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Review Article

Potential Application of Clodronate in Fibromyalgia

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Abstract

Fibromyalgia (FM) is a condition with an uncertain etiology, primarily characterized by chronic widespread pain, particularly in the axial muscles and skeleton, alongside fatigue, sleep disturbances, and mood disorders. This pathology is thought to result from heightened central nervous system (CNS) sensitivity, which amplifies peripheral signals and reflects an altered function of antinociceptive pathways. Although the pathogenesis of FM remains incompletely understood, emerging research highlights the role of potential trigger events that may initiate CNS hypersensitivity.

Keywords: *Fibromyalgia; Clodronate; Microglia; Nociplastic Pain*

Introduction

Pain is among the most ancient biological responses, yet it remains one of the least understood in terms of pathophysiology and effective treatment. Even recent advances in pain research have left unanswered questions and therapeutic challenges, likely due to the complex interplay of biological, psychological, and environmental factors contributing to pain symptomatology [1]. In this paper, we wanted to highlight some of the events responsible for the typical symptomatology of FM and emphasize how the pharmacological characteristics of a particular bisphosphonate, Clodronate, can potentially counteract its pathogenesis.

Nociplastic pain

Various pain classifications based on etiology, duration, and anatomical location have evolved over time. In 2017, the International Association for the Study of Pain introduced a new classification, distinguishing between nociceptive, neuropathic, and nociplastic pain. Nociplastic pain occurs without clear peripheral or sensory nervous system damage but is instead attributed to CNS sensitization, leading to neural signal amplification and central modulation resulting in hypersensitivity [2,3]. This category includes conditions such as FM, migraine, irritable bowel syndrome, and chronic back pain. Fibromyalgia is considered a prototype of nociplastic pain due to its symptoms, including generalized muscle pain, fatigue, depression, sleep disturbances, allodynia, and hyperalgesia [4].

Central sensitization in FM may result from chronic increases in substance P and glutamate followed by NMDA and AMPA receptor hyperactivation, microglial activation and polarization to a proinflammatory M1 phenotype, and diminished central neuroinhibitors like GABA [5,6].

Microglia and pain

Microglia may represent a critical CNS interface between both peripheral nerves and higher CNS centers. A prominent role of microglia in Nociplastic pain, as well as in Fibromyalgia, is also demonstrated by the imbalance between microglial cells with M1 versus M2 phenotype and the presence of numerous cytokines and chemokines responsible for a state of neuroinflammation with consequences for central modulation of pain [3,7].

Experimental data suggest that activated spinal microglia, particularly through ATP, cytokines, and substance P, contribute to nociplastic pain [8].

In FM, ATP sensitizes purinergic receptors, including P2Y12, P2Y13, P2X4, and P2X7 and activate microglial cells stimulating TNF-α expression [9,10]. Although FM is not classified as an immune disease, FM patients exhibit a systemic inflammatory profile with elevated Th1 cells, reduced Th2 and presence of anti-inflammatory cytokines (IL-4, IL-5, IL-13), and systemic inflammatory biomarkers (e.g. ESR, CRP) [11].

Microglial activation, an ATP-triggered process involving peripheral nerve and microglial interactions, underscores the need to identify therapies modulating immune factors and blocking adverse signaling at spinal synapses, thereby potentially disrupting pain signaling pathways to the brain.

In addition to ATP and cytokines, in the pathophysiology of FM substance P is also important. Substance P is a peptide usually produced in the nervous system and both peripherally (Aδ and C fibers) and in the brain and is functionally related to pain; moreover, substance P is one of the first neuropeptides to be released from nociceptive fibers following stimulation of TRKA receptors [12].

There is ample evidence that various neurological diseases such as Alzheimer's, Parkinson's, and others recognize an inflammatory component although there is uncertainty as to whether this may be the trigger or rather an epiphenomenon [13,14]. However, some animal studies show that inflammation of microglia and astrocytes may contribute to aggravating neurological disorders. Therefore, it is not unreasonable to believe that an inhibition of microglia activity with inhibition of related neuroinflammation may slow down the course of the above-mentioned pathologies and of altered central activity in general [15].

Under normal conditions, microglia cells are resident and phenotypically inactive macrophages, producing anti-inflammatory substances and neurotrophic factors. In the presence of foreign factors or damage to peripheral fibers or by chronically activating signals due to overstimulation of peripheral Aδ and C nerve fibers, microglia enter a state of morphological change with polarization to the inflammatory M1 phenotype responsible for chronic inflammatory processes damaging the involved tissues [16].

Given the importance of microglia as a central node between the periphery and the higher centers of the brain and the possibility that they may be sensitized by neuroinflammatory processes and numerous mediators of pain, it is desirable to identify agents that can modulate the immune system and the interaction of various factors activating medullary postsynaptic receptors so as to interrupt the flow of noxious stimuli to brain structures.

Fibromyalgia and analgesic response

However, it should be noted that the symptomatology peculiar to Fibromyalgia also suggests a deficient or altered endogenous analgesic response. Therefore, if we were to draw conclusions, based on the albeit partial knowledge, of the pathophysiology of Fibromyalgia, we could say that the mechanisms contributing to CS are mainly as follows: 1) enhancement of NMDA and AMPA receptor response; 2) microglia activation with macrophage polarization to M1 phenotype; 3) increased concentrations of ATP, glutamate and Substance P; and 4) decreased or altered secretion of central inhibitory signals [17-23].

It is well known how activation of tropomyosin receptor kinase A receptors on the peripheral terminals of Aδ and C fibers by NGF induces the expression of CGRP and Substance P to affect pain and circulatory symptoms. However, the same substance P is also expressed by activated microglia with direct effects on pain. It is also known how the release of ATP and Glutamate at medullary synapses between peripheral nerves and central transmitters occurs predominantly by degranulation of transport vesicles. We also know how the activation of macrophage-type microglial cells, but also Th lymphocytes, are activated by the action of ATP with production of cytokines, chemokines, free radicals, etc. Microglia themselves are activated as a result of stimulation induced by ATP produced and transported to the periphery via vesicles equipped with SLC17A9 channels effectively blocked by clodronate.

It is widely recognized that ATP is, not only the most important source of cellular energy, but also an extracellular messenger that participates in immune response and inflammatory processes together with its degradation products (ADP, AMP and Adenosine) through modulation of the various purinergic receptors, P2X, P2Y, P present on all immune cells including spinal microglia cells [24,25]. In fact, activation of spinal microglia in response to peripheral stimuli involves morphological changes and the expression of signaling molecules in addition to the expression of numerous purinergic receptors whose stimulation by ATP results in allodynia [20,26].

Recent data show how ATP is directly involved in processes responsible for the proper functioning of the nervous, cardiovascular, immune as well as bone and skin systems and how its altered presence results in extensive organic dysfunction [21,27].

Clodronate and analgesic mechanism

Clodronate, a bisphosphonate with unique characteristics, exhibits a longer systemic presence, enhanced penetration into neurons of primary afferent fibers where it prevents ATP and glutamate from entering transport vesicles with the effect of limiting interaction with purinergic receptors and with AMPA and NMDA on the button of secondary afferent fibers [28]. Clodronate has demonstrated an ability to attenuate pain by inhibiting ATP vesicular transport via VNUT (SLC17A9), with a notable effect in conditions such as neuropathic pain. Additionally, clodronate's anti-inflammatory effects, both peripheral and within nervous system, reduce inflammatory mediators from immune cells and spinal microglia [29].

Unlike other bisphosphonates, Clodronate is able to easily penetrate neurons, microglia, and immune cells and at concentrations sufficient to prevent ATP from entering transport vesicles (IC50-15.6 nM) by limiting the presence of the nucleotide in the synaptic space in the posterior horns of the medulla as well as on the cell membrane of immune cells. At similar, though somewhat higher, concentrations, glutamate transit is also inhibited [30-32].

It is the opinion of these authors that blocking purinergic transmission may be effective in the treatment of various chronic diseases such as diabetes and neurological disorders. A study in an animal model of neuropathic pain (von Frey's test) showed that Clodronate exhibits pain-relieving activity superior to that of Gabapentin and similar to Pregabalin although somewhat more prolonged than the latter.

It should also be noted how neuroplasticity related to alterations in the nerve conduction system is linked to chronic and neuropathic pain through modulation of microglia [33].

Following this therapeutic direction, numerous clinical trials have been performed in recent years aimed at reducing microglia activaton. The therapeutic choice was motivated by the absence of other targets [34] apparently responsible for the pain symptoms.

Among the various drugs used minocycline, galantamine, and dextromethorphan have been employed with partial positive results and directed toward an inhibition of neuroinflammatory processes, as well as tending to inhibit glutamate (NMDA) receptors but always in consideration of potential abnormal processing of nociceptive pain.

Clinical data, including studies on CRPS, chronic back pain and gonarthrosis, support clodronate's analgesic efficacy, making it a well-tolerated option for FM and related pain syndromes. In a study by Varenna M., *et al*. [35] clodronate was shown to rapidly reduce the pain symptom in subjects with CRPS after intravenous administrations. Similar findings are reported by Gatti D., *et al*. [36]. Recent work by Frediani B., *et al*. definitively demonstrated the pain-relieving activity of clodronate after intramuscular administration in patients with painful gonarthrosis. The study was conducted so that the antalgic effect of clodronate and the slow recovery (after several months) of pain after treatment discontinuation were evident [37,38]. The drug's pharmacokinetics, however, warrant attention in FM given its rapid osseous binding and renal excretion.

Conclusion

The available data and current knowledge on the pathophysiology of fibromyalgia, along with pharmacodynamic insights on clodronate, support the rationale for evaluating the potential effects of extended clodronate therapy. This is especially relevant given its documented multifunctional actions, notably its role as an inhibitor of the immune system and peripheral and spinal microglial inflammatory processes. These effects are further enhanced by the inhibition of ATP and glutamate release at spinal synapses, which in turn attenuates ascending fiber activation and central sensitization. Clodronate demonstrates potential as a versatile drug with a high tolerability profile and minimal risk of inducing jaw osteonecrosis, a concern sometimes associated with other bisphosphonates with distinct chemical structures.

For the informed and effective therapeutic application of clodronate, however, it is essential to account for this drug's pharmacokinetic characteristics. As is common with bisphosphonates, clodronate exhibits rapid plasma clearance due to rapid binding to bone and urinary excretion. These characteristics might reduce its suitability for conditions in which bone is not the primary target. This consideration warrants further investigation in the context of fibromyalgia treatment, particularly given the promising results seen in managing other osteometabolic conditions, well recognizing that any therapeutic intervention on chronic conditions succeeds in achieving better results the earlier therapy is initiated at the first appearance of related symptoms.

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