signaling pathways of NF-κB and MAPK, leading to catabolic reactions (degradation of proteoglycans and collagen rupture). They also inhibit the synthesis of type II collagen, increase the expression of chemokines, and stimulate the release of vascular endothelial growth factors in synovial fibroblasts (Table 1).

Table 1. Main cytokines involved in the pathophysiology of osteoarthritis

Cytokines	Source	Effects	Pharmacological Therapy	References
TNF-α	Macrophages/monocytes	Degradation by inducing collagenases and aggrecanases including MMP-1, MMP-3, MMP-13 and ADAMTS-4. Production of iNOS, COX-2 and PGE-2 synthase.	Infliximab, etanercept and adalimumab	Kloppenburg (2018)[38]
IL-1β	Synoviocytes, osteoblasts, osteoclasts, and inflammatory cells such as macrophages	Activation of NF-κB and MAPK, increases the expression of MMP-1, MMP-3, MMP-13 and ADAMTS-4, IL-8, CCL2 and CCL5, IL-6 and TNF-α and inhibits type II collagen.	Arthrokinex and Orthokine	Barreto; Braun (2016)[39]
IL-6	Chondrocytes, osteoblasts and synoviocytes	Activation of PI3K, JAK/STAT and MAPK pathways, regulates the production of TIMP-1, MMP-1 and ADAMTS and decreases the synthesis of type II collagen and proteoglycans.	Tofacitinib and MR16-1	Kjelgaard-Petersen et al (2019)[40]
IL-8	Chondrocytes	Promote release of matrix metalloproteinase-13 (MMP-13), neutrophil accumulation leukocyte migration.		
IL-15	Fibroblasts, synoviocytes, phagocytes, skeletal muscle, inflammatory cells	Enhances the production of MMP-1, 3, 7 and 9.		
IL-17	Fibroblast-like Synoviocytes, natural killer (NK) cells, osteoblastos and macrophages	Enhance the levels of TNF-α, IL-1 and IL-6 and estimulates the release of VEGF.	Not found	
IL-18	Chondrocytes, osteoblasts, synoviocytes, dendritic cells and osteoblasts	Increase the synthesis MMP-1, MMP-3 and MMP-13. Activates NF-κB and MAPK-p38-AP1 pathways, upregulates COX-2, PGE-2, IL-6 and TNF-α in chondrocytes and synoviocytes.		

TNF-α: tumor necrosis alpha, MMP-1: metalloproteinase-1, MMP-3: metalloproteinase-3, MMP-13: metalloproteinase-13, ADAMTS-4: metalloproteinase with thrombospondin motifs 4, iNOS: inducible nitric oxide synthase, COX-2: cyclooxygenase-2, PGE2: prostaglandin E2, IL- 1β: Interleukin-1 beta, NF-κB: factor nuclear kappa B, MAPK: map quinase, CCL2: chemokine ligand 2, CCL5: chemokine ligand 5, IL-6: Interleukin-6, PI3K: fosfatidil-inositol 3-quinase, TIMP-1: metallopeptidase inhibitor 1, IL-8: interleukin-8, IL-15: interleukin-15, MMP-7: metalloproteinase-7, MMP-9: metalloproteinase-9, Il-17: interleukin-17, IL-18: interleukin-18, VEGF: vascular endothelial growth factor.

The literature demonstrates therapies that target cytokines (TNF-α, IL-1β, and IL-6) in OA. The TNF-α inhibitor (infliximab and etanecerpt) has effects on modifying the structure in OA joints with the presence of inflammation, neutralization of target proteins, but also mediates signals through unexpected receptors, such as tmTNF and/or Fc receptors and manipulation of proteases. The IL-1β inhibitors (arthrokinex and orthokine) were shown to have a chondroprotective effect in the joint, and IL-6 inhibitor (tofacitinib and MR16-1) blocked cytokine-induced proteoglycan loss and restored collagen type II synthesis, reducing the cartilage destruction, osteophyte formation and synovitis.

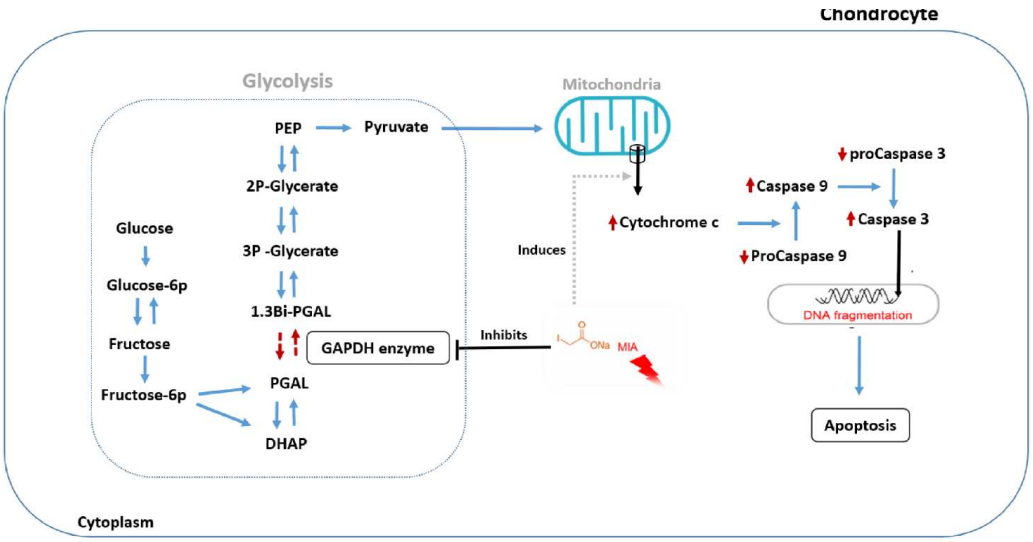
MIA-induced osteoarthritis model

The sodium monoiodoacetate-induced OA model was first described by Kalbhen and Blum5 (1977) as a model of experimental articular osteoarthritis in rats. The application

of intra-articular MIA causes a chronic degeneration of the articular hyaline cartilage, with signs of hypernociception and inflammatory process, inducing severe damage with marked aspects of hyperalgesia and tissue degeneration, simulating chronic studies with animals[6].

Recent experimental studies point out MIA as an OA inducer closer to clinical practice for altering chondrocyte metabolism by inhibiting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in chondrocytes; MIA blocks glycolysis, stopping ATP synthesis, causing the death of these cells. In vitro, MIA inhibits cell proliferation and increases oxidative stress and apoptosis by activation of the caspase pathway in chondrocytes[7] (Figure 2).

Figure 2. Cascading effects on chondrocytes caused by MIA

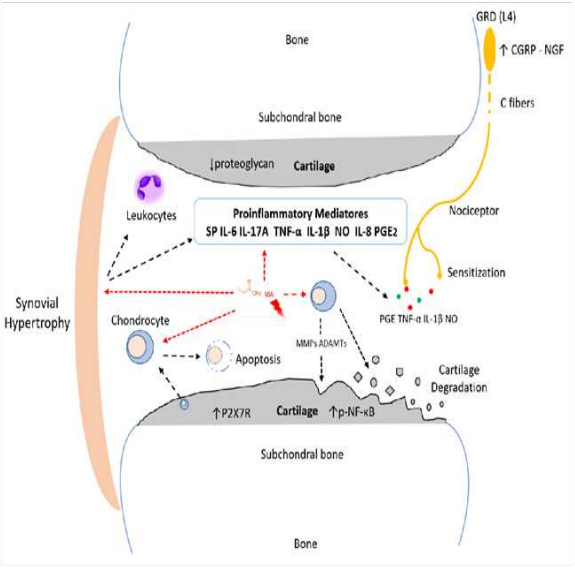


Cascading effects on chondrocytes caused by MIA. MIA inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in chondrocytes, blocking glycolysis, stopping ATP synthesis, enhancing cytochrome c, and activating the caspases pathway.

In addition, exposure to MIA causes lesions in the subchondral bone, an innervated and vascularized structure, resulting in nociception due to the expression of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-17A, TNFα in type C fibers as well such as matrix metalloproteinases (MMP1, MMP-3, and MMP-13) in articular cartilage. MIA is capable of inducing the maximum release of TNF-α and IL-6 in synovial tissue and the joint capsule four days after injection and remains elevated for 28 days. Consequently, the presence of these cytokines sensitizes primary nociceptors, contributing to joint hypernociception and tissue changes in the synovium and potential catabolic effect on articular cartilage components[3,8].

Many of the apoptotic events involving chondrocytes induced by MIA exhibited dependence on the mitochondria due to the increase in the concentrations of reactive oxygen species (ROS) and activation of caspases. Altogether, these MIA effects manifested in joint damage and inflammatory processes similar to human osteoarthritis, mainly because it induces severe chondrocyte apoptosis, destroying articular cartilage, very similar to what is observed in advanced cases of OA7 (Figure 3).

Figure 3. Main effects of MIA on synovial joint.

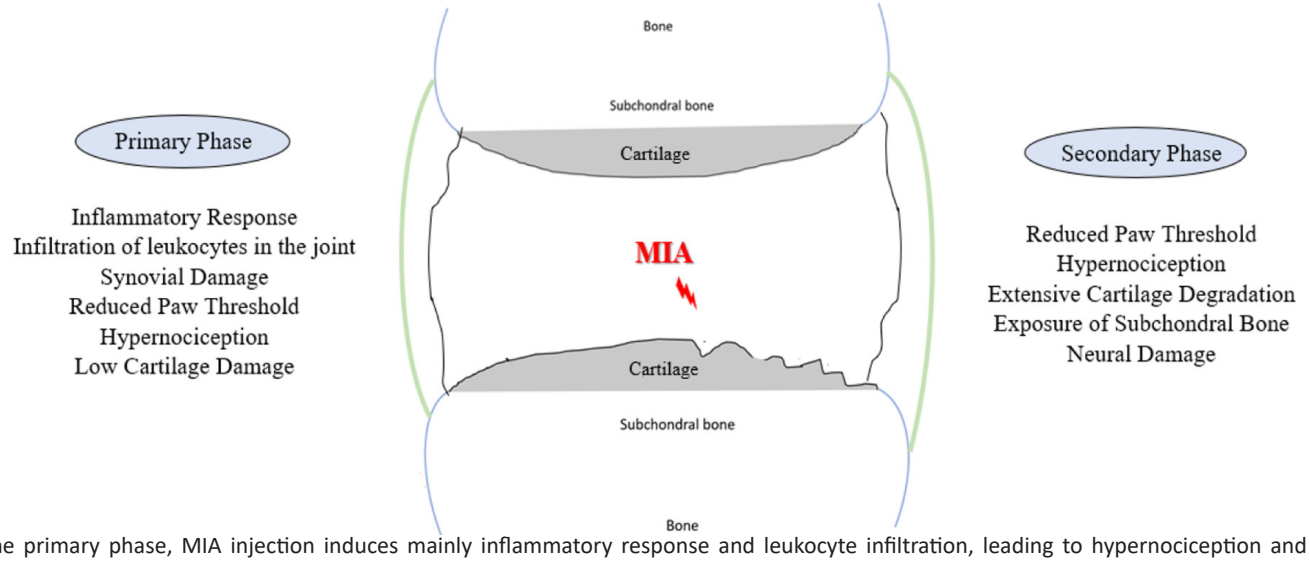


Main effects of MIA on the synovial joint. MIA induces synovial hypertrophy, cytokines release by synovial cells, chondrocyte apoptosis, and cartilage degradation. The synovial cells activated in the inflamed synovium produce catabolic and pro-inflammatory mediators that lead to excessive production of the proteolytic enzymes responsible for the breakdown of cartilage. TNF-α, tumor necrosis fator alpha, IL-1β, Interleukin-1beta, NO, nitric oxide, PGE2, prostaglandin E2, MMPs, matrix metalloproteinase, IL-17A, Interleukin 17A.

Hypernociception in MIA-induced osteoarhritis model

Hypernociception in MIA-induced OA has a biphasic characteristic, where the primary phase is caused by infiltration of mononuclear and polymorphonuclear leukocytes, edema and several inflationary mediators, such as TNF-α, IL-1β, IL-6, SP and PGE2, initiating from the 5th day, being evidenced by the decrease in the mechanical threshold in the first two weeks in addition to the reduction in the weight distributed on the affected limb, with maximum effect on the 7th day after induction. In the secondary phase, nociception is also caused by inflammatory mediators, associated with bone exposure and a neuroinflammatory state in the dorsal root ganglia and spinal cord, beginning on the 21st day after induction with asymmetry in weight distribution[2,8] (Figure 4).

Figure 4. Major joint changes in the MIA-induced osteoarthritis model.



In the primary phase, MIA injection induces mainly inflammatory response and leukocyte infiltration, leading to hypernociception and low cartilage damage. The secondary phase is characterized by extensive degradation of the cartilage, exposure of the subchondral bone, and inflammation.

MIA induces nociceptive sensitization peripherally and in the spinal cord, with activation in specific subcortical and hippocampal areas and increased functional connectivity in the mediodorsal nucleus, hippocampal nucleus, and globus pallidus. The rapid induction of nociception in the OA-MIA model allows for careful evaluation of analgesic compounds. It is advantageous concerning existing surgical models and the spontaneous development of OA. Therefore, the use of the MIA chemical model in the development of compounds allows the use of preventive and therapeutic protocols in the development and maintenance of nociception similar to OA[6].

In this context, the literature demonstrates that CB1 and PPARα receptors are involved in mediating MIA-induced nociception in murine OA and that noradrenergic and serotonergic components contribute to the expression of nociceptive inhibitory controls in the offspring[2]. Furthermore, σ1R receptor blockade, by modulating microglial activity in the medial prefrontal cortex, reduces cognitive and emotional changes associated with MIA-induced nociception9. It is important to highlight that the induction of OA by MIA in mice in the ankle versus knee joint has different characteristics, which is similar to that found in human patients with OA, mainly because different joints of the same limb may present different markers of hypernociception and inflammation[10].

Evolution of the MIA-induced osteoarthritis model

Changes in the cartilage structure induced by MIA can be measured and classified into different scores, such as the OARSI scores, one of the most used to evaluate the physical state of cartilage. In several studies, histological evaluations with toluidine blue of these tissues also demonstrated significant losses of chondrocytes and proteoglycans in the femorotibial or tibiotarsal articular cartilage of rats. MIA induces areas of erosion, loss of cartilaginous matrix in the superficial and middle zone, areas of denudation with loss of cartilaginous coating, and similar damage to the articular cartilage coating and bone exposure[6].

In vitro assays with chondrocytes demonstrate that MIA inhibits cell proliferation and increases levels of oxidative stress, apoptosis, and loss of proteoglycans associated with high expression of pro-inflammatory cytokines such as IL-6, IL-17A, TNF-α, and matrix metalloproteinases (MMP1, MMP-3, and MMP-13), thus explaining the different levels of damage observed in cartilage[7].

The loss of type II collagen and the inflammatory process induced by MIA is a condition that can be reversed by physical exercise. However, physical exercise, when performed in exposure to

particles, can increase the severity of OA by exacerbating the inflammatory process systemically. Some studies that investigated the effects of resources from natural sources, such as galactomannans5, curcumin, isorhamnetin, and others, showed that these biomolecules reduce the inflammatory process and are capable of protecting articular cartilage from serious damage caused by MIA Although OA is associated with aging, there is a genetic character, which is why gene therapy with murine animals was explored in this model, realizing that this is another important tool to study and modulate the genetic components[11,12] (Table 2).

Table 2. Main inflammatory and nociceptive markers involved in MIA-induced OA

Methodology	Main results	References
OA induced by MIA (1 mg/kg). Hypernociception and histopathological evaluation, dosage of TNF, caspase-3 and NFkB.	Imbalance in weight support, damage to articular cartilage, destruction of chondrocytes, expressions of nitrotyrosine, TNF-α and caspase-3.	Park et al. (2019)[25]
OA induced by MIA (10 mg/ml). Mechanical hypernociception, cognitive, behavioral (anxiety and depression) test, study of the local effect of the σ1R receptor antagonist on cartilage degradation and its central effects on microglial reactivity in the medial prefrontal córtex.	Mechanical hypernociception, cognitive deficits and depressive states associated with OA hypernociception. These effects are associated with central modulation of glial activity.	Carcolé et al. (2019)[9]
OA induced by MIA (2 mg/kg). Electrophysiological evaluation in the dorsal horn of the spinal cord, mechanical hypernociception, mRNA levels of the α2-adrenergic receptor and 5-HT.	Rats induced to OA by late-stage MIA showed disregulation in the downward modulation of nociception and the activation of α2-adrenergic or 5-HT receptors restored downward nociceptive.	Lockwood et al. (2019)[2]
OA induced by MIA (3 mg/kg). Knee swelling test, histology, serum inflammatory biomarkers (NO, PGE2, expression of iNOS and COX 2) and western blot.	Isorhamnetin reduced knee swelling, inhibition of NO, PGE2, Inos, COX-2, COMP, CTX-II and osteopontin (OPN).	Tsai et al (2019)[11]
OA induced by MIA (4 mg/kg). Western blot of GLP-1R (PKA / CREB pathway). Immunoprecipitation to detect interactions between GLP-1R and PKA / CREB pathway	GLP-1R levels decreased, accompanied by negative regulation of PKA / CREB.	Que et al. (2019)[12]
OA induced MIA (2 mg/kg). Chondrocyte count and non-calcified cartilage thickness evaluated morphometrically on slides with hematoxylin and eosin (H&E)	The treatment with platelet-rich plasma in monoiodoacetate-induced OA increased the chondrocyte count and the height of the articular cartilage.	Asjid et al. (2019)[26]
OA induced by MIA (2 mg/0.05 ml). Hypernociception and histopathological evaluation, immunohistochemistry of the dorsal horn and the integrity of the articular cartilage.	Reduced optical densitometry of the cartilage in the superficial layers, reflecting the deceased in proteoglycans and chondrocytes. Enhanced activity spinal glial cells on hypernociception.	Balbinot et al. (2019)[27]
OA induced by MIA (2 mg/kg). Evaluation of mechanical hypernociception, weight support during walking (dynamic) and orthostatic (static).	MIA showed a dynamic weight reduction at different times. However, the different induction sites caused similar reductions in static weight during the initial phase.	Möller et al. (2019)[10]
OA induced by MIA (2 mg/kg). Hypernociception, immunohistochemical and levels of superoxide anion in the spinal cord determined using dihydroetide (DHE).	P47phox attenuated pain behaviors, cartilage damage and ROS production in the knee joints with MIA-induced OA.	Shin et al. (2020)[28]
OA induced by MIA (3 mg/kg). Evaluation of hypernociception and intravital microscope to measure leukocyte trafficking in the synovial microvasculature.	Local injection of KML29 reduced joint pain at day 14 Reduction in withdrawal threshold and leukocyte trafficking was seen after treatment with KML29 + CXB ameliorated the development of mechanical secondary allodynia.	Philpott et al. (2020)[29]

Methodology	Main results	References
OA induced by MIA (60 mg/ml). Evaluation of joint volume, oxidative stress and nitrosative biomarkers (MDA, GSH and NO), citokynes: IL-6, IL-1 and TNF-α, radiographic and histopathological analysis.	Enhaced serum levels of MDA, GSH, NOx, IL-6, IL-1β and the TNF-α. Changes in radiographic images and histopathological of the joint.	Jaleel et al (2020)[30]
OA induced by MIA (2mg/kg). Knee-Bend and CatWalk tests. Immunofluorescence for TLR4 and ATF-3 was performed in L3-L5 DRG and histopathological evaluation.	TLR4-A1 reduced movement-induced nociception in OA animals in the Knee-Bend test. Moreover, the increase of ATF-3 expression observed in DRG of OA animals	Ferreira-gomes et al (2021)[31]
OA induced by MIA (2mg/kg). Behavioral tests (open field test, von frey and weight bearing), histopatological analysis and immunohistochemistry.	Low optical densitometry cartilage was evident in superficial layers, likely reflecting the reduced proteoglycan and chondrocyte contents and enhanced spinal glial cells pain-like behavior	Balbinot et al (2021)[17]
OA induced by MIA (1mg/kg). Measurement of swelling (edema), gait test, determination of kellgren-lawrence score (cartilage evaluation), biochemical analysis, western blot and histopathology.	Serum IL-1β, IL-6, TNF α, COMP, and CRP increased in rats with OA and enhanced MDA and knee joint MMP 3, NF κB, and TGβ protein levels. Enhanced joint diameters with joint pain behavior.	Sahin et al (2021)[18]
OA induced by MIA (1 mg/kg). Serum levels of TNF-α, IL-1β, IL-6, cartilage oligomeric matrix protein (COMP), c-reactive protein (CRP), prostaglandin E2 (PGE2), and osteocalcin (OCN), gail test and joint swelling, western blotting radiographic and histopathological analysis.	Enhanced Kellgren-Lawrence scoring, serum levels of inflammatory cytokines IL-1β, IL-6, TNF-α, COMP, CRP, COX-2, MCP-1, NF-κB, MMP-3 and RANKL.	Orhan et al (2021)[20]
OA induced by MIA (0,05ml /2%). RT-PCR of Tlr2, Tlr4, Nfkb1 and Comp. Elisa assay kit of IL-6, IL-8, TGF-β1, IGF-1, COMP, ACAN, CHI3L1, CTSK, and TLR-2.	OA induced by MIA caused significant increase of TLR-2 soluble form and IL-6, IL-8, TGF-β1, COMP, ACAN, CHI3L1, and CTSK levels in the blood serum;	Korotkyi et al (2021)[21]
OA induced by MIA (1 mg/kg). Dynamic weight-bearing device for pain behavior, histopathology analysis, extracellular electrophysiological recordings of knee joint.	Early pain (3 day) in MIA-induced OA involves activation and sensitization of nerves that innervate the joint capsule but not the underlying subchondral bone, and pain in late MIA-induced OA (28 days) involves the additional recruitment of nerves that innervate the subchondral bone.	Morgan et al (2022)[32]
OA induced by MIA (0,5 mg/kg). Evaluation of hypernociception, histopathology and immunoreactive neurons for calcitonin gene-related peptide (CGRP) in dorsal root ganglia (DRG).	The OA-MIA induced hypernociception. Tramadol groups showed significant cartilage reduction and degeneration and supression of CGRP expression in DRG.	Kanno et al (2022)[33]
OA induced by MIA (2 mg/kg). Hypernociception, computed tomography, immunohistochemical of the DRG and Iba1 microglia in the spinal cord.	The OA-MIA elevated pain sensitivity and CGRP and Iba1 expression in the DRG and spinal cord.	Arai et al (2022)[34]
OA induced by MIA (2 mg/kg). Pain and behavior assessement, histopathological and immunohistochemical analysis.	The OA-MIA induced the cartilage degeneration, pain behavior, histopathological alterations and elevated MMP13 and Col10 expressions.	Chen et al (2022)[35]
OA induced by MIA (2 mg/kg). Joint diameter measure, radiographic analysis, Elisa assays (IL-β, IL-6, TNF-α, IL10, and TGF-β), RT-PCR (NF-Kb, iNOS, and type II collagen) and Western blot (caspase-3).	BM-MSCs reduced IL-1β, IL-6, and TNF-α) and increased levels of IL-10 and TGF-β. BM-MSCs decreased expression of NF-κB, iNOS, caspase-3 and increased expression of type II collagen. The hematoxylin/eosin-stained sections revealed that BM-MSC administration ameliorated the knee joint alterations in MIA-injected rats.	Hamdalla et al (2022)[36]

Methodology	Main results	References
OA induced by MIA (0.25, 0.5, 1.0, 2.0, and 4.0 mg) and radiographic and histological evaluations of the hip joint were performed.	The degree of OA changes increased as the dose of MIA increased. MIA (0.25 mg and 0.5 mg) induced both radiographic and histological changes in a time-dependent manner, whereas more than 2 mg of MIA provoked end-stage.	Yoh et al (2022)[37]
OA induced by MIA (2 mg/kg). Dosage of NO, MDA, MPO, GSH, catalase, TNF- α and histopathological analysis.	Treatment with NR in a similar dose with HC decreased blood/serum levels of oxidative stress biomarkers and the histological lesions. NR may exhibit chondroprotective and anti-inflammatory effects in MIA-induced KOA in rats.	Gherghina et al (2023)[13]
MIA induced OA (3mg). RNA extraction and RT-PCR, immunohistochemistry, immunoflorescence, primary culture of DRG neurons and whole cell patch clamp recordings, single nerve recording in C- or Aδ-afferent nerve fibers innervating knee joint, mechanical allodynia and dynamic weight bearing test.	TG-C alleviates MIA-induced pain behavior, suppresses the expression of NGF, neuronal sensitization factors and regulates the activation status of immune cells in DRG. TG-C also downregulates the expression of GAP43 and CGRP in knee joint tissues and neuronal hyperexcitabiities of DRG, afferent nerve fiber and spinal cord are attenuated.	Park et al (2023)[14]
MIA induced OA (3mg). Articular diameter, ELISA assay kit, histopathology, rotarod performance test RT-PCR and westernblot analysis.	Probenecid and/or L-carnitine reduced articular diameter and reestablished motor coordination and joint mobility. High levels of IL-1β, IL-18, IL-6 and TNF-α through the miRNA-373/P2X7/NLRP3/NF-κB pathway were suppressed. Reduction in protein expressions: P2X7, NLRP3, caspase -1 and NF-κB. An increase in expression of procaspase-1, miRNA-373 IκB proteins. In histopathology, a positive reverse of the joint structural changes.	Mahfouz et al (2023)[15]
MIA induced OA (0,75 mg/kg). Body weight and mechanical hypernociception, histopathology, radiographic analysis, RT PCR, ELISA kit assays, western blottling, cell culture and cell-counting kit 8 assay.	In vivo, PDL reduced pain, decreased OA-induced cartilage damage and degradation, decreased pro-inflammatory cytokine production in serum, and suppressed mRNA expression levels of IL-1β, IL-6, and TNF- α. In RAW264.7 cells, PDL prevented LPS-induced activation of ERK/Akt pathway and decreased the levels of TNF-α , IL-1β, IL-6.	Fang et al (2023)[16]

Nicotinamide riboside (NR), a precursor of NAD+, can improve oxidative stress and histological lesions, making it a high-potential treatment option in the early stages of OA. Its use as an adjunctive therapy is promising due to its potential to increase energy production, reduce inflammation, improve chondrocyte function, and neutralize and for its bioavailability and greater potential to increase NAD+ levels[13].

TG-C significantly alleviated pain-related behavior by restoring altered dynamic weight-bearing and reducing the mechanical threshold of the affected hindlimb in the MIA-induced OA model and recovered neuronal hyperexcitability by restoring RMP and firing threshold and the frequency of DRG neurons, attenuating the firing rates of C or Aδ nerve mechanosensitive fibers innervating the knee joint and decreasing the increase in miniature and evoked excitatory postsynaptic currents (mEPSCs and eEPSCs) in the spinal cord, by a single intra-articular injection of TG-C, thus being able to effectively modulate the positive regulation of pain mediators in peripheral tissues and the nervous system. Thus, TG-C can be a disease-modifying osteoarthritis drug (DMOADs), being a promising therapy for relieving chronic pain and improving joint function[14].

L-carnitine enhanced the anti-inflammatory effect of probenecid to attenuate MIA-induced osteoarthritis in rats by eliciting the level of miRNA-373 and inhibiting the P2X7/NLRP3/NF-κB milieu, leading to the suppression of serum inflammatory cytokines: IL-1β, IL-18, IL-6, and TNF-α. The combination therapy also had a more prominent effect in reducing joint edema, improving motor balance, and reversing structural changes in the joint. The most significant reductions in knee OA were observed in the combination therapy, demonstrating the importance of the new combination in the treatment of OA[15].

Pudilan Tablets (PDL) relieve joint pain, suppress the generation of pro-inflammatory cytokines and mediators, and preserve cartilage in the OA mouse model. PDL also shows anti-inflammatory effects in RAW264.7 cells treated with LPS,

decreasing the production of TNF-α, IL-1β, and IL-6 through the ERK/Akt signaling pathway, showing that PDL may be a candidate for the treatment of OA16.

It is worth mentioning that MIA can act directly on cartilage and alter weight bearing in addition to causing central sensitization in the spinal cord. At the tissue level, reactive astrogliosis is induced, which may be related to late nociception17, a highly relevant finding as they reproduce changes similar to the central sensitization observed in human OA. Other recent studies18 show increased production of cytokines MAPK signaling pathway19 and pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, COMP and CRP, IG6, COX2, NF-κB. Other works show microstructural deformations in the joint and some catabolic signaling pathways (NF-κB) and inflammatory mediators (COX-2, PGE2, IRF-7, MCP-1) and MMP3, RANKL20, suggesting new markers such as COMP, CRP and IG6 as a study tool in OA.
At the molecular level, MIA causes a significant increase in the soluble form of TLR-2 and the levels of TGF-β1, COMP, ACAN, CHI3L1, and CTSK in blood serum; the level of IGF-1, increased expression of the Tlr2, Tlr4, and NfkB1 genes, regulating the NF-κB pathway mediated by TLR-2/421. The results may provide evidence to support the effects of MIA on OA in ovariectomized rats22 and in expanding the understanding of the physiopathology of OA in different males and females.

It has been demonstrated that MIA inhibits chondrocytes proliferation and increases oxidative stress, apoptosis, and loss of proteoglycans, in addition to elevated concentrations of pro-inflammatory cytokines such as IL-6, IL-17A, TNF-α, and matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) and caspase activation6.

In in vivo studies, intra-articular infiltration with MIA causes biphasic mechanical hypernociception, the first associated with acute inflammatory processes in the synovial joint, hypomobility due to nociception with peripheral sensitization and synovial damage and the second phase related to damage to cartilaginous and bone tissue, inflammation characterized by expansion of the synovial membrane, protein edema, infiltration of neutrophils, macrophages, basophils, plasma cells, and lymphocytes, lasting seven (7) days, decreased acute inflammation, but there is continued nociception, progressive hypomobility, exposure of the subchondral bone and marginal osteophytes[2,6].

Thus, previous studies postulate that the first phase of joint nociception is mediated by the inflammatory infiltrate, while the second phase (above seven days) may be related to structural changes in the cartilage and subchondral bone. Subchondral bone and synovium, unlike cartilage, are innervated; therefore, in the late stages of OA, both exposed subchondral bone and synovium can produce joint hypernociception. The onset of secondary hypomobility characterizes the transition between the early silent stage and the late stage of this disease in rats, as has been observed in human OA23.

Although the inflammatory process reduces approximately 14 days after induction, concentrations of TNF-α and IL-6 remain elevated in synovial fluid for up to 28 days and result in exposure of the subchondral bone after 56 days of induction. In the MIA-induced OA model, progressive tactile allodynia and elevated concentrations of cytokines (TNF-α, IL-6, and NGF) in the femoral-tibial joint and increased spinal content of substance P (SP) and peptide related to the calcitonin gene (CGRP) have been demonstrated. Both neuropeptides are released from sensitized nociceptors and facilitate the generation of spinal hyperexcitability[3].

In the MIA-induced OA model, ipsilateral dorsal root ganglion (DRG) neurons showed high immunoreactivity for CGRP, reaching a peak 14 days after intra-articular injection with MIA, while there was high immunoreactivity in DRG neurons for markers of neuronal injury and axonal regeneration, ATF3 and GAP43. In addition to these changes in DRGs, MIA injection also induced significant proliferation of microglia in the ipsilateral dorsal horn of the spinal cord. Other in vivo studies detected high concentrations of TNF-α, IL-1β, IL-6, prostaglandin E2 (PGE2), substance P, MMP-13, and purinergic receptor (P2X7) in cartilage tissue during the early and late phases of the model, which may be related to hyperalgesia and joint wear, associated with increased concentrations of oxidative stress markers and reduced antioxidant reaction, both at joint and systemic levels[3].

Recent studies with dorsal root ganglia (DRG) and spinal cord in MIA-induced OA show that in the late phase (14-21 days), hyperalgesia may be the result of changes in the descending inhibitory and facilitatory control pathways in the brainstem, caused by the action of microglia in the dorsal horn of the spinal cord. The activation and proliferation of microglia causes the release of cytokines, mainly IL-1β, which contributes to central sensitization in the dorsal horn of the spinal cord24. Taken together, all these effects of MIA manifest themselves in hypernociception, joint damage, and inflammatory processes similar to human osteoarthritis. Therefore, the MIA-induced OA model mimics the clinical and histopathological signs of the human disease, that is, pain, joint wear, and functional impairment of the joint, as shown in Table 3.

Table 3. Comparison between the main inflammatory and nociceptive markers involved in human and MIA-induced OA

Human OA	MIA-induced OA	
Inflammatory mediators	TNF-α, IL-1β, IL-6, IL-15, IL-17, IL-18, IL-21, IL-22, LIF, CGRP, SP, NGF, TGF-β3, CCL2, CCL3, CCL 4 e CCL 5, IL-8, GROα, MCP-1, SDF1, NO, PGE2, IL-4, IL-10, IL-13,	TNF-α, IL-1β, IL-6, IL-17, CGRP, SP, NGF, SDF1, NO, PGE2.

Human OA	MIA-induced OA	
Histological changes	Synovial hypertrophy and hyperplasia, osteophytosis, bone sclerosis, cartilage destruction, subchondral bone exposure, bone marrow damage, neovascularization and innervation in cartilage.	Synovial hypertrophy, osteophytosis, bone sclerosis, cartilage destruction, subchondral bone exposure, bone marrow damage, neovascularization and cartilage innervation.
Clinical features	Persistent pain, edema, stiffness and reduced flexibility, muscle atrophy and radiographic changes	Hypernociception, edema, hypomobility, radiographic changes, rigidity and reduced flexibility
References	Molnar et al., 2021; Du et al., 2023	Morais et al., 2016; Orita et al., 2011,

FINAL CONSIDERATIONS

Osteoarthritis is an arthropathy with diverse manifestations involving inflammation and molecular and neurological mechanisms of hypernociception. Reproducing all the characteristics of the pathophysiology of OA in animal models has been challenging; even so, important advances in animal models of OA have achieved great discoveries. MIA, in a sufficient dose, is used to reproduce quickly OA-like lesions and functional impairment in rodents, similar to the ones seen in human diseases. These parameters, as well as the metabolism of proteoglycans, collagen, inflammatory, and nociceptive markers, can serve as indicators to study imaging techniques, chondroprotective or analgesic drugs, and to evaluate chondral lesions. In general, the osteoarthritis model induced by MIA has demonstrated several predictive characteristics for studies of experimental osteoarthritis and explored several relevant protocols and markers for understanding osteoarthritis and developing new therapies.

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