Cannabinoid derivatives and the pharmacological management of pain

Derivados canabinóides e o tratamento farmacológico da dor

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ABSTRACT

BACKGROUND AND OBJECTIVES: Medical properties of *Cannabis sativa* have been reported for centuries for the treatment of different disorders and, more recently, to manage pain. This study aimed at reviewing major pharmacological advances of the endocannabinoid system and the potential therapeutic use of some cannabinoid compounds to manage different types of pain.
CONTENTS: A search was carried out in Pubmed, Scielo and Lilacs databases to identify studies and literature reviews on the pharmacology and therapeutic use of cannabinoids for pain. The following keywords were used: *Cannabis sativa*, tetra-hydrocannabinol, cannabidiol, sativex˚, cannador˚, cannabinoids, endocannabinoid, pain and neuropathic pain. Synthetic cannabinoids and *Cannabis sativa* extracts have shown analgesic effects in several clinical trials, suggesting their potential role for pain management, especially neuropathic pain. Synthetic cannabinoids and CS extracts have also induced anxiolytic effects when used as adjuvants to treat cancer pain, rheumatoid arthritis and multiple sclerosis. However, significant adverse effects, such as euphoria, depression and sedation limit the clinical use of such cannabinoids.
CONCLUSION: Further understanding of endocannabinoid system pharmacology, together with study results involving pain management with cannabinoid substances may be very useful for the development of drugs allowing a significant advance in the treatment of patients with painful syndromes, especially difficult to control. However, further studies are needed to confirm such findings and to determine the safety of such compounds.
Keywords: *Cannabis*, Endocannabinoids, Management, Pain, Pharmacology,

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RESUMO

JUSTIFICATIVA E OBJETIVOS: As propriedades medicinais da *Cannabis sativa* têm sido relatadas por muitos séculos para o tratamento de diversos distúrbios e, mais recentemente, para o tratamento da dor. O objetivo deste estudo foi revisar os principais avanços na farmacologia do sistema endocanabinóide e no potencial uso terapêutico de alguns compostos canabinóides no tratamento de diversas formas de dor.
CONTEÚDO: Foi realizada uma busca nos bancos de dados Pubmed, Scielo e Lilacs, identificando-se estudos e revisões da literatura sobre a farmacologia e o uso terapêutico de substâncias canabinóides em dor. Nessa busca foram utilizadas as seguintes palavras-chaves: *Cannabis sativa*, tetra-hidrocanabinol, canabidiol, sativex˚, cannador˚, canabinóides, endocanabinóide, dor e dor neuropática. Os canabinóides sintéticos e os extratos de *Cannabis sativa* apresentaram efeito analgésico em diversos ensaios clínicos, sugerindo um potencial papel no tratamento da dor, em particular naquela de origem neuropática. Os canabinóides sintéticos e os extratos de *Cannabis sativa* também apresentaram efeitos ansiolíticos quando usados como adjuvantes no tratamento da dor no câncer, na artrite reumatoide e na esclerose múltipla. Porém, efeitos adversos significativos, como euforia, depressão e sedação limitam o uso clínico desses agentes canabinóides.
CONCLUSÃO: Um melhor conhecimento sobre a farmacologia do sistema endocanabinóide, juntamente com os resultados dos estudos envolvendo o tratamento da dor com substâncias de natureza canabinóide, podem ser de grande valor para o desenvolvimento de fármacos que permitam um avanço significativo na terapêutica de pacientes portadores de síndromes dolorosas, em particular nos casos de difícil controle. Porém, mais estudos são necessários para confirmar esses achados e determinar a segurança desses compostos.
Descritores: *Cannabis*, Dor, Endocanabinóides, Farmacologia, Tratamento.

INTRODUCTION

Among plant species domesticated by men, may be none is as versatile as *Cannabis sativa* (CS). Popularly known in Brazil by its African name (*maconha*), marijuana is part of humankind history for hundreds of years. From Gutenberg's Bible and paper money, to the original text of the American constitution, CS-derived fiber has been broadly used to manufacture paper. In addition to its psychoactive effect, CS has nutritional, medicinal and industrial importance as food, drug, fiber and fuel oil, in addition to its use in religious cere-

monies in different parts of the world. Recently, in Brazil, the controversial discussion about CS for medical use has been intensified due to the need for legal authorization to import cannabidiol for the treatment of children with seizures refractory to conventional therapies.

Medical use of CS has been recommended for different clinical conditions for many centuries[1]. In this sense, it is worth stressing that the two most widely used classes of drugs to manage pain (opioids and anti-inflammatory drugs), have vegetal origin. Popular consumption of willow bark to control pain and subsequent results of this plant have led to the development of aspirin and then to the discovery of the role of prostaglandins on inflammation and pain. Opium, obtained from poppy sap, has given origin to morphine, which is the prototype of opioid analgesics and which has allowed the characterization of several peptides, receptors, enzymes and signaling pathways which form the endogenous opioid system.

As from these breakthroughs there has been major scientific-technological development related to the manufacturing and use of these products and their derivatives. Similarly, studies related to CS pharmacological properties and its potential therapeutic use have gained major impulse in recent decades, especially as from the isolation in 1964 of its major psychoactive component, Δ^9-tetra-hydrocannabinol (THC). This advance has allowed for the discovery of the endogenous "cannabinergic" system, subsequently called endocannabinoid system (ECS) or endogenous cannabinoid. Several clinical and experimental evidences are suggesting the ECS participation in pain modulation[1], opening space for pharmaceutical developments in this area.

This study aimed at reviewing major pharmacological advances of endocannabinoid system pharmacology and the therapeutic use of some cannabinoid compounds to manage different types of pain.

CONTENTS

Selected articles for this review were identified by means of electronic query in Pubmed, Scielo and Lilacs databases. The following keywords were used: *Cannabis sativa,* tetra-hydro-cannabinol, cannabidiol, sativex*, cannador*, cannabinoids, endocannabinoid, pain and neuropathic pain. Selection was made up of studies and literature reviews on pharmacology and therapeutic use of cannabinoid derivatives for pain. Studies using drugs produced as from raw plant extract were also included.

Then, a review of references of articles was carried out and clinical and experimental studies were included. Considering the broad individual variation of different studied samples, dose or composition of different cannabinoids were not arbitrated. Studies using smoked CS were not included in this review due characteristics related to its use, such as previous experience of users, which impair the performance of a blind study, use of devices for plant combustion, etc.

PHARMACOLOGY OF THE ENDOCANNABINOID SYSTEM

In 1988, the first cannabinoid receptor was identified[2] and was susequently called endocannabinoid receptor 1 (CB_1). In 1993, a second receptor was discovered and called endocannabinoid receptor 2 (CB_2)[3]. Both receptors belong to the family of cell membrane proteins coupled to proteins Gi/o. Tissue distribution of CB_1, especially in basal ganglia, cerebellum, hippocampus, cortex, spinal cord and peripheral nerves, explains most part of psychotropic effects of endocannabinoid substances[4]. CB_2 receptors are found in immune system cells[5], which partially may explain the effects of these substances on pain and inflammation.

Cannabinoids are divided in three types: phytocannabinoids, synthetic cannabinoids and endogenous cannabinnoids or endocannabinoids, which are natural chemical substances especially represented by anandamide (N-arachidonoil ethanolamine) and by 2-arachidonoil glycerol. Anandamide and 2-arachidonoil glycerol are compounds found in several animals, especially those hibernating, and are physiologically related to functions such as "relax, eat, sleep, forget and protect"[6].

ECS includes endocannabinoids, their synthesis and catabolism enzymes and their corresponding receptors[7]. The name anandamide derives from the Sanskrit term *ananda*, which means ecstasy, supreme happiness, joy or blessedness. Both anandamide and 2-arachidonoil glycerol are agonists of receptors CB_1 and CB_2. However, due to the involvement in a larger number of metabolic pathways, cell and tissue levels of 2-arachidonoil glycerol are higher as compared to anandamide. Clinical and experimental evidences suggest that ECS, which is made up of endocannabinoid receptors, its endogenous ligands and synthesis and metabolic enzymes, may play important physiological role in regulating several signaling pathways, including those involved with pain pathophysiology.

Most endocannabinoids identified to date are derived from long chain poly-unsaturated fatty acids, specifically arachidonic acid. So, anandamide and 2-arachidonoil glycerol are formed by phospholipid-dependent pathways, the synthesizing enzymes of which are selective N-acyl phosphate diethanolamine phospholipase D and selective sn-1-diaglycerol lipase, respectively[8,9]. After release, anandamide and 2-arachinodoil glycerol suffer neuronal reuptake process and then are rapidly metabolized in inactive compounds by FAAH (fatty acid amide hydrolase) and by MGL lipase (monoacyl glycerol), respectively[10,11]. Anandamide is hydrolized by FAAH in arachidonic acid breakdown products and ethanolamine[12]. 2-arachidonoil glycerol is hydrolyzed by the MGL enzyme in arachidonic acid and glycerol[13]. FAAH is a post-synaptic enzyme which controls anandamide levels close to synthesis sites, and MGL is a pre-synaptic enzyme[14] controlling 2-arachidonoil glycerol levels after its action on CB_1 receptors. It is intriguing to notice that both endocannabinoids are degraded both in pre-synaptic (2-arachidonoil glycerol) and post-synaptic (anandamide) ways, thus making modulation of FAAH and MGL activity an important pharmacological target with potential therapeutic use.

ECS us active both in central (CNS) and peripheral nervous systems acting on spinal, supraspinal and peripheral pain modulation[15,16]. Endocannabinoid substances are produced in CNS by demand aiming at decreasing sensitivity to pain[17]. Several studies have already documented high ECS activity in pain integration key-centers[18-22]. Endocannabinoids seem to be mediators involved in the modulation of painful phenomena, such as wind up[23] and allodynia[24]. Peripherally, activation of CB_1 receptors seems to have important role in decreasing both hyperalgesia and allodynia[25,26].

By means of CB_1 and CB_2-mediated mechanisms, ECS seems to play important role also in peripheral pain, particularly in inflammatory processes and hyperalgesia[26]. Astrocytes and microglia-mediated inflammatory response depends on mechanisms involving activation of spinal CB_2 receptors[27]. THC inhibits prostaglandin E-2 synthesis[28] and stimulates lipoxygenase[29], however it does not affect cycloxigenase-1 and cycloxigenase-2 synthesis[30]. In addition to anti-inflammatory action, cannabinoids also have antioxidant activity via non-cannabinoid mechanisms[31].

Cannabidiol, which is a phytocannabinoid present in high concentrations in raw CS extract, inhibits both FAAH and anandamide reuptake[32], in addition to decreasing THC liver metabolism, thus decreasing psychotic changes and signs and symptoms of anxiety[33]. So, cannabidiol seems to act as ECS mediator, attenuating THC effects on behavior[34], appetite[35] and short term memory[36]. Cannabidiol seems to be effective to control endometriosis pain, among other conditions, especially those which may be considered ECS-mediated pain[37]. High cannabinoid activity has been already documented in different mediator areas of painful response in the gastrointestinal tract[38,39].

Cannabinoid substances specifically inhibit glutamate release in the hippocampus[40] decreasing NMDA-mediated painful response[28] so, they could be useful for the management of NMDA-mediated painful disorders[41], such as migraine, fibromyalgia and other diseases where glutamatergic mechanisms seem to be involved[42].

A promising pharmacological approach of particular interest for pain therapy is the combination of cannabinoids and opioids. Cannabinoid substances and ECS have different interaction levels with the endogenous opioid system. Known cannabinoid system interaction mechanism with the opioid system are: endorphin release[43]; opioid sparing effect[44]; decreased phenomena of opioids tolerance and withdrawal[45]; and analgesic rescue by opioids after the tolerance phenomenon[46]. It is interesting to notice that it seems to be pharmacological synergy between cannabinoid and opioid substances and that this phenomenon could potentiate analgesic effects of both drugs, thus decreasing doses without impairing therapeutic effects, in addition to significantly decreasing adverse effects of both drugs.

Based on above-mentioned action mechanisms, as well as on described pharmacological interactions for cannabinoid substances and ECS, it is possible to suggest that a functional ECS change may significantly contribute for the onset or worsening of pathological pain.

CLINICAL TRIALS ON THE USE OF SYNTHETIC CANNABINOIDS AND PAIN

Classically indicated for treating loss of appetite in human immunodeficiency virus (HIV) patients and to treat nausea and vomiting of patients under chemotherapy, dronabinol is available in the American market with the commercial name of marinol® in gelatin capsules of 2.5, 5 and 10mg. Dronabinol has been used in studies with neuropathic pain patients[47,48], but without significant benefit in pain control, in addition to presenting major adverse effects which have limited its use. For multiple sclerosis pain, dronabinol has produced significant relief[49], however there has been no evident effect on postoperative pain[50]. Dronabinol has been used to relieve itching in jaundice patients, however there are no controlled studies in this area, being this effect described only as case reports[51]. In a crossover study, dronabinol was evaluated in patients with chronic non-cancer pain under opioids and results were significant with regard to pain relief[52]. In a study with patients with spinal cord injury and neuropathic pain, dronabinol was not better than diphenhydramine[53].

Nabilone, with commercial name of Cesamet® is another THC semi-synthetic analog, available in oral capsules of 1 and 2mg in the United States and in Europe. It has more prolonged therapeutic effect as compared to THC for having pharmacological potency approximately 10 times higher, as well as for presenting longer half-life[54]. Notwithstanding reports of the use of nabilone to treat neuropathic pain[55] and other painful syndromes[56], its classic indication is as antiemetic agent for patients under chemotherapy. In polyneuropathy patients, nabilone has resulted in significant pain improvement after three months of use[57].

A controlled study with nabilone three times a day in patients with postoperative pain has shown increased visual analog scale (VAS) scores[58]. In a double-blind study with mixed spastic syndrome patients, nabilone has improved pain scores as compared to placebo[59], however there has been no improvement in other parameters such as spasticity, motor function or daily activities. In a double-blind crossover study comparing nabilone and dihydrocodeine for neuropathic pain[60], both drugs had no satisfactory results. In a different controlled study with fibromyalgia patients, nabilone versus placebo has shown significant improvement in VAS and anxiolytic effects[61].

A more recent study with nabilone versus amitriptyline with fibromyalgia patients has shown beneficial effects only for sleep-related parameters, without significant results for pain, mood or even quality of life[62]. Bestard & Toth, evaluating nabilone versus gabapentin, have found comparable effects in peripheral neuropathic pain improvement and in other symptoms[63]. However, in general, significant adverse effects, especially sedation and euphoria, have also limited its use in most studies.

Ajulemic acid, another synthetic THC analog[64], was used by Karst et al. in a controlled clinical trial with patients with peripheral neuropathic pain, showing possible improvement of pain-related symptoms[65].

CLINICAL TRIALS ON THE USE OF CANNABIS EXTRACTS AND PAIN

Cannador® is administered in oral capsules and is manufactured as from raw CS extract with different THC/cannabidiol percentages[33], but which in general is approximately 2:1. Cannador® was used in patients with spasticity changes in multiple sclerosis[66,67] and has shown slight postoperative pain relief[68]. However, side effects, such as sedation and psychoactive changes, were evident[68].

Sativex® is produced as from raw plant extract and is administered as oral spray which combines a partial agonist effect on CB_1 and CB_2. In addition to THC and cannabidiol, Sativex® has in its composition other minor cannabinoids, propylene glycol, terpenoids, ethanol and flavoring mint excipient[33,69]. Sativex® has been used to treat cancer pain refractory to opioids and to relieve symptoms related to multiple sclerosis, such as central neuropathic pain and spasticity. Sativex® is formulated as from two CS strains where THC and cannabidiol predominate[70]. Sativex® has shown satisfactory results in patients with pain refractory to conventional treatment and/or with neurogenic symptoms[71] and in patients with untreatable chronic pain[72]. In patients with chronic pain by brachial plexus avulsion, Sativex® has also significantly decreased pain[73]. Sativex® for rheumatoid arthritis patients has significantly improved pain both at rest and at movement[74]. Sativex® was also used in patients with peripheral neuropathic pain associated to allodynia and again has decreased pain and allodynia levels[75]. In virtually all chronic pain clinical trials, Sativex® has significantly improved quality of sleep, not due to drug sedative effect, but rather by significantly decreasing symptoms[76]. Sativex® adverse effects may be considered mild, being most common: bitter taste, oral burning, dry mouth, dizziness, nausea and fatigue. Psychoactive sequelae are early and transient and have been significantly decreased by a slower and less aggressive titration scheme.

CONCLUSION

Pharmacological studies and clinical trials partially support the use of cannabinoid agents as analgesics for chronic pain, creating the perspective that drugs based on phytocannabinoids and synthetic cannabinoids may be used as adjuvant for pain control, especially for that of neuropathic origin. Due to their unique pharmacological profile, with multimodal effect and low risk of adverse effects, cannabinoid agents have potential to offer health professionals a useful option to treat neuropathic pain. However, further studies are needed to confirm the efficacy and safety of these compounds for patients, especially with regard to the incidence and intensity of adverse effects during long term treatment.

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