Review

CB2 receptor as a potential target in age-related diseases

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(Received March 7, 2014; Accepted March 16, 2014; Published online: March 22, 2014)

Abstract: The plant Cannabis sativa containing psychoactive chemical compounds known as cannabinoids has been used for thousands of years in the treatment of different diseases and adverse conditions. Analgesic and anti-inflammatory properties of cannabinoids were deciphered experimentally a long time before the discovery of mammalian endocannabinoid system with cannabinoid-sensing receptors CB1 and CB2. Psychoactive effects of cannabinoids are commonly associated with the CB1 receptors, whereas the CB2 receptors primarily mediate anti-inflammatory and immunomodulatory effects. Cannabinoid receptors become upregulated in various pathological conditions and in many cases, their activation results in the alleviation of adverse effects. In this article, we will review the signaling of CB2 receptors with particular emphasis been placed on the associations with inflammation and autophagy. Increased inflammation and decreased autophagy are hallmarks of various age-related diseases which could potentially be treated by modulating the activity of the CB2 receptors.

Keywords: CB2 receptor, inflammation, autophagy, age-related diseases

Introduction

Pharmacological effects of cannabinoids have been known for thousands of years, and the primary source of cannabinoids has been the plant Cannabis sativa [1, 2]. In the earliest still existing Chinese pharmacopoeia, flowers of a female partner of the dioecious plant were recommended for treating adverse conditions such as menstrual ailments, absent-mindedness, beriberi, constipation, rheumatism, even malaria [2]. Later on, experimental trials have shown that cannabinoids e.g. relieve pain, inhibit nausea, increase appetite, decrease inflammation, reduce muscle weakness and spasticity, and alleviate intraocular pressure [1, 2]. In addition to various advantageous impacts, cannabinoids also cause several adverse effects, such as anxiety, depression, and hepatotoxicity [3]. C. sativa contains tens of different cannabinoids and in 1964, the main active constituent, Δ⁹-tetrahydrocannabinol (Δ⁹-THC, Fig. 1), was isolated [4]. Δ⁹-THC has strong effects on the central nervous system (CNS), which has increased the use of C. sativa for recreational intoxication purposes but also restricts its use for therapeutical intentions. Acute CNS responses upon Δ⁹-THC exposure at low doses include relaxation, reduced attention, and psychomotor impairment, which predispose to accidents [5, 6]. High doses can be more stimulatory causing anxiety, panic reactions, and psychotic symptoms [6]. Long-term use has been associated e.g. with attenuated psychososial development and defects in mental health [6, 7].
Inflammation is a protective response against danger signals encountered by a cell. Various endogenous and exogenous threats become recognized by pattern recognition receptors (PRRs) scattered throughout membranes and cytoplasm [8]. Aged people have higher basal level of inflammation with increased amounts of pro-inflammatory cytokines, clotting factors, and acute phase proteins [9, 10]. The number of innate immune cells does not seem to associate with the phenomenon since the populations of many central cells become rather diminished than expanded [10]. Instead, the cell phenotypes and functions become remodelled [9, 11-13]. Due to the age-related changes, inflammation gets more easily induced and prolonged. Chronic inflammation is present in a variety of phenomena associated with age-related diseases, such as physical frailty, homeostatic dysregulation, neurodegeneration, and changes in body composition and energy balance [14]. Suggested mechanisms for causing chronic inflammation in the elderly include dysregulation of NF-κB pathway, excessive reactive oxygen species (ROS) production due to impaired mitochondrial function, and decline in autophagy [14, 15].

Macroautophagy (referred here to as autophagy) is the most comprehensive intracellular degradation system [16, 17]. In autophagy, protein complexes and dysfunctional organelles become surrounded by double membranes forming autophagosomes [18, 19]. Thereafter, autophagosomes fuse with lysosomes and their cargo becomes degraded by lysosomal enzymes [18, 19]. Depending on the context and microenvironmental circumstances, autophagy can either maintain cellular homeostasis, promote cell survival, or contribute to cell death [20]. It is widely known that autophagy becomes declined during aging [16, 21]. For example, in the ocular retinal-pigment epithelial (RPE) cells, there is a significant accumulation of intralysosomal lipofuscin which disturbs the lytic function of lysosomal enzymes and promotes oxidative stress [16, 22-24]. Malfunctional autophagy is detrimental also in other post-mitotic cells, such as neurons [16, 25]. Attenuated autophagy tends to result in the accumulation of protein aggregates and dysfunctional, ROS-producing mitochondria [16]. Adverse conditions influenced by attenuated autophagy include aggregation diseases, such as age-related macular degeneration (AMD) [26]. The disease progressively destroying the central vision results from a decline in the RPE cell functions, which subsequently leads to photoreceptor death [26, 27]. Due to their high metabolical activity, lipid peroxidation products accumulating from the ingested photoreceptor outer segments (POS), and extensive exposure to light, RPE cells are predisposed to chronic oxidative stress [28]. Constant oxidative stress, in turn, disturbs autophagy and induces inflammation [26]. Other aggregation diseases associated with impaired autophagy include Alzheimer’s disease, Huntington’s disease, and Parkinson’s disease [17, 29]. Defective autophagy can also predispose to several cancers [29]. For counterbalancing the disadvantageous effects of defunct autophagy, there is a strong confidence that pharmacological revitalizing of autophagic clearance can delay the aging process and have therapeutic potential in age-related diseases [30, 31]. Autophagy becomes induced by caloric restriction, the best-known anti-aging method at the moment [31, 32].

**Endocannabinoid system**

Discovery of the endogenous cannabinoid system (ECS), which comprises of cannabinoid receptors CB1 and CB2, their natural ligands (endocannabinoids), and enzymes involved in the synthesis and degradation of endocannabinoids, has opened new possibilities in generating synthetic cannabinoid ligands with higher selectivity and fewer side-effects. The idea for cannabinoid-specific receptors initiated from a finding that centrally active cannabinoids decrease the activity of adenylyl cyclase in neuroblastoma cells [33]. It was shown that the effect was not mediated through prostacyclin receptors [33] but a requirement for a functional Gi protein arisen in further studies, implicated towards G-protein-coupled receptors (GPCRs) [34, 35]. In 1988, Devane et al. demonstrated a specific cannabinoid receptor in rat brain with CP-55,940 (Fig. 2), a synthetic cannabinoid originally developed by Pfizer for analgesic [36]. A couple of years later, the first cannabinoid-specific G-protein-coupled receptor was cloned from both rat [37] and human [38]. This receptor was observed to be highly expressed in the CNS but at lower...
levels in periphery, which resulted in searching for an alternative receptor from peripheral tissues in order to explain the known non-psychoactive effects of cannabinoids. Peripheral responses included e.g. cannabinoid-mediated suppression of immune responses in which the regulation by the CNS was more unlikely involved than in findings concerning e.g. suppression of hormone release or antiemesis [39, 40]. In 1993, Munro et al. cloned another cannabinoid-specific G-protein-coupled receptor from the human leukemic cell line HL60 [41]. They suggested that the CNS receptor would be named as a cannabinoid CB1 receptor, and their finding as a cannabinoid CB2 receptor. Although prevailing in peripheral tissues, especially on immune and hematopoetic cells [3], the CB2 receptor has more recently found also in the CNS [42, 43]. On the other hand, the CB1 receptor has subsequently been found to be expressed also in several peripheral tissues [44]. CB1 and CB2 are still the principal cannabinoid receptors in human although some additional receptors, e.g. GPR55 [45], peroxisome proliferator-activated receptors (PPARs), and transient receptor potential (TRP) channels [46] have also been suggested to mediate cannabinoid signaling.

Three most prominent of about ten known endogenous cannabinoid ligands (endocannabinoids) are N-arachidonylethanolamine (anandamide, AEA), 2-arachidonoylglycerol (2-AG), and 2-arachidonoylglycerol (noladin) ether [2, 3, 47] (Fig. 3). Although the CB1 and CB2 receptors are related to each other and share certain principles, such as seven transmembrane-spanning domains, their sequences exhibit only 44% amino acid identity and they are selective to different agonists and antagonists [41]. For example, AEA favors the binding to the CB1, whereas 2-AG is more selective towards the CB2 [3, 41, 48, 49]. Δ⁹-THC also binds both receptor types but with clearly higher affinity to the CB1 than to the CB2 [50].

**Signaling via CB2 receptors**

Inhibition of the adenylyl cyclase pathway

Adenylyl (adenylate) cyclase is a G-protein-dependent enzyme responsible for catalyzing the synthesis of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP) [51]. Both the CB1 and CB2 receptors are linked to adenylyl cyclase through G<sub>i/o</sub> proteins but the CB2 receptors seem not to associate with ion channels similarly to the CB1 receptors [2, 46, 47, 52-54]. Generally, stimulation through cannabinoid receptors is considered to inhibit the cAMP-mediated intracellular signaling [54-59] (Fig. 4). It has been noticed that the type of enzyme isofrom and sometimes also the stimulant may influence on the capacity of cannabinoid receptors to inhibit the adenylyl cyclase activity [60].

Condie et al. showed that Δ⁹-THC and the more strongly CB2-selective cannabinol decreased IL-2 production in thymoma-derived T-cells by inhibiting adenylyl cyclase/cAMP pathway [61]. Decreased production of intracellular cAMP levels inhibited the protein kinase A (PKA)-mediated activation of transcription factors cAMP response element-binding protein (CREB) and activator protein 1 (AP-1) (Fig. 4). Since IL-2 promoter does not have binding sites for CREB, they suggested that heterodimers of CREB and Fos or Jun regulated the IL-2 production by binding to the AP-1 binding sites of IL-2 promoter [61] (Fig. 4). In addition to CREB, other members belonging to same family, i.e. activating transcription factors (ATF) and cyclic AMP response element modulator (CREM), can also become regulated by cannabinoids [61]. The effect of Δ⁹-THC is not restricted to cancer cells but can be extended to primary leucocytes, as well [62]. Jeon et al. demonstrated that Δ⁹-THC decreased the NF-κB-mediated iNOS activation and subsequent nitric oxide (NO) production by inhibiting either lipopolysaccharide (LPS) or forskolin-induced production of cAMP in macrophages [58]. Decreased levels of intracellular cAMP levels, in turn, prevented PKA-mediated activation of transcription factors CREB and nuclear factor kappa B (NF-κB) [58] (Fig. 4). Despite the rather low selectivity of Δ⁹-THC, the response was mediated through the CB2 receptors since RAW 264.7 cells did not express the CB1 receptors [58]. Herring et al. also demonstrated cannabino to inhibit anti-CD3, LPS, and phorbol-12-myristate-13-acetate (PMA)/ionomycin-induced responses in splenocytes and thymocytes with the similar

Fig. 3. Molecular structures of endocannabinoids.
mechanism presented by Jeon et al. [63].

Regulation of mitogen-activated protein kinases

Mitogen-activated protein kinases (MAPKs) are serine-threonine kinases whose principal members are p38 MAPKs, c-Jun N-terminal kinases (JNKs), and extracellular signal-regulated kinases (ERKs) [64]. p38 and JNK are also called Stress-Activated Protein Kinases (SAPKs) since they become activated by cytokines and stress stimuli [65, 66]. ERKs, in turn, become induced mainly by growth factors [65]. MAPKs function by regulating other protein kinases and transcription factors, and thereby contribute to various cellular functions, such as inflammation, cell cycle, metabolism, differentiation, and cell movement [64].

Ligand binding by the CB2 receptors can activate MAP kinases. It is not surprising when considered that MAPK pathway is known to become triggered by signaling through G-protein-coupled receptors [67, 68]. Bouaboula et al. used Chinese hamster ovary (CHO) cells transfected to express human CB2 for showing that cannabinoids can activate MAPKs in time- and dose-dependent manner [67]. They showed similar pathway to function also in human promyelotic HL60 cells, which express the CB2 receptors endogenously [67]. In their experiments with CB2-expressing cells, MAPK activation was observed to be protein kinase C (PKC)-dependent [67]. Sánchez et al. presented an indirect pathway in which ligand binding by the CB2 receptors induced Raf1 (MAP3K/MEKK)-mediated phosphorylation of ERK MAPKs by activating phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB/Akt) signaling in human prostate epithelial PC-3 cells (Fig. 4) [69]. Activation of ERK MAPKs by CB2 ligands has been promising in treating neural cancers, such as glioma and astrocytoma [70, 71]. Although ERK signaling is usually associated with proliferation, a long-term stimulus may alter it to prefer cell death instead of cell division [70]. When administered intratumorally, Δ⁹-THC, synthetic and nonselective agonist WIN55212-2, and CB2 selective agonist JWH-133 (Fig. 5) activated ERK MAPKs via ceramide accumulation and Raf1 activation resulting in the apoptosis of cancer cells [70, 71]. Ceramide-dependent apoptosis by the CB2 receptor activation has also been observed in the Jurkat leukemia cell line, and CB2-mediated growth inhibition also in lymphoma and skin tumors [72-74]. However, immunosuppressive properties of CB2 ligands may restrain the feasibility of CB2 agonists in cancer therapy [75].

In addition to the ERK MAPK signaling pathway, other MAPK pathways can also be affected by the CB2 activation. In a study with human leukemia cells, CB2 receptor-mediated apoptosis was dependent on the activity of p38 MAPK [76] (Fig. 4). Yamaori et al. also showed that p38 MAPK was responsible for CB2-mediated cytotoxicity in J774-1 macrophages [77]. Due to different intracellular signaling routes, the same ligand binding may also activate several MAPKs with varying outcomes [68]. For example, Yamaori demonstrated in the same study with p38 MAPK-dependent cytotoxicity that JNK signaling induced by the CB2 ligand binding protected from cell death [77]. In an in vivo murine study, CB2 receptor-mediated JNK activation was also associated with neuroprotection after an axonal
damage in cerebellar neurons [78]. Interestingly, the PI3K/Akt signaling was involved in the process [78].

Modulation of intracellular calcium levels

Unlike the CB1 receptors, CB2 receptors have not traditionally been linked to changes in ion balances [2, 46, 47, 52-54]. However, there is some evidence showing that ligand binding to the CB2 receptors would result in transient increase in cellular Ca\textsuperscript{2+} levels [50, 79]. First observations were made using HL-60 cells from which the CB2 receptor was cloned [50]. Thereafter, Zoratti et al. associated the CB2-induced Ca\textsuperscript{2+} release from endoplasmic reticulum with the activation of phospholipase C (PLC) in endothelial cells [79] (Fig. 4). They also showed that the Ca\textsuperscript{2+} release was preceded by a PLC-mediated activation of inositol 1,4,5-trisphosphate (IP\textsubscript{3}) [79]. It is also possible for cannabinoids to release intracellular Ca\textsuperscript{2+} in a nonspecific way [80]. Physiological function of the CB2-induced intracellular Ca\textsuperscript{2+} release remains to be fully elucidated but with the CB1 receptor, it has been shown e.g. to stimulate formation of endocannabinoids and activate other GPCRs [54]. Increased cellular Ca\textsuperscript{2+} levels are known to activate PKC [81] which could result in the activation of ERK MAPK (Fig. 4) [67].

Regulation of inflammation through the CB2 receptors

Central residence on various immune cell types, such as monocytes, macrophages, neutrophils, and microglia [49], as well as auspicious intracellular signaling upon activation make the CB2 receptors as attractive therapeutic targets for regulating inflammation (Fig. 4). In addition, a remarkably lower risk for psychoactive reactions increases interest in developing modulatory ligands to the CB2 rather than to the CB1 receptors. The expression of the CB2 receptors is also strongly upregulated during pathological processes making the inflammatory pathways accessible for modulation [82]. On the other hand, it is challenging to decide whether receptor agonists or antagonists are more preferable in regulating inflammatory responses. It is partly due to the fact that the physiological role of the CB2 receptors under normal or pathological conditions is not fully known [82]. As a lipid-binding G-protein coupled receptor, the CB2 receptors can bind several structurally divergent ligands and conversely, a molecule supposed to be specific to a CB2 receptor may also be prone to bind somewhere else [49, 82, 83]. There is also a phenomenon called functional selectivity indicating that different ligands can regulate separate intracellular signaling pathways through the same receptor [49, 84]. In a study with murine J774 macrophages, which are known to express the CB2 receptors, Δ\textsubscript{9}-THC, CB2 receptor inverse agonist indomethacin morpholinyl amide (IMMA), and AEA inhibited LPS-induced NO and IL-6 production, whereas 2-AG inhibited only the production of IL-6 and slightly increased the NO production [85]. In addition to iNOS, 2-AG induced cyclooxygenase (COX)-2, whereas Δ\textsubscript{2}-THC and IMMA (Fig. 6) inhibited it [85]. The results are in line with a suggestion that cannabinoids can become metabolized in different ways resulting in the formation of other bioactive molecules. In the study with Δ\textsubscript{9}-THC, IMMA, AEA, and 2-AG, researchers concluded that 2-AG could serve as a substrate for a COX-catalyzing production of bioactive prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) that also could modulate the function of the CB2 receptors [85]. PGE\textsubscript{2} can, e.g. counteract the inhibitory effect of 2-AG on

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Fig. 6. Molecular structures of the CB2 inverse agonists indomethacin morpholinyl amide (IMMA), SR144528, and AM-630.
For inhibiting inflammation through adenylyl cyclase/cAMP pathway, the use of the CB2 agonists could be advantageous (Fig. 4). As described above, Kaminski et al. have made groundbreaking work in revealing anti-inflammatory effects of CB2 agonists through adenylyl cyclase pathway. Also in mouse splenocyte cultures, 2-AG inhibited the PMA/ionomycin-induced IL-2 expression by decreasing the activity of transcription factors nuclear factor of activated T cells (NF-AT) and NF-κB [87]. Rinaldi-Carmona et al. synthesized the first, orally active CB2-selective inverse agonist SR144528 (Fig. 6) for the CB2 receptors [88]. They demonstrated that SR144528 abolishes the agonist-induced inhibition of adenylyl cyclase pathway but also to prevent the MAPK activation in Chinese hamster ovary (CHO) cells expressing human CB2 as well as in human tonsillar B cells [88, 89]. AM630 (Fig. 6), another CB2 antagonist has also been observed to act as an inverse agonist [46]. It has been shown e.g. to counteract the agonist JWH015-induced inhibition of MAPK activation, IL-2 secretion, and cell proliferation on T lymphocytes [90].

In addition to activation, CB2 ligation can inhibit MAPK signaling. It is noteworthy that the inhibition of MAPK signaling through the CB2 receptors is often associated with another external stimulation [91-93], which naturally fits in with pathological processes. Moreover, the magnitude of cellular activation seems to participate in determining, whether cannabinoid receptor-mediated signaling activates or inhibits MAPK pathways. It was shown, for example, with primary murine splenocytes and EL4.T-cell activation induced a MAPK-mediated production of IL-2, whereas together with stronger T-cell activators, cannabidiol suppressed the cytokine production [92]. Similar effect is applicable also with other cellular events, such as cell fate between proliferation and apoptosis [91].

Regulation of autophagy by cannabinoids

PI3K/PKB (Akt) signaling is known to activate mTOR (mammalian target of rapamycin), which inhibits autophagy. Therefore, the presence of that pathway downstream of the CB2 receptors proposes that the ligand binding might also affect autophagy. Effects of cannabinoid receptor activation on autophagy have been studied largely in cancer models since experimental evidence suggests that at least in some cancer types, CB2 modulators act advantageously by inducing autophagy-mediated cell death [94, 95]. It was recently revealed that Δ⁹-THC inhibits the interaction of Akt with mTOR complex 2 (mTORC2), which by phosphorylating contributes to the full activation of the kinase [96, 97]. Inhibition of Akt induces autophagy by preventing the mTORC1 signaling [96, 97]. Interestingly, the inhibition of Akt was mediated by Tribbles homolog 3 (Trib3), a pseudokinase upregulated upon cellular stress and able to regulate inflammation e.g. by inhibiting NF-κB [96, 98]. In that sense, Trib3-mediated autophagy activation may concurrently inhibit inflammation, which is in line the idea that autophagy and inflammation counterregulate each other. The work of Salazar et al., in which Δ⁹-THC induced autophagy-related cell death in tumors, did not pay attention to the receptor type mediating the effect of cannabinoid. It is not, however, ruled out that the CB2 receptors were involved since the Trib3 expression is known to be regulated by IL-3 [98]. IL-3 significantly increased the chemotactic migration of CB2-overexpressing murine cells when administered together with the potent CB2 agonist 2-AG [99]. There are also other studies showing that CB2-selective agonists can decrease the tumor growth. For example JWH-133 has been proven effective e.g. on glioma, astrocytoma, skin, and breast cancer cells [71, 74, 87, 95, 100-102].

Along with treatment of cancers, neuroprotective properties of cannabinoids have raised interest and stimulated research. A study with the commercial Sativex®...
product serves as a good example of the autophagy point of view [103]. The product was administered intraperitoneally to mice having a complex frontotemporal dementia, Parkinsonism, and lower motor neuron disease. Along with various other beneficial effects, Sativex® increased autophagy and diminished the deposition of tau and amyloid in the hippocampus and cerebral cortex [103]. Protective effects were interpreted to result, at least partially, from the induction of autophagy since the treatment increased the levels of LC3-II and beclin, and decreased the levels of p62 in cerebral cortex [103]. There were also indications of improved lysosomal function [103]. Although involvement of autophagy was not revealed, findings are in accordance with another study in which the CB2 agonist JWH-015 (Fig. 7) induced the removal of β-amyloid from tissue samples of human Alzheimer’s patients [104]. The result was similar also with JWH-015-treated THP-1 macrophages and synthetic β-amyloid [104]. While Δ⁹-THC and JWH-015 are agonists, cannabidiol acts as an inverse agonist on the CB2 receptors [105]. CB2 antagonists may also be applicable when autophagy is concerned. Palazuelos et al. have shown that CB2 activation induces PI3K/Akt/mTORC1-mediated proliferation of neural progenitor cells and therefore, inhibition of aberrant neurogenesis in epileptogenesis could have therapeutical significance [106].

Possible therapeutic applications of CB2 receptor ligands in the treatment of age-related diseases

Discovery of the ECS speeded up the research on using cannabinoids for therapeutical purposes [3]. Although Δ⁹-THC is a partial agonist also to the CB2 receptor, its psychoactive properties have forced to search for alternatives that would function more selectively on the CB2 receptors [107]. Selectivity would be important especially in the treatment of neurodegenerative diseases in which the compound need to pass the blood-brain barrier to the CNS. Therapeutic potential of CB2 ligands have been shown in various human tissue and animal models of neurodegenerative diseases, such as Alzheimer’s [104], Huntington’s [108], and Parkinson’s diseases [109], multiple sclerosis [110], amyloid lateral sclerosis (ALS) [111], and cerebral ischemia/reperfusion injury [112]. In CNS-related diseases, restraining the overactivation of microglia and infiltrating macrophages is a major mechanism by which CB2 receptors exert their effects [104, 108-112]. AMD resembles Alzheimer’s disease in its clinical and pathological features, and is also counted into neurodegenerative diseases despite of its residence outside the CNS [113]. Results published on the modulation of CB2-mediated signaling in RPE cells are scanty but in line with other studies. Wei et al. reported that the CB2-selective agonist JWH-015 protected human RPE cells from oxidative damage and cytotoxicity induced by H₂O₂ [114]. Meanwhile, the CB1 receptor agonist N-arachidonoyl-2-chloroethylamine (ACEA) (Fig. 8) was not cytoprotective suggesting that the effect of JWH-015 would be specific to the CB2 receptor [114]. Cancer studies have revealed that CB2 agonists are effective also in preventing angiogenesis [74, 100, 115]. In addition to cancers, inhibitions of proangiogenic factor production and vascular endothelial cell migration could play a therapeutical role also in the wet (exudative) form of AMD [116] (Fig. 4). It is conceivable that CB2 agonists could also inhibit inflammation and/or induce autophagy in RPE cells but they need to be clarified in future studies.

One way to avoid psychoactivity is to generate cannabinoids that do not enter the CNS [107]. Several potential compounds have failed due to adverse effects on cardiovascular system [3]. However, those compounds have been acted also upon CB1 receptors, the activation on which is known to decrease blood pressure and myocardial contractility [3]. Quite contrary, signaling through CB2 receptors seems beneficial rather than harmful by activating cardioprotective mechanisms and limiting inflammation [3, 112]. For example, orally administered Δ⁹-THC at low doses inhibited atherosclerotic plaque progression, lymphoid cell proliferation, interferon gamma (IFN-γ) production, and macrophage chemotaxis in apolipoprotein E (ApoE) knockout mice, and the effects were reversed by the CB2 inverse agonist SR144528 [117]. Similarly, the synthetic nonselective agonist WIN55,212-2 showed anti-atherosclerotic effects when injected in mice, and the reduced plaque size, macrophage levels, and adhesion markers were abolished by the CB2 inverse agonist AM630 [118].

Physiological effects of cannabinoids can also be modified by administering several compounds at the same time. For example, cannabis extract nabiximols (Sativex®) contain nearly equal amounts of Δ⁹-THC and cannabidiol, and it is a licensed cannabis-based drug for treating spasticity and pain [107]. Endocannabinoids are also good to keep in mind for the joint effects. Walter et al. observed that pathological stimulation of nerve cells induced the production of 2-AG, which attracted microglia towards dying neurons [119]. Interestingly, plant-derived cannabiol and cannabidiol acted as antagonists preventing the 2-AG-induced cell migration [119].
Conclusions

Increasing life expectancy is contributing to the fact that age-related diseases are becoming as a major public health burden with severe socio-economic impacts. The situation is challenging since efficient treatment options are largely missing. There is an increasing interest in the endogenous cannabinoid system in the treatment of age-related diseases. Especially CB2 receptors, the signaling pathways of which are closely linked to the regulation of inflammation and autophagy, are of great interest. Inflammation has been proposed to increase the expression of CB2 receptors, which could offer possibilities also for the CNS-targeted drug design without concern over psychoactive symptoms. However, trials on generating effective drugs have revealed the complexity of signaling by cannabinoid receptors. Despite of promising targets and applications, pharmacology and signaling of CB2 receptors, as well as effects in different disease states need to be fully revealed prior to clinical application of cannabinoid derivatives on age-related pathologies.

Acknowledgements

This work was financially supported by the Academy of Finland (grants 138151 and 139140), the Päiviikki ja Sakari Sohlberg Foundation, Finnish Cultural Foundation, North Savo Regional fund, CIMO, and the EVO grants of Kuopio University Hospital.

Conflict of interests

The authors declare no conflict of interest.

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