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The Endocannabinoid System a Turning Point in Optimizing Physiotherapy Procedures in Knee Osteoarthritis

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Abstract: ***Introduction:*** *Knee Osteoarthritis (KOA) is characterized by wear, tear, and it's a slowly progressive loss of cartilage, that becomes finally disabling. KOA is one of the most analyzed diseases by many medical specialties such as rheumatology, orthopedics, rehabilitation medicine, and physiotherapy. Major symptoms of KOA such as pain, dysfunction, and chronic low-grade inflammation will decrease the quality of life and eventually lead to locomotor disability. Since there are no effective ways to limit KOA progression, involvement of the endocannabinoid system (ECS) may be a non-pharmacological therapeutic alternative in the management of this disease. This study debate aspects of ways to modulate the ECS in KOA, using physiotherapeutic (PT) means such as TENS electroanalgesia, LASER biostimulation, and physical exercises with analgesic effects.*
Materials and Methods: *In the study, we included 82 sources, with the following keywords in the title: knee osteoarthritis, cannabidiol, endocannabinoid, inflammatory pain, analgesia, neuropathic pain, physiotherapy, electrotherapy, and LASER. To perform this review, we searched for the most relevant articles in the field of medicine and physiotherapy in 7 international databases applying inclusion and exclusion criteria.*
Results: *The application of TENS currents in certain doses and frequencies together with LASER biostimulation stimulates the production of endocannabinoids thus controlling pain, and stimulating the ECS. Physical exercise has an antioxidant, and anti-inflammatory role and stimulates the release of endogenous opioids.*
Conclusions: *The results obtained from this meta-analysis may contribute to paradigm shifts in clinical practice related to the treatment of pain by PT. TENS, LASER, and physical exercise are effective clinical tool that limits chronic inflammation and pain by involving the ECS. More studies are needed to understand endocannabinoid system involvements in KOA, and that will inspire medical doctors and physiotherapists to improve long-term treatment strategies.*

Keywords: *Knee Osteoarthritis, endocannabinoid system, TENS, LASER, physical exercise.*

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1. INTRODUCTION

Osteoarthritis (OA) is a most debated and analyzed disease by many medical specialties such as rheumatology, orthopedics, geriatrics, family medicine, rehabilitation medicine, and physiotherapy. Major symptoms of osteoarthritis (OA) such as pain, dysfunction, and chronic inflammation will decrease the quality of life and eventually lead to locomotor disability and several other social problems that burden the health systems around the world (Berenbaum, 2013). Some authors suggest that OA is not a disease but a combination of predisposing factors such as the onset of acute inflammation with the perpetuation of mechanisms that maintain a low-grade chronic inflammation (Musumeci et al., 2015). This chronic inflammation, over time, will develop a destructive effect on articular cartilage, that maintains a vicious circle: inflammation → enzyme production → chondrolysis → inflammation (Gherghel et al., 2021).

Among the many treatment methods to limit the progression of OA, it seems that weight loss, lifestyle changes, and hyaluronic acid intraarticular viscosupplementation in combination with physical therapy have given the best results which are recognized by specialists in the field (Onu et al., 2022). However, the progression of OA is modestly influenced by the therapies listed above, and in the end, total arthroplasty of the affected joints is the last solution. Unfortunately, there is no effective strategy for understanding the biochemical and biophysical phenomena underlying low-grade inflammation, and the mechanisms have not been fully elucidated. Current pharmacological treatments have extremely limited efficacy in controlling disease progression and analgesic treatment is rather temporary (Akkiraju & Nohe, 2015; Loeser, 2011; Mathiessen & Conaghan, 2017).

Knee Osteoarthritis (KOA) is the result of wear and tear and slow progressive loss of articular cartilage that eventually the disease becomes disabling. It is common in older people, and in the last stage, the final solution is total knee arthroplasty. KOA is caused by a multitude of factors that are involved in the destroy articular cartilage, especially in the condyles. Clinical manifestations of KOA are specific pain including nociceptive and neuropathic mechanisms, limited mobility, and decreased muscle strength in the quadriceps (Hsu & Siwiec, 2022; Maldonado & Nam, 2013). An alternative and noninvasive approach to reducing pain in KOA are to exploit the antinociceptive effects of cannabinoids by actively involving the endocannabinoid system (ECS) in the pathophysiological mechanisms. Studies suggest that the physiological role of the ECS, along with the allocation of cannabinoid receptors in the regulation of low-grade

inflammation, is massive (Manzanares et al., 2006). The successful therapeutic use of cannabinoids in the management of KOA promises new directions in pharmacological and other treatment approaches (La Porta et al., 2014). Certain physical therapies are available whose effects on endocannabinoid stimulation are known.

2. METHOD

Systematic Search Strategy. For this systematic review, we searched open-access articles in the fields of medicine, biochemistry, physiotherapy, and exercise physiology. We use 7 international databases: Elsevier, ISI Web of Knowledge, PEDro, NCBI / PubMed, NCBI / PMC, Doaj, and Cochrane. Keywords combinations searched in the context were: knee Osteoarthritis, cannabidiol, endocannabinoid, inflammatory pain, analgesia, neuropathic pain, physiotherapy, electrotherapy, and LASER. Eligible articles were analyzed in detail regarding the involvement of the endocannabinoid system with physiotherapy techniques, in KOA management.

Inclusion and Exclusion Criteria. Articles included in this review use the methodology outlined above, in all keyword combinations present in the title. We included non-randomized, cross-sectional, randomized controlled trials and meta-analyses. Exclusion criteria were articles studied in the next phase but fulfilling the above criteria.

3. RESULTS

Considering the niche area of this systematic review, we read 108 articles from 2023 -to 2012. This study included 82 bibliographic sources, which were obtained after applying NCBI selection filters and removing duplicates and irrelevant ones from a total of 108. These 82 sources passed the relevant criteria in the areas listed above and the keywords. Word combinations like "endocannabinoid System, TENS"; "endocannabinoid system, physical exercises" and "endocannabinoid system, LASER" - one result, show us how narrow this area is. This study debate aspects of ways to modulate the ECS in KOA, using PT such as TENS electroanalgesia, LASER biostimulation, and physical exercises with analgesic antioxidant effects.

The following variables (V) were extracted from articles considered eligible for systematic review:

(V1) population: age, sex, and diagnosis;

(V2) types of physiotherapy related to the ECS;

(V3) biochemical parameters: types of receptors (in particular CB1) and endocannabinoids (in particular anandamide), assessment of blood levels (pre and post-physiotherapy intervention), and method of measurement used;

(V4) methodological information.

Endocannabinoid system

ECS was identified in the early 1990s by researchers studying the cannabinoid - trans-Δ9-tetrahydrocannabinol (THC). ECS is a neuromodulatory and cell signaling system that plays key roles in the central nervous system (CNS), in neural functions, including motor coordination, control of movement, and the response to environmental and endogenous threats. ECS interacts with several neurotransmitters that are responsible for most of the neuronal effects of cannabinoids. The most important neurotransmitter is acetylcholine followed by dopamine, opioid peptides, norepinephrine, GABA, histamine, serotonin as well as prostaglandins. ECS is active in the body even if a person does not consume cannabis products, and this phenomenon is not fully understood. ECS plays a key role in regulating functions and processes, such as mood, appetite, sleep, memory, and reproduction. ECS also intervenes in the mechanism of pain reduction (Gonsiorek et al., 2000; Lu & Mackie, 2016).

Endocannabinoids (EC), also called endogenous cannabinoids, are molecules naturally produced by the human body and are similar to the cannabinoids in cannabis. ECs help the proper functioning of internal functions and are produced according to the body needs the most important EC are anandamide (AEA) and 2-arahydonoylglycerol (2-AG) (Gonsiorek et al., 2000; Mackie et al., 1993).

Receptors are found throughout the human body, and ECs bind to them to signal ECS. The most important EC receptors are CB1 and CB2. CB1 - is found mainly in the CNS; and CB2 - is found in the peripheral nervous system (PNS), but mostly in immune cells. EC have a unique property of binding to either of these two specific receptors. The effects produced by this binding depend on where the receptor is located and which EC binds to it. EC that target CB1 receptors on a spinal nerve will be involved in the pain mechanism, thus modulating the perception of pain. EC targeting CB2 receptors will bind to immune cells to signal inflammation (Bodor et al., 2005; Howlett et al., 2002; Luk et al., 2004; Mackie, 2005; Norrod & Puffenbarger, 2007; Suarez et al., 2008; Uchigashima et al., 2007).

Endocannabinoid: Pain: Analgesia

It is known that the most effective analgesics available in pharmacies and hospitals are opioids that exploit an endogenous pain control pathway within the CNS. However, the use of opioids in many countries is banned because they generate significant problems in terms of addiction, tolerance, depression, opioid-induced hyperalgesia, and respiratory distress. In the last four decades, the existence of a second endogenous anti-nociceptive ECS pathway has been revealed that could be a valid alternative to opioid use. Studies show that this endogenous anti-nociceptive pathway can be stimulated by various non-pharmacological mechanisms using physical agents and exercise in certain doses (Angst & Clark, 2006; Di Marzo, 1998; Guindon & Hohmann, 2009).

Cannabis sativa extracts have been used as an analgesic since ancient Egypt, and the psychotropic effects of this drug have been described as being associated with religious rituals or recreational purposes, and it was banned in the early 20th century. The cannabis plant contains more than 100 cannabinoids out of a total of more than 480 compounds, the best known is THC, and cannabidiol (CBD). THC is the main psychoactive element in cannabis, while CBD has neither intoxicating nor addictive properties (Abel, 1980; Zias et al., 1993).

Devane was the first to identify the cannabinoid receptor and subsequently AEA, which is the main endogenous ligand. More than 5000 articles deal with the ECS, and as a general line, they indicate that this system plays an essential role in multiple physiological processes and in physiological and pathophysiological functioning (Devane et al., 1988; Herkenham et al., 1991; Mechoulam & Gaoni, 1967).

The ECS is omnipresent across all components in almost all pain processing pathways with a key role in modulating the nociception. Both receptors and ligands can be detected in the nociceptive regions of the brain and peripherally in the spinal cord, meaning that CB1 is predominantly located in neurons, while CB2 is found in immune cells. Increased peripheral AEA levels have been shown to reduce nociceptive effects in inflammatory and neuropathic pain due to CB1 receptor inhibition of primary neurons that transmit nociceptive signals. Increased 2-AG signaling at peripheral CB1 receptors has antinociceptive effects, but CB2, too, is thought to be involved in inhibiting pro-nociceptive actions of immune cells (Brownjohn & Ashton, 2012; Cencioni et al., 2010; Han et al., 2009; Hao et al., 2010; Nomura et al., 2011; Racz et al., 2008; Salio et al., 2002; Samson et al., 2003).

Involvement of the endocannabinoid system in osteoarthritis pain

Pain is the main symptom of KOA and comprises manifestations of nociceptive and neuropathic mechanisms. Several authors support the interest in ECS as a therapeutic option in reducing pain is KOA. Schuelert & McDougall in 2008, along with Yao et al. demonstrated the anti-nociceptive effects of CB1R and CB2R agonists in rodent models with OA. Schuelert et al. 2011 alongside the initial 2008 findings of McDougall et al. show that the knee joint possesses an active ECS component, that contributes to the regulation of joint pain and synovial blood flow. The findings of the authors Mbvundula et al. in 2006, and Idris & Ralston in 2012 suggest that cannabinoids have a key role in the regulation of cartilage degradation and bone remodeling processes that occur during OA. These processes are possible due to the presence of cannabinoid receptors in bone and on chondrocytes (Idris & Ralston, 2012; Mbvundula et al., 2006; Schuelert & McDougall, 2008; Schuelert et al., 2010; Schuelert et al., 2011; Yao et al., 2008).

Carmen La Porta et al. (2015) demonstrated that significant differences were observed between KOA patients and healthy subjects in Huskisson knee scale scores, correlating with a significant increase in plasma 2-AG levels in KOA patients. In contrast, no significant increases in AEA were observed in KOA patients. The authors also observed an increase in CB1R and CB2R gene expression levels in blood lymphocytes in KOA patients compared to control subjects. Significantly positive correlations were found between 2-AG levels and pain in KOA.

Burston JJ et al. demonstrated in 2013 that CB2 inhibitory cannabinoid receptors attenuate peripheral immune cell function which in turn will modulate central neuroimmune responses in neurodegeneration. OA-induced pain and changes in circulating pro-and anti-inflammatory cytokines were attenuated by systemic administration of the CB2 receptor agonist JWH133. These data offer new insights into the treatment of OA pain by targeting CB2 receptors that inhibit central sensitization thereby controlling chronic pain (Burston et al., 2013).

Physiotherapy involving the endocannabinoid system in the treatment of Knee Osteoarthritis

Although not life-threatening, major symptoms of KOA such as pain, intermittent inflammation, and dysfunction will slowly decrease quality of life and performance, eventually leading to disability. Conservative treatments for KOA pain reduction are oral, topical medication, intramuscular, intra-articular injection therapy, and non-pharmacological

therapies such as physiotherapy. Some of the physiotherapy procedures reduce pain and here we list TENS, interferential currents, ultrasound, LASER, phototherapy, thermotherapy, cryotherapy, TECAR, Deep Oscillation, massage, and physical exercises.

The results found in the meta-analysis of the studies showed that the application of TENS currents, LASER, and physiotherapy exercises directly involve the ECS thus controlling the pain in KOA. This new information opens new horizons of knowledge in improving pain therapy in clinical practice, without the use of pharmacological substances that have negative long-term effects.

TENS current therapy activates antinociception, thereby reducing pain by activating the descending pain modulation pathway. TENS is responsible for the release of endogenous analgesic substances when low frequencies are used. A plausible hypothesis is that ECS may be positively influenced by TENS-induced antinociception. Herrick Ulisses de Oliveira et al. demonstrated that low- and high-frequency TENS induced antinociception by activating the descending pain control pathway through EC release, which activates the cannabinoid CB1 receptor (de Oliveira et al., 2019; Maeda et al., 2007; Radhakrishnan et al., 2003; Rice et al., 2002; Sabino et al., 2008).

Gonçalves et al. demonstrated in 2014 that the application of TENS currents has modified the effect of cannabidiol, diazepam, and naloxone in combination with 10-150 Hz TENS current pulses in rodents, which were subjected to a 30-minute tail-friction test, that produced pain. The 10 Hz current increased the nociceptive threshold during the evaluation period being abolished considerably by cannabidiol pretreatment (1.5mg/kg), while at 150 Hz the inhibition given by cannabidiol was total. These new data suggest the involvement of ECS and cannabinoid-mediated neuromodulation in antinociception induced by TENS electroanalgesia at 10 Hz and 150 Hz in animals (Bushlin et al., 2010; Parik et al., 2011; Prado & Roberts, 1985; Resende et al., 2004; Teixeira Gonçalves et al., 2014).

Riley T. Paulsen and Brian D. Burrell suggested that the analgesic effects of TENS are due to the contribution of cannabinoid signaling to the anti-nociceptive effects of non-nociceptive repetitive stimulation (2019). Sluka et al. demonstrated that TENS produces different antihyperalgesic at high and low frequencies. High-frequency 100 Hz TENS produces anti-hyperalgesia via delta-opioid receptors in the spinal cord and low-frequency 4 Hz TENS produces anti-hyperalgesia via mu receptors (Sluka et al., 1999). Sabino et al. demonstrated on rodents models that the application of high and low-frequency TENS has significant analgesic and anti-inflammatory

effects, of which 10 Hz showed a longer-lasting analgesic effect than 100 Hz. The data obtained show that both forms of TENS induced anti-hyperalgesia, of which 10 Hz TENS was more effective due to the local release of endogenous opioids (2008).

Recent studies show that physical exercise increases EC concentrations in serum EC concentrations but factors such as type of exercise, exercise duration, and volume, exercise intensity, gender, and age will influence the EC response. Cannabinoids produce psychological states described as "runner's high", and compared to opioid analgesics, the analgesia produced by ECS is more consistent with exercise-induced analgesia. ECS activation also produces sedation, a feeling of well-being, reduces alertness, impairs memory capacity, and produces difficulties in time estimation and management. This "runner's high" phenomenon is reported by long-distance runners who modulate their behavioral profile when ECS is activated through significant increases in serum EC concentrations. The ECS is involved in the control of basal ganglia-mediated motor activity via central anandamide. During physical exercise, ECS mediates peripheral effects such as vasodilation and bronchodilation, which play a key role in the EC-exercise interaction relationship (Calignano et al., 2000; Carmack & Martens, 1979; Charytoniuk et al., 2020; Cook & Koltyn, 2000; Fernández-Ruiz et al., 2002; Giuffrida et al., 1999; Mechoulam et al., 1995; Unu et al., 2021; Richardson, 2000; Scully et al., 1998; Walker et al., 1999).

Sparling et al. demonstrated that exercise activates the ECS, resulting in exercise-induced analgesia on a 45 min cycle ergometer program. Twenty-four healthy men aged 23 years; height 183.7 ± 6.2 cm, BMI 74.5 ± 7.9 kg, divided into 3 groups entered the study. After one hour, blood samples were collected, and the results of the analyses showed that AEA levels were significantly elevated in runner cyclists $p<0.05$, and low in the inactive control group. These new data show that moderate-intensity exercise activates the ECS, thereby inducing analgesia (Sparling et al., 2003). Marin Bosch et al. showed that moderate-intensity exercise was correlated with increased circulating levels of AEA and increased activity in the caudate nucleus and hippocampus and concluded that AEA stimulates hippocampal and striatal activity and function, thereby enhancing memory for motor sequences. High levels of AEA are associated with improved motor sequence memory (Marin Bosch et al., 2020; Thomas et al., 2016). Stensson et al. demonstrated that exercise raises AEA levels in fibromyalgia patients, succeeding in controlling chronic pain in a group of 37 women aged 20-65 years. After a 15-week program of progressively increasing exercise volume, intensity, and complexity, increases in plasma levels of AEA were recorded

and stearoyl ethanolamide levels decreased, suggesting that chronic exercise has analgesic and pain-controlling effects (82). Barbosa et al. confirmed that physical exercise in a resistance training program is an effective method that can ameliorate the symptoms of fibromyalgia in adult women as an alternative to pharmacological therapies (Barbosa et al., 2021).

Several authors have hypothesized that moderate physical exertion with time between 30-90 minutes/per workout will increase plasma levels of circulating EC which generate a system-wide response to seek, consume, and store energy. This hypothesis that increased energy use results in an increase in circulating EC to replenish energy stores are confirmed by the fact that immediately after the exercise period, AEA elevates (Hill et al., 2013; Raichlen et al., 2013; Ramaekers et al., 2006; St-Onge et al., 2011). Fernandez-Aranda et al. 2004 examined the effects of chronic exercise on obese and normal-weight women and determined that moderate-vigorous physical activity measured over 6 days is positively correlated with high levels of AEA. This study showed that chronic exercise exerts particular effects on AEA in patients with high BMI.

Gabriela Xavier Santos et al. in 2020 in a placebo-controlled trial study demonstrated that supraspinal photobiomodulation performed with LASER reduces pain by engaging the CB1 receptor in antinociception rodent models. The LASER used is infrared AsALGa with 830 nm, an output power of 30 mW with a dose of 50 J/cm^2, and with continuous wavelength. Thirty-five male Swiss albino mice were used in the study, and eighteen eligible animals were included and divided into three groups. The mice were operated on the sciatic nerve using the technique that creates chronic constriction injury (CCI). The groups consisted of 6 animals in each group and received the following therapies: (G1) CCI + LASER 0J/cm^2, (G2) CCI+LASER 50 J/cm^2, and (G3) CCI + SALINE + 50 J/cm^2. The authors of the study conclude that CB1 receptors located in supraspinal structures, participate in the control of neuropathic pain following LASER treatment in animals that have suffered CCI lesions (Xavier Santos et al., 2020).

4. CONCLUSIONS

More than 80 articles from peer-reviewed journals were entered into this study, looking for all elements that encompassed "Effects of physiotherapy procedures on the ECS on KOA". The results found in the meta-analysis of studies showed that the application of TENS currents, LASER, and exercises directly involve the ECS thus controlling pain. TENS

promotes antinociception by activating the descending pain modulation pathway and consequently releasing endogenous analgesic substances. The results also show that physical exercise has a stimulatory effect on the ECS. Central opioidergic mechanisms can modulate the positive effects of exercise, which have the main effect of reducing pain, and stress and improving mental mood. The results obtained from this meta-analysis may contribute to paradigm shifts in clinical practice related to the treatment of pain by PT. The application of TENS currents in certain doses and frequencies together with LASER biostimulation stimulates the production of EC thus controlling pain, and stimulating the ECS. Exercise has an antioxidant, and anti-inflammatory role and stimulates endogenous opioid release.

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