Retrograde inhibition of hyperactive central pathways in nociplastic pain

Inibição retrógrada das vias centrais hiperativas nas dores nociplásticas

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ABSTRACT

BACKGROUND AND OBJECTIVES: Nociplastic pain occurs due to a combination of hyperexcitability and decreased inhibitory activity in the central nervous system, responsible for a state of amplification of different stimuli, present in many chronic disorders. Among them: fibromyalgia, chronic migraine, irritable bowel syndrome, myofascial pain syndrome and complex regional pain syndrome. Often, several of these diseases are associated. Nociplastic pain therapy is a challenge in clinical practice, since most traditional treatments are not effective in controlling symptoms, often causing difficulty in adherence or even interruption of treatment due to undesirable adverse effects. The objective of this article was to demonstrate the importance of identifying the presence of nociplastic pain in the patient's condition, and also the pathophysiological mechanisms involved. Thus, due to retrograde neuromodulation, a unique feature of the endocannabinoid system until now, evaluate the use of pharmaceutical grade medicines based on the cannabis plant as an adjunct in the therapy of pain and other symptoms associated with this disorder.

CONTENTS: This article was addressed the pathophysiology of nociplastic pain, the physiology to the endocannabinoid system, the cannabis plant with its components and its use as an adjuvant medication in the multimodal treatment of nociplastic pain (due to retrograde neuromodulation), based on published scientific articles between 1981 and 2022.

CONCLUSION: Although the scientific evidence supporting the use of medical cannabis in nociplastic pain therapy is insufficient so far, it can and should be considered as a possible adjuvant medication in multimodal pain therapy, always on an individual basis, when recommended treatments fail or are not tolerated.

Keywords: Cannabis, Chronic pain, Endocannabinoid system, Nociplastic pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor nociplástica ocorre por uma combinação de hiperexcitabilidade e diminuição da atividade inibitória no sistema nervoso central, responsável por um estado de amplificação de estímulos diversos, presente em muitas doenças crônicas. Entre essas doenças estão: fibromialgia, migrânea crônica, síndrome do intestino irritável, síndrome dolorosa miofascial e síndrome de dor complexa regional. Frequentemente, várias dessas doenças se apresentam associadas. A terapia da dor nociplástica é um desafio na prática clínica, uma vez que a maioria dos tratamentos tradicionais não são eficazes no controle dos sintomas, causando muitas vezes dificuldade de adesão ou até mesmo interrupção do tratamento, devido aos efeitos adversos indesejáveis. O objetivo deste artigo foi demonstrar a importância da identificação da presença da dor nociplástica no quadro do paciente, e do conhecimento dos mecanismos fisiopatológicos envolvidos. Dessa forma, devido à neuromodulação retrógrada, característica exclusiva do sistema endocanabinoide até o momento, avaliar a utilização de fármacos de grau farmacêutico à base da planta cannabis como coadjuvante na terapia da dor e dos outros sintomas associados a essa doença.

CONTEÚDO: Este artigo abordou a fisiopatologia da dor nociplástica, a fisiologia do sistema endocanabinoide, a planta cannabis com seus componentes e sua utilização como medicação coadjuvante no tratamento multimodal da dor nociplástica (decorrente da neuromodulação retrógrada), com base em artigos científicos publicados entre 1981 e 2022.

CONCLUSÃO: Apesar das evidências científicas que apoiam o uso da cannabis medicinal na terapia da dor nociplástica serem insuficientes até o momento, ela pode e deve ser considerada como um possível fármaco coadjuvante na terapia multimodal da dor, sempre de forma individualizada, quando os tratamentos preconizados falharem ou não forem tolerados.

Descritores: Cannabis, Dor crônica, Dor nociplástica, Sistema endocanabinoide.

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HIGHLIGHTS

- Importance of identifying the presence of nociplastic pain.
- Relationship between nociplastic pain and endocannabinoid system.
- Importance of treating nociplastic pain through retrograde modulation on central hyperexcitability.

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INTRODUCTION

The term Nociplastic Pain (NP) was introduced by the International Association for the Study of Pain (IASP) in 2017 as a third pain descriptor. NP is defined by IASP as "pain that arises from increased responsiveness of nociceptive neurons in the central nervous system (CNS) to normal or subthreshold afferent input, without any evidence of actual or potential tissue or somatosensory system injury, causing pain"[1].

NP is a state of sensory stimuli supraspinal amplification from different organ systems, giving rise to central symptoms such as sleep disturbance, fatigue, and cognitive alterations. It is present in a large number of chronic diseases that are difficult to explain due to the absence of identifiable tissue alteration.

The term NP is used both scientifically and clinically, referring to individuals who complain of pain and hypersensitivity in regions with apparently normal tissues and without any signs of neuropathy[2]. Among the various chronic pain disorders that present with NP are fibromyalgia (FM), chronic migraine (CM), chronic visceral pain (CVP), irritable bowel syndrome (IBS), atypical facial pain (AFP), myofascial pain syndrome (MPS), and complex regional pain syndrome (CRPS). It is common for patients to have the association of more than one of these diseases in some period of their lives[3]. A study[4] described the association between FM, CM and IBS for the first time in 1981. In 2007, the author of that study proposed the term "central sensitization syndromes" for the diseases already described, as a clinical and pathophysiological term[5]. In recent decades, functional magnetic resonance imaging examinations have contributed to elucidation of the pathophysiological mechanism related to NP[3,6].

General chronic pain (CP), and specially neuropathic pain and NP, are a challenge in clinical practice. Most traditional treatments for CP are not effective in controlling symptoms and often cause adverse effects that prevent adherence to treatment. Thus, there is a constant need, both from the scientific community and from the patients, to search for new therapeutic options that are more effective and improve the quality of life of the person with CP. In this context, drugs based on cannabis plant have drawn attention as a potential treatment to fill this therapeutic gap.

With a better understanding of NP neurophysiological basis and endocannabinoid system (ECS), in addition to evidence of cannabis-based drugs effects on various nociplastic conditions, it is noted that such therapeutics hold promise to NP treatment[7].

NOCIPLASTIC PAIN

NP is currently considered a third type of pain, with a different pathophysiology from nociceptive pain and neuropathic pain. Its pathophysiology is probably the factor responsible for numerous chronic diseases that were previously difficult to understand, categorize, and treat.

There is probably a sensitization to peripheral afferent in spinal cord posterior horn, responsible for allodynia and hyperpathia, characteristic symptoms of neuronal hyperexcitability in spinal cord posterior horn, and a supra-spinal central sensitization responsible for sensations such as fatigue, cognitive dysfunction, mood swings, hypersensitivity to external stimuli (sound, light), non-painful stimuli coming from the body itself and external stimuli, in addition to pain. In general, NP can be considered a combination of hyperexcitability and decreased inhibitory activity.

NP is neither nociceptive nor neuropathic. NP is characterized by the absence of current or former tissue lesion, responsible for activation of nociceptors, or somatosensory lesion, responsible for pain. NP is different from neuropathic pain because there is no central or peripheral nervous system lesion, nor an underlying disease that can cause this type of lesion[8].

However, patients may present with a combination of nociceptive pain and NP. Evidence indicates that continuous nociceptive pain is a risk factor for the development of NP because hypersensitivity is associated with a longer duration of nociceptive pain. Thus, high NP rates are observed in patients with osteoarthritis, rheumatoid arthritis, and other disorders that present persistent nociceptive pain[9,10].

Although central sensitization is probably a dominant mechanism in NP conditions, the term NP should not be considered synonymous with the neurophysiological term "central sensitization"[1]. In the last decades, functional neuroimaging examinations (positron emission tomography, functional magnetic resonance imaging, spectroscopy) have shown structural, chemical, and functional changes in brain areas of patients with CP, compatible with a state of hyperactivity, in addition to changes in spinal cord posterior horn. Studies have also shown alterations in the pain matrix substance (thalamus, periaqueductal gray, insula, anterior cingulate cortex, and somatosensory cortex) in these patients[11]. Neurochemical alterations were also observed, with an increase in excitatory neurotransmitters (glutamate) and a decrease in inhibitory neurotransmitters (Gamma-aminobutyric acid - GABA) in several cortical and subcortical areas[12-14].

Some cases are considered risk factors for NP development, such as chronic diseases, autoimmune diseases, family history of CP or mental health diseases, infections, or significant emotional trauma in childhood[15].

This type of pain can occur as a one-off case in conditions such as FM or CM, or as part of a mixed pain state, in combination with ongoing nociceptive or neuropathic pain, as in chronic low back pain. It is important to recognize the presence of this type of pain in chronic conditions, since it will not respond in the same way as nociceptive pain to the therapies recommended for the latter, such as anti-inflammatory and analgesic drugs, surgery, or other procedures effective against nociceptive pain[16].

In summary, it is possible to highlight the central changes related to NP: hyper-responsiveness to painful stimuli, hyperactivity and connectivity within and between brain and regions involved in pain, decreased activity of brain regions involved in pain, inefficient descending inhibitory pathways, elevation of substance P and glutamate in cerebrospinal fluid, decreased GABAergic concentration, gray and white matter changes in cortical regions involved in pain processing, and glial activation.

ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) plays important roles in CNS development, synaptic plasticity, and response to endogenous and exogenous insults. ECS is extremely complex and is present in all organ cells, playing an essential role in homeostasis. In the last 25 years, ECS has gained prominence as an important neuromodulatory system.

ECS is composed of three components:

1- Endocannabinoids,

2- Receptors,

3- Synthesis and degradation metabolizing enzymes.

The most studied endocannabinoids are anandamide (N-arachidonoylethanolamide or AEA) and 2-araquidonoylglycerol (2-AG). The efficacy of endogenous cannabinoids depends on their affinity for receptors. 2-AG is a highly effective agonist of CB1 and CB2 receptors, while AEA is a low efficacy agonist at CB1 receptors and a very low efficacy agonist at CB2 receptors. Consequently, in systems with low receptor expression or when receptors are weakly coupled to signaling pathways, AEA can antagonize the effects of more effective agonists.

Other endocannabinoids have recently been isolated such as virodhamine ("reverse anandamide"), noladin ether, and N-arachidonoyl dopamine (NADA). However, the biology of these compounds is not as clear as that of AEA and 2-AG. Also important are the so-called endocannabinoid-like compounds, N-oleoylethanolamide (OEA) and N-palmitoylethanolamide (PEA), which in addition to reducing the hydrolysis of AEA and 2-AG, act synergistically with these endocannabinoids. Nevertheless, this synergism occurs through the action of endocannabinoid-like on G-protein-coupled receptors (GPR55, GPR18, GPR119), TRPV1 and PPARs.

CB1 and CB2 receptors are present throughout the body. CB1 receptor is the most abundant in human body, predominating in CNS and peripheral nervous system (PNS). CB1 receptor action depends on its location in nervous system. CB2 receptor is more present in peripheral areas and is important in immuno-modulation and control of inflammation. CB1 and CB2 receptors were the first to be identified and studied, but endocannabinoids also interact with transient potential receptors (TRPs) and peroxisome proliferator-activated receptors (PPARs), particularly with TRPV1 and GPR55.

Although the AEA and 2-AG contain arachidonic acid, synthesis and degradation *in vivo* are virtually distinct, and mediated by different enzymes. AEA is synthesized by NAPE-specific phospholipase D (NAPE-PLD) and 2-AG by DAG lipase (DAGL). The degradation enzymes are fatty acid amide hydrolase (FAAH), which degrades AEA and monoacylglycerol lipase (MAGL), which metabolizes 2-AG.

2-AG, in addition to serving as an endogenous ligand for cannabinoid receptors, is an important metabolic intermediate in lipid synthesis and serves as an important source of arachidonic acid in prostaglandin synthesis.

The precursors of endocannabinoids are present in lipid membranes. Endocannabinoids are synthesized only when needed, i.e., on demand, in one or two rapid enzymatic steps, and released into extracellular space by activation of certain G-protein-coupled receptors or by depolarization. Therefore, ECS contrasts with the production and release of classical neurotransmitters, since these are synthesized in advance and stored in synaptic vesicles. Another unique feature of the ECS is that endocannabinoids are produced in postsynaptic membrane and will act on presynaptic receptors modulating neuronal hyperexcitability, that is, they act in a retrograde manner.

ECS action on pain pathways occurs both independently and by synergistic action with other endogenous pain circuit systems, represented by inflammatory molecules, endorphins, enkephalin, and various ion channels. The endocannabinoid system functions at various levels in the nervous system as an alternative pathway to the inflammatory prostaglandin pathway, with potential to modulate pain and inflammation. The effect on pain modulation occurs via descending supraspinal inhibitory pathways through a complex mechanism of multiple ligand interaction, cross-reaction with non-cannabinoid receptors, response plasticity dependent on local tissue characteristics, and presence of other molecules such as opioids[7,17-20].

A more recent hypothesis has suggested that many pain conditions characterized by NP may be related to endocannabinoid system deficiencies. In 2004, a research first linked a possible deficiency of the endocannabinoid system to one of the pathophysiological mechanisms involved in diseases such as FM, CM, and IBS. At that time, the presence of several of these diseases was already observed as comorbidities, and studies already showed a possible central hyperactivity as part of the pathophysiological mechanism[21,22]. Given this hypothesis, the aforementioned research suggested that these and other diseases in which EBS deficiency was present could be adequately treated with cannabis-based drugs by rebalancing EBS deficiency and restoring central modulation[23].

In 2010, with a deeper understanding of the ECS, a research[24] presented experimental and clinical data that demonstrated a link between endocannabinoids and migraine, a neurovascular disorder caused by abnormal processing of sensory information due to peripheral and/or central sensitization. Even though the ECS-dependent mechanisms involved in migraine pathophysiology were not fully clarified, the results available at the time strongly suggested that ECS activation could represent a promising therapeutic tool to reduce the physiological and inflammatory components of pain involved in migraine attacks.

In 2016, a review of the aforementioned 2004 study[25] showed statically significant differences in cerebrospinal fluid AEA levels in chronic migraine sufferers. Another study, mentioned in this review, demonstrated ECS hypofunction in different cortical and subcortical areas of Huntington's disease patients, with significant reductions in CB1 receptor availability versus controls ($p<0.0001$). These reductions ranged from 15% in the cerebellum to 25% in the frontal cortex, confirming ECS hypoactivity inversely related to disease severity. The profound early and widespread reduction in CB1 availability *in vivo* is consistent with the hypothesis that gene alteration represses CB1 transcription. This was probably the first *in vivo* demons-

tration of ECS disorder in a human neurological disease[26]. These studies reinforced the 2004 theory, and contributed greatly to the comprehension of CP pathophysiology, especially neuropathic and nociplastic.

In addition to the probable impairment of ECS confirmed by these studies, the therapeutic response to medical cannabis use for CM was also evaluated. A statistically significant decrease in CM seizures was proven after the introduction of cannabinoids. Another interesting proof was the efficacy of medical cannabis treatment in patients with FM when compared to the use of Duloxetine, Pregabalin, and Minalcipran, drugs approved for this disease by Food and Drug Administration (FDA) and European Medicines Agency (EMA)[27].

Endocannabinoid system and pain

The action potential generated in the presynaptic terminal causes cytoplasmic vesicles to fuse with the presynaptic membrane and the release of excitatory neurotransmitters takes place. Endocannabinoids are then synthesized in response to the increased activity in postsynaptic neuron. The neurotransmitter binding to receptors on postsynaptic membrane causes Ca2+ accumulation, membrane depolarization and activation of calcium-dependent enzymes, responsible for the synthesis of NAPE-PLD and DAGL endocannabinoids.

The synthesized AEA and 2-AG then act in a retrograde manner on the presynaptic membrane receptors. These endocannabinoids bind to cannabinoid receptors on presynaptic membrane and on cell membrane of the microglia cells in posterior horn of spinal cord.

CB1 receptors are present predominantly in presynaptic terminal neurons, and their activation decreases vesicular release, reducing glutamate release in nociceptive projection neurons. This mechanism is known as retrograde signaling.

CB2 receptors are present predominantly in microglia, and their activation suppresses microglial activation, responsible for the classics symptons of central sensitization (allodynia and hyperpathia), so that microglia starts producing more anti-inflammatory mediators and less pro-inflammatory mediators. The activation of neuronal and microglial cannabinoid receptors leads to nociception modulation.

After acting, endogenous cannabinoids present in synaptic cleft are captured by cellular cannabinoid transporters, where they are broken down by degradation enzymes, FAAH and MAGL. The inactivation of endocannabinoids AEA by FAAH and 2-AG by MAGL occurs by hydrolysis, forming arachidonic acid and ethanolamine or glycerol, respectively[28].

A study published in 2020 suggests that maintenance and potentiation of mechanical allodynia in prelimbic cortex is due to stimulation of NMDA and TRPV1 receptors. This hyperexcitability may be attenuated by activation of cortical CB1 receptors[29].

Medical cannabis in central hyperactivity treatment

Cannabis has been used for medicinal purposes for thousands of years. With prohibition in the mid 20th century, research into the plant use for medicinal purposes was interrupted. In recent decades, there has been a growing debate about the use of cannabis for various chronic diseases refractory to conventional treatment, most notably CP[30].

There are several preclinical studies on the use of cannabinoids for pain, but clinical studies still remain somewhat limited. There is plenty of evidence in observational studies, anecdotal reports, and even systematic reviews. However, as in the case of other chronic diseases refractory to conventional treatments, more randomized clinical trials on pain are also needed.

The term ”medical cannabis” refers to the use of the plant and its components, mainly cannabinoids, under medical recommendation and monitoring, to treat or improve the symptoms of different diseases. Recent studies have proved that phytocannabinoids exert their therapeutic actions on pain through different targets, both in periphery and in CNS, in the same way as endocannabinoids. These targets include not only CB1 and CB2 receptors, present along the entire pain pathway, but also other G protein-coupled receptors important in the analgesic pathway, such as GPR55, GPR18, opioid receptors, serotoninergic receptors (5-HT), as well as transient potential receptors (TRVP, TRPA and subfamilies, and TRPM).

Several studies have reported the ability of certain cannabinoids in modulating PPARs receptors, important as analgesic, neuroprotective and modulators of neuronal function. Studies have also demonstrated interaction between μ-opioid receptors and CB1 receptors, which potentiates the action of phytocannabinoids[31-33].

Cannabinoids have multimodal mechanisms of action in pain treatment, including: modulation of neuronal nociceptive processing, inhibition of pro-inflammatory molecules release, inhibition of mast cell activation, and modulation of endogenous opioid receptors in primary afferent pathways[34-36].

Similarly, cannabis can also provide relief for groups of symptoms that accompany conditions of NP, such as nausea, anxiety, insomnia, and depression, through its effects on the endocannabinoid system. This group of symptoms can be difficult to relieve using traditional pharmaceutical agents, which often focus on a single symptom. Therefore, in addition to improving pain by improving associated symptoms in NP sufferers, it helps to reduce the psychological distress associated with NP[37].

Tetrahydrocannabinol

THC is responsible for most of cannabis pharmacological actions, such as analgesic, anti-inflammatory, antioxidant, antispasmodic, muscle relaxant, bronchodilator, and antipruritic action. Although all cannabinoids are psychoactive, because they act in CNS, THC is the only one that has a dysleptic effect, probably because it is a partial CB1 receptor agonist, with high affinity for CB1 receptor[34].

In addition to modulating the release of excitatory neurotransmitters at overactive synapses, THC inhibits COX-2 and activates CB2 receptors in microglia with control and decrease of hyperpathia and allodynia. THC also acts on PPARs receptors, important in analgesia.

Although the role of CB2 receptors in mediating the effects of THC on analgesia has not been fully elucidated, the effects

of CB2 receptor agonists on inflammation-induced pain are better described than their effects on pain related to nervous system disorders[38,39].

Cannabidiol

There are few clinical trials exploring the analgesic effects of cannabidiol (CBD) in humans. A recent observational study retrospectively evaluated changes in quality of life in a subset of the first 400 patients in New Zealand to be prescribed CBD (primarily 100 mg CBD/mL oil administered via dropper)[40]. In that study, patients with non-cancer pain (n=53) reported significant improvements in pain-related quality of life, improved mobility, and reduced anxiety and depression. User surveys in countries where cannabis products are more freely available (e.g., North America) suggest that CBD-predominant products tend to be consumed more often for anxiety and depression, while THC-predominant products are preferentially used for pain and sleep[41].

The current Special Access Scheme Category B data indicates that nearly a quarter of current approvals for CP involve CBD-dominant products, despite minimal available evidence regarding their efficacy (SAS-B, April 2021).

Considering the current evidence, a panel of 20 experts from nine countries recommended the use of medical cannabis for neuropathic and nociplastic pain mechanisms and not for nociceptive pain[42]. There is an extensive number of preclinical studies on the effects of cannabinoids in CP, but clinical studies remain limited. There are many observational studies, anecdotal reports and even systematic reviews, but few randomized clinical trials[43].

The challenges are considerable in terms of reliable evidence on the medical effects of cannabinoids in neuropathic CP and NP due to the heterogeneity of cannabis products and different methods of administration in various populations. There is also a lack of commitment from the cannabis industry to support better quality research that confirms what the observational studies, anecdotal reports, and systematic reviews demonstrate[44].

CONCLUSION

Medical cannabis and cannabis-based drugs can potentially fill the therapeutic gap in treatment of neuropathic CP and NP treatment. Their mechanism of action on NP is important due to retrograde neuromodulation in central nerve pathways, decreasing hyperexcitability. In addition, it also modulates microglial neuronal inflammation, potentiates the opioid system and other central inhibitory mechanisms (across the pathway involved in pain pathophysiology), and has peripheral analgesic actions. Although the evidence supporting its recommendation for NP is insufficient to endorse its general use, cannabis can and should be considered as a possible adjunct drug in multimodal pain therapy, always on an individual basis, when the recommended treatments fail or are not tolerated.

AUTHORS' CONTRIBUTIONS

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