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REVIEW

The influence of cannabinoids on generic traits of neurodegeneration

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In an increasingly ageing population, the incidence of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease are rising. While the aetiologies of these disorders are different, a number of common mechanisms that underlie their neurodegenerative components have been elucidated; namely neuroinflammation, excitotoxicity, mitochondrial dysfunction and reduced trophic support. Current therapies focus on treatment of the symptoms and attempt to delay the progression of these diseases but there is currently no cure. Modulation of the endogenous cannabinoid system is emerging as a potentially viable option in the treatment of neurodegeneration. Endocannabinoid signalling has been found to be altered in many neurodegenerative disorders. To this end, pharmacological manipulation of the endogenous cannabinoid system, as well as application of phytocannabinoids and synthetic cannabinoids have been investigated. Signalling from the CB_1 and CB_2 receptors are known to be involved in the regulation of Ca^{2+} homeostasis, mitochondrial function, trophic support and inflammatory status, respectively, while other receptors gated by cannabinoids such as PPARγ, are gaining interest in their anti-inflammatory properties. Through multiple lines of evidence, this evolutionarily conserved neurosignalling system has shown neuroprotective capabilities and is therefore a potential target for neurodegenerative disorders. This review details the mechanisms of neurodegeneration and highlights the beneficial effects of cannabinoid treatment.

LINKED ARTICLES

This article is part of a themed section on Cannabinoids 2013. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-6

Abbreviations

2AG, 2-arachidonoyl glycerol; Aβ, amyloid-β peptide; AD, Alzheimer's disease; AEA, anandamide; BDNF, brain derived neurotrophic factor; CB, cannabinoid; CBD, cannabidiol; DAMP, damage associated molecular pattern; DGLα, diacylglycerol lipase-α; DGLβ, diacylglycerol lipase-β; eCB, endocannabinoid; FAAH, fatty acid amide hydrolase; HD, Huntington's disease; HTT, huntingtin protein; KA, kainic acid; MGL, monoacylglycerol; PAMP, pathogen associated molecular pattern; PD, Parkinson's disease; RAGE, receptor for advanced glycation end-products; RNS, reactive nitrogen species; ROS, reactive oxygen species; SN, substantia nigra; SR141716A, N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride; SR144528, N-([1S]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; THC, Δ^9-tetrahydrocannabinol; TLR, Toll-like receptor

Introduction

Neurodegeneration is the culmination of progressive loss of structure and function in neuronal cells, resulting in severe neuronal death. The widespread prevalence of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), and the lack of effective treatments, pose a significant social and

economic burden (Brookmeyer *et al.*, 2007; Zuccato *et al.*, 2010; Taylor *et al.*, 2013). Age remains the highest risk factor for these diseases and with a degree of neurodegeneration also occurring during normal ageing the threat to the quality of life and health of the global population is ever present (Marchalant *et al.*, 2009). Although neurodegenerative diseases are a heterogeneous group of disorders, current research has identified a number of common underlying mechanisms namely protein misfolding, neuroinflammation, excitotoxicity and oxidative stress. These triggers are known to contribute to the progression of symptoms, functional alteration and microanatomical deficits found in neurodegenerative states.

Inflammation within the CNS is centred around the activation of the resident immune cells, the microglia (Akiyama *et al.*, 2000; Taylor *et al.*, 2013). Maintained in a quiescent state and associated with the production of neurotrophic and anti-inflammatory factors, microglia become activated by the recognition of highly conserved structural motifs on either pathogens (pathogen associated molecular patterns; PAMPs) or from damaged or stressed cells (damage associated molecular patterns; DAMPs) (Arroyo *et al.*, 2011). The binding of PAMPs or DAMPS to pattern-recognition receptors, such as the Toll-like receptors (TLR) or receptors for advanced glycation end-products (RAGE), cause the migration of microglia followed by the synthesis and release of proinflammatory cytokines and reactive oxygen species (ROS) (Yan *et al.*, 1996; Arroyo *et al.*, 2011). Oxidative stress is a cytotoxic condition brought on by the increased intracellular production or accumulation of ROS and reactive nitrogen species (RNS) (Taylor *et al.*, 2013). ROS are normal products of the mitochondrial respiratory chain but activated microglia generate excessive amounts as a result of intracellular peroxidases, oxidative processes and NADPH oxidase activity (Block and Hong, 2007). Regulation of ROS and RNS is vital to cell survival as their increased production leads to the damage of proteins, lipids, carbohydrates and nucleic acids resulting in significant disruption of cellular function (Mehta *et al.*, 2013). Furthermore, oxidative stress can lead to the activation of the mitochondrial permeability transition pore causing the collapse of the *trans*-membrane electrochemical gradient and the release of proapoptotic factors like cytochrome c, procaspases and caspase activated DNase (Emerit *et al.*, 2004). Excitotoxicity is the pathological process of damaging and killing neuronal cells as a result of excessive stimulation of ionotrophic receptors by glutamate and similar substances (Mehta *et al.*, 2013). This process leads to impairment of intracellular Ca^{2+} buffering, generation of ROS and RNS, activation of the mitochondrial permeability transition pore and secondary excitotoxicity (Dong *et al.*, 2009). In an attempt to reduce the intracellular Ca^{2+} load, neurons expend considerable energy using ion pumps on the endoplasmic reticulum, plasma membrane and mitochondria, reducing ATP levels and causing excitotoxic lesions (Beal, 2000). Activation of the proapoptotic cascade is associated with a number of insults such as generation of ROS/RNS, mitochondrial dysfunction, excitotoxicity and trophic factor withdrawal. This process depends upon initiator and effector caspases which cause DNA cleavage, proteolytic cascades and mitochondrial permeability resulting in the release of proapoptotic factors such as cytochrome c and DIABLO (Bredesen *et al.*, 2006). A dynamic interplay between these neurodegenerative processes has been reported in AD, PD and HD and is the focus of many prospective therapeutic agents (Bredesen *et al.*, 2006; Lin and Beal, 2006). Decreased neurogenesis and neurotrophic support has also emerged as a common characteristic in neurodegenerative states often presenting early in disease progression (Simuni and Sethi, 2008). Genes which have been identified as problematic in neurodegenerative disorders such as those for α-synuclein, presenilin 1, tau and huntingtin are also involved in brain plasticity and their aberrant aggregation is detrimental to adult neurogenesis (Winner *et al.*, 2011).

The endogenous cannabinoid (eCB) system

The eCB system is composed of the endocannabinoid signalling molecules, 2-arachidonoyl glycerol (2AG) and anandamide (AEA) and their G-protein coupled cannabinoid CB_1 and CB_2 receptors (Piomelli, 2003: receptor nomenclature follows Alexander *et al.*, 2013). Endocannabinoid signalling molecules are synthesized in the post-synaptic terminal as a result of depolarization and work in a retrograde fashion on presynaptic CB receptors. The primary pathway through which AEA is synthesized involves the Ca^{2+}-dependent cleavage of its membrane precursor N-arachidonoyl phosphatidylethanolamine by phospholipase D (Di Marzo *et al.*, 1994). In most cases, 2AG is synthesized by the hydrolysis of two *sn*-1 diacylglycerol lipase isozymes, diacylglycerol lipase-α (DGLα) and diacylglycerol lipase-β (DGLβ) (Bisogno *et al.*, 2003). The CB_1 receptor is highly expressed in the CNS at the terminals of central and peripheral neurons where they regulate neurotransmitter release and psychoactivity (Sanchez and Garcia-Merino, 2012). CB_2 receptor expression is associated with the peripheral immune system, neurons within the brainstem and microglia during neuroinflammation (Van Sickle *et al.*, 2005; Nunez *et al.*, 2008). CB_1 and CB_2 receptors have also been associated with postnatal oligodendrogenesis. CB_1 activation increases the number of glial precursors in the subventricular zone of postnatal rats while CB_2 activation increases polysialylated neural cell adhesion molecule expression which is necessary for the migration of oligodendrocyte precursors (Arevalo-Martin *et al.*, 2007). CB receptors act via the G_i or G_o protein to stimulate the MAPK pathway and inhibit adenylate cyclase, attenuating the conversion of ATP to cyclic AMP (Howlett *et al.*, 2002). CB receptor activation is also tightly linked to ion channel regulation through inhibition of voltage-dependent Ca^{2+} channels and activation of K^+ channels (Mackie *et al.*, 1993; Deadwyler *et al.*, 1995; Hampson *et al.*, 2000). The TRPV1 receptor is also activated by the endocannabinoid AEA and has been linked to its anti-inflammatory actions (Zygmunt *et al.*, 1999). Degradation of endocannabinoids is carried out by two enzymes: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) which act upon AEA and 2AG respectively (Cravatt *et al.*, 1996; Ben-Shabat *et al.*, 1998). A number of exogenous ligands to CB receptors are also known such as the phytocannabinoids derived from the *Cannabis sativa* plant as well as synthetic CB_1/CB_2 agonists and antagonists. Manipulation of the eCB system has also been carried out by the inhibition of

	CB_1 receptor	CB_2 receptor	Endocannabinoid levels	Endocannabinoid synthesis	Endocannabinoid degradation
Alzheimer's disease	CB_1 receptor expression initially rises followed by decline during disease progression (Farkas *et al.*, 2012). CB_1 receptor functionally impaired (Ramirez *et al.*, 2005).	CB_2 receptor expression increases in the entorhinal cortex and parahippocampus (Benito *et al.*, 2003; Solas *et al.*, 2013).	Decreased AEA levels in the midfrontal and temporal coretex (Jung *et al.*, 2012).	DGLα and DGLβ levels are increased in AD patients (Braak stage IV) (Mulder *et al.*, 2011).	Increased FAAH levels (Benito *et al.*, 2003). Increased MGL levels in AD patients (Braak stage IV) (Mulder *et al.*, 2011).
Parkinson's disease	CB_1 receptor expression decreases in the substantia nigra (Van Laere *et al.*, 2012). CB_1 receptor expression increases in dopaminergic projecting areas (Van Laere *et al.*, 2012).		AEA levels increased in cerebrospinal fluid (Pisani *et al.*, 2010). Sevenfold increase in 2AG levels in the globus pallidus (Di Marzo *et al.*, 2000).		Decreased levels of anandamide membrane transporter and FAAH (Gubellini *et al.*, 2002).
Huntington's disease	CB_1 receptor expression decreases in the caudate nucleus, putamen and globus pallidus (Glass *et al.*, 2000).	CB_2 receptor expression increases in striatal microglia (Palazuelos *et al.*, 2009).	AEA and 2AG levels decrease in striatum (Bari *et al.*, 2013; Bisogno *et al.*, 2008). AEA levels increase and 2AG levels decrease in the cortex(Bari *et al.*, 2013; Bisogno *et al.*, 2008).	NAPE-PLD and DGL levels decrease in the striatum (Bari *et al.*, 2013; Bisogno *et al.*, 2008).	FAAH levels increase and MGL levels decrease in the cortex (Bari *et al.*, 2013; Bisogno *et al.*, 2008).

Figure 1
Summary of changes to the endogenous cannabinoid system in neurodegenerative conditions.

endocannabinoid biosynthesis, membrane transport and degradation (Bisogno *et al.*, 2005). The eCB system has been identified as a possible therapeutic target against neurodegeneration as a number of alterations in the eCB system have been noted in AD, PD and HD, as discussed below (Figure 1).

Alzheimer's disease

AD is a progressive age-related neurodegenerative disorder that affects over 26 million people worldwide (Brookmeyer *et al.*, 2007). It is estimated that 10% of people over 65 and 25% of people over 80 years of age are afflicted by this debilitating disease, and that number is set to rise to 1 in every 85 people by 2050 (Hebert *et al.*, 2003; Brookmeyer *et al.*, 2007). AD is defined by the progressive deterioration of cognition and memory and is the most common form of dementia among the elderly (Minati *et al.*, 2009). The characteristic hallmarks of AD include the formation of neuritic plaques, containing aggregated forms of the amyloid-β (Aβ) peptide and dystrophic neurites, and neurofibrillary tangles caused by the hyperphosphorylation of the microtubule associated protein, tau, resulting in severe neurodegeneration.

Over the past two decades, neuroinflammation has emerged as an integral process in the pathogenesis of AD. Post-mortem analysis of the brains of AD patients has revealed an increase in the amount of activated microglia and astrocytes as well as a significantly higher levels of proinflammatory cytokines, IL-1, IL-6 and TNF-α and ROS (Akiyama *et al.*, 2000; Rojo *et al.*, 2008). Furthermore, clinical studies have identified a positive correlation between TNF-α levels and cognitive decline (Holmes *et al.*, 2009) and numerous trials have shown that anti-inflammatory drugs delay the onset or slow the progression of AD (Arroyo *et al.*, 2011). Fibrillated Aβ can be recognized by immune cells and phagocytosed. However, once the peptides oligomerize, aggregate and form neuritic plaques this is not possible, leading to the chronic activation of the immune system (Salminen *et al.*, 2009). Activation of TLR, nucleotide-binding oligomerization domain-like receptors and RAGE by Aβ can stimulate phagocytosis but also results in reduced antioxidant defence and the release of proinflammatory cytokines and proapoptotic mediators (Salminen *et al.*, 2009; Heneka *et al.*, 2010). The pathophysiological relevance of neuroinflammation to neurodegeneration in AD has been well established through multiple lines of evidence. Direct evidence of neurotoxicity has

been shown as a result of the release of IL-1, IL-6 and TNF-α (Allan and Rothwell, 2001). Colocalization of the inflammatory response to areas most affected by AD pathology and the absence of such a response in areas less affected implies a strong relationship between the two (Akiyama *et al.*, 2000).

The dysregulation of intracellular Ca^{2+} concentration and excessive activation of NMDA receptors are characteristic of AD (Sonkusare *et al.*, 2005). Accumulation of glutamate as a result of Aβ-mediated reduction in astrocytic uptake, as well as direct activation of NMDA receptors, leads to excessive NMDA activity and excitotoxicity (Sonkusare *et al.*, 2005; Texido *et al.*, 2011). Aβ has been shown to increase voltage-dependant Ca^{2+} channel activity (MacManus, 2000) and to form Ca^{2+} permeable pores in membrane bilayers (Alarcon *et al.*, 2006). Aβ-induced excitotoxicity has long been associated with the neurodegenerative process as rises in intracellular Ca^{2+} concentration have been shown to activate a number of apoptotic pathways including the activation of caspase-3, calpain and lysosomal cathepsins (Hajnoczky *et al.*, 2003; Harvey *et al.*, 2012). Activated microglia, which can be seen in excess around neuritic plaques, are a major source of ROS production and oxidative stress in the CNS. ROS can further perpetuate the inflammatory response by activating proinflammatory pathways (Taylor *et al.*, 2013).

Several components of the eCB system are altered in AD. In the post-mortem brains of patients with AD, CB_2 receptor expression was significantly increased in areas containing microglia associated with the neuritic plaques, such as the entorhinal cortex and parahippocampus (Benito *et al.*, 2003; Solas *et al.*, 2013). This increase in CB_2 expression is thought to be an attempt to counteract the chronic inflammation found in AD as CB_2 receptor activation reduces microglial activation and cytokine production (Ramirez *et al.*, 2005; Koppel and Davies, 2010). CB_1 receptor expression in the AD brain remains a contentious issue with reports of both intact and increased expression levels (Lee *et al.*, 2010; Solas *et al.*, 2013). However, Farkas *et al.* (2012) have recently reported an initial rise, followed by a steady decline in CB_1 receptor expression in the prefrontal cortex of AD patients. When patients were grouped depending on the progression of AD, at the earliest stages of disease progression (Braak stages I-II) CB_1 receptor density was at its highest when compared to aged-matched controls and those CB_1 receptor levels were found to decline with the progression of AD while remaining above age-matched control levels (Farkas *et al.*, 2012). Furthermore, pharmacological investigation has shown that the CB_1 receptor becomes functionally impaired by nitrosylation in the AD brain, affecting the G protein coupling and downstream signaling (Ramirez *et al.*, 2005). Lipidomic analysis of post-mortem brain tissue from AD patients has revealed significantly reduced levels of AEA and its precursors in the midfrontal and temporal cortex when compared to age-matched controls (Jung *et al.*, 2012). Interestingly, increased degradation of AEA may also occur as a consequence of the up-regulation of the metabolizing enzyme, FAAH, on plaque-associated astrocytes that has been noted in the AD brain (Benito *et al.*, 2003). Inhibition of MGL in an *in vivo* model of AD has recently been shown to suppress the production and accumulation of Aβ via reduced expression of β-site amyloid precursor protein cleaving enzyme 1, a key enzyme in the synthesis of Aβ (Chen *et al.*, 2012). 2AG signalling in AD patients (Braak stage VI) is functionally impaired with increased expression of DGLα and DGLβ as well as the hydrolyzing enzyme MGL although membrane-associated 2AG hydrolysis by MGL was decreased (Mulder *et al.*, 2011).

Parkinson's disease

PD is the second most common neurodegenerative disease affecting 1% of people over 60 and 4% of people over 80 years of age (de Lau and Breteler, 2006). PD is characterized by the progressive loss of dopaminergic neurons primarily in the substantia nigra (SN) affecting the circuits of the basal ganglia resulting in bradykinesia, rigidity and tremors (Bartels and Leenders, 2009). In a rat model of PD, symptomatology followed an approximate 50% reduction of dopaminergic neurons in the SN combined with an 80% loss of dopamine levels in the striatum (Deumens *et al.*, 2002). In degenerating neurons, Lewy bodies form containing neurofilaments with aggregated α-synuclein (Wakabayashi *et al.*, 2007). The disease has been associated with genetic mutations, inflammation, exogenous toxins and oxidative stress (Bartels and Leenders, 2009).

The link between PD and dopamine loss has been affirmed by PET studies showing a presynaptic dopamine deficit in PD patients and *post mortem* biochemical analysis revealing decreased levels of dopamine metabolites in the affected areas (Bartels and Leenders, 2009). Intracellular degradation of dopamine generates high levels of ROS, promotes H^+ leakage from the mitochondria and reduces levels of glutathione, a key antioxidant enzyme (Hald and Lotharius, 2005). This intrinsic increase in ROS and concomitant decrease in antioxidant enzymes may be the reason for the high levels of oxidative stress found in PD patients. Furthermore, ROS have been shown to induce excitotoxicity through the activation of NMDA receptors and induction of proinflammatory cascades (Barnham *et al.*, 2004). Indeed, PET scans and post-mortem analysis have reported an increased number of activated microglia in the PD brain (McGeer *et al.*, 1988; Gerhard *et al.*, 2006). In line with this, *post mortem* analysis has also revealed an increased amount of proinflammatory cytokines, namely IL1-β, IL-2, IL-4, IL-6 and TNF-α (Taylor *et al.*, 2013).

The eCB system has been shown to modulate GABAergic and glutamatergic transmission in the basal ganglia (Kofalvi *et al.*, 2005) which affects motor function (Fernández-Ruiz, 2009) and has therefore gained interest as a possible therapeutic target for motor disorders. A recent study has shown a decrease in the availability of CB_1 receptors in the SN of PD patients when compared with healthy controls (Van Laere *et al.*, 2012). However, a marked increase in CB_1 receptors was found in the nigrostriatal, mesolimbic and mesocortical dopaminergic projection areas of the same patients. It is important to note that no difference in CB_1 availability was found between patients that had developed levodopa-induced dyskinesias and those without such symptoms (Van Laere *et al.*, 2012). AEA levels in the cerebrospinal fluid of untreated PD patients were found to be more than double that found in age-matched controls. Interestingly, AEA levels returned to control levels in patients receiving chronic dopa-

mine replacement therapy (Pisani *et al.*, 2010). Furthermore, a sevenfold increase in 2AG levels was found in the globus pallidus of the reserpine-treated animal model of PD and this has been linked to suppression of locomotion (Di Marzo *et al.*, 2000). A decrease in endocannabinoid degradation has also been noted in an animal model of PD with reduced levels of FAAH and AEA membrane transporter found in the striatum (Gubellini *et al.*, 2002). This increase in endocannabinoid tone and CB_1 receptor activity in the brain of PD patients has been proposed to be an attempt to normalize striatal function following dopamine depletion as enhanced CB_1 receptor signalling reduces glutamate release and activates the pool of G-proteins usually activated by the dopamine D_2 receptor (Meschler and Howlett, 2001; Brotchie, 2003).

Huntington's disease

HD is a progressive neurodegenerative disease that affects 4–10 people per 100 000. The average age of onset is 40 years and it is fatal within 15–20 years (Ross and Tabrizi, 2011). The disease is inherited in an autosomal dominant fashion and is caused by an expanded cytosine, adenine, guanine repeat in the huntingtin gene. Expansion of this gene results in an elongated glutamine repeat at the NH_2 terminus of the huntingtin protein (HTT) (Macdonald, 1993). The exact functions of HTT are not fully known although it is believed to play a role in vesicular transport and regulation of gene transcription (Cattaneo *et al.*, 2005; Sadri-Vakili and Cha, 2006). Mutation of HTT can result in intracellular toxic protein aggregation through the formation of abnormal conformations, typically β-sheet structures, protein modifications and the disruption of cellular processes such as protein degradation and metabolic pathways (Ross and Tabrizi, 2011). The resulting clinical features of this are atrophy of the cerebral cortex, severe striatal neuronal loss and up to a 95% reduction of GABAergic medium spiny projection neurons (Halliday *et al.*, 1998; Vonsattel, 2008). The pathological processes implicated in HD are the loss of trophic factors, specifically brain-derived neurotrophic factor (BDNF), excitotoxicity, oxidative stress and inflammation resulting in progressive neurodegeneration. Symptoms associated with HD include progressive motor dysfunction, cognitive decline and psychiatric disturbance (Ross and Tabrizi, 2011).

A number of studies have reported the dependency of medium spiny neurons on BDNF which is depleted by approximately 35% in animal models of HD (Baquet *et al.*, 2004; Zuccato and Cattaneo, 2007). Reduced BDNF mRNA expression has also been reported in the *post mortem* analysis of brain tissue from HD patients (Zuccato *et al.*, 2008). Decreased levels of BDNF have been closely linked to the HD phenotype since BDNF partial knock-out mice showed very similar phenotypes to HD models, namely progressive brain damage and hindlimb clasping as well as reduced striatal volumes (Baquet *et al.*, 2004). Indeed, BDNF replacement is believed to be a possible therapeutic for HD and has been shown to decrease excitotoxicity and attenuate motor dysfunction and cell loss in animal models of HD (Kells *et al.*, 2004; Kells *et al.*, 2008). This may prove beneficial as mounting evidence implicates excitotoxicity in the pathophysiology of HD. Hassel *et al.* (2008) have reported a 43% decrease in glutamate uptake in HD patients and defective activity of the glutamate transporter, GLT1. The subsequent accumulation of extracellular glutamate could well be the cause of excessive NMDA activity and excitotoxicity. Mutant HTT has also been found to bind directly to mitochondria, disrupting metabolic activity and up-regulating the proapoptotic factors Bcl2-associated X protein and p53-up-regulated modulator of apoptosis (Bae *et al.*, 2005). Neuroinflammatory processes are also gaining interest in the investigation of HD. PET imaging, *in vitro* studies and post-mortem analysis have reported an increase in microglial activation in HD which correlates with neurodegeneration and the severity of the condition (Ross and Tabrizi, 2011).

A clear parallel has been made between the graded progression of HD and decreasing CB_1 receptor density, particularly in the caudate nucleus, putamen and the globus pallidus (Glass *et al.*, 2000). Recently, it has been reported that CB_1 receptor down-regulation is specific to certain striatal subpopulation such as medium spiny neurons and neuropeptide Y/neuronal nitric oxide synthase-expressing interneurons (Horne *et al.*, 2013). Much work has been carried out in analysing the components of the eCB system in R6/2 transgenic mice, a common model of HD. A loss of CB_1 receptor density was found presymptomatically (Denovan-Wright and Robertson, 2000) as a result of mutant HTT-associated impairment of CB_1 receptor gene expression (Blazquez *et al.*, 2011). Genetic ablation of CB_1 receptors aggravated HD symptoms in mice while pharmacological activation by Δ^9-tetrahydrocannabinol (THC) attenuated symptomatology indicating that impairment of CB_1 receptor function may be a primary pathogenic feature of HD (Blazquez *et al.*, 2011). CB_2 receptor expression, however, was found to increase in the striatal microglia of these transgenic mice and HD patients and this may confer neuroprotection as genetic ablation of CB_2 receptors in transgenic HD mice results in increased microglial activation, aggravation of disease symptomatology and decreased life span (Palazuelos *et al.*, 2009). In the striatum, a reduction in AEA, 2AG and their respective biosynthetic enzymes N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D and diacylglycerol lipase activity was found (Bisogno *et al.*, 2008; Bari *et al.*, 2013). In the cortex, a reduction in 2AG levels was accompanied by an increase in AEA levels while their respective hydrolytic enzymes MGL, was decreased, and FAAH increased (Bisogno *et al.*, 2008; Bari *et al.*, 2013). These data clearly indicate the alteration of multiple components of the eCB system in the progression of HD.

Ageing

Ageing is a time-dependent and progressive deterioration of biological function that leads to death. The typical characteristics of ageing include a decrease in physiological capacity, reduced adaptive capabilities to changes in environment and an increased vulnerability to disease and death (Farooqui and Farooqui, 2009). Indeed, normal ageing presents many of the same pathophysiologic mechanisms found in neurodegenerative diseases and is believed to further aggravate disease progression. Many theories have been put forward to explain

the degenerating nature of age such as Ca^{2+} dyshomeostasis, oxidative stress and mitochondrial dysfunction but a consensus is yet to be reached.

The atrophy of the human brain with age is believed to be as a result of neurodegeneration and the loss of myelinated axons (Peters, 2002). Increased Ca^{2+} influx has been reported in the CA1 hippocampal region of aged rats, mediated by increased voltage-operated Ca^{2+} channels (Landfield and Pitler, 1984; Thibault and Landfield, 1996). Furthermore, intracellular Ca^{2+} regulation is altered in the aged brain. Efflux of Ca^{2+} through plasma membrane pumps as well as its uptake to mitochondrial sinks is affected by ageing (Michaelis *et al.*, 1996; Toescu, 2005) resulting in impairments in intracellular Ca^{2+} homeostasis. Oxidative stress is also prominent in the aged brain. Membrane lipid peroxidation coupled with oxidative damage of proteins and DNA is reported to increase with age (Sohal and Weindruch, 1996). Prolonged oxidative damage of mitochondrial DNA and lipids increases ROS generation resulting in further oxidative damage and vulnerability towards apoptosis (Paradies *et al.*, 2011). Chronic activation of microglia and alterations in their morphologic and immunophenotypic nature have also been reported. Normal ageing is believed to prime microglia for an exaggerated response, preferentially releasing proinflammatory cytokines. Increased basal levels of IL-6 and enhanced LPS-induced levels of IL-6 and IL-1β have been reported in the aged brain (Nakanishi and Wu, 2009).

Conflicting reports have emerged on the state of the eCB system as a result of ageing. Decreased CB_1 receptor density has been reported in the cerebellum and cerebral cortex of aged rats, while reduced CB_1 mRNA levels were found in the hippocampus and brainstem (Berrendero *et al.*, 1998). Conversely, Wang *et al.* (2003) have shown that there is no change in endocannabinoid tone or CB_1 receptor density in the hippocampus limbic forebrain, amygdala or cerebellum of aged mice. However, decreased coupling of CB_1 receptor to G-proteins was reported in the limbic forebrain.

The eCB system as a therapeutic target

The use of cannabinoids as a therapeutic remains a controversial issue. However, some success has been gained with the use of cannabinoid-based drugs to regulate appetite, sleep, pain and some psychotic tendencies. Dronabinol, derived from the phytocannabinoid THC, is beneficial in reducing anorexia, increasing body weight and improving behaviour in elderly AD patients (Volicer *et al.*, 1997). Dronabinol has more recently been assessed in a pilot study with AD patients where it improved nocturnal motor activity and reduced agitation and aggression, without undesired side effects (Walther *et al.*, 2006). In animal models of PD, THC attenuates motor inhibition and the loss of tyrosine hydroxylase-positive (dopamine producing) neurons. Furthermore, preclinical studies have investigated the anti-inflammatory and antioxidant capabilities of the phytocannabinoid cannabidiol (CBD), combined with THC, in the form of the cannabis-based medicine Sativex, which is already used as a therapeutic agent for multiple sclerosis. Sativex has been shown to successfully treat neuropathic pain and spasticity in multiple sclerosis patients (Nurmikko *et al.*, 2007; Notcutt *et al.*, 2012). Maresz *et al.* (2007) have demonstrated that CB_1 and CB_2 receptors are required for mediation of the immune system in animal models of multiple sclerosis. This combination is now emerging as a viable therapeutic option for PD and HD (Valdeolivas *et al.*, 2012; Fernandez-Ruiz *et al.*, 2013). The eCB system is believed to be a promising therapeutic target for delaying disease progression and ameliorating Parkinsonian symptoms (Garcia *et al.*, 2011).

Cannabinoids and neuroinflammation

Chronic neuroinflammation has been identified as a key mediator of neurodegeneration in AD, PD and HD. Various models of inflammation have reported the beneficial effects of cannabinoid action on reducing the inflammatory burden (Figure 2). The CB_2 selective agonist, JWH015 a synthetic cannabinoid, has been shown to reduce interferon-γ-induced up-regulation of CD40 in cultured mouse microglial cell through interfering with the JAK/STAT pathway. Furthermore, this intervention suppressed the production of proinflammatory cytokines and promoted the phagocytosis of Aβ (Ehrhart *et al.*, 2005). Mobilization of intracellular Ca^{2+} in response to ATP is a key mediator of microglial activation and inducer of the inflammatory response. CBD, along with the synthetic cannabinoids WIN 55212-2, a mixed CB_1/CB_2 receptor agonist and JWH-133, a CB_2 receptor selective agonist, were all shown to decrease the ATP-induced rise in intracellular Ca^{2+} concentration in the N13 microglial cell line (Martin-Moreno *et al.*, 2011). The effects of WIN 55212-2 and JWH-133 were fully reversed by the selective CB_2 antagonist, SR144528 (100 nM) indicating a CB_2 receptor-mediated effect. This antagonism was not seen in CBD-treated cells suggesting that CB_2-independent mechanisms may also be beneficial. Furthermore, the Aβ-induced rise in the proinflammatory cytokine IL-6 was reduced almost sixfold by 20 mg kg^{-1} CBD or 0.5 mg kg^{-1} WIN 55212-2 *in vivo* (Martin-Moreno *et al.*, 2011). Further *in vivo* studies using transgenic APP 2576 mice have reported that oral administration of JWH-133 (0.2 mg kg^{-1} day^{-1} for 4 months) decreased microglial activation, reduced COX-2 and TNF-α mRNA and reduced cortical levels of Aβ, with no impact on cognitive performance (Martin-Moreno *et al.*, 2012). A number of studies have identified the PPARγ as a key mediator of the cannabinoid anti-inflammatory effect. The PPAR family are a group of nuclear hormone receptors known to be involved in gene expression, lipid and glucose metabolism and the inflammatory response. In cultured rat astrocytes, reactive gliosis was induced by treatment with 1 mg mL^{-1} Aβ for 24 h and this was significantly reduced by CBD in a concentration-dependant manner. The beneficial effects of CBD were blunted by PPARγ antagonism by GW9662, suggesting the involvement of PPARγ in the anti-inflammatory effects of CBD (Esposito *et al.*, 2011). Hippocampal fractions isolated from adult rats injected with Aβ (10 μg mL^{-1}) to the CA1 region and treated with CBD (10 mg kg^{-1}) intraperitoneally for 15 days replicated the results found *in vitro*. Fakhfouri *et al.* (2012) have further elucidated the relationship between cannabinoids and PPARγ *in vivo* and have

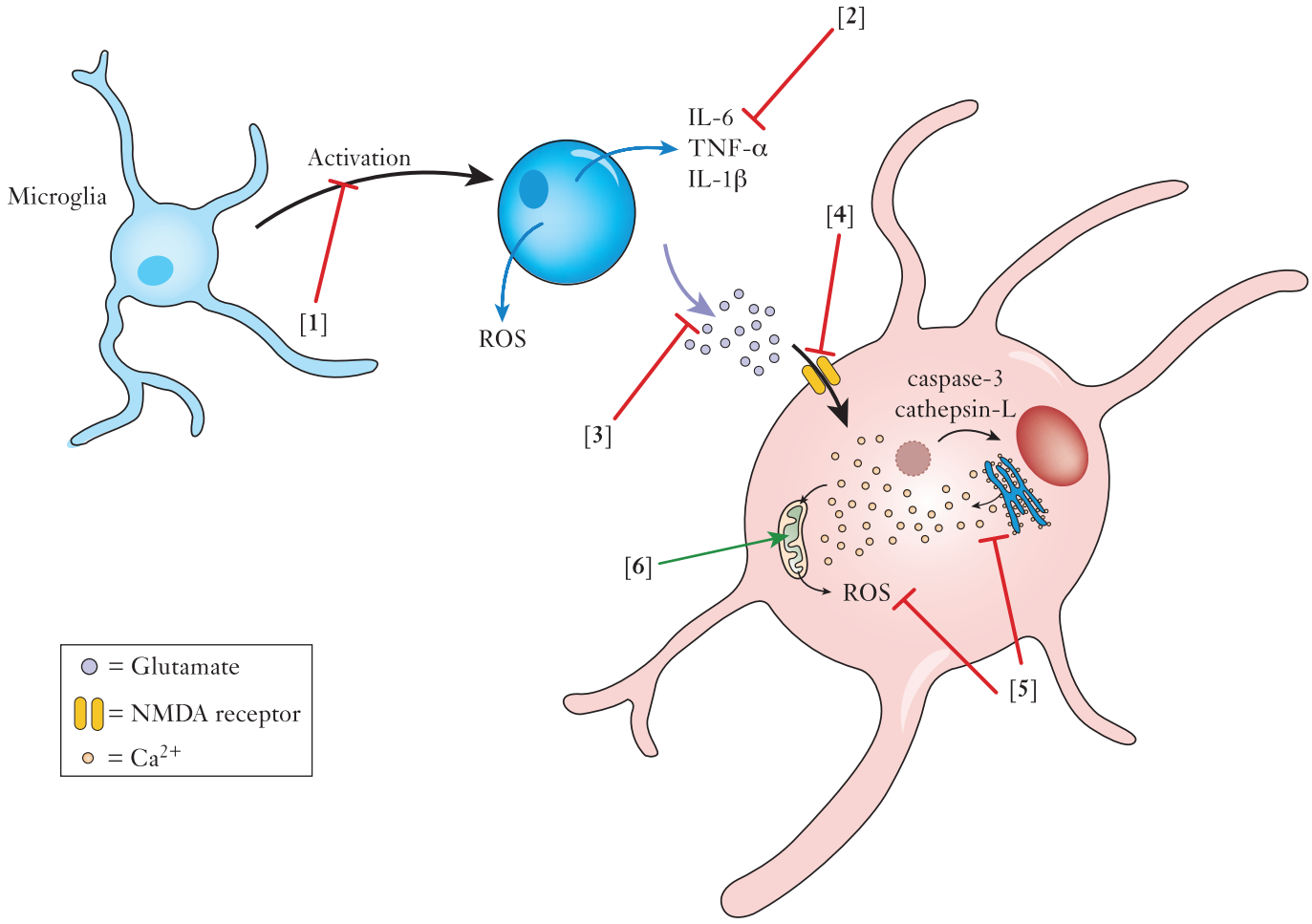

Figure 2

The beneficial effects from modulation of the eCB system showing [1] inhibition of microglial activation by CB_2 receptor agonists [2] reduction of proinflammatory cytokine release from activated microglia by CB_2 receptor agonists [3] inhibition of glutamate release from synaptosomes by mixed CB_1/CB_2 agonist [4] reduction of cell death by excitotoxicity through the inhibition of NO signalling and PKA in a CB_1 receptor-mediated fashion [5] reduction of the NMDA-mediated release of Ca^{2+} from intracellular stores resulting in mitochondrial dysfunction and ROS release by mixed CB_1/CB_2 agonists and [6] promotion of Ca^{2+} uptake into mitochondrial sinks.

identified that Aβ, when administered intrahippocampally to adult rats, increased PPARγ transcriptional activity and protein expression is observed which was further increased as a result of i.c.v. administration of WIN 55212-2. The beneficial effects caused by WIN 55212-2 were partially halted by the antagonism of PPARγ by i.c.v. administration of GW9662.

A common model for inflammation in the brain is the infusion of lipopolysaccharide into the fourth ventricle of young rats. Marchalant *et al.* (2007) have shown that daily i.p. injections of WIN 55212-2 (0.5 mg kg^{-1}) successfully reduced microglial activation in this model. However, when the dosing regimen was raised to 1 mg kg^{-1} day^{-1}, microglial activation was potentiated by WIN 55212-2. Normal aging has also been shown to cause neuroinflammation and in this context cannabinoids have also been shown to confer neuroprotection. In rats aged 23 months, WIN 55212-2 injections of 2 mg kg^{-1} i.p. for 4 weeks reduced the number of activated microglia in the hippocampus and dentate gyrus (Marchalant *et al.*, 2009). Interestingly, when incubated with the CB_1 receptor antagonists SR141716A and SR144528, WIN 55212-2 had no effect. The same treatment was found to decrease the mRNA levels of the proinflammatory cytokine IL-6 as well as the anti-inflammatory cytokine IL1-RA. Protein levels of TNF-α and IL-1β were decreased while an increase in IL1-RA was seen (Marchalant *et al.*, 2009). It is now clear that at multiple steps throughout the inflammatory process, cannabinoids can help to reduce the inflammatory burden during neurodegeneration.

Cannabinoids, excitotoxicity and mitochondrial dysfunction

The excitotoxic increase of intracellular Ca^{2+} concentration in neurodegenerative disorders can lead to the activation of apoptotic and proinflammatory pathways, as well as disrupting metabolic processes leading to cell death.

Endocannabinoids are most commonly synthesized in a Ca^{2+}-dependent fashion as a result of depolarization and are believed to help reduce excitotoxic damage. Indeed, AEA levels increase rapidly in the hippocampi of mice after administration of the excitotoxin kainic acid (KA) (30 mg kg^{-1}) and genetic ablation of the CB_1 receptor lowered the threshold for KA-induced seizures with more than 75% of CB_1-null mice dying within 1 h of KA injection. The neuroprotective capabilities of CB_1 are suggested to act primarily on principal glutamatergic neurons. Furthermore, the intracellular events involved in this neuroprotection have been attributed to the CB_1-mediated activation of ERKs and the subsequent expression of the immediate early genes c-*fos* and *zif268* (Marsicano *et al.*, 2003). Cannabinoid action, via CB_1 receptors in particular, regulates intracellular Ca^{2+} levels through a number of mechanisms (Figure 2). Exposure of murine cortical cultures to 20 μM NMDA for 24 h results in 70% cell death and WIN 55212-2 has been shown to decrease cell death though the inhibition of nitric oxide signalling and PKA (Kim *et al.*, 2006a). This CB_1 receptor-mediated regulation of PKA has long been associated with neuroprotection against excitotoxicity (Kim *et al.*, 2005). Another route for Ca^{2+} influx is through TNF-α mediated surface delivery of Ca^{2+} permeable AMPA receptors which contribute to *in vitro* excitotoxicity. WIN 55212-2 inhibits this TNF-α-induced increase in surface AMPA receptors and reduces excitotoxic damage in rat hippocampal cultures (Zhao *et al.*, 2010). TNF-α also increased PKA activity (Zhang *et al.*, 2002) which in turn can phosphorylate AMPA receptors at Ser^{845} and traffic them to the plasma membrane (Oh *et al.*, 2006). It is therefore believed that the inhibition of PKA by CB_1 receptor stimulation is beneficial in reducing excitotoxic damage by interfering with AMPA trafficking. Furthermore, the CB_1 receptor agonists, WIN 55212-2 and AEA, inhibited glutamate release from rat hippocampal synaptosomes which would reduce NMDA activation and the resulting Ca^{2+} influx (Wang, 2003). As well as reducing the influx of Ca^{2+}, cannabinoid action regulates intracellular Ca^{2+} homeostasis. WIN 55212-2 reduced the NMDA-mediated release of Ca^{2+} from intracellular stores in cultured rat hippocampal cells thereby increasing cell viability. This involved the CB_1-mediated reduction in cAMP-dependant PKA phosphorylation of ryanodine receptors (Zhuang *et al.*, 2005). Furthermore, in high-excitability conditions CBD (1 μM) increased the levels of Ca^{2+} uptake by mitochondria in cultured rat hippocampal neurons (Ryan *et al.*, 2009). Intense elevation of intracellular Ca^{2+} is known to induce proapoptotic cascades. Activation of cytosolic calpains by Ca^{2+} results in permeabilization of the lysosome and the release of proapoptotic proteins such as the caspase and cathepsin family (Yamashima and Oikawa, 2009). Noonan *et al.* (2010) have shown *in vitro* that increasing endocannabinoid tone through inhibiting FAAH degradation of 2AG prevented the Aβ-induced increase in calpain activation, permeabilization of the lysosome and the resulting neurodegeneration.

Mitochondrial dysfunction has also been addressed by cannabinoid research (Figure 2). Oxygen-glucose deprivation/reoxygenation of neuronal-glial cultures causes mitochondrial depolarization and oxidative stress. In rat neuronal-glial cultures, the cannabinoid *trans*-caryophyllene (1 μM) has been shown to increase neuronal viability through a reduction of mitochondrial depolarization and oxidative stress, and by increasing the expression of BDNF. This study has identified CB_2 receptor activation as a mechanism for enhancing the phosphorylation of AMP-activated protein kinase and cAMP responsive element-binding protein and increasing expression of the CREB target protein, BDNF (Choi *et al.*, 2013). In an *in vitro* model of PD, 1-methyl-4-phenylpyridinium iodide, paraquat and lactacystin were used to inhibit mitochondrial function, generate free radicals and inhibit the ubiquitin proteasome respectively. These treatments resulted in cell death brought on by ROS generation, caspase-3 activation and cytotoxicity. THC (10 μM) was shown to reduce these effects in human neuroblastoma cells (SH-SY5Y) while increasing cell viability. This result was not reproduced by the CB_1 receptor agonist WIN 55212-2 (1 μM) but was blocked by inhibition of PPARγ, the activity of which was increased by THC treatment (Carroll *et al.*, 2012).

Cannabinoids and adult neurogenesis

Adult neurogenesis is the process by which new neurons are generated and integrated into the developed brain. Regulation of neurogenesis is strictly controlled through a number of different factors such as adrenal and sex hormones, neurotransmitter systems, trophic factors and inflammatory cytokines. The formation of new neurons and neuronal connections may prove vital to sustaining neuronal function in neurodegenerative disorders where neurogenesis is impaired such as AD and HD (Molero *et al.*, 2009; Crews *et al.*, 2010). The eCB system has been closely linked to the process of adult neurogenesis. DGLα and DGLβ synthesize the endocannabinoid 2AG, and DGLα and DGLβ null mice have an 80 and 50% reduction in 2AG respectively. These transgenic mice were shown to have impaired neurogenesis, believed to be as a result of the loss of 2AG-mediated transient suppression of GABAergic transmission at inhibitory synapses (Gao *et al.*, 2010). Furthermore, mice lacking CB_1 receptors displayed an almost 50% reduction in neurogenesis in the dentate gyrus and subventricular zone when compared to wild type. In line with this, the mixed CB_1/CB_2 receptor agonist WIN 55212-2 enhanced BrdU incorporation into murine neuronal culture in a CB_1 receptor-mediated fashion (Kim *et al.*, 2006b). CB_1 receptor-mediated stimulation of adult neurogenesis has been shown to act through its opposition of the antineurogenic effect of nitric oxide (Kim *et al.*, 2006b; Marchalant *et al.*, 2009). Neuronal precursor cell proliferation and the number of migrating neurons have been shown to increase in neurogenic regions in response to seizure, ischaemia and excitotoxic and mechanical lesions indicating a possible contributing factor in the repair of lesioned circuits (Gould and Tanapat, 1997; Arvidsson *et al.*, 2001; Parent *et al.*, 2002; Lie *et al.*, 2004). KA-induced neural progenitor proliferation is reduced in CB_1 receptor deficient mice as well as in wild-type mice administered with the selective CB_1 receptor antagonist SR141716A. This effect was attributed to the CB_1-dependent expression of basic fibroblast growth factor and epidermal growth factor (Aguado *et al.*, 2007). BDNF is vital for the survival of new neurons and is significantly reduced in neurodegenerative conditions such as HD (Zuccato and Cattaneo, 2007). De March *et al.* (2008) have shown that 2 weeks post-excitotoxic lesion in rats, tran-

sient up-regulation of BDNF coincides with higher binding activity and protein expression of CB_1 receptor. This is believed to be an attempt to rescue the striatal neuronal population. In a reciprocal fashion, BDNF (10 ng mL^{-1}) was shown *in vitro* to increase neuronal sensitivity to the endocannabinoids 2AG and noladin ether as measured by the phosphorylation of Akt (Maison *et al.*, 2009). Indeed, CB_1 receptor activation has been implicated in neural precursor proliferation and neurogenesis while CB_1 and CB_2 receptor activation is involved in neural progenitor cell proliferation, both of which are vital to the generation and survival of new neurons (Palazuelos *et al.*, 2006; Aguado *et al.*, 2007).

Summary

Neurodegenerative diseases are a heterogeneous group of age-related disorders. While AD, PD and HD have a variety of different genetic and environmental causes, the principal factor involved is the progressive and severe loss of neurons. It is widely accepted that neuroinflammation, excitotoxicity and oxidative stress are key mediators of neurodegeneration, and impaired neurogenesis as well as reduced trophic support leave neuronal systems unable to cope. The eCB system is emerging as a key regulator of many neuronal systems that are relevant to neurodegenerative disorders. Activation of CB_1 receptors regulates many neuronal functions such as Ca^{2+} homeostasis and metabolic activity while the CB_2 receptor is mainly involved in regulating the inflammatory response.

Here, we have put forward the mechanisms of neurodegeneration in the three most prevalent neurodegenerative disorders, AD, PD and HD, as well as showing the vulnerability of the brain as a result of age. We have summarized evidence of the beneficial role of modulating the cannabinoid system to reduce the burden of neurodegeneration. Pharmacological modulation of the eCB system (Figure 3) has been shown to reduce chronic activation of the neuroinflammatory response, aid in Ca^{2+} homeostasis, reduce oxidative stress, mitochondrial dysfunction and the resulting proapoptotic cascade, while promoting neurotrophic support.

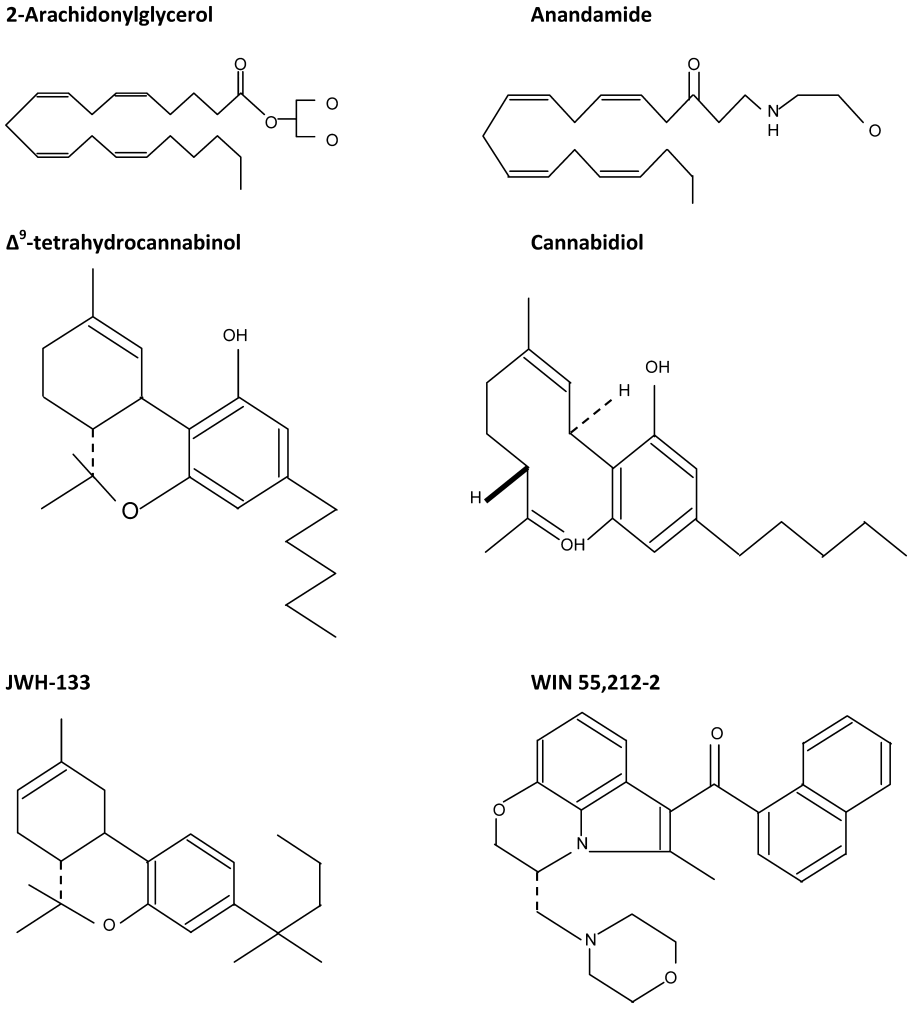

Figure 3
Chemical structures of the common CB receptor agonists.

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Conflict of interest

There are no conflicts of interest associated with this paper.

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