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The Endocannabinoid System and Oligodendrocytes in Health and Disease

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Cannabinoid-based interventions are being explored for central nervous system (CNS) pathologies such as neurodegeneration, demyelination, epilepsy, stroke, and trauma. As these disease states involve dysregulation of myelin integrity and/or remyelination, it is important to consider effects of the endocannabinoid system on oligodendrocytes and their precursors. In this review, we examine research reports on the effects of the endocannabinoid system (ECS) components on oligodendrocytes and their precursors, with a focus on therapeutic implications. Cannabinoid ligands and modulators of the endocannabinoid system promote cell signaling in oligodendrocyte precursor survival, proliferation, migration and differentiation, and mature oligodendrocyte survival and myelination. Agonist stimulation of oligodendrocyte precursor cells (OPCs) at both CB_1 and CB_2 receptors counter apoptotic processes via Akt/PI3K, and promote proliferation via Akt/mTOR and ERK pathways. CB_1 receptors in radial glia promote proliferation and conversion to progenitors fated to become oligodendroglia, whereas CB_2 receptors promote OPC migration in neonatal development. OPCs produce 2-arachidonoylglycerol (2-AG), stimulating cannabinoid receptor-mediated ERK pathways responsible for differentiation to arborized, myelin basic protein (MBP)-producing oligodendrocytes. In cell culture models of excitotoxicity, increased reactive oxygen species, and depolarization-dependent calcium influx, CB_1 agonists improved viability of oligodendrocytes. In transient and permanent middle cerebral artery occlusion models of anoxic stroke, WIN55212-2 increased OPC proliferation and maturation to oligodendroglia, thereby reducing cerebral tissue damage. In several models of rodent encephalomyelitis, chronic treatment with cannabinoid agonists ameliorated the damage by promoting OPC survival and oligodendrocyte function. Pharmacotherapeutic strategies based upon ECS and oligodendrocyte production and survival should be considered.

Keywords: 2-arachidonoylglycerol (2-AG), CP55940, HU210, multiple sclerosis (MS), neural stem cells (NSCs), oligodendrocyte precursor cells (OPCs), SR141716, WIN55212-2

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INTRODUCTION

Phytocannabinoid use in management of multiple sclerosis (MS) symptoms (Consroe et al., 1997) has led to clinical trial evidence for the efficacy of tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (Sativex) in controlling spasticity and pain (Wade et al., 2010; Giacoppo et al., 2017). MS, a demyelinating disease characterized by persistent neuroinflammation and progressive central nervous system (CNS) demyelination (Kutzelnigg and Lassmann, 2014), is only one of many demyelinating neurodegenerative diseases involving oligodendrocytes, the myelinating cells of the CNS. The endocannabinoid system (ECS) (Howlett et al., 2002; Pertwee et al., 2010) involvement in neuroprotection (Panikashvili et al., 2001; van der Stelt and Di Marzo, 2005; Martinez-Orgado et al., 2007; Sanchez and García-Merino, 2012) and the immune system in CNS diseases (Croxford and Yamamura, 2005; Rom and Persidsky, 2013; Chiurchiu et al., 2015; Olah et al., 2017) have been reviewed. Here, we address ECS effects on oligodendrocytes and their precursors, in order to evaluate the evolving research around cannabinoids in healthy development and in demyelinating neurodegenerative diseases.

CANNABINOIDS, OLIGODENDROCYTE PRECURSOR CELLS AND OLIGODENDROCYTES IN HEALTH

Oligodendrocytes, myelinating cells of the vertebrate CNS, enable neurons to signal more energy-efficiently and at higher speed due to saltatory conduction, and maintain axonal integrity through trophic and metabolic support (Michalski and Kothary, 2015; Simons and Nave, 2015). Generation of oligodendrocytes is an ongoing process, starting in embryonic development and continuing throughout life (Baumann and Pham-Dinh, 2001; Trotter et al., 2010; Dimou and Gallo, 2015; Michalski and Kothary, 2015). In brief, oligodendrocyte precursor cells (OPCs), also known as NG2-glia, O-2A progenitors, polydendrocytes, or synantocytes, arise from neural stem cells (NSCs), and preferentially populate distinct areas of the developing CNS in lineage- and time-specific waves (Richardson et al., 2006). Upon arrival, many undergo apoptosis, while many others either mature into myelinating oligodendrocytes or persist as progenitors and remain capable of self-renewal as well as production of mature oligodendrocytes well into adulthood (Dawson et al., 2003). These progenitors become distributed throughout gray and white matter and maintain their respective domains by continuously sampling their environment, able to expand to neighboring areas vacated by other OPCs (Kirby et al., 2006; Hughes et al., 2013).

Despite this interchangeability, it is becoming increasingly clear that oligodendrocyte precursors represent a heterogeneous group, distinct in their origin, signaling, and ability to revert differentiation to produce neurons and astrocytes (Trotter et al., 2010; Dimou and Gallo, 2015; Nishiyama et al., 2016; Vigano and Dimou, 2016). Regardless of the differences, all OPCs rely on the processes of proliferation, migration, and differentiation to become mature, functioning oligodendrocytes (Baumann and Pham-Dinh, 2001; Miron et al., 2011; Dubois et al., 2014; Sampaio-Baptista and Johansen-Berg, 2017). As these steps are differentially regulated (Marinelli et al., 2016), it is important to look at the effects of cannabinoid agonists on each (see **Figure 1**).

Survival

Reports of cannabinoid receptors in newborn rat white matter by immunostaining (Berrendero et al., 1999), led to subsequent studies exploring cells *in vitro*. OPCs were isolated from newborn Wistar rat forebrains and expanded by incubation in serum-free defined media with supplements including platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) (Molina-Holgado et al., 2002). OPCs could be differentiated into myelin basic protein (MBP)-producing mature oligodendrocytes by incubation in serum-free defined media in which PDGF and FGF were replaced by triiodothyronine (T3). As ascertained by RT-PCR, Western blot, and immunohistochemistry, both OPC and mature oligodendrocytes expressed both CB_1 and CB_2 cannabinoid receptors (Molina-Holgado et al., 2002). Because activation of cannabinoid receptors confers neuroprotection (van der Stelt and Di Marzo, 2005; Martinez-Orgado et al., 2007; Sanchez and García-Merino, 2012), the influence of cannabinoid agonists on viability of OPCs was investigated. Upon incubation in serum-free DMEM/F12 media for 12 h, nearly half of OPCs underwent apoptosis (Molina-Holgado et al., 2002). However, most were rescued by concurrent supplementation with CB_1 agonist arachidonyl-2′-chloroethylamide (ACEA, 25 nM) or CB_1/CB_2 agonists WIN55212-2 (25 nM) or HU210 (500 nM). Co-treatment with CB_1 antagonist SR141716 (1 μM) abolished the anti-apoptotic effect of ACEA, but not of WIN55212-2 or HU210. Both SR141716 plus CB_2 antagonist SR144528 (1 μM) were required to nullify the pro-survival effect of HU210. These results show that the activation of either CB_1 or CB_2 receptors

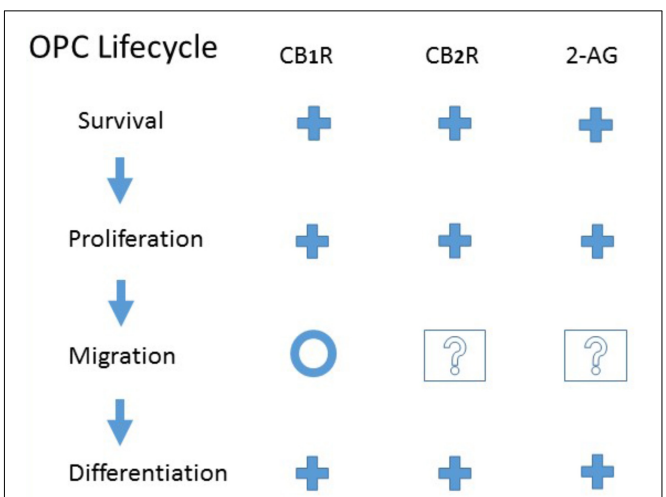

FIGURE 1 | Evidence for CB_1 or CB_2 receptor activation or endogenous 2-Arachidonoylglycerol modulation of Oligodendrocyte Precursor Cell Life Cycle. **+**, Promote; **O**, No effect; **?**, Unknown. See the text for details and original references.

could be sufficient in promoting OPC survival under conditions of trophic factor deprivation. The mechanism includes activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, a known modulator of OPC survival (Vemuri and McMorris, 1996; Ebner et al., 2000). Applying each of the three agonists correlated with increased Akt phosphorylation, while co-treatment with PI3K inhibitors LY294002 (10 μM) or wortmannin (100 nM) nullified the effects of WIN55212-2 and HU210 on both Akt phosphorylation and cell survival (Molina-Holgado et al., 2002). Thus, stimulation of Akt/PI3K pathways via CB_1 and CB_2 receptors present in OPCs can curtail apoptotic processes and promote survival.

Proliferation

Molina-Holgado and colleagues explored the ability of the endocannabinoid system to modulate OPC proliferation and self-renewal (Gomez et al., 2015). In cultured OPCs (Molina-Holgado et al., 2002), 24-h blockade of CB_1 receptors with AM281 (1 μM), CB_2 receptors with AM630 (1 μM), or synthesis of 2-arachidonoylglycerol (2-AG) by diacylglycerol lipase α and β (DAGLs) with RHC80267 (5 μM), led to reduction in PDGF/FGF-stimulated OPC proliferation. In the absence of PDGF and FGF, OPC proliferation increased in response to 24-h application of CB_1 agonist ACEA (0.5 μM), CB_2 agonist JWH133 (0.5 μM), 2-AG (1 μM), or JZL184 (1 μM) which blocks the 2-AG metabolizing enzyme monoacylglycerol lipase (MAGL). The effect depended on phosphorylation of Akt and mammalian target of rapamycin (mTOR), as their blockers LY294002 (5 μM) and rapamycin (3 nM), respectively (24 h), decreased the proliferative effects of ACEA, JWH133, and JZL184. Extracellular signal regulated-kinase (ERK) 1/2 phosphorylation was decreased in cells treated with the 2-AG synthesis inhibitor RHC80267, as well as with CB_1 and CB_2 antagonists AM281 and AM630, respectively. These results extend the impact of cannabinoid receptor activation from promoting OPC survival (Molina-Holgado et al., 2002) to increasing proliferation, while also implicating cannabinoid-mediated Akt/mTOR and ERK pathways, known to play a role throughout OPC development to myelination (Gonsalvez et al., 2016; Figlia et al., 2018).

Migration

NSCs of postnatal subventricular zone (SVZ) emigrate the neurogenic niche in the form of neuroblasts or OPCs (Marshall et al., 2003). In rat CNS, both myelination and SVZ gliogenesis peak at postnatal day (PD) 15 (Bjelke and Seiger, 1989; Hamano et al., 1996), making this an optimal time-point for exploring cannabinoid effects on OPC proliferation and migration from postnatal SVZ. Immunohistochemical analysis of PD7 and PD15 Wistar rat brain revealed that the CB_1 receptor was primarily expressed by radial glia (Aré-Martín et al., 2007), which can transform to NSCs (Merkle et al., 2004). However, the CB_2 receptor co-stained with poly-sialylated neural cell adhesion molecule (PSA-NCAM) (Aré-Martín et al., 2007), a marker of migration in OPCs and neuroblasts (Doetsch et al., 1999; Menn et al., 2006). The CB_1 agonist ACEA (escalating dose 1.25–2.5 mg/kg, SC daily PD1 to PD14) increased PD15 SVZ staining for 4A4, a marker of radial glia proliferation (Howard et al., 2006), and Olig2 (Aré-Martín et al., 2007), which is expressed in glial precursors fated to become oligodendrocytes (Mitew et al., 2014). Similar treatment with CB_2 agonist JWH056 (escalating dose 2.5–5.0 mg/kg, SC) increased SVZ staining for PSA-NCAM. Activation of both CB_1 and CB_2 receptors by WIN55212-2 (escalating dose 2.5–5.0 mg/kg, SC) increased MBP staining in the external capsule, which was inhibited below control values by concurrent administration of either SR141716 (CB_1) or SR144528 (CB_2) antagonists (escalating dose 2–4 mg/kg, SC) (Aré-Martín et al., 2007). These results support the involvement of CB_1 receptors in radial glia proliferation and conversion to oligodendrocytes, but CB_2 receptors in OPC migration, leading to functional oligodendrocytes in neonatal myelination.

Studies have examined cannabinoid agonist impact on rodent SVZ proliferation beyond the newborn stage. In juvenile (PD35-PD48) Lewis rats, WIN55212-2 (2 mg/kg, IP bid, 2-weeks) increased SVZ BrdU staining, without changing the ratio of progenitors committed to neuronal or OPC fates, or the number of cells undergoing caspase-3 mediated apoptosis (Bortolato et al., 2014). These results are consistent with findings that genetic ablation of CB_1 receptors decreased progenitor proliferation in adult mouse SVZ (Jin et al., 2004; Kim et al., 2006). In adult mice, cannabidiol (CBD; 3 mg/kg IP daily for 14 days) increased SVZ proliferative markers Ki67 and BrdU staining (Schiavon et al., 2016). However, CBD at 30 mg/kg decreased proliferation markers (Schiavon et al., 2016), highlighting the importance of dose.

Differentiation to Mature Oligodendrocytes

Molina-Holgado et al. (2002) investigated OPC differentiation using isolated OPCs differentiated with T3 (30 ng/mL, 48 h) in the absence of PDGF/FGF (Gomez et al., 2011). Activating either cannabinoid receptor (ACEA for CB_1 and JWH133 for CB_2, 0.5 μM) increased OPC branching and accumulation of MBP (Western blot). The CB_1/CB_2 agonist HU210 (0.5 μM) evoked the same responses, which could be abolished by either AM281 (CB_1) or AM630 (CB_2; 1 μM). The mechanism for HU210-mediated OPC arborization and production of MBP involved PI3K/Akt and mTOR pathways, as these effects were blocked with LY290042 (2.5 μM) and rapamycin (0.75 nM), respectively. Gomez et al. (2010) found the Western blot level of DAGLs to be higher in OPCs, whereas the level of MAGL was higher in mature oligodendrocytes, culminating in the finding that OPCs accumulated a greater content of 2-AG than mature oligodendrocytes. Levels of anandamide (AEA) were low and did not differ between the cell stages (Gomez et al., 2010). Differentiation, denoted by branching morphology and levels of MBP after 96 h, was increased by MAGL inhibitor JZL184 (1 μM), and decreased by DAGL inhibitor RHC80267 (5 μM), with exogenous 2-AG (2 μM) abolishing the effect of blocking its synthesis. Inhibition of the ERK pathway by the MEK blocker PD98059 (10 μM) abolished Western blot staining for MBP, implicating the ERK pathway in differentiation. In a CB_1

receptor mRNA-expressing human oligodendrocyte precursor line HOG16, WIN55212-2 (1 μM, 24 h) increased MBP mRNA expression, particularly in cells treated with T3-supplemented differentiating medium (Tomas-Roig et al., 2016). Collectively, these studies suggest that endogenous 2-AG in OPCs triggers the ERK pathway, leading to the maturation of arborized, MBP-producing oligodendrocytes.

THE ECS AND OPCS-OLIGODENDROCYTES IN MODELS OF DISEASE

The role of cannabinoids in OPCs and oligodendrocytes under stress has been evaluated in models of insults such as excitotoxicity (Shouman et al., 2006; Bernal-Chico et al., 2015), reactive oxygen species (ROS) toxicity (Ribeiro et al., 2013), KCl-induced depolarization (Mato et al., 2009), as well as in models of stroke (Fernández-López et al., 2010; Sun et al., 2013a,b), spinal cord injury (SCI) (Marsicano et al., 2003; Arevalo-Martin et al., 2010), and demyelination (Solbrig et al., 2010; Ribeiro et al., 2013; Bernal-Chico et al., 2015; Wen et al., 2015; Feliu et al., 2017).

Cannabinoids and OPC-Oligodendrocytes in Cytopathology Models

The ability of cannabinoid agonists to protect neurons from excitotoxicity is well known (Shen and Thayer, 1998; Hansen et al., 2002; Marsicano et al., 2003; van der Stelt and Di Marzo, 2005). Likewise, ECS involvement in OPC and oligodendrocyte excitotoxicity has recently been explored (Shouman et al., 2006; Bernal-Chico et al., 2015). Newborn (PD5) Sprague Dawley rats received AMPA/kainate agonist bromowillardine (15 μg, IC), immediately followed by AEA (10 mg/kg, IP) (Shouman et al., 2006). AEA significantly increased OPC density within the periventricular white matter lesion after 1 day, and increased MBP staining after 5 days. The ECS in excitotoxicity was also investigated in mature oligodendrocytes (Bernal-Chico et al., 2015). OPCs were isolated from the cerebral cortex of newborn wildtype or CB_1-KO Sprague-Dawley rats and differentiated with T3 minus growth factors. Oligodendrocytes were exposed to AMPA plus cyclothiazide (10 μM:100 μM) for 15 min, resulting in excessive cytosolic calcium, reactive oxygen species (ROS) production, and cell death (Bernal-Chico et al., 2015). A 30-min pretreatment with CB_1 agonist ACEA (25 nM), endocannabinoids AEA or 2-AG (1 μM), or MAGL inhibitor JZL184 (25 nM) reduced cell death (Bernal-Chico et al., 2015). No protection occurred in oligodendrocytes lacking CB_1 receptors, or pretreated with CB_2 agonist JWH133 (25 nM) or the inhibitor of AEA metabolizing enzyme fatty acid amide hydrolase (FAAH) URB597 (10 nM – 1 μM). These findings implicate endocannabinoids and CB_1 receptors in improved viability of oligodendrocytes in excitotoxic conditions.

Due to their high metabolic demand, oligodendrocytes are vulnerable to elevated levels of ROS (McTigue and Tripathi, 2008; Roth and Nunez, 2016), although less so than their precursors (Back et al., 1998). To investigate how cannabinoid agonists affect oligodendrocyte survival, precursors isolated from PD2-PD3 Sprague-Dawley rat brains were differentiated by T3 plus ciliary neurotrophic factor for 2 weeks, and exposed to a peroxynitrite generator SIN-1 (1 mM) (Zhang et al., 2006, 2007) for 2 h (Ribeiro et al., 2013). Concurrent treatment with CB_1/CB_2 agonists CP55940 (1–3 μM), WIN55212-2 (10 μM), or anandamide/THC hybrid CB52 (3–10 μM), reduced cell death. CB52's mechanism included activation of CB_2 receptors, as CB_2 antagonist AM630 (10 μM), but not CB_1 antagonist AM281 (10 μM) reduced its effectiveness, while CB_2 agonists AM1241 and JWH015 partially replicated it (Ribeiro et al., 2013).

The ability of CB_1 agonists to inhibit depolarization-dependent calcium channels, as observed in neurons (Howlett et al., 2002), was explored in oligodendrocytes (Mato et al., 2009). Precursors were isolated from optic nerve of PD12 Sprague-Dawley rats, differentiated by 2-day incubation in defined media, and exposed to KCl (50 mM, 1 min) to induce depolarization (Mato et al., 2009). Resulting calcium influx was decreased by CB_1 agonist ACEA (1 μM) or CB_1/CB_2 agonists THC (3 μM), CP55940 (3 μM), AEA (3 μM) or 2-AG (3 μM), but not CB_2 agonist JWH133 (3 μM). Oligodendrocytes from CB_1-KO mice were less responsive to AEA and ACEA, although not completely unresponsive, suggesting other targets exist such as transient receptor potential vanilloid receptor-1 (TRPV1) (Ross, 2003; Ruparel et al., 2011), expressed in oligodendrocytes (Gonzalez-Reyes et al., 2013). In contrast, CBD (100 nM, 20–30 min) reduced oligodendrocyte viability, in part through an increase in intracellular calcium (Mato et al., 2010). CBD (1 μM, 10 min) increased oligodendrocyte production of ROS, and induced apoptosis through mitochondria-mediated activation of caspase-8 and -9 and their downstream effector caspase-3, as well as poly-(ADP ribose) polymerase-1 (PARP-1), triggered by caspase-independent mitochondrial apoptosis-induced factor (AIF) (Hong et al., 2004).

ECS and Oligodendrocytes in Stroke and Traumatic Injury

Oligodendrocytes are vulnerable to ischemic conditions and their replacement via OPCs has been found to aid recovery (Dewar et al., 2003; Zhang et al., 2013, 2016). The impact of the ECS was studied in adult (Sun et al., 2013a,b) and neonatal (Fernández-López et al., 2010) rat models of middle cerebral artery occlusion (MCAO). In transient (2 h) MCAO (Sun et al., 2013a), WIN55212-2 (9 mg/kg, IP immediately after reperfusion and daily) increased staining for penumbral OPCs and mature oligodendrocytes at 4, 7, and 14 days post ischemia (DPI), and penumbral myelin density at 14 DPI. WIN55212-2 reduced penumbral expression of caspase-3 in OPCs at 7 DPI, which correlated with reduced ERK1/2 phosphorylation. These effects were ameliorated by CB_1 antagonist SR141716 (1 mg/kg, IV). In adult male Sprague-Dawley rats, WIN55212-2 (9 mg/kg, IV) was given within 2 h after permanent MCAO, with anoxia damage quantitated after 24 h (Sun et al., 2013b). WIN55212-2 treatment increased OPC proliferation within the penumbra and ipsilateral SVZ, and decreased penumbral OPC expression of tau-1, an oligodendrocyte marker of ischemic

stress (Dewar and Dawson, 1995; Irving et al., 1996). Both effects were partially due to CB_1 receptor activation (Sun et al., 2013b). In a permanent MCAO model in neonatal PD7 Wistar rats (Fernández-López et al., 2010), WIN55212-2 (1 mg/kg, IP daily for 7 days) increased ipsilateral SVZ OPC proliferation and number of penumbral OPCs at 7 DPI. WIN55212-2 increased the number of mature penumbral oligodendrocytes at 14 and 28 DPI, and accelerated complete MBP recovery. Consistent with earlier findings (Goncalves et al., 2008; Bortolato et al., 2014), WIN55212-2 increased SVZ OPC proliferation even in the absence of ischemia. Although preclinical results appear promising for cannabinoid pharmacotherapies for anoxic demyelination, SVZ neurogenic response to stroke varies greatly between rodents and humans (Kahle and Bix, 2013).

The endocannabinoid 2-AG has been shown to be neuroprotective after traumatic brain injury (Panikashvili et al., 2001), and 2-AG is elevated after spinal trauma (Marsicano et al., 2003; Garcia-Ovejero et al., 2009). Thus, the impact of 2-AG on oligodendrocyte survival was explored in a model of contusive SCI generated by a dropped weight in male adult Wistar rats (Arevalo-Martin et al., 2010). 2-AG (5 mg/kg, IP 30 min after injury) preserved myelin integrity and reduced oligodendrocyte death at the epicenter (1 day post-injury), with the same effects seen as far as 10 mm rostral of epicenter (1 and 7 days post-injury). Co-administration of both CB_1 and CB_2 antagonists (AM281 and AM630, respectively; 3 mg/kg, IP), but not by either alone, could reverse the effects of 2-AG. These results support the idea that improved oligodendrocyte survival and preserved white matter integrity underlie the cannabinoid-mediated improvement in SCI recovery (Arevalo-Martin et al., 2012).

ECS and Models of Demyelination

To investigate demyelination in a mouse model of experimental autoimmune encephalomyelitis (EAE), PD49 or PD56 C57BL/6 mice received a single injection of myelin oligodendrocyte glycoprotein peptide (MOG 35-55), followed by injections of pertussis toxin on the day of MOG inoculation and again 2 days afterward (Bernal-Chico et al., 2015). MAGL inhibitor JZL184 (8 mg/kg, IP daily for 3 weeks, starting on day 14 postinoculation) ameliorated the reduction in spinal cord white matter staining (Bernal-Chico et al., 2015). Similar results in the EAE model were achieved by THC (Moreno-Martet et al., 2015), CBD (Giacoppo et al., 2015), cannabigerol quinone (Carrillo-Salinas et al., 2014), and CB_2 agonist HU308 (Shao et al., 2014). The effects of CB52 on demyelination EAE (Ribeiro et al., 2013) showed that when initiated before symptom development (3 days) or after clinical disease onset (12 or 20 days), CB52 (2 mg/kg, IP daily) ameliorated the loss of staining for spinal cord myelin and mature oligodendrocytes at day-30. In contrast to CB52's action on cultured oligodendrocytes *in vitro* (Ribeiro et al., 2013), both of its effects *in vivo* were blocked by CB_1 antagonist AM281 (2 mg/kg), but not by CB_2 antagonist AM630 (2 mg/kg).

Microglia are an integral part of demyelinating diseases' neuroimmune complex (Gonzalez et al., 2014). In microglia, CB_1 receptors are expressed at low levels constitutively; however, CB_2 receptors become upregulated when microglia become activated (Cabral et al., 2008). Endocannabinoids 2-AG and AEA have been shown to drive microglia toward alternative, anti-inflammatory activation state, M2, and away from classic, pro-inflammatory polarization, M1, which in turn causes microglia to upregulate its own 2-AG synthesizing enzymes (Mecha et al., 2015). Because microglial 2-AG has been shown to promote OPC differentiation (Miron et al., 2013), blocking its degradation could be of use in counteracting demyelination. This has been explored in a mouse model of EAE (Wen et al., 2015), by inhibiting the 2-AG hydrolyzing microglial enzyme ABHD6 (Li et al., 2007; Marrs et al., 2010; Murataeva et al., 2014) with WWL70 (10 mg/kg, IP daily starting at the onset of clinical symptoms on day-11 postinoculation). WWL70 increased cerebral 2-AG at day-21, and ameliorated the loss of staining of spinal cord myelin and mature oligodendrocytes in wildtype mice on day-28 (Wen et al., 2015). These results were not seen in CB_2-KO mice, nor when WWL70 was co-administered with CB_2 antagonist AM630 (3 mg/kg), suggesting that microglial 2-AG accumulation is dependent upon CB_2 receptor signaling. Co-administration with CB_1 antagonist AM281 failed to interfere with WWL70's effects.

OPC gliogenesis in Borna Disease Virus (BDV) encephalomyelitis, generated in PD28 male Lewis rats (Solbrig et al., 2010), demonstrated that WIN55212-2 (1 mg/kg, IP daily for 7-days starting 1 week after virus inoculation) increased OPC proliferation in striatum, decreased apoptosis of proliferating cells, skewed precursor differentiation away from astrocytes and toward oligodendrocytes, and promoted OPC maturation. In uninfected controls, WIN55212-2 increased proliferation in both PFC and striatum.

In Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD), PD28 female CJL/J mice received an intracerebral injection of the Daniel strain virus (Feliu et al., 2017). When started after symptom onset at day-75, a 10-day treatment with MAGL inhibitor UCM03025 (5 mg/kg, IP) increased the spinal cord populations of both mature oligodendrocytes and OPCs, and restored MBP level to that of sham controls (Feliu et al., 2017).

In the cuprizone oligodendrotoxic model (Bernal-Chico et al., 2015), PD56 C57BL/6 mice were fed a cuprizone-supplemented diet (0.3%) for 3 weeks. Concurrent MAGL inhibitor JZL184 (8 mg/kg, IP daily) ameliorated cuprizone-induced reduction in corpus callosum MBP staining (Bernal-Chico et al., 2015), implicating 2-AG-mediated protection.

Seizures are known to accompany demyelination in experimental models (DePaula-Silva et al., 2017; Lapato et al., 2017; Spatola and Dalmau, 2017) as well as MS (Koch et al., 2008; Anderson and Rodriguez, 2011; Sponsler and Kendrick-Adey, 2011). The ECS promotion of OPCs (Solbrig et al., 2010; Feliu et al., 2017) and mature oligodendrocytes (Ribeiro et al., 2013; Wen et al., 2015; Feliu et al., 2017) may counteract demyelination observed in patients with intractable epilepsy (Hu et al., 2016).

CBD and OPCs in Inflammation

CBD has been promoted for potential therapeutic applications (Devinsky et al., 2014; Blessing et al., 2015; Ibeas Bih et al., 2015)

including anti-inflammation (Burstein, 2015). Inflammation underlies a range of pathologies including neurodegeneration (Glass et al., 2010; Cunningham, 2013), stroke (Turner and Vink, 2007; Ahmad et al., 2014), and demyelination (Popescu and Lucchinetti, 2012; Kutzelnigg and Lassmann, 2014). To examine CBD's anti-inflammatory impact on OPC survival, cultured OPCs isolated from the forebrain of newborn Wistar rats were exposed to inflammation-related stressors (Mecha et al., 2012). Treatment with CBD (1 μM) reduced: (1) caspase-3-mediated apoptosis resulting from lipopolysaccharides (LPS) and interferon-γ (IFNγ)-mediated inflammation (48 h); (2) cell death induced by endoplasmic reticulum stress instigated by tunicamycin (1 μg/ml, 24 h); and (3) cell detachment and ROS production in response to hydrogen peroxide (2 h). CBD was unable to increase OPC proliferation in culture (Mecha et al., 2012), in contrast to its chronic administration in SVZ of adult Swiss mice (Schiavon et al., 2016). CBD did not promote apoptosis in culture, as observed in unstressed cultured oligodendrocytes (Mato et al., 2010). CBD's cellular mechanism(s) have yet to be established for OPC and oligodendrocyte function, but might counter the endocannabinoid responses at their receptors. Further, CBD may target other cell types in the neuro-immune complex, explaining differences between *in vitro* vs. *in vivo* models.

PERSPECTIVES

Although much has been learned about the impact of cannabinoid agonists on oligodendrocytes in health and disease, many questions remain unexplored, such as the cannabinoid impact on OPC local migration (Kirby et al., 2006; Hughes et al., 2013) and glutamate signaling (Spitzer et al., 2016), the oligodendrocyte's ability to produce myelin and provide metabolic support to axons (Zecca et al., 2004; Saab et al., 2013; Simons and Nave, 2015). Cannabinoid agonists also comprise structurally and functional distinct ligands (Howlett et al., 2002; Pertwee et al., 2010; Laprairie et al., 2017; Priestley et al., 2017), and as such, it is important to characterize their pharmacological profiles in cell pathologies related to oligodendrocytes and other cell types in the neuro-immune complex. Although the impact of cannabinoid extracts on MS disease progression remains inconclusive (Pertwee, 2007; Pryce et al., 2015), the outlook is optimistic (Arévalo-Martin et al., 2008; Chiurchiu et al., 2015, 2018). Evidence of cannabinoid agonist effects on oligodendrocyte survival and OPC lifecycle suggests their usefulness in CNS pathologies such as demyelination (Popescu and Lucchinetti, 2012; Kutzelnigg and Lassmann, 2014), neurodegeneration (Ettle et al., 2016; Tauheed et al., 2016), ischemia (Dewar et al., 2003; Mifsud et al., 2014), epilepsy (Friedman and Devinsky, 2015; Stockings et al., 2018), and traumatic injuries to spinal cord (Alizadeh and Abdolrezaee-Karimi, 2016; Levine, 2016; Arevalo-Martin et al., 2016) and brain (Armstrong et al., 2016; Takase et al., 2018).

AUTHOR CONTRIBUTIONS

AI conceived the idea and approach to the review, wrote and edited the manuscript. CM and EP provided the feedback and edited the manuscript. AH developed approach to the review, structured, wrote and edited the manuscript.

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