Cannabinoid-based drugs targeting CB_1 and TRPV1, the sympathetic nervous system, and arthritis

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Abstract

Chronic inflammation in rheumatoid arthritis (RA) is accompanied by activation of the sympathetic nervous system, which can support the immune system to perpetuate inflammation. Several animal models of arthritis already demonstrated a profound influence of adrenergic signaling on the course of RA. Peripheral norepinephrine release from sympathetic terminals is controlled by cannabinoid receptor type 1 (CB_1), which is activated by two major endocannabinoids (ECs), arachidonylethanolamine (anandamide) and 2-arachidonylglycerol. These ECs also modulate function of transient receptor potential channels (TRPs) located on sensory nerve fibers, which are abundant in arthritic synovial tissue. TRPs not only induce the sensation of pain but also support inflammation via secretion of pro-inflammatory neuropeptides. In addition, many cell types in synovial tissue express CB_1 and TRPs. In this review, we focus on CB_1 and transient receptor potential vanilloid 1 (TRPV1)-mediated effects on RA since most anti-inflammatory mechanisms induced by cannabinoids are attributed to cannabinoid receptor type 2 (CB_2) activation. We demonstrate how CB_1 agonism or antagonism can modulate arthritic disease. The concept of functional antagonism with continuous CB_1 activation is discussed. Since fatty acid amide hydrolase (FAAH) is a major EC-degrading enzyme, the therapeutic possibility of FAAH inhibition is studied. Finally, the therapeutic potential of ECs is examined since they interact with cannabinoid receptors and TRPs but do not produce central side effects.

Introduction

Rheumatoid arthritis (RA) is a debilitating disease that affects around 1.3 million people in the US alone [1]. Important characteristics of RA are inflammation of the joint with subsequent destruction of cartilage, pannus formation and infiltrates of immune cells [2–4]. Ongoing inflammation also leads to systemic changes manifesting in co-morbidities like dyslipidemia, depression, fatigue, insulin resistance, activation of the sympathetic nervous system, and cachexia [5, 6]. Changes in sympathetic activity lead to a metabolic switch, which is in part responsible for the perpetuation of inflammation and the increase in cardiovascular risk in RA patients [7].

Cannabis has been used since 4000 BC for the treatment of spasms and post-operative pain [8]. In the 1990s, the two main receptors for cannabinoids (cannabinoid receptors I and II; CB_1 and CB_2) were identified [9, 10]. Both receptors are activated by the psychoactive component of cannabis, tetrahydrocannabinol (THC), and several other synthetic and plant-derived cannabinoids [11]. Two major endogenous cannabinoids (endocannabinoids, ECs), arachidonylethanolamine (anandamide, AEA) and 2-arachidonylglycerol (2-AG), were described shortly after the discovery of CB_1 and CB_2 [12, 13]. In recent years, other receptors such as transient receptor potential vanilloid 1 (TRPV1), GPR55, or GPR18 were found to bind cannabinoids, and activation of these receptors is responsible for the off-target effects of several cannabinoids [14–18]. Transient receptor potential channel (TRP) modulation by cannabinoids might be explicitly important since these receptors not only influence sensation of pain, but also support inflammation [19].

This review describes physiological aspects of CB_1 receptors, pharmacological roles of ECs and the EC-
degrading enzyme fatty acid amid hydrolase (FAAH),
functional crosstalk between ECs and TRPV1, the
interaction between ECs and the sympathetic nervous
system in RA, the influence of ECs on arthritis disease
sequelae in mice and humans, and direct immuno-
modulatory effects of CB₁ signaling in the periphery
and in the brain. Considering this knowledge we finally
try to demonstrate an optimum therapeutic EC ap-
proach in RA.

Physiology

CB₁ influences cell function by controlling
neurotransmitter levels

The classic function of ECs in the nervous system is the
regulation of neurotransmitter release via CB₁, which is
also responsible for the psychotropic effects of cannabis
[20–23]. CB₁ is mainly located on presynaptic nerve ter-
minals, and activation of this receptor reduces the re-
lease of neurotransmitter from corresponding neurons
in a heteroreceptor-typical way [24]. Thus, cannabinoids
can increase or decrease neuronal excitability depending
on neurotransmitter and brain region affected. CB₁
receptors are also abundant on peripheral sympathetic
nerve terminals, where they modulate adrenergic sig-
naling. This influence on sympathetic nerves can alter
lipolysis, cytokine production, ghrelin production, heart
rate and bone resorption [20, 25–28]. The effects of CB₁
activation or inhibition on neurotransmitter release in a
given peripheral tissue are depicted in Fig. 1. In addition,
CB₁ receptors are located on nociceptive nerve fibers.
Here, CB₁ agonism increases the threshold for the
generation of action potentials via modulation of ion
channels and TRPs [29, 30].

Direct effects of CB₁ activation on immune cells have
only been scarcely described. Our group but also others
demonstrated an influence of cell adhesion in response
to CB₁ agonism; this effect might also modulate immune
function by regulating cell trafficking and tissue extra-
vasation [31, 32].

CB₂ regulates immune cell function directly

While CB₁ functions mainly through modulation of
central and peripheral neurotransmitter release, ac-
tivation of CB₂ elicits direct anti-inflammatory effects in
target cells [33]. This includes reduction of cytokine and
matrix metalloproteinase production, modulation of
adhesion and migration but also induction of apoptosis
[33]. The anti-inflammatory potential of CB₂ was also
confirmed in mouse models of arthritis [34, 35]. While
the impact of CB₂ on immune function has already been
investigated and reviewed elsewhere [33, 36], this review
focuses on CB₁.

![sympathetic nerve fiber](image-url)

**Fig. 1** Effects of CB₁ activation or inhibition on norepinephrine (NE) release in tissue. CB₁ regulates the amount of NE released from sympathetic nerve terminals. The red zone depicts the effects of CB₁ agonism, which decreases NE release. Only cells within the red line boundary can be modulated by β-adrenergic receptors under CB₁ activation. Beyond the dotted ‘β-adrenergic zone’, α-adrenergic effects prevail. Under basal conditions, the β-adrenergic area is increased (black dotted line). Under CB₁ inhibition, NE release is boosted and maximal β-adrenergic effects can be achieved (green dotted line). Beta receptor activation on immune cells decreases production of pro-inflammatory mediators, for example, tumor necrosis factor.
Pharmacology

Role of the ECs anandamide and 2-AG

The action of ECs is limited by rapid degradation involving FAAH, which degrades AEA and related N-acylethanolamines, and monoacylglycerol-lipase (MAGL), which degrades 2-AG [37]. In addition, several enzymes like cyclooxygenase-2, lipooxygenase or cytochrome P450 and others contribute to EC metabolism [38]. Characteristics of AEA, 2-AG, THC and the CB1 antagonist rimonabant are given in Table 1. Inhibition of FAAH raises the levels of the N-acylethanolamines AEA, palmitoylethanolamine (PEA) and oleoylethanolamine (OEA) [39]. While AEA is responsible for maintaining basal EC signaling, 2-AG mediates strong and rapid feedback via CB1 receptors [40]. This is also reflected by the fact that AEA is a partial agonist at CB1, while 2-AG acts as full agonist [41]. Due to its full agonistic properties, elevation of 2-AG by inhibition of MAGL leads to functional antagonism (discussed below) of CB1, although this might be prevented by reduced dosing [42, 43]. Furthermore, MAGL inhibition might be detrimental in some situations, since 2-AG is also degraded by cyclooxygenase-2 leading to pro-inflammatory metabolites [44]. Therefore, this review only covers the consequences of FAAH inhibition.

The conundrum of functional antagonism at CB1 and TRPV1

Throughout this review, similar effects of CB1 agonists and CB1 antagonists on features of arthritic inflammation are described. This conundrum can be explained by rapid desensitization and downregulation/internalization of CB1 upon agonist exposure [45–47]. If desensitization is disturbed due to mutations in crucial CB1 phosphorylation sites, CB1 agonism leads to enhanced acute effects and delayed tolerance [48]. Consequently, CB1 signaling diminishes in response to repeated agonist exposure [49]. This feature of CB1 explains functional antagonism: administration of exogenous cannabinoids or elevation of endogenous levels of the full CB1 agonist 2-AG leads to downregulation of CB1. If levels drop low enough, production of ECs is not sufficient to activate CB1 or CB1 signaling pathways. This phenomenon was described with MAGL inhibitors, which increase levels of 2-AG [42]. Another possibility to achieve antagonistic effects with agonists is the use of CB1 partial agonists like AEA, which lack full activation of CB1 signaling pathways. These partial agonists act as antagonists when full agonists are also present [50].

TRPs, in particular TRPV1, TRPV2, TRPV3, TRPV4, TRPA1 and TRPM8, serve as ionotropic cannabinoid receptors and they also desensitize upon agonist exposure [51–55]. The EC AEA is an agonist at TRPV1 with a binding affinity similar to that of the hot pepper ingredient capsaicin, although it does not activate the receptor like capsaicin [56]. Therefore, although being an agonist itself, AEA prevents the effects of high efficacy agonists like capsaicin, thus serving as antagonist in this setting. Furthermore, AEA rapidly desensitizes TRPV1, which results in reduced calcium influx [57]. In addition, the AEA congeners and FAAH substrates PEA and OEA also desensitize TRPV1 [58, 59]. Although there are no data available regarding the desensitization of other TRPs by N-acylethanolamines, it is likely that this also occurs since there is extensive crosstalk between, for example, TRPV1 and TRPA1 via intracellular calcium [60]. Moreover, it has been demonstrated that synthetic cannabinoid ligands binding TRPA1 also desensitized target cells to the action of TRPV1 agonists [61].

FAAH inhibition does not produce central side effects and bridges TRPs and cannabinoid receptors

Central activation of CB1 has psychotropic side effects and this problem is circumvented by the use of FAAH inhibitors [62]. In contrast to exogenous cannabinoids, AEA does not lead to tolerance at CB1 or psychotropic effects [63]. Therapeutically, reduction of tolerance to CB1 agonists with FAAH inhibitors can be important since this process leads to a loss of efficacy when repeatedly

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**Table 1 Characteristics of selected cannabinoid receptor ligands**

| Ligand          | Target receptors | Ki at CB1 in nM | Ki at CB2 in nM | Emax/IC50 at TRPV1 (nM) | Route of degradation |
|-----------------|------------------|-----------------|-----------------|-------------------------|---------------------|
| Anandamide      | CB1, CB2, GPR55, TRPV1, TRPA1, TRPM8 (antagonist) | 239.2 ± 61.77 [158] | 439.5 ± 95.89 [158] | 458 (Emax) [159] | FAAH, FAAH-2, NAAA, COX-2, LOX [160] |
| 2-AG            | CB2, CB3, TRPV1, GABAA | 3423.6 ± 3288.24 [158] | 1193.8 ± 327.71 [158] | 750 ± 40 (IC50) [161] | MAGL, COX-2, LOX, ABHD6/12 [160, 162] |
| Delta9-THC      | CB1, CB2, GPR18 | 25.1 ± 5.54 [158] | 35.2 ± 5.86 [158] | NA | CYP2C [163] |
| Rimonabant      | CB1, MOR        | 1.98 ± 0.36 [164] | NA              | NA | CYP3A [165] |

Anandamide, 2-arachidonylethanolamine (2-AG) and tetrahydrocannabinol (THC) are CB1/CB2 agonists, rimonabant is a CB1/MOR antagonist/inverse agonist. Anandamide and THC are partial CB1/CB2 agonists, 2-AG is a full agonist at both receptors. The main degrading enzyme for each compound is highlighted in bold. ABHD6/12; αβ-Hydrolase domain; CB1/CB2; cannabinoid receptor 1/2; COX-2; cyclooxygenase-2; CYP; cytochrome P450; Delta9 THC; Delta9 tetrahydrocannabinol; Emax; maximal functional response; FAAH; fatty acid amide hydrolase; IC50, half maximal inhibitory concentration; Ki; dissociation constant; LOX; lipoxygenase; MAGL, monoacylglycerol lipase; MOR, μ opioid receptor; NA, not applicable; NAAA, N-acyl ethanolamine-hydrlyzing acid amidase; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanillioid 1.
administered [63]. In addition, elevation of OEA and PEA also provide anti-inflammatory, neuroprotective effects and they enhance neurogenesis mostly via peroxisome-proliferator activated receptors [64–66]. FAAH inhibition has already been demonstrated to be effective in collagen-induced arthritis in mice, although this was attributed to CB2 activation [34]. Furthermore, FAAH inhibition not only combines anti-inflammatory effects of several N-acylethanolamines but also targets additional receptors such as TRPV1 and peroxisome proliferator-activated receptors [65, 67–69]. One important receptor for AEA and its congeners OEA and PEA is the TRPV1 cation channel, although other TRPs are similarly activated by AEA [69–71].

Besides CB1 and CB2, ECs as well as synthetic and phytocannabinoids bind to members of the TRP family [54, 61, 72–74]. Several of these non-selective cation channels integrate external and endogenous stimuli and are sensitized and activated during inflammation [19, 75]. Pharmacological elevation of AEA in the rat leads to activation but also desensitization of TRPV1, resulting in increased pain thresholds [69]. In contrast to CB1 activation, TRP activation increases cell excitability leading to increased release of neurotransmitters [76–78]. When co-expressed, CB1 agonist decreases TRPV1 channel activity by dephosphorylation, which increases the threshold for agonists [78]. Although mainly located on sensory Aδ and C-fibers, TRPs are also expressed on peripheral cells such as synoviocytes, and activation results in increased expression of inflammatory mediators [75, 79, 80]. The best described example of subsequent TRPV1 and CB1 activation is the regulation of blood pressure, where only the CB1/TRPV1 agonist AEA elicited a triphasic response involving both receptors [81]. First, AEA activates TRPV1 causing hypotension and bradycardia followed by a pressor phase with increased heart rate. In the final phase, prolonged hypotension by AEA is observed and this effect was inhibited by CB1 antagonism. The sequential activation of TRPV1 and CB1 in the context of blood pressure regulation has been reviewed elsewhere [81].

Clinical relevance
The sympathetic nervous system supports chronic inflammation in arthritis - links to endocannabinoids
Sympathectomy in arthritic patients has already been performed in the 1920s and follow-up studies showed reduced joint swelling and pain in sympathectomized patients [82]. The neuroinflammatory component of arthritis has been revealed in studies by Levine and colleagues [83, 84]. In the mouse model of collagen-induced arthritis it was shown that chemical sympathectomy before or during the time of immunization results in less severe disease [85]. Late sympathectomy, however, results in exacerbation of experimental arthritis, which might be due to deletion of tyrosine hydroxylase-positive catecholamine-producing cells that appear in synovial tissue during the course of the disease [86]. The beneficial effects of tyrosine hydroxylase-positive cells on the development of collagen-induced arthritis was demonstrated by our group. In vitro, tyrosine hydroxylase controls cytokine production in mixed synovial cells, whereas in vivo introduction of these cells into arthritic mice reduced arthritic score [87]. During arthritic inflammation in mice and humans, production of nerve repulsion factors by macrophages leads to the retraction of sympathetic but not sensory fibers from synovial tissue [88]. As a result, synovial concentration of norepinephrine falls under the threshold for anti-inflammatory β2 receptor activation and this favors pro-inflammatory effects via α-adrenergic signaling [89, 90]. However, sympathetic signaling is increased in adipose tissue surrounding the synovium, which is responsible for generating energy-rich substrates to support inflammation [91]. These changes in sympathetic activity during the course of arthritis might be limited or even reversed by altering either EC production or CB1 function, since this receptor controls norepinephrine release. Reduction of EC production by blocking appropriate synthesizing enzymes leads to a functional loss of CB1 since low levels of ECs can no longer activate the receptor. This was already demonstrated in a mouse model of constipation, where inhibition of diacylglycerol lipase α lowered levels of the CB1 agonist 2-AG with concomitant increases in gut motility [92]. The same effect is achieved by antagonizing CB1 directly [93]. The loss of sympathetic nerves, altered adrenergic signaling and the possible influence of ECs in the joint is visualized in Fig. 2. In parallel with the disappearance of sympathetic nerve fibers in the joint, hypothalamic norepinephrine, interleukin (IL)-6 and IL-1β increase during the induction phase of experimental arthritis [94] (Fig. 3). In addition, these changes in cytokine levels and disruption of adrenergic signaling are not accompanied by an adequate response of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in low cortisol levels in relation to inflammation in humans and rodents [94]. A more detailed description of the influence of the sympathetic nervous system on inflammation has recently been published by our group [95].

Modulation of adrenergic signaling via CB1 might be beneficial in arthritis
In adjuvant arthritis, immune cells respond to adrenergic β2 receptor stimulation with decreased production of tumor necrosis factor (TNF), an increase in anti-inflammatory IL-10, and a shift to a T-helper type 2 and T-regulatory immune response [96]. Antagonism of CB1 at splenic sympathetic terminals provides strong anti-inflammatory effects and ameliorates collagen-induced arthritis in mice via reduction of TNF levels, which was inhibited by β2 adrenergic antagonism [26] (Fig. 4).
Furthermore, β2 adrenergic activation on murine B-lymphocytes increases production of the anti-inflammatory cytokine IL-10, which inhibits inflammation [97]. The time window for anti-arthritic β2 adrenergic effects in mice is crucial since early activation (during the induction phase of experimental arthritis) of sympathetic signaling in the spleen increases interferon (IFN)-γ production [98]. Sympathetic innervation of the spleen is reduced during the course of experimental arthritis, comparable to the situation in synovial tissue [99]. This has profound effects on local adrenergic signaling since low concentrations of norepinephrine favor pro-inflammatory α-adrenergic receptor activation [100, 101] (Fig. 4). Although the beneficial outcome of CB1 receptor antagonism in collagen-induced arthritis in mice was attributed to β2-receptor activation on splenocytes, several other mechanisms might contribute to the therapeutic effects. CB1 antagonism at sympathetic terminals surrounding the synovium might have different outcomes depending on the magnitude of recovery of norepinephrine levels in the joint [102, 103] (Fig. 2). On the other hand, since we demonstrated an
increase of sympathetic fibers in human synovial adipose tissue, increased norepinephrine release might further increase lipolysis and thereby fuel inflammation [91]. Thus, it is imperative to maintain norepinephrine levels over a certain \( \beta_2 \) activation threshold in the synovium, which might only be achieved with continuous high doses of CB\(_1\) antagonists. Consequences of enhanced \( \beta_2 \) signaling by CB\(_1\) antagonism are depicted in Fig. 2.

Although the above mentioned stimulating effects of CB\(_1\) antagonism on adrenergic signaling are evident, CB\(_1\) agonists might also prove useful in modulating arthritis. As mentioned earlier, sympathectomy in the early phase ameliorates experimental arthritis in mice [85]. This indicates a pro-inflammatory influence of adrenergic signaling at the beginning of the disease, which might be counteracted by CB\(_1\) agonists decreasing norepinephrine levels [20]. Arthritis is accompanied by a loss of sympathetic nerve fibers from sites of inflammation and this might also be counteracted by CB\(_1\) activation, since neurogenesis is disturbed in CB\(_1\) knock-out mice, although we do not know whether this also applies for sympathetic nerve fibers [104].

The development of comorbidities such as bone resorption, depression and water retention/volume expansion in RA is partly driven by changes in sympathetic activity [19, 105]. Osteoporosis is a major contributor to RA-associated complications and osteoclasts and osteoblasts respond to cannabinoid receptor activation [106, 107]. Activation of CB\(_1\) results in enhanced osteoblast differentiation, which leads to reduced osteoporosis. Blockade of CB\(_1\) disturbs osteoclast function and increases bone mass in the young, but leads to osteoporosis later on due to decreased bone formation [108].

One major disability associated with RA is the development of depression, which affects around 17 % of patients and is associated with poorer disease outcome [109]. Depression and CB\(_1\) are connected since side effects of rimonabant, a first generation CB\(_1\) inverse agonist/antagonist, include depression and anxiety while CB\(_1\) agonism has anxiolytic-like and antidepressant-like activities [110, 111]. The effects of CB\(_1\) agonism by FAAH inhibition in the brain are depicted in Fig. 3.

Overactivity of the sympathetic nervous system in RA also leads to water retention via activation of the renin-
ally activates CB1 antagonism in the hypothalamus and stimulates pro-inflammatory cytokine production [115]. CB1 antagonism might also support beneficial systemic changes. One of the hallmarks of RA is an inadequate cortisol secretion in relation to inflammation [114]. Antagonism at CB1 might counteract this phenomenon, since CB2 knock-out mice had higher levels of adrenocorticotropic hormone and corticosterone under basal but also under stressed conditions [115]. ECs control glucocorticoid feedback and, therefore, CB1 antagonism increases circulating adrenocorticotropic hormone levels [116]. Interestingly, high doses of a CB1 agonist also increase the activity of the HPA axis, although this is due to alteration of serotonergic and adrenergic transmission [117]. The same outcome using CB1 antagonism or agonism on HPA axis activation might also depend on the concentration of CB1 agonists and whether central or peripheral CB1 receptors are targeted. Peripheral agonism at CB1 leads to subsequent activation of α and β adrenoreceptors, which are linked to the antinociceptive effects of CB1 in a rat pain model [118]. Increases in adrenergic signaling by CB1 agonists might be due to decreased inhibitory gamma-aminobutyric acid (GABA) signaling since release of this neurotransmitter is also controlled by CB1 [22]. Thus, enhanced GABA signaling reduces sympathetic activity and vice versa [119]. Central activation of CB1 mediates the rapid effect of glucocorticoid negative feedback and this might explain the necessity for high peripheral doses of the CB1 antagonist rimonabant to increase cortisol levels [120, 121].

A major problem during the course of RA is the development of insulin resistance with systemic metabolic changes [122, 123]. Insulin resistance is a direct consequence of enhanced pro-inflammatory cytokine signaling and TNF, IL-6, IL-1β as well as other cytokines are responsible for these changes [124]. From 2006 to 2008 the CB1 antagonist rimonabant was marketed for use against obesity but was withdrawn due to central side effects [125]. However, the drug proved to be effective at decreasing important parameters associated with metabolic syndrome. Rimonabant reduces leptin expression, decreases atherosclerosis, and reverses insulin resistance in rodents and humans [126, 127]. In this respect, CB1 antagonism might also be beneficial in reversing metabolic changes in RA. Insulin resistance is induced by the immune system to divert energy to active immune cells, which are not dependent on insulin for glucose utilization.
agonists or antagonists is limited. Agonists are most prominent when injected on immune cells, where rimonabant decreased TNF and other pro-inflammatory cytokines [136]. Furthermore, the TRPV1 agonist capsaicin which reduced TNF production and provided anti-arthritis effects in the rat [150]. Interestingly, this effect was mediated by TRPV1 located on sensory neurons, emphasizing the neuronal component of arthritis [150]. This might disrupt a positive feedback loop, since TNF and other pro-inflammatory cytokines sensitize TRPV1 and enhance its activity [102]. The paradoxical finding that TRPV1 agonists also act in an anti-inflammatory fashion is explained by rapid desensitization of TRPV1 in response to agonist treatment, which depends on the agonist used [151]. Findings in synovial fibroblasts support this notion, where the TRPV1 agonist capsaicin increases IL-6 production, while AEA, a low efficacy TRPV1 agonist, decreased IL-6 levels under TNF stimulation (T Lowin, unpublished data) [80].

Since some peripheral effects of TRPV1 are attributed to receptors located on sensory nerve terminals which co-express CB1, crosstalk between both receptors might define the outcome of inflammation [152]. This can be important in RA, since elevated synovial levels of nerve growth factor sensitize TRPV1 to inflammatory stimuli and CB1 agonism counteracts this response [153, 154]. In this respect, FAAH inhibition might be superior to selective CB1 agonists since AEA or its metabolites not only activate CB1 but also desensitize TRPV1, leading to analgesia [69]. Neuronal TRPV1 increases neurotransmitter and pro-inflammatory neuropeptide release via elevation of intracellular calcium levels and the same mechanism often induces the secretion of cytokines
from immune cells [155–157]. Inhibition of TRPV1 function by concomitant CB1 activation and AEA-induced desensitization (FAAH inhibition) might be a promising strategy to reduce RA disease activity and pain.

Conclusion: is there a perfect cannabinoid-based therapy for the treatment of RA? The question arises how to modulate the EC system for the treatment of RA. The best treatment option might be a combination of a peripherally restricted CB1 antagonist and a FAAH inhibitor raising systemic levels of N-acylethanolamines. CB1 antagonism has already been shown to result in anti-arithmetic effects in mice and this treatment might also increase adrenergic signaling in RA, thereby reducing TNF and IFN-γ and decreasing joint inflammation and cartilage destruction. Potential effects of CB1 antagonism (also of FAAH inhibition) in arthritic synovium and spleen are shown in Figs. 1 and 3, respectively.

Furthermore, CB1 antagonists might reverse metabolic alterations associated with RA: for example, insulin resistance, enhanced leptin expression, depression/fatigue or atherosclerosis. FAAH inhibition on the other hand can counteract the neuroinflammatory component of RA by activating neuronal CB1 and TRPV1 (Fig. 3). Furthermore, the FAAH substrates OEA and PEA can support anti-inflammatory and neurogenic effects of central CB1 activation via peroxisome-proliferator activated receptors. In addition, CB1 activation in the brain lowers sympathetic activity, which can decrease disease-related problems like hypertension. In addition, increases in brain AEA can have antidepressant effects and since many RA patients suffer from mood disorders, FAAH inhibition might help to counteract this central nervous system problem.

In the periphery, FAAH inhibition leads to analgesic and anti-inflammatory effects via desensitization of TRPV1. Moreover, FAAH inhibition has been shown to have high efficacy in arthritic mice through activation of CB2, which might also be beneficial in patients by downregulating cytokine production. In summary, therapeutic intervention in RA with a peripherally restricted CB1 antagonist and a FAAH inhibitor might offer a promising strategy to ameliorate RA.

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Competing interests The authors declare that they have no competing interests.

Abbreviations
2-AG: 2-arachidonylethanol; AEA: Arachidonylethanolamine; EC: Endocannabinoid; FAAH: Fatty acid amid hydrolase; GABA: Gamma-aminobutyric acid; HPA: Hypothalamus-pituitary-adrenal; IFN: Interferon; IL: Interleukin; MAGL: Monoaclyglycerol lipase; OA: Oleoyylethanolamine; PEA: Palmitoylethanolamine; RA: Rheumatoid arthritis; THC: Tetrahydrocannabinol; TNF: Tumor necrosis factor; TRP: Transient receptor potential channel.
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