Cannabinoid receptors as therapeutic targets for autoimmune diseases: where do we stand?

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Described during the late 1980s and 1990s, cannabinoid receptors (CB1R and CB2R) are G-protein-coupled receptors (GPCRs) activated by endogenous ligands and cannabinoid drug compounds, such as Δ9-THC. Whereas CB1R has a role in the regulation of neurotransmission in different brain regions and mainly mediates the psychoactive effects of cannabinoids, CB2R is found predominantly in the cells and tissues of the immune system and mediates anti-inflammatory and immunomodulatory processes. Studies have demonstrated that CB1R and CB2R can affect the activation of T cells, B cells, monocytes, and microglial cells, inhibiting proinflammatory cytokine expression and upregulating proresolution mediators. Thus, in this review, we summarize the mechanisms by which CBRs interact with the autoimmune environment and the potential to suppress the development and activation of autoreactive cells. Finally, we highlight how the modulation of CB1R and CB2R is advantageous in the treatment of autoimmune diseases, including multiple sclerosis (MS), type 1 diabetes mellitus (T1DM) and rheumatoid arthritis (RA).

Introduction

Mammalian tissues contain an endogenous cannabinoid system (the endocannabinoid system, ECS), comprising: (i) GPCRs CB1R and CB2R; (ii) endogenous cannabinoid ligands; and (iii) enzymes involved in their synthesis and inactivation (endocannabinoid metabolism) [1]. Additionally, other receptors have been reported to be activated by cannabinoid drugs and related molecules, including GPCR 55 (GPR55), GPR18, and GPR119 [2–4]. GPR55 has gained attention as a potential receptor for cannabinoid ligands that mediates effects independently of CB1R and CB2R, suggesting a third CBR (i.e., CB3R). However, according to Pertwee and co-authors, CB3R does not meet the criteria that would classify it as a cannabinoid receptor [4]. According to the current classification by the International Union of Basic and Clinical Pharmacology (IUPHAR), endocannabinoids are those compounds with significant affinity for CB1R or CB2R [5]. However, their molecular

targets go far beyond classical CBR and include a range of receptors, such as GPR55, GPR18, GPR119, transient receptor potential ankyrin 1 (TRPA1), transient receptor potential channel type V1 (TRPV1), and peroxisome proliferator-activated receptors (PPARs), as well as several nonreceptor targets, which makes them active in different processes, such as inflammation and autoimmunity [4,6].

The ECS acts as a regulator of immune homeostasis, in cortical development [7], the sleep–wake cycle, memory, and emotional responses [8]. Moreover, it exerts regulatory effects on neuroendocrine function, including the regulation of the stress response, food intake, fluid homeostasis, and reproductive function [9]. Thus, the dysregulation of ECS signaling can leads to immune-mediated psychiatric disorders [10], obesity, insulin resistance, and dyslipidemia [11]. The ECS also has an important role in neuroprotection and central nervous system (CNS) homeostasis. Previous studies suggested that the ECS participates in immune control in the CNS [12], maintaining the overall 'fine-tuning' of immune homeostatic balance [13] and influencing neuroendocrine responses to

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inflammation and infection [14]. Thus, pharmacological modulation of CBR and/or the enzymes that control its synthesis, transport, and degradation is an option for the treatment of numerous neurological disorders [15], reinforcing the role of the ECS in neuroinflammatory conditions [16].

After synthesis, the ECS acts locally by regulating multiple presynaptic neurotransmitters. In this context, it is synthesized and released from postsynaptic cells and travels backward in the 'retrograde' direction across the synapse, maintaining homeostasis and preventing excessive neuronal activity [10]. N-arachidonoyl-ethanolamine, also called anandamide (AEA), and 2-arachidonoyl glycerol (2-AG) are both lipid molecules, but are not stored in vesicles similar to other neurotransmitters [17]. Instead, they are synthesized and released on demand, a process that can be regulated either physiologically or under pathological conditions (Fig. 1). The two-step process that includes transport into cells and hydrolysis by specific enzymatic systems degrades the ECS. The biological activities of anandamide at CBR are halted by their removal from the extracellular space through cellular uptake by a transporter. However, the molecular identity of the AEA and 2-AG transporters remains elusive [18–20]. Once taken up by cells, AEA is the substrate for fatty acid amide hydrolase (FAAH), which breaks the amide bond and releases arachidonic acid and ethanolamine. 2-AG is subjected to rapid transport across the plasma membrane and is degraded by FAAH or, more efficiently, by specific monoacylglycerol lipase (MAGL) (Fig. 1) [10].

The CB1R was initially considered a CNS receptor, although it occurs at central and peripheral nerve terminals in both excitatory and inhibitory neurons (Fig. 2) [21]. The expression of CB1R in skeletal muscle, liver, and pancreatic islets has also been described, as well as its role in metabolism [22]. CB1R demonstrates neuroprotective roles [23] in disorders such as chronic intermittent hypoxia [24], neurodegenerative diseases [25], and neuronal damage caused by HIV-1 infection [26]. These neuroprotective effects are mediated by the downregulation of PGE2, PGD2, and reactive oxygen species (ROS), through the reduction of COX-1- and COX-2 activity in microglial cells [27], although many other mechanisms and targets are known. Intriguingly, the anti-inflammatory properties of CB1R extend to skin diseases and wound healing. CB1R is capable of limiting the secretion of proinflammatory chemokines in cells such as keratinocytes, suggesting that CB1R also regulates T cell-dependent inflammatory diseases of the skin [28]. Furthermore, CB1R agonists could be good options for the treatment of psoriasis, vitiligo, and atopic dermatitis because they downregulate mast cell activation and relieve inflammatory symptoms mediated by hypersensitivity and autoimmune diseases [29], although their use is minimal because of their psychotropic properties (Fig. 3). Peripherally selective CB1R agonists, such as indole and indene compounds with limited CNS penetration, have emerged to solve this limitation and represent a possible pharmacological intervention to explore the beneficial effects of CB1R without undesirable consequences [30].

Recent reports suggested that endocannabinoid levels at inflammatory sites can be rapidly elevated and in turn regulate fast signaling responses in immune and other cells, modulating their crucial functions. Thus, previous reports investigated CB2R for the treatment of chronic neuroinflammatory disorders [31], traumatic brain injury (TBI) [32], ischemic injury, spinal cord injury [33], and Parkinson's disease (PD) [34] (Fig. 3). Extending from these observations, Castaneda et al. showed that CB2R expression in human leukocytes is regulated by cellular location (extracellular or intracellular), cell lineage, and activation state, suggesting that CB2R location activates different signaling pathways [35]. Surprisingly, CB2R is distributed in the CNS, and its expression has been identified in areas including the prefrontal cortex [36], globus pallidus [37], substantia nigra [36], brain stem [38], and cerebellum [39], justifying its possible neuroprotective role [40]. Additionally, CB2R demonstrates analgesic effects in cancer, MS, fibromyalgia, painful diabetic neuropathy, migraine, and both acute and persistent inflammatory pain [41] through the downregulation of cytokines such as interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor (TNF), and monocyte chemoattractant protein 1 (MCP-1). Moreover, CB2R activation inhibits astrocyte and glial cell activation, leading to the control of chronic pain by modulating neuronal activity and inhibiting pain transmission [42] (Fig. 3). Additionally, early studies demonstrated that cannabinoids and their receptors constitute a novel, innovative, and clinically relevant control element of keratin upregulation and keratinocyte proliferation [43]. In the same way, AEA suppresses human epidermal keratinocyte proliferation and induces cell death, demonstrating that cutaneous ECS activation could become a therapeutic strategy for hyperproliferative human skin lesions, such as psoriasis [44]. More recently, Noroznezhad and colleagues showed that the cannabinoid JWH-133 inhibited psoriatic pathogenesis (angiogenesis and inflammation) [44]. In this context, both receptors have been studied for their relevance in autoimmune conditions, such as MS, T1DM, RA, and others (Fig. 4). Herein, we discuss how CBR and cannabinoid ligands could modulate the genesis, onset, and progression of autoimmunity.

Therapeutic strategies targeting the CBR pathway in multiple sclerosis

Autoimmune diseases, including MS, result from aberrant activation of the immune system, whereby the immune response is directed against harmless self-antigens. This results in inflammation, tissue damage, and loss of tissue function [45]. Evidence supports the use of cannabis and its active ingredients as immunomodulatory agents by affecting T cell, B cell, monocyte, and microglial activation, inhibiting proinflammatory cytokine expression, and upregulating proresolution mediators [46]. MS is a chronic, degenerative, autoimmune disease of the CNS that affects ~2.5 million people worldwide [47]. It is considered the most common nontraumatic disability in the world, with a high prevalence in young people, with associated personal and socioeconomic burdens [48]. According to Dendrou and Fugger, MS is an inflammatory disease, characterized by the infiltration of immune cells into the CNS. This discovery lead to research into the etiology of autoimmune disease, as well as guided treatments with immunomodulatory agents [49]. Commonly, demyelinated plaques are present in white and gray matter, such as the cerebral or cerebellar cortex and brainstem nuclei. The pathophysiological processes involve the formation of plaques, neuroinflammation, myelin breakdown, astrogliosis, oligodendrocyte injury, neurodegeneration, axonal loss, and remyelination. The presence of immune mediators, such as complement proteins, and autoreactive cells,
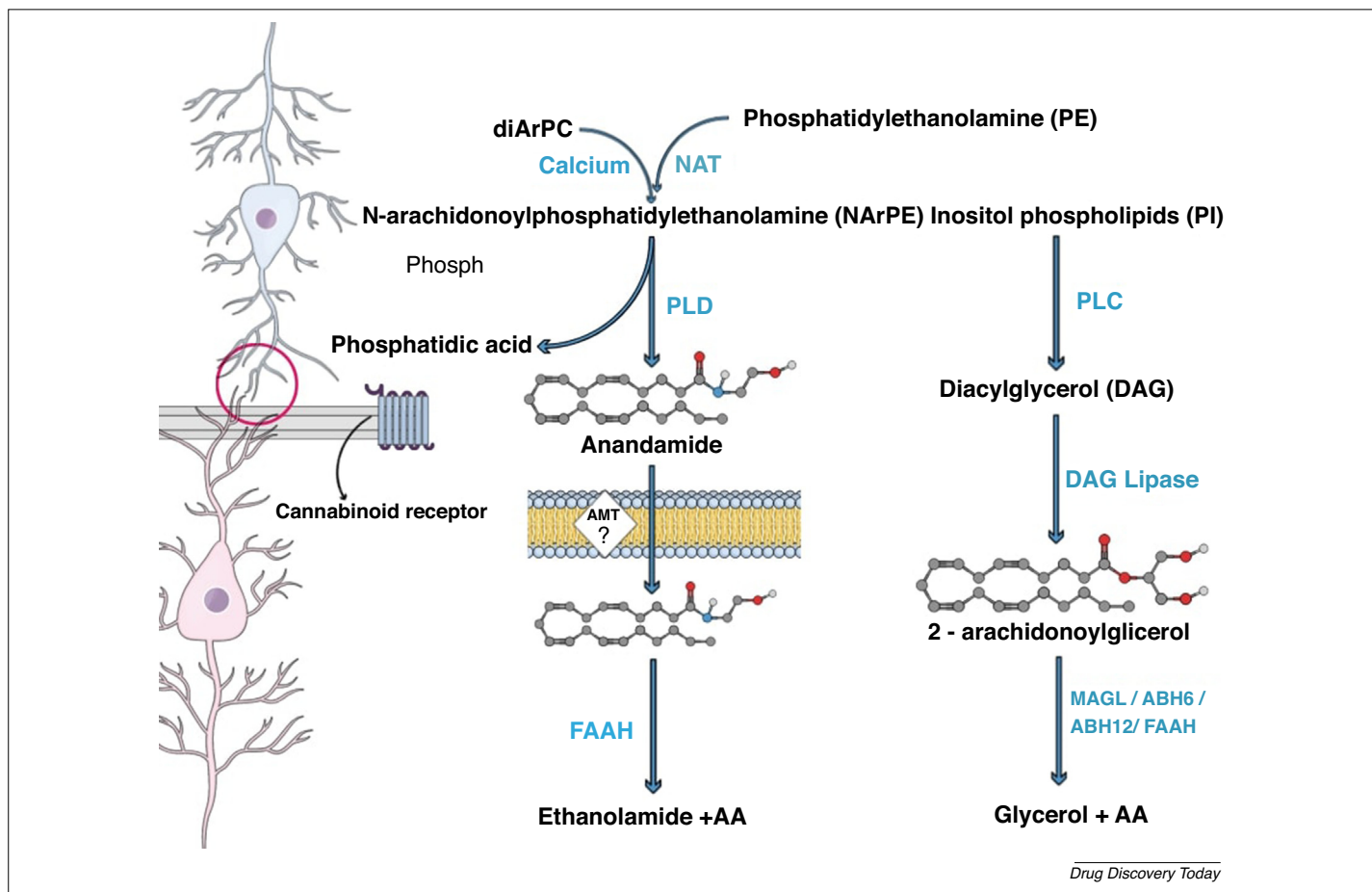
FIGURE 1

Biosynthesis and degradation of endocannabinoids (ECS). Pathways involved in the synthesis and degradation of two main endocannabinoids: arachidonoyl ethanolamine (anandamide; AEA) and 2-arachidonoyl glycerol (2-AG). AEA is synthesized from N-arachidonoyl phosphatidylethanolamine (NArPE), which is derived from the enzymatic transfer, catalyzed by N-acyltransferase (NAT), of an acyl group from the sn-1 position of arachidonoyl phosphatidylcholine (diArPC) to the amino group of a phosphatidylethanolamine (PE). In turn, NArPE is hydrolyzed to AEA and phosphatidic acid by a specific phospholipase D (NAPE-PLD) and degraded by fatty acid amide hydrolase (FAAH), producing ethanolamide and arachidonic acid. Synthesis of 2-AG depends on conversion of phosphatidylinositol (PI) to diacylglycerol by phospholipase C (PLC) and their subsequent transformation to 2-AG by the action of diacylglycerol lipase (DAGL). 2-AG is inactivated by the activity of monoacylglycerol lipase (MAGL) at glycerol and arachidonic acid. Finally, 2-AG and AEA might be taken back into the cell by a transporter mechanism that is currently poorly defined. Here, we illustrate the possible role of AEA membrane transporter (AMT) in the removal of AEA from the extracellular space. Figure created using the Mind the Graph platform.

including B cells, T cells, and macrophages, drives autoimmune-mediated inflammatory diseases, such as MS [47]. Moreover, there is evidence demonstrating that hypofunction or dysregulation of the ECS might be responsible for the onset or progression of MS symptomatology, and that modulation of the cannabinoid system could provide potential therapeutics for inflammatory and auto-immune diseases such as MS [50–52].

Recently, Brindisi *et al.* demonstrated that compound 4a, a potent β-lactam-based monoacylglycerol lipase inhibitor (MAGL), upregulated 2-AG and acted as an indirect cannabinoid (CB1R/CB2R) receptor agonist. Interestingly, administration of compound 4a during experimental autoimmune encephalomyelitis (EAE), an MS model, improved the severity of clinical symptoms in a CB1/CB2-dependent manner [53]. Another study demonstrated that mice with lower levels of FAAH showed severity of symptoms similarly to wild-type mice, with important clinical remission [54]. MAGL blockade is a useful strategy for the treatment of white matter lesions via the inhibition of oligodendrocyte death, prevent-

ing demyelination and reducing EAE severity in mice [55]. Moreover, WWL70, a potent inhibitor of α/β-hydrolase domain 6 (ABHD6), modulates CB2R by inducing a neuroprotective effect, and upregulates 2-AG in microglia and macrophages. In addition, WWL70 inhibited EAE-induced symptoms and reduced iNOS, COX-2, TNF, and IL-1β expression, as well as nuclear factor (NF)-κB phosphorylation in the CNS [56]. Another cannabinoid compound, UCM707, a potent and selective inhibitor of endocannabinoid uptake, reduced microglial activation, proinflammatory mediator levels, major histocompatibility complex class II antigen expression, and cellular infiltrates in the spinal cord of mice with Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD), a typical murine model of MS [57]. Moreover, CB2R activation is a prospective alternative to treat neuroinflammatory responses in neurological disorders such as MS, cerebral ischemia, Alzheimer's disease (AD), and PD, given that CB2R ligands do not induce the adverse psychotropic effects related to CB1R activation in the brain, which are mediated by microglia and neurons [58].
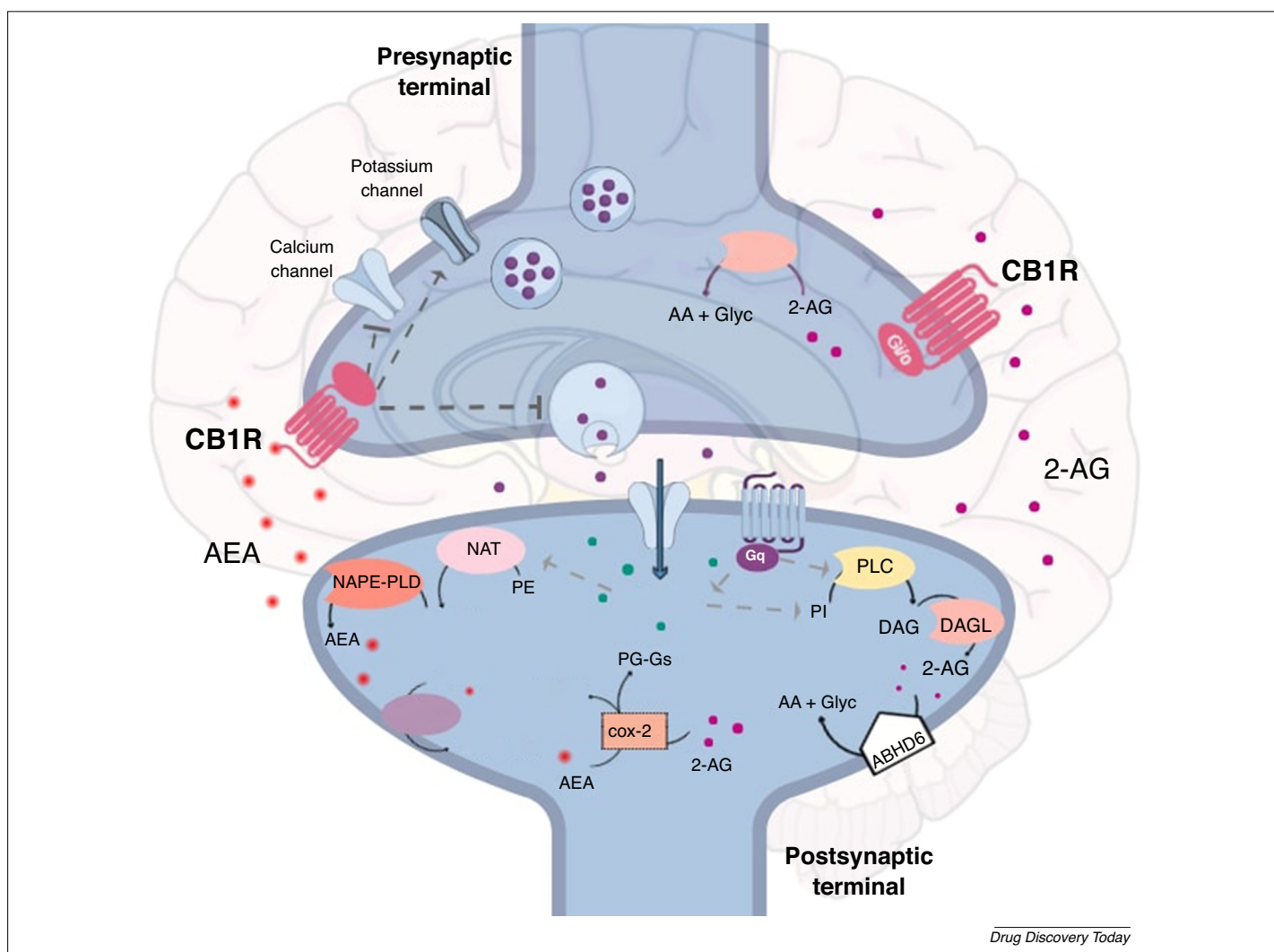
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FIGURE 2

Neuromodulatory activity of cannabinoid type 1 receptor (CB1R). The action potential stimulates glutamate (Glu) release. After release into extracellular space, Glu binds to glutamate receptors such as AMPAR and mGLUR expressed in membranes of both postsynaptic and presynaptic neurons. Endocannabinoids (ECSs) are mobilized from postsynaptic neurons and target presynaptic CB1R to suppress neurotransmitter release. After synthesis, ECSs regulate multiple presynaptic neurotransmitters and travel backward (in the 'retrograde' direction) across the synapse, maintaining homeostasis and preventing excessive neuronal activity. ECSs are synthesized and released 'on demand', and this can be regulated either physiologically or under pathological conditions. Biological activities of arachidonoyl ethanolamine (anandamide; AEA) at CBRs are stopped by their removal from the extracellular space through cellular uptake by a transporter. Once taken up by cells, AEA is a substrate for fatty acid amide hydrolase (FAAH), which breaks the amide bond and releases arachidonic acid (AA) and ethanolamine. By contrast, 2-arachidonoyglicerol (2-AG) is subjected to rapid transport across the plasma membrane and is degraded by FAAH or, more efficiently, by a specific monoacylglycerol lipase (MAGL). CB1R commonly is coupled to Gi/o and inhibits presynaptic Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs), the activity of adenylyl cyclase (AC), the formation of cAMP, and activity of protein kinase A (PKA), as well as activating ERK1/2, inhibiting neurotransmitter release. Abbreviations: COX, cyclooxygenase; DAGL diacylglycerol lipase; NArPE, N-arachidonoyl phosphatidylethanolamine; PLD, phospholipase D. Figure created using the Mind the Graph platform.

In terms of the relevance of the CBR pathway in MS, Annunziata *et al.* recently reported that COR167, a selective CB2 agonist, led to an atypical and incomplete shift in the Th1 phenotype towards a Th2 phenotype, associated with a slight reduction in IL-4 and IL-5 levels, as well as markedly reduced Th17-related cytokine levels [59]. CB2R knockout mice showed exacerbated clinical EAE scores compared with wild-type mice. Interestingly, these animals also showed extended axonal loss, T lymphocyte (CD4+) infiltration, and microglial (CD11b+) activation, whereas CB2-deficient T cells exhibited reduced levels of apoptosis, a higher rate of proliferation. and increased production of inflammatory cytokines. These findings indicate that CB2R expression by encephalitogenic T cells is

crucial for the control of neuroinflammation associated with EAE [60]. Lago *et al.* showed that CB1R mediated anti-inflammatory effects in the EAE model through the downregulation of COX-2, iNOS, and TNF expression in the spinal cord and brainstem [61]. Moreover, administration of Rimonabant® (20 mg), a CB1R inverse agonist, increased motor system excitability in the cortex and spinal cord, revealing its role as a potential therapeutic agent in neuroinflammatory and motor neuron diseases, including MS, PD, and traumatic brain injury [62].

Interestingly, a clinical report demonstrated a positive impact of a Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) Sativex® oromucosal spray, a mix of 2.7 mg Δ9-THC and 2.5 mg
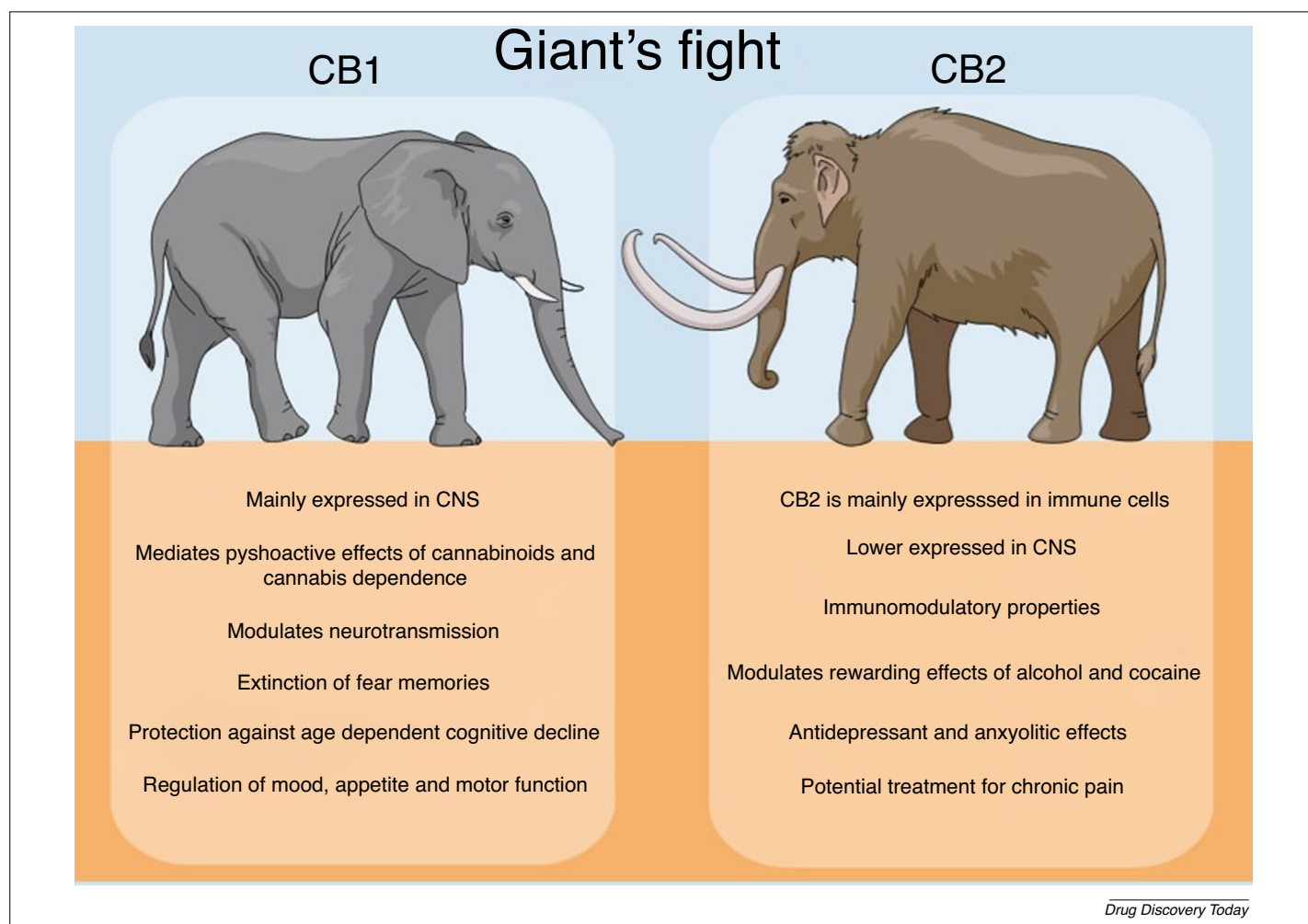
FIGURE 3

Giant's fight. This figure illustrates the main differences and physiology mechanism between cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) and highlights the strengths and weaknesses. Abbreviation: CNS, central nervous system. Figure created using the Mind the Graph platform.

CBD extracted from *Cannabis sativa*, in patients with MS [63]. It was an effective and well-tolerated treatment for patients with treatment-resistant MS spasticity [64,65]. Furthermore, Patti and co-authors demonstrated that Sativex® treatment inhibited spasticity (70.5% reduction) in 1615 patients with MS, although 39.5% of patients discontinued treatment for lack of effectiveness (26.2%) and/or adverse events (18.7%) [66]. Other groups demonstrated that the Δ9-THC/CBD Sativex® oromucosal spray improved spasticity-related symptoms independently of the number of prior failed therapy attempts; in addition, tolerability was not influenced by pretreatment history [67]. Additionally, Sativex® oromucosal spray improved neuropathic pain, sleeping, walking, and treatment-refractory symptoms [68]. According to Gras and Broughton, Sativex® oromucosal spray is cost-effective for the treatment of spasticity in MS [69]. Additionally, Carotenuto *et al.* showed corticospinal tract (CST) damage in patients with MS with spasticity symptoms, but they could not show correlations that could explain the clinical effects of Sativex® [70]. Another study demonstrated that patients with MS treated with IFN-β1b associated with Sativex® showed specific downregulation of CB2R expression, suggesting that IFN-β contributes to the difference in CBR expression in leukocytes during Sativex® treatment [71]. Finally, Δ9-THC and CBD have

immunosuppressive activity [72]. THC/CBD has low abuse potential and few psychoactive effects, and the approval of Sativex® for the management of MS spasticity has opened new opportunities for many patients [73]. These relevant clinical trials are reviewed in details elsewhere [74]. Altogether, these data reinforce the hypothesis that pharmacological manipulation of the ECS represents a potential target for the treatment of autoimmune diseases, such as MS.

The impact of cannabinoid receptor signaling in type 1 diabetes mellitus

T1DM is a chronic autoimmune disease that leads to the destruction of insulin-producing pancreatic β cells, the glucose thermostats of the body, such that they are not able to produce sufficient amounts of insulin, resulting in hyperglycemia, clinical symptoms, and damage to organs and tissues. Classical symptoms include hyperglycemia, polyuria, polydipsia, weight loss, abdominal symptoms, headaches, and ketoacidosis, as well as visual impairment, nephropathy, neuropathy, heart disease, and stroke. An unfortunate combination of genetic and environmental factors contributes to the differentiation and proliferation of autoimmune cells against pancreatic β cells, leading to the autodestruction of pancreatic β-cells and hyperglycemia
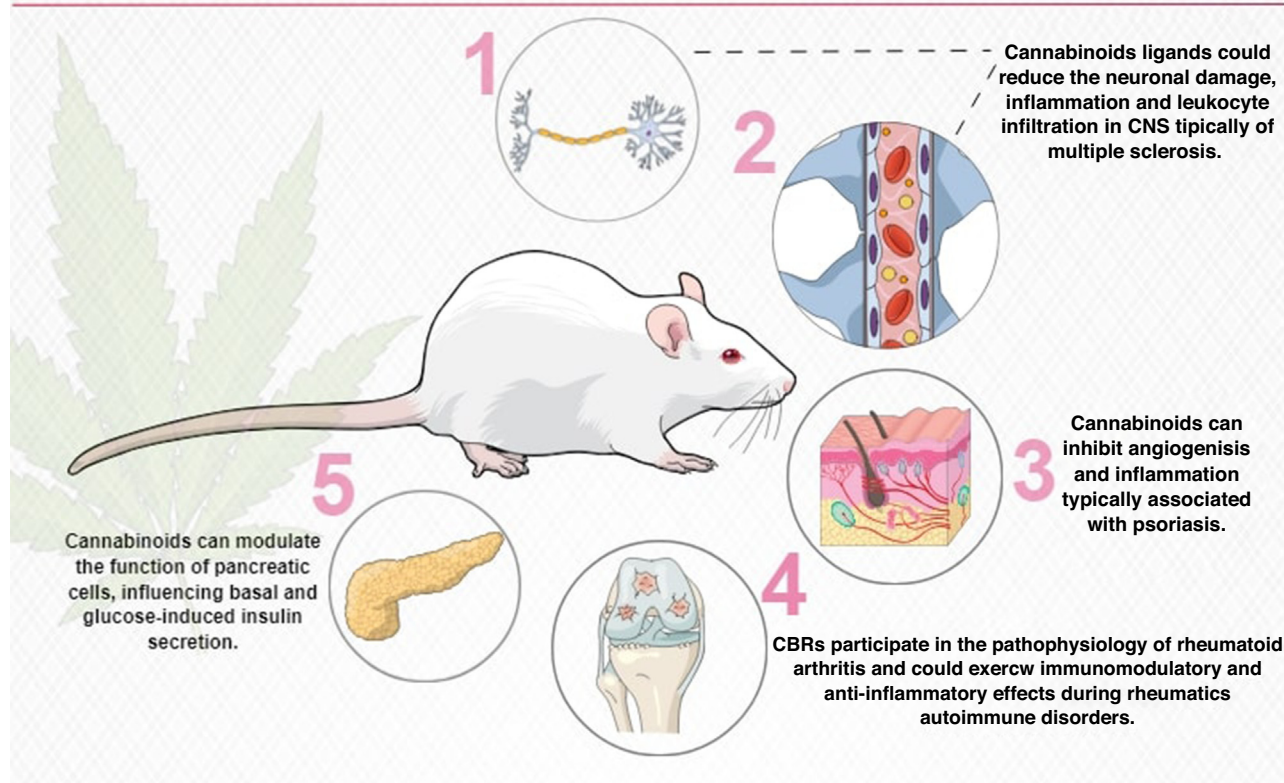
FIGURE 4

Cannabinoid receptor (CBR) ligands and autoimmune diseases. This illustration summarizes the main findings from this review article regarding the interaction between cannabinoid receptor ligands in autoimmunity, especially multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis, and psoriasis. Figure created using the Mind the Graph platform. Abbreviation: CNS, central nervous system.

symptoms. The autoimmune response during T1DM involves humoral and cellular immunity, possibly from a loss of tolerance to tissue self-antigens caused by deficiencies in both central and peripheral tolerance as well as the production of autoantibodies against pancreatic islets [75]. T1DM has no cure, but the crucial involvement of the endocannabinoid/cannabinoid receptor system in DM and its complications has been recognized [76].

CB1Rs are expressed mainly in the brain and modulate food intake and energy balance. Moreover, the ECS modulates the function of pancreatic β cells by influencing basal and glucose-induced insulin secretion, as well as their proliferation and survival. Evidence indicates that CB1R signaling contributes to insulin resistance in both T1DM and T2DM. However, is not entirely understood whether CB1R has a harmful or beneficial effect during hyperglycemia. Whereas Δ9-THC induced glucose tolerance in mice when chronically administered, CB1R blockade inhibited hyperglycemia and controlled obesity in mice [77]; this was also observed in cannabis users [78]. Finally, previous reports

have shown that CBD administration ameliorates T1DM symptoms in nonobese diabetic (NOD) mice [79].

Other evidence suggests that CB1R is upregulated in podocytes, a highly specialized cell of the kidney glomerulus. CB1R signaling has an essential role in nephropathy development in Zucker diabetic fatty (ZDF) rats. Also, CB1R blockade ameliorated albuminuria in an experimental T1DM model [80]. By contrast, CB2R expression is downregulated in kidney biopsies from patients in advanced stages of diabetic nephropathy, and CB2R deletion worsens nephropathy and reduces albuminuria in diabetic mice, confirming a protective role of CB2R signaling during T1DM progression [76]. Lastly, dual therapy using AM6545, a peripherally restricted CB1R antagonist, or AM1241, a CB2R agonist, in experimental diabetic nephropathy showed positive effects on albuminuria, inflammation, tubular injury, and renal fibrosis [81].

Additionally, Bartolozzi et al. demonstrated the antinociceptive effect of CB2R agonists in a streptozotocin (STZ)-induced diabetic neuropathy model [82]. Duarte et al. showed an increase in CB1R density in the hippocampus of STZ-induced

diabetic rats, associated with diabetic encephalopathy [83]. Two years later, Zhang et al. showed that high glucose levels decreased CB1R expression in nerve cells, although its function was preserved [84]. Moriarty et al. showed that STZ-diabetic rats have altered CB1R functionality in the substantia nigra, which might be related to a negative impact on cognitive function, associated with diabetes and diabetic neuropathic pain [85]. Recently, Jadoon et al. published a randomized, double-blind, placebo-controlled study using 62 subjects with noninsulin-treated T2DM, and demonstrated that tetra-hydrocannabivarin treatment (THCV, THV; 5 mg twice daily), a homolog of THC, significantly decreased plasma glucose and increased β cell function, and adiponectin and apolipoprotein A (Apo-A) levels, and was well tolerated in patients [86]. Altogether, these findings suggest beneficial effects of cannabinoid ligands on T1DM, given the relationship between the ECS and T1DM, partly because this system modulates food intake and energy balance and regulates pancreatic β cell function, reinforcing its involvement in diabetes pathophysiology and diabetic complications. However, despite these results, questions remain. For instance, what is the mechanism by which CBR modulates metabolic disorders, including T1DM? Does CBR mediate T1DM through the inhibition of autoreactive B cells or are other CBR-related pathways significantly involved? Further studies are needed to answer these and other questions.

Modulation of rheumatoid arthritis by cannabinoid receptors

RA is human leukocyte antigen (HLA) class II-associated autoimmune rheumatic disease, in which arthritogenic T cells drive to progressive inflammation and destruction of synovial joints. RA is characterized by progressive disability, systemic disturbances, early death, and socioeconomic costs. Furthermore, genetic, female sex, and environmental factors contribute to disease susceptibility, development, and progression. Although the cause of RA has yet to be elucidated, molecular mimicry between self-proteins and microbial pathogens has been implicated as a possible factor in the induction or exacerbation of RA [87]. In this context, earlier evidence suggested the participation of CBR in the pathophysiology of RA. Previously, Bellini et al. demonstrated an association between CB2R variant Q63R and susceptibility to oligo/polyarticular juvenile idiopathic arthritis [88]. Others showed the potential anti-inflammatory activity of CB2R agonists during RA; for instance, ajulemic acid, a synthetic nonpsychoactive cannabinoid acid, induced T cell apoptosis and increased selectively and markedly 15d-PGJ(2), an eicosanoid that facilitates the resolution of inflammation during experimental RA [89]. Moreover, Selvi et al. demonstrated that the cannabinoid CP55,940 and WIN55,212-2 (both nonselective cannabinoids agonists) inhibited IL-6 and IL-8 expression from IL-1β stimulated fibroblast-like synoviocytes through a CBR-independent pathway [90]. Another randomized, parallel group, double-blind study compared the pharmacological effects of Sativex®,

which contains Δ9-THC and CBD, with placebo in 58 patients with RA over 5 weeks of treatment. Relevantly, a significant analgesic effect was observed, and disease activity was markedly reduced following Sativex® treatment [91]. These findings suggest that CB2R is upregulated in synovial tissue and cultured fibroblast-like synoviocytes from patients with RA.

Thus, CB2R activation might have immunomodulatory and anti-inflammatory effects during rheumatic autoimmune disorders, such as RA. In this way, the modulation of endocannabinoid metabolism represents another target to control arthritic inflammation. The N-acylethanolamines, as well as FAAH inhibitors, exert anti-inflammatory effects in synovial fibroblasts [92]. Moreover, FAAH inhibition reduced collagen-induced arthritis hyperalgesia in a CB1R dependent-manner and this analgesic effect was associated with a COX-2 inhibitor [92]. These reports suggest that CBR and the ECS offer a promising therapeutic target for the development of innovative pharmacological approaches to the treatment of RA and other rheumatic disorders.

Concluding remarks and future perspectives

Autoimmune diseases are related to the impairment of health-related quality of life and depression-like symptoms [2,3]. Additionally, although currently available treatments have brought about significant advances in medicine and significant clinical benefits, they can have considerable adverse effects, and optimal treatment for these conditions remains a work in progress. Given the involvement of the ECS in the pathophysiology of autoimmune diseases, CBR ligands and pharmacological modulation of the ECS have emerged as potential therapies because of their anti-inflammatory, immunomodulatory, and analgesic properties. Thus, CB1R and CB2R ligands, including phytocannabinoids beyound the Cannabis species, have caught the attention of the medical community and further preclinical and clinical studies are needed to investigate their beneficial effects on autoimmune diseases such as MS, T1DM, and RA, and their comorbidities. Finally, these reports highlight recent advances in research into therapies going beyond Sativex® and Rimonabant®, pointing to other exciting and prospective compounds that have opened new therapeutic windows for the treatment of autoimmune diseases (Fig. 4).

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