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Review

The endocannabinoid system and its therapeutic implications in rheumatoid arthritis

Huan Gui [a,b], Qiang Tong [b], Wenchun Qu [c,d], Chen-Mei Mao [a,*], Sheng-Ming Dai [b,**]

[a] Department of Pharmacy, Children's Hospital of Soochow University, Suzhou, China
[b] Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, Shanghai, China
[c] Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA
[d] Division of Pain Medicine, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Since the discovery of the endogenous receptor for Δ^9-tetrahydrocannabinol, a main constituent of marijuana, the endocannabinoid system (comprising cannabinoid receptors and their endogenous ligands, as well as the enzymes involved in their metabolic processes) has been implicated as having multiple regulatory functions in many central and peripheral conditions, including rheumatoid arthritis (RA). RA is an immune-mediated inflammatory disease that is associated with the involvement of many kinds of cells (such as fibroblastlike synoviocytes [FLSs], osteoclasts, T cells, B cells, and macrophages) and molecules (such as interleukin-1β, tumor necrosis factor-α, interleukin-6, matrix metalloproteinases [MMPs], and chemokines). Increasing evidence suggests that the endocannabinoid system, especially cannabinoid receptor 2 (CB2), has an important role in the pathophysiology of RA. Many members of the endocannabinoid system are reported to inhibit synovial inflammation, hyperplasia, and cartilage destruction in RA. In particular, specific activation of CB2 may relieve RA by inhibiting not only the production of autoantibodies, proinflammatory cytokines, and MMPs, but also bone erosion, immune response mediated by T cells, and the proliferation of FLSs. In this review, we will discuss the possible functions of the endocannabinoid system in the modulation of RA, which may be a potential target for treatment.

Contents

Abbreviations: AEA, arachidonoyl ethanolamide; 2-AG, 2-arachidonoylglycerol; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; FAAH, fatty acid amide hydrolase; FLS, fibroblastlike synoviocyte; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; RA, rheumatoid arthritis; Th, T helper cells; THC, Δ^9-tetrahydrocannabinol; TNF, tumor necrosis factor

* Correspondence to: C.-M. Mao, Department of Pharmacy, Children's Hospital of Soochow University, 303 Jingde Road, Suzhou 215003, Jiangsu Province, China. Tel.: +86 0512 67786318.
** Correspondence to: S.-M. Dai, MD, PhD, Department of Rheumatology & Immunology, Changhai Hospital, Second Military Medical University, 168 Changhai Road, Shanghai 200433, China. Tel.: +86 21 31161557; fax: +86 21 65492727.
E-mail addresses: maocm68@163.com (C.-M. Mao), dsm@medmail.com.cn (S.-M. Dai).

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1. Introduction

As early as the 18th century BCE, cannabis/marijuana was recorded in "Shen Nong's Herbal Classic" by the Chinese emperor Shen Nong as a drug for menstrual symptoms, gout, rheumatism, malaria, and constipation. In the 19th century, British physicians started to prescribe it widely for conditions ranging from epilepsy to rheumatism and abdominal symptoms. The psychological addiction resulting from the abuse of cannabis is the main concern limiting its therapeutic use. In the 20th century, Δ^9-tetrahydrocannabinol (THC) was identified as the main bioactive constituent of cannabis, and its molecular targets in the human body, the cannabinoid receptor family, were discovered. Since then, the cannabinoid system has attracted more and more attention from physicians and scientific researchers. Current studies focus on the function of this unique system and the synthesis of cannabinoid-based drugs. In this review, we will discuss the possible function of the endogenous cannabinoid system in the modulation of rheumatoid arthritis (RA), which may be a potential target for treatment.

2. The endocannabinoid system

After the identification of plant-derived constituents of cannabis, endogenous cannabinoid binding sites, called cannabinoid receptors, were found and cloned in the early 1990s. Shortly thereafter, substances were found occurring naturally in the body that could mimic the activity of THC; these are called endocannabinoids. Endocannabinoids and their receptors, as well as the enzymes that mediate their synthesis and degradation, constitute the endocannabinoid system. In recent years, more and more components have been classified into the endocannabinoid system.

2.1. Cannabinoid receptors

After identification of the pharmacologic properties of constituents of the marijuana plant, the cannabinoid receptor 1 (CB1) gene was cloned from rat cerebral cortex and sequenced in 1990 [1]. The CB1 protein is a Gi protein-coupled receptor with 473 amino acids. Activation of CB1 inhibits cAMP accumulation, and this can be prevented by pretreatment with pertussis toxin. The inhibitory potency of CB1 varies when responding to different cannabinoids. Briefly, CB1 is more responsive to psychoactive cannabinoids (eg, THC) than to nonpsychoactive cannabinoids (eg, cannabidiol). This suggests that CB1 is likely to be the molecular target through which marijuana produces its psychiatric effects. This assumption was proved by later studies showing that CB1 exists mainly, although not exclusively, in the central nervous system [2] and is correlated with the motor and reward systems [3].

The peripheral effects of marijuana and THC—analgesia, anti-inflammation, immunosuppression, and anticonvulsant activity—suggested the possibility of a novel cannabinoid receptor type. In 1993, cannabinoid receptor 2 (CB2) was identified from macrophages in the marginal zone of mouse spleen; CB2 shares 44% homology with CB1 and also belongs to the Gi protein-coupled receptor family [4]. Mouse CB2 has an 82% sequence identity to human CB2 [5]. Unlike CB1, CB2 is predominantly present in the peripheral immune system under normal conditions. A recent study showed no differences in the intensity of CB2 mRNA expression among human peripheral blood leukocytes such as B cells, T cells, and monocytes [6]. Differences were seen, however, in the cell-surface expression of CB2; only B cells have been shown to express membrane-bound CB2 protein, whereas T cells and monocytes expressed only intracellular CB2 protein. CB1 and CB2 are also expressed by other kinds of cells, at relatively lower levels, and are regulated by many pathophysiologic changes. For example, in addition to immunocytes, CB2 is also detectable in fibroblastlike synoviocytes (FLSs) [7,8], osteoclasts [9], osteoblasts [10], and smooth muscle cells [11]. All these data demonstrate the expression of CB2 in various cells that are involved in the physiopathology of RA. Outside the central nervous system, CB1 is also present in hepatic cells [12] and macrophages [13].

Besides the 2 classic cannabinoid receptor types, pharmacologic evidence for the existence of additional types of cannabinoid receptors has already emerged. Among them, orphan receptor GPR55 [14,15], peroxisome proliferation-activated receptor-γ [16], and transient receptor potential vanilloid 1 [17,18] seem to be possible candidates. However, there has been no solid evidence to demonstrate any effects of cannabinoids mediated by these candidate receptors yet.

2.2. Endocannabinoids

Identification of specific receptors for plant-derived cannabinoids was followed in the 1990s by the isolation of 2 endogenous arachidonic acid-derived ligands. Anandamide (arachidonoyl ethanolamide [AEA]) was the first endocannabinoid isolated from porcine brain [19], followed by 2-arachidonoylglycerol (2-AG), found in canine intestines [20]. Subsequently, other bioactive endocannabinoids such as 2-AG ether (noladin ether) [21], O-arachidonoyl ethanolamine (virodhamine) [22], and N-arachidonoyl dopamine [23] were identified, but their functions and mechanisms of action remain poorly characterized. More recently, 2 omega-3 fatty acid ethanolamides, docosahexaenoyl ethanolamide and eicosapentaenoyl ethanolamide, were discovered as having considerable potency to activate CB1 and CB2 in vitro [24], which indicates that the endocannabinoid family has 2 other members.

Endocannabinoid synthesis can be induced by numerous stimuli (eg, neuronal activity, glucocorticoids, insulin, and cytokines) and secreted by various cells throughout the body, from central brain [25] to peripheral tissues such as the adipose tissue [26], muscle [27], liver [28], and immune cells [29]. The biological activity of endocannabinoids is tightly regulated by their metabolism. In a classic pattern, the biosynthesis of AEA is catalyzed by Ca^{2+}-dependent N-acyl-phosphatidylethanolamine–hydrolyzing phospholipase D [30], but AEA can also be produced by other routes [25,31]. The process for AEA clearance consists of 2 steps. AEA is first transported into the plasma by cellular uptake and then hydrolyzed by fatty acid amide hydrolase (FAAH) into arachidonic acid and ethanolamine [32]. 2-AG is synthesized from its phospholipid precursor diacylglycerol by diacylglycerol lipases [25]. The major degradative pathway of 2-AG is its hydrolysis to arachidonic acid and glycerol [33]. The hydrolysis of 2-AG in the brain is mainly catalyzed by monoacylglycerol lipase; other hydrolases such as ABHD6, ABHD12, and FAAH contribute to less than 15% of the hydrolysis [34]. Although the hydrolysis pathway seems to be the primary fate of AEA and 2-AG, they can also be oxidized by cyclooxygenase-2 and lipoxygenase isozymes, thus producing oxidized endocannabinoids, which are involved in regulating brain synaptic transmission and other biological processes [35,36]. Both AEA and 2-AG are cannabinoid receptor agonists, but they display different affinity for CB1 and CB2. AEA has more affinity to CB1 than CB2, whereas 2-AG shows similar affinity for CB1 and CB2.

2.3. The endocannabinoid system in inflammatory conditions

From central brain to peripheral organs, the endocannabinoid system has been found to be involved in many inflammation-related conditions, such as multiple sclerosis [37,38], atherosclerosis [29,39], inflammatory bowel disease [40], RA [7,41], sepsis [42,43], and allergic inflammation [44]. Evidence shows that exogenous application of AEA and 2-AG exerts anti-inflammatory effects by decreasing the production of inflammatory mediators. Upregulating the level of endogenous cannabinoids by inhibiting their common metabolic enzyme, FAAH, becomes an important strategy in the treatment process of inflammation-related diseases. Meanwhile, blockage of CB1 and activation of CB2 could also inhibit inflammation in various animal models, mainly through restraining the activity of the immune system.