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CBD & Δ⁹-THC - the two faces of cannabis

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Cannabidiol (CBD) and Δ⁹-tetrahydrocannabinol (Δ⁹-THC) are phytocannabinoids produced by the plant *Cannabis sativa* which have both shown promising therapeutic value as anti-inflammatory and neuroprotective agents in a variety of neurological disorders. However, the molecular mechanisms involved in their protective function are thought to be distinctly different probably due to their divergent receptor pharmacology. Δ⁹-THC is a potent agonist at the cannabinoid receptors 1 and 2 through which it is thought to modulate synaptic plasticity and inflammatory responses respectively. CBD on the other hand exhibits negligible affinity for both receptors prompting research into cannabinoid receptor independent mechanisms of action such as modulation of endogenous cannabinoid tone and calcium signalling. This review aims to give an introduction into the pharmacological and biological effects of Δ⁹-THC and CBD with particular reference to neurological disease.

Introduction

After alcohol and tobacco, cannabis is one of the most commonly used recreational drugs worldwide. Although its deleterious effects on cognitive brain function have been well described, cannabis has also been shown to have potential as an anti-inflammatory, anxiolytic and neuroprotective agent. Cannabidiol (CBD) and Δ⁹-tetrahydrocannabinol (Δ⁹-THC) are the two most abundant compounds out of over 70 phytocannabinoids produced by the plant *Cannabis sativa* [1]. Because of its apparent psychoactivity, Δ⁹-THC was the first cannabinoid to be studied in detail and led to the discovery of the first cannabinoid receptors, CB1 and CB2 [2, 3]. Synthetic as well as endogenous cannabinoids (endocannabinoids) are defined by their characteristic ability to bind to either of these receptors whereas phytocannabinoids are identified by carrying a distinct C_{21} group [1].

The therapeutic potential of cannabinoids has been widely recognised and they have been clinically trialled in the treatment of a range of neurological symptoms and disorders including

spasticity [4], neurogenic pain [5], dyskinesia [6], tremor [7], schizophrenia [8, 9] and psychosis [10-12].

Although both Δ^9-THC and CBD have anti-inflammatory and neuroprotective properties, their effects are thought to be mediated through distinctly different pathways. A key difference between Δ^9-THC and CBD is that while Δ^9-THC readily agonises CB1 and CB2 receptors, CBD exhibits negligible affinity for both. Furthermore, the binding properties of Δ^9-THC and CBD differ for the newly identified G-protein receptor GPR55 receptor which is agonised by both the endocannabinoid anandamide (AEA) and Δ^9-THC but antagonised by CBD [13]. In this review, we will examine the differential pharmacological and biological effects of Δ^9-THC and CBD, mainly as a result of this discrepancy, with particular reference to neurological disease. The role of GPR55 in neuroprotective mechanisms is thus far unknown and will therefore not be further discussed in this review.

2. The psychoactivity and cognitive effects of Δ^9-THC

The potentially long lasting detrimental effects on cognitive function induced by the use of cannabis are thought to be due to Δ^9-THC, its major psychoactive component [14-16]. Concern regarding psychotropic and cognitive side-effects has limited therapeutic use of cannabinoids in the treatment of neurodegenerative diseases. It has been found that Δ^9-THC can influence memory formation, impair psychomotor control, trigger anxiety and psychosis and affect social interaction [17, 18]. It has been shown that regular exposure of rats to Δ^9-THC as well as a single injection of as little as 1 µg/kg Δ^9-THC into the cerebellum can lead to significant impairment of spatial learning [19, 20]. It is widely accepted that these psychoactive activities are CB1 receptor mediated as behavioural symptoms as well as cognitive impairment can be mimicked by CB1 receptor agonists whereas specific antagonists such as SR141716A are protective [14, 19, 21-23]. Activation of CB1 receptors modulates long term potentiation and depression (LTP and LTD) and thus has a profound effect on synaptic plasticity and memory formation. This is in accordance with reports of high CB1 receptor expression levels in brain regions associated with cognitive function [24]. Δ^9-THC has been reported to manipulate LTP and LTD directly through CB1 receptor activation but may also affect the retrograde signalling of endogenous CB1 ligands (endocannabinoids) [25, 26]. When acting directly through the CB1 receptor, a depression of neurotransmitter release is initiated as a result of receptor coupling to inhibitory G-proteins preventing the activation of voltage-gated Ca^{2+} [27-29] and K^+ channels [30, 31]. The nature of the long term effect is dependent on the neurotransmitter released at the synapse. Thus CB1 receptor stimulation leads to inhibition of LTD in GABAergic synapses and inhibition of LTP at glutamatergic synapses [32-35].

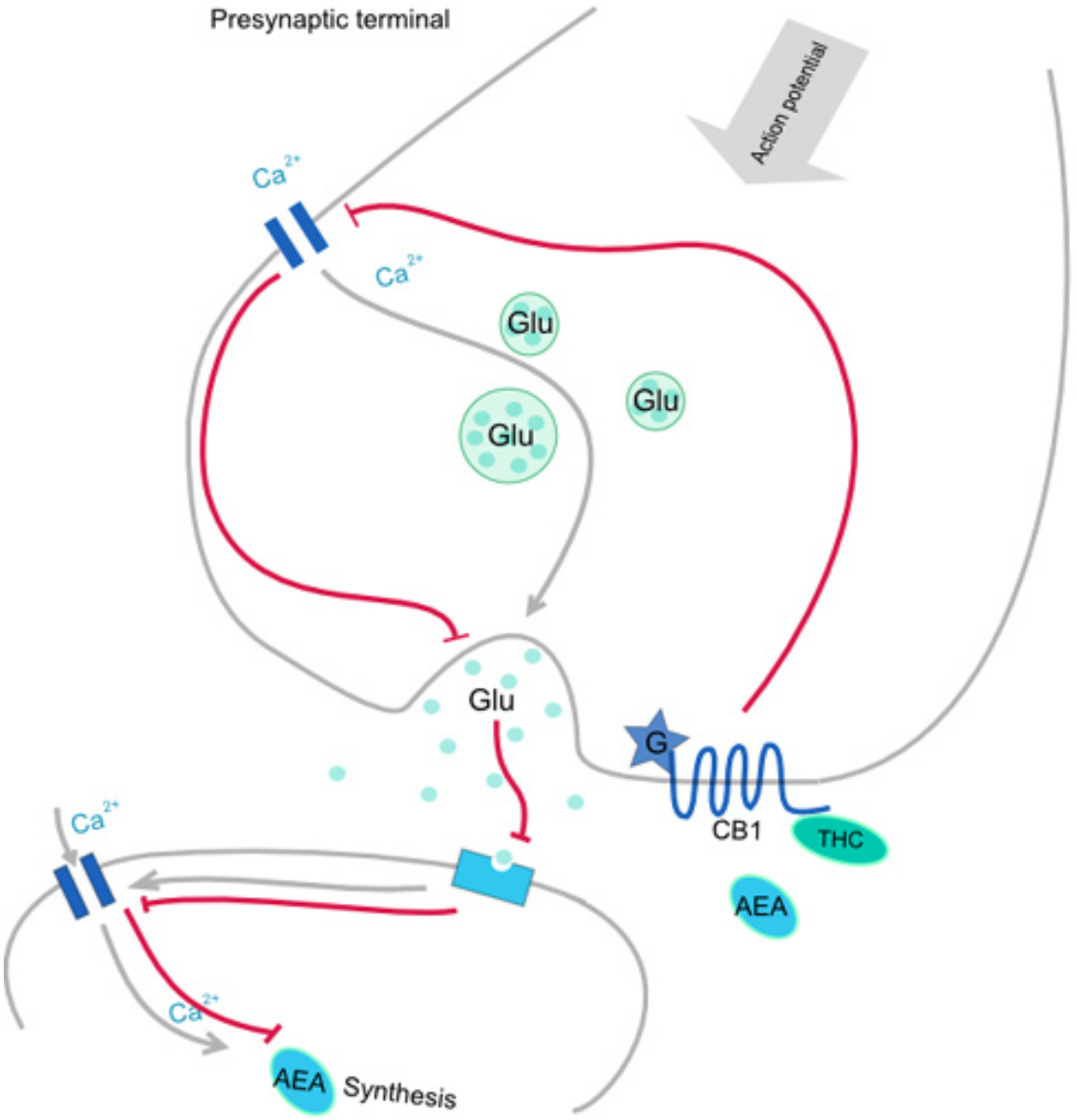

Figure 1. Activation of CB1 at the presynaptic terminal by THC leads to an inhibition of neurotransmitter release and postsynaptic endocannabinoid; Glutamate (glu), G-protein (G).

Endocannabinoids can be released either as a result of postsynaptic depolarisation stimulated by the resultant Ca^{2+} influx (depolarization induced suppression of inhibition (DSI) or depolarisation induced suppression of excitation (DSE)) or through activation of postsynaptic G-coupled receptors such as the metabotropic glutamate receptor 1 (mGlu1). Using hippocampal and nucleus accumbens tissue slices it has been shown that a single injection of Δ^9-THC leads to a short term but significant reduction of DSI and DSE as well as mGlu1-mediated LTD [25]; this effect was rescued with the specific CB1 receptor antagonist SR141716A [25]. Interestingly, chronic exposure to Δ^9-THC led to down-regulation of CB1 receptor expression and reduced coupling efficiency, thereby desensitising the brain to activation of the receptor by the drug as well as its endogenous ligands [36, 37]. Additionally, Δ^9-THC can lead to a desensitisation of the CB1 receptor even if applied in doses that do not trigger internalisation of the receptor [25, 37]. Therefore, given their central role in the mediation of psychoactivity, it has been proposed that

the activity of CB1 receptors is tightly linked to tolerance of and dependence on cannabinoids.

The molecular differences observed following acute versus chronic administration could be the major factor in the modulation of cannabinoid tolerance as well as dose-dependent differences [38]. These differences are particularly pronounced in the activation of downstream signalling pathways. The extracellular-regulated kinase (ERK), cyclic adenosine monophosphate (cAMP) and mitogen-actiated protein kinase (MAPK) pathways all lead to the phosphorylation of CREB (cAMP-response element-binding protein) which is an activator of transcription. Low doses of Δ^9-THC activate ERK 1/2, which play an important role in the regulation of cell survival, whereas high doses do not [20]. Similarly, acute treatment significantly increases CREB phosphorylation [33, 39] whereas chronic treatment with Δ^9-THC reduces CREB phosphorylation, which mediates transcription by binding to cAMP response elements (CRE) via CB1 receptors, both in the hippocampus and the cerebellum [38]. However, both chronic and acute treatments with Δ^9-THC lead to an increase in ERK1/2 protein levels and activation of ERK1/2 in the dorsal striatum, nucleus accumbens and the hippocampus [38, 40, 41]. Thus CB1 activation leads to ERK1/2 activation [41]. During the process of desensitisation of the receptor, CB1 is phosphorylated, inhibiting G-protein coupling and promoting β-arrestin binding to the receptor which in turn initiates internalisation [42]. Phosphorylation of the CB1 receptor is critical for inactivating ERK1/2. By contrast, internalisation of the receptor has no effect on ERK1/2 activation patterns, a phenomenon that may be cell specific [43, 44].

Unlike Δ^9-THC, CBD does not appear to affect behavioural and cognitive brain function, which is not surprising considering the key role CB1 plays in these mechanisms. However, CBD may be able to influence the psychoactivity of Δ^9-THC via as yet unknown mechanisms [45]. For example CBD inhibits up to 50% of the breakdown of Δ^9-THC into its metabolites by hepatic microsomes [46]. In the 1970s a series of studies reported the ability of CBD to attenuate the detrimental effect of Δ^9-THC on cognitive function, as well as Δ^9-THC-induced symptoms such as anxiety and paranoia [47-49]. Additionally, CBD is able to reverse perceptive changes caused by nabilone, a structural analogue of Δ^9-THC [50]. Furthermore, mice treated with CBD-supplemented Δ^9-THC performed better in spatial memory tests than when treated with Δ^9-THC alone, whereas CBD alone had no effect [45, 51]. Dosage seems to be important as the modulating effects of CBD on Δ^9-THC seem to be dependent on the ratio of CBD to Δ^9-THC [12, 51, 52]. A recent study using functional magnetic resonance imaging (fMRI) in humans confirmed that CBD and Δ^9-THC have distinctly opposite effects on neuronal activity during cognitive tasks [53]. CBD is thus considered a possible treatment for cognitive impairments associated with marijuana consumption.

CBD has also been suggested as a treatment of psychosis such as occurs in schizophrenia and drug-induced psychosis. A pilot study found that CBD significantly reduced levodopa-induced psychosis in Parkinson’s disease patients [10] and may thus be a useful treatment as it was well tolerated with almost no side effects. However, it was found that CBD monotherapy for treatment resistant schizophrenia had no effect in 2 out of three cases [54].

Commonly, anti-psychotic drugs induce *c-fos* expression in the limbic system which is mimicked by CBD providing molecular evidence of the anti-psychotic activity of CBD [55].

On a cellular level the ability of CBD to attenuate or even reverse the psychoactive effects of Δ^9-THC may be linked to its CB1 receptor pharmacology. Although CBD is a weak agonist at the CB1 receptor it has been repeatedly reported that CBD may be a partial antagonist at the receptor, marked by the displacement of the CB1 receptor agonists CP559540 and Win55212-2, but lacking receptor activation. Furthermore, agonists at the CB1 receptor are usually able to increase binding of the G-protein GTPγS. CBD inhibits the binding of GTPγS to mouse brain membranes thus displaying signs of inverse agonism at the receptor at a concentration of 10μM [56-58]. Although this finding remains controversial, as others have reported GTPγS binding to be unaffected by cannabidiol (reviewed in [59]), this may provide a possible mechanism by which CBD is able to attenuate some of the CB1 receptor-mediated psychoactive properties of Δ^9-THC.

Neuroprotection

The diverse mechanisms of action underlying the neuroprotective properties of cannabinoids can be divided into three broad categories:

(1) Receptor-mediated. In the case of Δ^9-THC this can be either CB1 or CB2 mediated, whereby CB1 activation is usually protective against excitotoxicity [60, 61] and CB2 activation is associated with an anti-inflammatory response.

(2) Anti-oxidant activity. Both CBD and Δ^9-THC are protective, at least in part, due to their inherent antioxidant activity conferred by the structural presence of a phenolic ring.

(3) Modulation of endocannabinoid tone and other mechanisms. There is evidence that CBD, which has negligible affinity at the CB1 and CB2 receptor, may affect endocannabinoid tone and intracellular calcium signalling, which could be relevant to its neuroprotective effects.

(1) Receptor-mediated neuroprotection

Studies in a range of *in vivo* and *in vitro* excitotoxicity models have suggested that the neuroprotective effect of cannabinoids may be mediated via the CB1 receptor [62-69]. CB1 receptors are widely expressed throughout the brain [24, 70, 71] where they co-localise with glutamatergic and GABAergic synapses [70, 72]. In motor diseases such as Huntington’s disease (HD) and Parkinson’s disease (PD) CB1 expression pattern changes, implicating an important role for the receptor [73-75].

Excitotoxicity occurs as a result of intense synaptic firing which leads to changes in dendrite morphology, synapse loss and can promote cell death. Even non-toxic increases in synaptic activity can cause an increase in dendrites and alter the shape of synaptic spines which can be crucial in pathological processes [61, 76-78]. One mechanism by which Δ^9-THC may be exerting its protective effects is via CB1 receptor-mediated presynaptic inhibition of glutamate release and suppression of excitotoxic mechanisms [28, 64, 67], although another study found a direct post-synaptic CB1 receptor-mediated protective effect of Δ^9-THC against kainate-induced

excitotoxicity [65].

Excitotoxicity is thought to be a relevant mechanism of cell death in conditions such as epilepsy, multiple sclerosis and cerebral ischaemia, in models of which CB1-receptor-mediated protective effects have been demonstrated [63, 66, 69]. However, the therapeutic use of Δ^9-THC or other CB1 agonists in excitotoxicity-induced neurodegeneration may be limited by agonist-induced desensitisation of the CB1 receptor due to internalisation as well as reduced coupling efficiency [36, 37], which has been shown to occur within 24hrs in a cell culture model [60]. Excitotoxicity has also been postulated to be relevant in the pathogenesis of neurodegenerative conditions such as motor neurone disease [79]. However, in the case of Parkinson's disease (PD), it is likely that other mechanisms of cell death are more relevant and in this case the protective effects of cannabinoids appear to be non-CB1 receptor-mediated [80-83].

The role of the CB2 receptor in mediating neuro-protective effects via modulation of inflammation is discussed in Section 4 below.

(2) Antioxidant effects

It is likely that some of the neuroprotective effects of Δ^9-THC are non-CB1 receptor mediated. This has particularly been demonstrated in models of PD, where *in vivo* and *in vitro* studies have demonstrated neuroprotective effects of Δ^9-THC that could not be blocked by specific CB1 receptor antagonists [80-82]. A *Drosophila* model of PD also implicated non-receptor mediated mechanisms of neuroprotection as CB1 receptor agonists were neuroprotective even though *Drosophila* do not express CB1 or CB2 receptors [83].

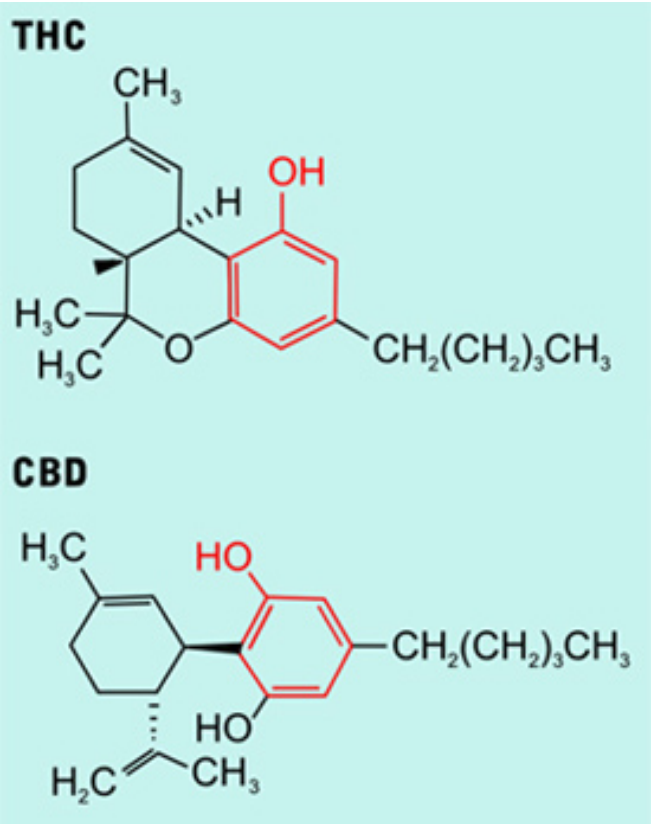

Figure 2. Antioxidant properties of THC and CBD are conferred by a phenol ring structure (red).

Commonly, neurodegenerative diseases lead to the formation of reactive oxygen species (ROS). Both CBD and Δ^9-THC as well as many other cannabinoids are inherently antioxidant due to the presence of a phenolic ring in their chemical structure [80, 81, 83, 84] (see figure 2) and it has been suggested that this underlies their neuroprotective effects.

(3) Modulation of endocannabinoid tone and other mechanisms

Modulation of endocannabinoid tone may be a relevant neuroprotective mechanism. In some conditions an increase in endocannabinoid level has been observed,

and it is thought that this may be a protective response. For example in a model of epilepsy, kainate-induced excitotoxicity acutely increased anandamide levels within the mouse brain and application of the CB1 receptor antagonist, SR141716A, increased seizure severity, suggesting a CB1-receptor-mediated protective effect of AEA against excitotoxicity. Furthermore, the AEA uptake inhibitor UCM707 was also protective [69]. Increase in endocannabinoid level has also been demonstrated in PD [85, 86].

In contrast, in animal models of another neurodegenerative disease, Huntington's disease (HD), endocannabinoid levels are markedly reduced [87]. In this condition transient receptor potential cation channel, subfamily V, member 1 (TRPV1) receptor activation has been shown to reduce motor symptoms such as hyperkinesia [88]. Although a neuroprotective effect may be exerted by CB1 receptor agonists as described above, there is loss of CB1 receptor-expressing neurones in the later stages of the disease [75, 88-90]; however, AEA uptake inhibitors as well as inhibitors of the hydrolysing enzyme FAAH have been shown to be neuroprotective [91]. This illustrates that in neurodegenerative conditions such PD and HD, cannabinoids may exert both neuroprotective effects as well as relieving symptoms - effects mediated by different receptors or non-receptor dependent mechanisms. Greater clinical benefit may therefore be achieved by modulating endocannabinoid tone rather than targeting specific receptors.

Although CBD has a limited direct effect on CB1 receptors due to its low affinity, it modulates endocannabinoid tone by increasing AEA levels which in turn may act at the CB1 receptor. However, the exact mechanism by which CBD modulates endocannabinoid tone remains unclear. One possibility is that CBD acts via the intracellular vannilloid receptor, TRPV1, which is a non-selective cation channel that facilitates the entry of Ca^{2+} into the cell [92]. Activation of the TRPV1 receptor can trigger Ca^{2+} dependent synthesis of endocannabinoids such as anandamide (AEA) which are also ligands at the receptor [93-95]. CBD leads to an influx in intracellular Ca^{2+}. However, there is evidence that CBD may not be acting via the TRPV1 receptor as the Ca^{2+} rise it generates is not blocked by the specific TRPV1 antagonist capsazepine [96]. On the contrary, the Ca^{2+} influx significantly increased when the TRPV1 receptor was blocked indicating that TRPV1 receptor activation causes downregulation of the CBD-induced Ca^{2+} rise [96]. Thus AEA, which is a potent activator of the TRPV1 receptor and causes the opening of its cation channel allowing Ca^{2+} to enter [93], inhibited the CBD-mediated Ca^{2+} response [97, 98]. This led to the hypothesis that in diseases where an increase of AEA levels is observed, CBD may be less effective. However, this is the subject of ongoing investigation as CBD is neuroprotective in models of PD [80], a disease in which AEA levels are enhanced [85, 86].

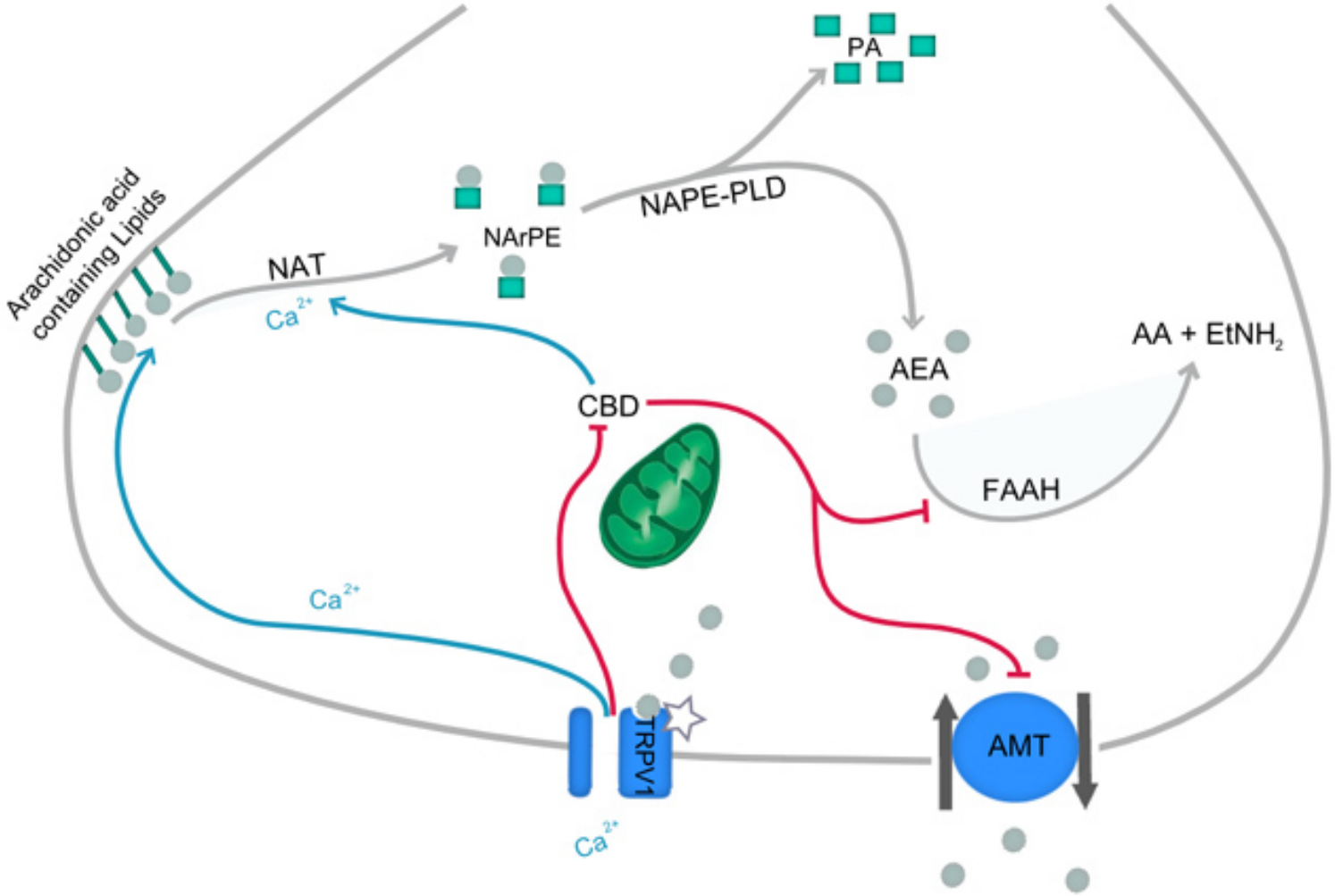

Figure 3. Endocannabinoid system of the postsynaptic terminal. N-acyltransferase (NAT) transfers arachidonic acid (AA) onto NArPE in a calcium dependent manner which is then cleaved by NAPE-specific phopholipase D (NAPE-PLD) into AEA and phosphatidic acid (PA). Fatty acid amide hydrolase (FAAH) hydrolyses AEA into AA and $EtNH_2$. The existence of an AEA membrane transporter (AMT) is still under debate but it may aid the movement of AEA across the plasma membrane. Grey lines - basic metabolism of AEA as described above, red lines – inhibitory actions of CBD on AEA hydrolysis and transport as well as inhibitory action of TRPV1 activation on mitochondrial calcium release, blue lines - release of calcium from mitochondria and TRPV1.

Evidence now suggests that Ca^{2+} may be released by CBD from mitochondrial stores [99]. Presumably as a response to CBD, AEA levels are increased either due to CBD's inhibitory function on AEA hydrolysis or due to Ca^{2+} influx resulting in a negative feedback cycle. Interestingly, the application of specific fatty-acid amide hydrolase inhibitors (FAAHI) (which inhibit hydrolysis of AEA and to some extent 2AG) does not cause a reduction in CBD response which may be due to the fact that CBD already acts as an inhibitor of hydrolysis [97] (summarised in Figure 3).

Therefore by increasing AEA levels within the cell, CBD may indirectly increase CB1 receptor activation, thus providing a potential mechanism by which CBD exerts its neuroprotective effects.

However, a more specific protective effect of CBD against mitochondrial toxins has also been proposed. A detailed study was published in 2007 evaluating the effect of CBD on 3-nitropropionic acid (3NP)-induced GABAergic neurone depletion [100]. 3NP is a mitochondrial toxin, inhibiting mitochondrial complex 2. It is used to model Huntington's disease (HD) as loss of function of the mitochondrial complex is its primary genetic cause [101]. In Sagredo's study, CBD completely reversed toxin-induced GABA depletion, whereas the specific CB1 receptor agonist, ACEA, and the specific CB2 agonist, HU-308, were not protective. Furthermore, coapplication of specific TRPV1 antagonists had no effect on the actions of CBD. Thus it is unlikely that the protective effect of CBD was exerted via the TRPV1 receptor despite its ability to agonise it [100]. This supports the findings of Ryan *et al* that CBD does not act via the TRPV1 receptor [102]. They have demonstrated that CBD prevents the membrane depolarisation caused by mitochondrial toxins. Furthermore, protection afforded by CBD against the mitochondrial toxin FCCP was potentiated by coapplication of the antioxidant BHT, indicating that the protective effect of CBD was not primarily exerted via its antioxidant properties [102].

In summary, CBD may not exert neuroprotective effects mediated by TRPV1 or antioxidant mechanisms but may uniquely protect against mitochondria-depolarising toxins through its calcium signalling abilities or through manipulating endocannabinoid tone. By contrast, unlike CBD where alternative modes of action were pursued due to its inability to bind CB1 or CB2 receptor, very little is known about the action of Δ^9-THC on intracellular calcium and endocannabinoids. Nevertheless it has been shown that Δ^9-THC modulates intracellular calcium levels in smooth muscle cells [103] and in the brain [104].

4. Inflammation

Inflammation plays an important part in many neurodegenerative diseases. Both Δ^9-THC and CBD have anti-inflammatory actions and might therefore be useful therapeutic agents in these conditions.

The anti-inflammatory action of Δ^9-THC is thought to be mediated through the CB2 receptor which is mainly located on cells of the immune system [105], with the highest levels being found in B lymphocytes and natural killer cells. The main CB2 expressing cells of the CNS are microglia, which are related to macrophages. Like macrophages, they are attracted to sites of injury where they are activated and proliferate [106, 107]. Once activated, microglia start to display a more phagocytic phenotype with amoeboid morphology. At this stage they produce various inflammatory cytokines including IL-1, IL-6 and TNF-α and express major histocompatability complex class 1 and 2 as well as the complement receptors CD11/CD18. The recruitment of microglia plays a major role in many neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis.

The expression pattern of CB2 by microglia is dependent on the activation status of the cells: inactivated, resting microglia express low levels of CB2 which is markedly increased in intermediate activation states where cells are responsive and primed, and reduced in fully activated glial cells [108]. Cannabinoids are known to suppress some of the immune functions of microglia such as phagocytosis, cytolysis and cytokine secretion and may therefore potentially

reduce potentiation of neurodegeneration attributable to microglial activation [109-111].

The cannabinoids Δ^9-THC and AEA are able to inhibit the secretion of the inflammatory cytokines TNF-α, IL-α, IL-β and IL-6 by activated microglia [112, 113]. It is thought that cannabinoid-induced reduction in microglial chemotaxis and motility is primarily mediated by CB2 receptor activation [114-117]. Δ^9-THC has also been shown to reduce the production of inflammatory cytokines by peripheral immune cells in a mouse model of autoimmune hepatitis; this response was CB2 receptor dependent as shown by the co-application of specific antagonists [118]. Blocking FAAH activity also had an immune-suppressive effect [118]. Thus it is thought that anti-inflammatory actions of cannabinoids are mainly mediated via the CB2 receptor which actively prevents the activation of glial cells [109]. However, even though specific CB2 receptor agonists such as BML-190 and JWH-015 as well as Δ^9-THC and AEA are able to protect neuronal cells from co-cultured, stimulated microglia, BML-190 caused a distinctly different cytokine profile compared with the other compounds indicating that regulation of inflammatory cytokine production may not directly influence neuronal cell viability [113].

Anti-inflammatory responses may also be partly mediated via the CB1 receptor, as indicated by a study using CB1 specific agonists which showed a dose dependent inhibition of nitric oxide production (a marker of microglial activation) [119]. Others have reported that CB1 agonists are able to reverse the morphological change of macrophages to a mobile amoeboid phenotype in a CB1 receptor-dependent manner [120, 121]. However, unlike in the rat, human microglia do not appear to express CB1 receptors which may limit the relevance of these findings to human disease [113].

Another potential mediator of Δ^9-THC-associated anti-inflammatory effects is the peroxisome proliferator-activated receptor-gamma (PPAR-γ), a receptor involved in lipid homeostasis, which is widely expressed in neuronal and glial cells [122]. PPAR-γ is a nuclear receptor that through binding to DNA promoter regions can regulate microglial activation [123], expression of inflammatory cytokines [124], nitric oxide synthase [125] and antioxidative enzymes [126]. In a mouse model of PD, the PPAR-γ receptor agonist, pioglitazone, prevented dopaminergic cell loss and attenuated glial activation [127]. Both Δ^9-THC and anandamide activate PPAR-γ [128, 129]. Although AEA itself is a PPAR-γ receptor agonist, evidence suggests that it inhibits IL-2 secretion via its COX-2 metabolites, an effect that can be attenuated by co-application of PPAR-γ antagonists [124, 130]. Thus it is unclear whether PPAR-γ activation alone is sufficient to mediate some of its anti-inflammatory effects.

CBD is a poor agonist at the CB2 receptor and thus mediates its anti-inflammatory actions through other, cannabinoid receptor-independent, mechanisms or through modulation of endocannabinoid levels as previously described. Carrier *et al* have proposed that CBD may act through modifying adenosine signalling [131, 132]. They showed that CBD inhibited the uptake of adenosine by nucleoside transporters in murine microglia, thereby increasing the activation of adenosine A2A receptors. A2A knock-out mice and antagonism of the A2A receptor lead to attenuation of the CBD-mediated effect, suggesting its importance in CBD-mediated anti-inflammatory actions [131, 132]. Further downstream, CBD prevents MAPK activation and

translocation of the nuclear factor NF-κB into the nucleus thus preventing the expression of inflammatory cytokines and nitric oxide synthase [133].

5. Pharmacokinetics

There are currently three cannabis-based medications clinically available, two of which contain Δ^9-THC, whose licensed indications vary between countries. These include dronabinol (trade name Marinol®), formulated as capsules containing synthetic Δ^9-THC; and Nabiximols oral spray (trade name Sativex®), a mixture of both CBD and Δ^9-THC. The third medication is Nabilone, a synthetic Δ^9-THC analogue. The potential therapeutic benefit of any drug is dependent on its pharmacokinetics which determines the onset, magnitude and duration of any effect depending on drug absorption by tissues, hepatic metabolism and excretion in bodily fluids and faeces. Thus, the route of administration makes a considerable difference to the bioavailability of Δ^9-THC such that smoked cannabis leads to a quicker and higher peak of drug plasma levels compared with oral intake. Compared with intravenous administration of Δ^9-THC, bioavailability by the oral route ranges between 4% and 20% [134-136], probably as a result of first pass metabolism by the liver into its over 80 different metabolites, the most abundant of which are the psychoactive metabolite 11-OH-THC and its inactive carboxylated form THC-COOH [135]. When smoked, mean plasma concentration of Δ^9-THC peaks after approximately 6 minutes, followed by a rapid decrease to less than a quarter of its maximum concentration [134]. This effect, accompanied by a steady increase in 11-OH-THC, led researchers to believe that it was its metabolite rather than Δ^9-THC itself that causes psychotic symptoms after consumption of the drug [137]. However, it is now known that, due its lipophilic properties, the majority of Δ^9-THC is quickly absorbed by adipose tissue and then slowly released back into the bloodstream [138].

The extent to which CBD exerts clinically relevant positive effects when co-administered with Δ^9-THC is the subject of ongoing debate, extensively reviewed by Russo *et al* [12]; the attenuating effect of CBD on the psychoactive effects of Δ^9-THC is discussed in section 2. Nabiximols (Sativex®) contains Δ^9-THC and CBD in almost equal proportions (2.7mg Δ^9-THC to 2.5mg CBD ratio per spray) and is composed of the standardized Δ^9-THC and CBD extracts Tetranabinex® and Nabidiolex® respectively. However, this does not mean that plasma levels of the drugs are equal following dose administration as both may be metabolised at different rates. Indeed, lower plasma concentrations of CBD have been found in comparison with Δ^9-THC after administration of equal amounts of both compounds despite the fact that CBD is metabolised at a slower rate and, unlike Δ^9-THC, the majority of CBD is excreted unchanged [134]. However, there is evidence that CBD may inhibit the conversion of Δ^9-THC into its metabolite 11-OH-THC by the enzyme CYP450 [46, 134, 139, 140]. Accordingly it was found that metabolism of Δ^9-THC to 11-OH-THC was reduced when CBD and Δ^9-THC extracts were co-administered. Furthermore a 1:1 mixture delayed Δ^9-THC absorption compared with Δ^9-THC high ratios [141, 142].

6. Conclusion

Here we have discussed the diverse mechanisms of action of Δ^9-THC and CBD and how these relate to their potential therapeutic role in neurological disorders. Although both compounds exhibit neuroprotective and anti-inflammatory effects their receptor pharmacology distinctly differs, indicating divergent mechanisms of action. These are probably mediated by the CB1 and CB2 receptors in the case of Δ^9-THC, but are much less clear in relation to CBD as the compound displays negligible affinity for both cannabinoid receptors. Thus CBD research has focused on non-receptor mediated mechanisms of actions such as Ca^{2+} and endocannabinoid tone modulation whereas the effect of Δ^9-THC on these two variables is uncertain. The clinical utility of Δ^9-THC may be limited by its psychoactive potential, whereas CBD not only appears to have antipsychotic effects but may also counteract the psychoactive properties of Δ^9-THC. Thus it may be of interest to study the pharmacological properties of these two compounds not only separately but also in conjunction to further evaluate their clinical potential.

Abbreviations

2AG - 2-acylglycerol
3NP - 3-nitropropionic acid
A2A - Adenosine A2A receptor
AEA - Anandamide
BHT - Butylated hydroxytoluene
CBD - Cannabidiol
CNS - Central nervous system
DSE - Depolarisation induced suppression of excitation
DSI - Depolarisation induced suppression of inhibition
FAAH - Fatty acid amide hydrolase
FCCP - carbonylcyanide-*p*-trifluoromethoxyphenylhydrazone
fMRI - Functional magnetic resonance imaging
HD - Huntington’s Disease
LTD - Long term depression
LTP - Long term potentiation
mGlu1 - Metabotropic glutamate receptor 1
PD - Parkinson’s disease
TRPV1 - transient receptor potential cation channel, subfamily V, member 1
Δ^9-THC - Δ^9-Tetrahydrocannabinol

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