ROLE OF CANNABINOIDS IN ALCOHOL-INDUCED NEUROINFLAMMATION

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Abbreviations

AEA	N-arachidonoylethanolamine or anandamide
AP-1	Activator protein 1
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic adenosine monophosphate
CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBG	Cannabigerol
CBGV	Cannabigivarin
CNS	Central nervous system
COX-2	Cyclooxigenase-2
DAGL	Diacylglycerol lipase
DAMPs	Danger associated molecular patterns
eCB	Endocannabinoid
ECS	Endocannabinoid system
ERK	Extracellular signal-regulated kinase
FAAH	Fatty acid amide hydrolase
GFAP	Glial fibrillary acidic protein
GPCR	G protein-coupled receptor
HMGB1	High mobility group box 1
HPC	Hippocampus
Iba1	Ionized calcium binding adaptor molecule 1
IL	Interleukin
INF-γ	Interferon gamma
iNOS	Inducible nitric oxide synthase
IκBα	Inhibitory kappa Bα
LPS	Lipopolysaccharide
MAGL	Monoacylglycerol lipase
MCP-1	Monocyte chemoattractant protein 1
MCSF	Macrophage colony-stimulating factor
MD2	Myeloid differentiation protein-2
MHCII	Major histocompatibility complex II
MIP-1α	Macrophage inflammatory protein 1α
miRNA	MicroRNA
MRF-1	Microglia response factor 1
MyD88	Myeloid differentiation factor 88
NAPE-PDL	N-acylphosphatidylethanolamine-specific phospholipase d-like hydrolase
Nrf2	Nuclear factor erythroid 2-related factor 2
NF-κB	Nuclear factor-kappa B
OEA	Oleoylethanolamide

PFC	Prefrontal cortex
PKA	Protein kinase A
PPAR	Proliferator-activated receptor
ROS	Reactive oxygen species
RXR-γ	Retinoid X receptor-γ
SDF-1α/CXCL1	Chemokine stromal cell-derived factor 1
SOC	Suppressors of cytokine signalling
TAK1	Transforming growth factor beta-activated kinase 1
TFG	Transforming growth factor
THC	Tetrahydrocannabinol
THCA	Tetrahydrocannabinolic acid
THCV	Tetrahydrocannabivarin
TLR4	Toll-like receptor 4
TNF-α	Tumour necrosis factor alpha
TrkB	Tropomyosin receptor kinase B
TRPV	Transient receptor potential vanilloid type

Highlights

- Alcohol exposure leads to a chronic pro-inflammatory profile in the CNS.
- The expanded endocannabinoid system is a key regulator of the neuroimmune response.
- CB1 activation is related to deterioration of alcohol-induced neuroinflammation.
- Cannabinoids modulate the pro-inflammatory and the anti-inflammatory signalling pathways.
- Targeting the PPARγ or the usage of OEA leads to promising outcomes.

Abstract

Alcohol is a psychoactive substance highly used worldwide, whose harmful use might cause a broad range of mental and behavioural disorders. Underlying brain impact, the neuroinflammatory response induced by alcohol is recognised as a key contributing factor in the progression of other neuropathological processes, such as neurodegeneration. These sequels are determined by multiple factors, including age of exposure. Strikingly, it seems that the endocannabinoid system modulation could regulate the alcohol-induced neuroinflammation. Although direct CB1 activation can worsen alcohol consequences, targeting other components of the expanded endocannabinoid system may counterbalance the pro-inflammatory response. Indeed, specific modulations of the expanded endocannabinoid system have been proved to exert anti-inflammatory effects, primarily through the CB2 and PPARγ signalling. Among them, some endo- and exogeneous cannabinoids can block certain pro-inflammatory mediators, such as NF-κB, thereby neutralizing the neuroinflammatory intracellular cascades. Furthermore, a number of cannabinoids are able to activate complementary anti-inflammatory pathways, which are necessary for the transition from chronically overactivated microglia to a regenerative microglial phenotype. Thus, cannabinoid modulation provides cooperative anti-inflammatory mechanisms that may be advantageous to resolve a pathological neuroinflammation in an alcohol-dependent context.

1. Introduction

Alcohol is one of the most consumed psychoactive drugs worldwide, with 2.3 billion ocurrent drinkers. Indeed, alcohol use is among the leading causes of global disease burden (Rehm and Shield, 2019). Around 3 million deaths per year occur due to the harmful use of alcohol, which represents 5.3% of total deaths (World Health Organization, 2018). Alcohol abuse affects most body organs, although severe alcohol-induced diseases are most notable in the liver, pancreas and brain. This is due to alcohol's direct neurotoxic effect on neurons through different mechanisms, including oxidative stress (Qin and Crews, 2012) and neuroinflammation (Crews and Vetreno, 2014).

Even though alcohol exposure may have a different impact in the central nervous system (CNS) determined by several factors, such as the developmental period of exposure, route of administration or pattern of consumption, there might be a common neuroinflammatory mechanism underlying such alterations. The endocannabinoid system (ECS) has been observed to play a key role in the modulation of neuroinflammatory responses (Chiurchiù et al., 2015; Cristino et al., 2020). In this context, we review and discuss the role of cannabinoids in the regulation of alcohol-induced neuroinflammation.

In this review, we first outline the mechanisms by which alcohol exposure induces a neuroinflammatory response. We also provide an overview on the ECS and its role in regards with the regulation of neuroinflammation. Then, we discuss the molecular mechanisms by which endocannabinoids, phytocannabinoids and synthetic cannabinoids may regulate alcohol-induced neuroinflammatory responses. Additionally, we are interested in alcohol impact on different neurobehavioral outcomes focused on preclinical studies, using cannabinoid-based approaches to modulate the alcohol-induced brain damage (i.e. neuroinflammation, oxidative damage or neurodegeneration) in two different developmental stages: adolescence and adulthood. Finally, we propose a mechanism by which cannabinoid-based therapies could modulate alcohol-induced neuroinflammatory signalling.

2. Alcohol-induced neuroinflammatory response.

The immune response within the CNS involves peripheral and local elements, primarily microglia and astrocytes, together forming the so-called glia (Gilhus and Deuschl, 2019).

Both cell types are highly reactive to changes in the brain, actively producing signalling molecules that can either participate in homeostasis or contribute to disease if an insult is present (Greenhalgh et al., 2020). Evidence suggests the existence of crosstalk between activated microglia and astrocytes that amplifies the inflammatory response, contributing to the production of neurotoxic factors (Saijo and Glass, 2011).

2.1. Evidence from clinical studies

Clinical studies have shown an upregulation of immune-related genes in post-mortem brains of alcoholic patients (Lewohl et al., 2000). Increased protein levels of Monocyte chemoattractant protein 1 (MCP-1) in the ventral tegmental area, substantia nigra, hippocampus (HPC) and amygdala have been found in alcoholic post-mortem brains as compared with controls (He and Crews, 2008). In addition, enriched expression of genes associated with interferon signalling pathway in prefrontal cortex (PFC) has been shown in alcohol use disorder (AUD) post-mortem brains (Kapoor et al., 2019).

Other clinical studies have shown changes in pro-inflammatory cytokines levels in plasma of current alcohol drinkers. Circulating levels of interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) were increased on the first day of withdrawal in alcohol-dependent patients without cirrhotic liver disease (Heberlein et al., 2014), suggesting a direct induction of pro-inflammatory cytokines in blood by alcohol. By contrast, other authors highlighted the importance of alcohol-induced secondary disorders to promote the enhancement of circulating inflammatory molecules in alcoholic patients (Achur et al., 2010; González-Reimers et al., 2011). Additionally, at least one clinical study has pointed out that intestinal permeability and lipopolysaccharide (LPS) circulating levels were largely increased in alcohol-dependent patients at the onset of withdrawal, which positively correlated with systemic pro-inflammatory cytokines. Interestingly, pro-inflammatory cytokines (TNF-α, IL-6, and C-reactive protein) remained increased after 3 weeks of withdrawal (Leclercq et al., 2012).

2.2. Evidence from preclinical studies

In accordance with clinical data, some preclinical studies have displayed an increase of pro-inflammatory markers after alcohol exposure even though several factors can influence the alcohol's effect on neuroimmune activation. Vallés and colleagues

117 demonstrated an enhanced expression of inducible nitric oxide synthase (iNOS),
118 cyclooxigenase-2 (COX-2) and IL-1β, within the cerebral cortex of female Wistar rats,
119 following a 5-months chronic alcohol treatment (Vallés et al., 2004). 10-days of alcohol
120 treatment (5 g/kg; i.g.) increased brain TNF-α and MCP-1 levels, whereas it reduced IL-
121 10, which is an anti-inflammatory cytokine, in adult male C57BL/6 mice (Qin et al.,
122 2008).

123 Other authors have suggested an age- and region-specific susceptibility to alcohol
124 regulation of neuroinflammatory response (Kane et al., 2014; Pascual et al., 2007; Perkins
125 et al., 2019). Although divergences could also be due to the usage of different models of
126 alcohol exposure, highlighting the importance of dose, route of administration and timing
127 of exposure in the alcohol-induced neuroinflammatory response. Nevertheless, aging-
128 associated changes in neuroimmune response are known to play a key role in adolescent
129 *versus* adult alcohol-induced neuroinflammation, which are to take into account (Perkins
130 et al., 2019). Hence, the period of lifetime in which alcohol exposure occurs is important
131 in terms of the severity of neuroinflammatory response and the following negative
132 consequences.

133 Sex factor seems to be relevant as well. When male and female mice were compared,
134 iNOS, COX-2, IL-1β and TNF-α were increased in cerebral cortex of both sexes.
135 However, alcohol induced higher glial fibrillary acidic protein (GFAP) levels in females
136 *versus* males (Alfonso-Loeches et al., 2013). On the other hand, concerning the
137 methodology, the time point examining post-exposure, the techniques to analyse the
138 protein and mRNA content, and the species used can also influence the changes on
139 immune signature (see (Melbourne et al., 2019) for more information).

140 Thus, the interaction between alcohol and neuroimmune system is complex and still
141 remains unclear. Although the number of studies focused on this field has been increasing
142 in the last decades, reports are not particularly consistent because of the influence of many
143 external factors.

144 *2.3. Mechanisms of alcohol-induced neuroinflammation*

145 *2.3.1. Central mechanisms*

Taken together, it seems that alcohol exposure can be defined as an insult that leads to neuroimmune dysregulation in some situations. These neuroimmune alterations are mostly mediated by central mechanisms that lead to the activation of microglia, which can persist for long periods once activated by excessive alcohol consumption (Liu et al., 2008; Vetreno et al., 2013). Alcohol molecule can cross the blood-brain barrier (BBB) to induce a local pro-inflammatory response due to the activation of Toll-like receptors (TLRs) in glial cells (Coleman and Crews, 2018; Crews and Vetreno, 2016). In addition, alcohol exposure may induce the release of endogenous danger associated molecular patterns (DAMPs), such as the high mobility group box 1 (HMGB1), by neurons and glia during glutamate hyperexcitation (Maroso et al., 2011; Zou and Crews, 2005) or by necrotic dead cells (Crews and Vetreno, 2016). DAMPs in extracellular space activate TLRs and other pro-inflammatory-associated receptors, such as the receptor for advanced glycation end products (Park et al., 2004). The activation of these receptors induces the stimulation of pro-inflammatory signalling pathways and activation of transcriptional factors, such as nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), through the myeloid differentiation factor 88 (Myd88)-dependent pathway. Furthermore, a hyperactivation of pro-inflammatory oxidases occurs when alcohol is metabolized, resulting in the formation of reactive oxygen species (ROS). Altogether cause positive loops of pro-inflammatory responses in the brain that converge upon NF-κB activation and its subsequent translocation into the nucleus, which will keep on amplifying the neuroimmune gene induction through autocrine and paracrine positive feedbacks (Crews and Vetreno, 2016).

During such periods of activation, microglia suffers morphological and functional changes. Thus, authors suggested that a single period of binge alcohol drinking does not induce a full microglial-driven neuroinflammatory response, but a partial microglial activation that persists until adulthood (McClain et al., 2011). In a chronic but moderate alcohol exposure model using a vapor chamber for 5 weeks, increased number of Iba1-positive cells were observed at the first day of withdrawal in many brain regions, including frontal cortex, HPC, amygdala, substantia nigra and cerebellum. Furthermore, Iba1 staining remained elevated after 28 days of withdrawal in amygdala, frontal cortex and substantia nigra (Sanchez-Alavez et al., 2019). Accordingly, a chronic alcohol drinking model over 6 months induced long-lasting partial microglial activation in rat HPC (Cruz et al., 2017). On the other hand, other authors have shown an increased

number of MHCII-, CD45- and CD68-positive cells in a chronic alcohol-drinking model over 5 months in mice, suggesting an activated ameboid phenotype in this case. Elevated levels of pro-inflammatory cytokines and chemokines, including chemokine ligand 2 and fractalkine, were reported in this study following a chronic alcohol exposure (Alfonso-Loeches et al., 2016).

Therefore, one may confirm that there is no clear consensus about the activated microglial phenotype induced by alcohol and its functional implications. Again, there are several factors that might lead to a different neuroinflammatory response. Interestingly, evidence suggests a possible association between chronic or excessive alcohol consumption with pro-inflammatory microglial phenotypes, whereas single or moderate drinking episodes could be accompanied by homeostatic responses. However, further studies should be addressed to clarify the influence of the factors mentioned upon the microglial phenotype, alongside the role of this microglial activation following alcohol exposure. Thus, whether this neuroimmune activation is detrimental or neuroprotective remains a subject of debate.

However, some studies in attempt to assess causality have exhibited that the deletion of TLR4 prevents the neurotoxicity through the blockade of alcohol-induced activation of microglia (Erickson et al., 2019). TLR4 deletion prevented alcohol-induced upregulation of CD11b (microglial marker) and GFAP immunoreactivity. Furthermore, in this knockout mouse model the increase of caspase-3 and iNOS activity, as well as the increase of COX-2, IL-1β, TNF-α and IL-6 in the cerebral cortex of female mice, were also prevented following a 5-month chronic alcohol treatment (Alfonso-Loeches et al., 2010). Another study has shown that the inflammatory response induced by alcohol treatment was completely abolished in microglia of TLR4-deficient mice (Fernandez-Lizarbe et al., 2009). Altogether, it is relatively clear that the activation of microglia under certain alcohol exposure conditions could be somehow detrimental for the CNS, supporting the hypothesis of neuroimmune activation in the pathophysiology of AUDs. Noteworthy, microglia may as well promote repair under many homeostatic and pathological conditions, including other certain types of alcohol exposure mentioned above.

2.3.2. *Peripheral mechanisms*

The presence of alcohol increases blood's innate immune signals released from peripheral organs. The gut and liver are especially affected by alcohol intake as it has been reported in different studies; therefore, pro-inflammatory markers can be released when they are dramatically affected by alcohol exposure (de Timary et al., 2017; Ferrier et al., 2006; Gao et al., 2011). Alcohol increases the intestinal permeability (Antón et al., 2018), allowing the release of pathogen-associated molecular patterns into the bloodstream, such as LPS endotoxin, stimulating pro-inflammatory cytokine production. These circulating immune signals, primarily cytokines and chemokines (i.e.:TNF-α, IL-6, IL-1β and chemokine stromal cell-derived factor 1 (SDF-1α/CXCL1)), are proposed to contribute to neuroimmune activation in AUD as various immune-to-brain communication pathways have been described (Banks and Erickson, 2010; Crews et al., 2006; de Timary et al., 2017). First, circulating pro-inflammatory cytokines may activate the hypothalamus-pituitary-adrenal axis through the vagus nerve stimulation (so-called 'neural pathway'). Moreover, peripheral signals can reach the brain via circumventricular organs, meninges and the choroid plexus, structures with a 'leaky' BBB, and they can also act on brain endothelium to induce the release of secondary mediators eliciting a response into the brain (named 'humoral pathway). In addition, endothelial cells may become activated by circulating cytokines and secrete inflammatory mediators that alter the permeability of the BBB, allowing the recruitment of peripheral immune cells (known as 'cellular pathway') (Capuron and Miller, 2011; D'Mello and Swain, 2017; Dantzer et al., 2008).

3. Cannabinoids and neuroinflammation

3.1. The endocannabinoid system

The search for specific binding sites for tetrahydrocannabinol (THC) lead to the first identification of cannabinoid receptor 1 (CB1) (Devane et al., 1988) and cannabinoid receptor 2 (CB2) (Matsuda et al., 1990; Munro et al., 1993). CB1 is considered to be the most abundant G-protein coupled receptor (GPCR) within the CNS (Irving et al., 2008) being primarily expressed in axon terminals (Freund et al., 2003). When activated, CB1 inhibits neurotransmitter release from both presynaptic glutamatergic (Katona et al., 2006) and GABAergic neurons (Katona et al., 1999). CB2 is found in lower levels in the brain, being mostly located in microglia (Atwood and Mackie, 2010; Walter et al., 2003).

The spread localization among immune cells confers CB2 a key role in the modulation of inflammatory processes.

The most studied endogenous ligands to CB1 and CB2 are N-arachidonoylethanolamine or anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Lu and MacKie, 2016). Endocannabinoids (eCB) are synthesized on demand and, unlike classic neurotransmitters, are not stored into vesicles, but immediately released from postsynaptic cells (Di Marzo et al., 1998). The main enzymes involved in the synthesis of eCB are N-acylphosphatidylethanolamine-specific phospholipase d-like hydrolase (NAPE-PLD) (Okamoto et al., 2004) and diacylglycerol lipase (DAGL) α and β (Bisogno et al., 2003), for AEA and 2-AG respectively. The canonical metabolic pathway for eCBs degradation is the hydrolysis of AEA by fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996) and 2-AG by monoacylglycerol lipase (MAGL) (Dinh et al., 2002). However, eCBs can also be degraded by oxygenation via cyclooxygenase-2 (COX-2), among others (Di Marzo et al., 2000).

These receptors, ligands and enzymes responsible for their synthesis and degradation constitute the ECS, which is a neuromodulatory system engaged in a wide range of physiological roles, such as brain development, homeostasis, neurotransmitter release, synaptic plasticity and immune response (Lu and MacKie, 2016). In order to develop its function, the ECS directly or indirectly interplays with other components of the CNS leading to what some authors have called the expanded endocannabinoid system (Cristino et al., 2020). Therefore, other N-acylethanolamines, such as oleoylethanolamide (OEA), or 2-acylglycerols molecules, as well as long-chain N-acyl-amides can also interact with cannabinoid and cannabinoid-like receptors, such as peroxisome proliferator-activated receptor (PPAR), orphan receptor GPR or transient receptor potential (TRP) channel (Cristino et al., 2020).

3.2. Cannabinoid signalling in neuroinflammation

The wide distribution of ECS throughout the CNS and the immune system confers cannabinoids a privileged position for the regulation of neuroinflammatory responses. Although CB1 is most expressed in neurons, it can also be found in glial cells in the brain (Stella, 2010). The stimulation of CB1 has been shown to diminish the release of pro-inflammatory cytokines, iNOS and ROS via NF-κB pathway inhibition (Lou et al., 2016;

Ribeiro et al., 2013) and protect from excitotoxicity (Marsicano, 2003). Besides, some studies have also proved that CB1 antagonists can indirectly induce an anti-inflammatory response (Kaplan, 2013).

Due to its microglial localization, CB2 is highly involved in the modulation of neuroimmune responses. CB2 levels in the CNS increase drastically in neurodegenerative disorders (Aymerich et al., 2018; Cassano et al., 2017) or after brain insults (Cabral and Griffin-Thomas, 2009). Nevertheless, the range of the alcohol-induced neuroinflammatory response is probably less profound and so, its effects on central CB2 levels might be fewer. Still, CNR2 gene expression is increased in alcohol users and in human monocyte-derived dendritic cells treated with alcohol (Agudelo et al., 2013), although more studies focusing on the alcohol effects on central CB2 levels would be clarifying. In fact, CB2 levels in microglia are phenotype-dependent, being principally expressed in activated and primed microglia (Stella, 2010). The activation of CB2 is related to decreases in pro-inflammatory cytokines (TNF-α, interferon gamma (IFN-ɣ), IL-1, IL-2, IL-6 or IL-12) (Croxford and Yamamura, 2005; Mecha et al., 2016; Yuan et al., 2002), chemokines (Bátkai et al., 2012; Sheng et al., 2005) and iNOS (Wen et al., 2015; Zarruk et al., 2012) via inhibition of the NF-κB pathway (Fakhfouri et al., 2012; Jeon et al., 1996). Hence, CB2 would act as a homeostatic regulator, bringing the system back to physiological states.

Cannabinoids also bind to other non-cannabinoid receptors in the so-called expanded cannabinoid system in order to exert its anti-inflammatory and homeostatic functions. eCBs (AEA and other endocannabinoid-like mediators) (Cristino et al., 2020), phytocannabinoids (cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerol (CBG), tetrahydrocannabinolic acid (THCA)) (Di Marzo, 2018) and synthetic cannabinoids (WIN55,212-2) (Fakhfouri et al., 2012) are agonist of PPARs, which are nuclear receptors that inhibit NF-κB and AP1-mediated inflammation (Varga et al., 2011a). In the CNS, PPARs are expressed in neurons and glial cells (Moreno et al., 2004). Out of its three isoforms, PPARα and specially PPARɣ are involved in the regulation of neuroinflammation and lipid metabolism, whereas PPARβ/δ remains the least studied one (Varga et al., 2011a). Interestingly, their activation has been shown to exert protective effects in different alcohol intake models (Alen et al., 2018; Blednov et al., 2015; Cippitelli et al., 2017).

TRP channels are highly related to the eCB signalling. Indeed, TRP vanilloid 1 (TRPV1), TRPV2, TRPV3, TRPV4, TRP ankyrin 1 and TRP melastatin 8 have all been reported to mediate cannabinoid activity (Muller et al., 2018). TRPV1 has recently been shown to control microglial activation and glutamate release from microglial microvesicles (Marrone et al., 2017). Another recent study also found that TRPV1 regulate cytokine release from activated microglia (Bassi et al., 2019). The eCBs AEA and 2-AG (Lowin and Straub, 2015; Petrosino et al., 2016), some phytocannabinoids, such as tetrahydrocannabivarin (THCV), CBD, CBG or cannabigivarin (CBGV) (De Petrocellis et al., 2011), and several synthetic cannabinoids, such as WIN55,212-2 (Soethoudt et al., 2017), bind to TRPV1.

The orphan receptor GPR55 has also been proposed as an eCB receptor. Some studies have revealed that AEA and 2-AG bind and activate GPR55 (Lauckner et al., 2008; Ryberg et al., 2007), whereas CBD acts as an antagonist (Kaplan et al., 2017) and THC as an agonist (Lauckner et al., 2008). Furthermore, atypical synthetic cannabinoids, other than WIN55,212-2, can also activate this receptor (Johns et al., 2007). GPR55 levels are microglia-activation dependent, mimicking the regulatory pattern of CB2 and conferring a potential role in the regulation of inflammatory responses (Pietr et al., 2009). Other orphan receptors could also play an important role in neuroinflammation: GPR18 due to its microglial localization (McHugh, 2012), or GPR119 due to the binding of OEA, among other cannabinoid-like mediators (Hansen et al., 2012). Nevertheless, little is known about the physiological roles of these receptors as wells as their interactions with the endocannabinoid system and the immune response which are yet to be elucidated.

Besides, due to their lipidic nature, eCBs are highly related to the eicosanoid system (Grabner et al., 2017). Prostaglandins, a classical eicosanoid, are arachidonic acid-derived bioactive lipid mediators synthetized by COX-1/2 that have a prominent role in the regulation of inflammatory processes (Aoki and Narumiya, 2012; Dennis and Norris, 2015). Indeed, prostaglandins are thought to mediate the transition to chronic inflammation via different mechanisms including the amplification of pro-inflammatory cytokines (Chiurchiù et al., 2018). Although phospholipase A2 is considered to be the main source of the prostaglandin precursor arachidonic acid, the hydrolysis of 2-AG by MAGL has also been proved to generate it (Grabner et al., 2017; Long et al., 2009; Schlosburg et al., 2010). In this line, MAGL inhibition might protect from the

prostaglandin-induced neuroinflammation, as evidenced in a mouse model of Parkinson disease (Nomura et al., 2011).

The neuroimmune modulatory profile of cannabinoids has led to the emergence of a wide range of studies exploiting these molecules for the treatment of neurological and neurodegenerative diseases. Endogenous, phytogenic and synthetic cannabinoids have been proved to ameliorate neuroinflammation induced by different pathologies, such as Alzheimer's disease (Maroof et al., 2013; Vallée et al., 2017), Parkinson's disease (Kelly et al., 2020; Little et al., 2011), multiple sclerosis (Al-Ghezi et al., 2019; Correa et al., 2007), neuropathic pain (Donvito et al., 2018), autism spectrum disorder (Araujo et al., 2019) or addiction (Rodrigues et al., 2014).

4. Cannabinoids in alcohol-induced neuroinflammation

Alcohol exposure may have a different impact on neurobehavioral outcomes depending on the developmental timing of exposure. Subsequently, we divided our discussion about the role of cannabinoids in alcohol-induced neuroinflammation by the developmental period at which alcohol exposure took place.

4.1. Adolescent alcohol exposure

Adolescence represents a period in which the brain is undergoing extensive maturational processes. Therefore, alcohol consumption during this time can cause structural and functional changes in immature brain areas resulting in cognitive and behavioural deficits (Kyzar et al., 2016). Compelling evidence has shown that the activation of the immune system plays a crucial role in the disruptive effects induced by adolescent alcohol use (Guerri and Pascual, 2019; Lamont et al., 2020; Pascual et al., 2018). Accordingly, Sanchez-Marin et al. (2017) have shown that 4-week intermittent alcohol exposure (3 g/kg injections for 4 days/week) during adolescence induces anxiogenic-like responses and impairs recognition memory later in life. Furthermore, these behavioural alterations were associated with changes in the ECS and neuroinflammation-related factors. Increased levels of the enzymes that mediate the synthesis of AEA and 2-AG, NAPE-PLD and DAGLs, were found in the medial prefrontal cortex (mPFC) of alcohol-exposed rats. In addition, an up-regulation of pro-inflammatory mediators, such as TLR4, TNF-α, COX-2 and GFAP, was induced by alcohol exposure in the mPFC. Notwithstanding,

lower mRNA levels of the receptors CB1 and CB2, as well as, decreased expression of COX-2, GFAP, microglia response factor 1 (MRF-1) and NF-κB were observed in the striatum. Therefore, brain region-dependent changes of the ECS and neuroinflammation were induced by adolescent intoxication in rats.

Some modulations of the eCBs have been described to confer neuroprotective effects against the oxidative damage induced by binge alcohol drinking in adolescence. Selective pharmacological inhibition of the FAAH enzyme, which metabolizes the N-acylethanolamines, blocked the induction of oxidative stress resulting from binge alcohol consumption (Pelição et al., 2016). Pre-treatment with a single dose of the FAAH inhibitor URB597 (0.3 mg/kg; i.p.) was able to prevent the production of free radicals after acute (3 consecutive sessions) or chronic (3 consecutive sessions over 4 weeks) alcohol bingeing (6 g/kg; i.g.) in the PFC of young rats, avoiding the neurotoxicity of alcohol abuse. Similarly, Bellozi et al. (2019) reported the ability of URB597 pre-treatment (0.3 mg/kg; i.p.) to modulate neuroinflammation induced by binge alcohol consumption during adolescence. The blockade of FAAH prevented the increase of IFN-γ and TNF-α levels in the PFC and HPC induced by chronic alcohol bingeing (3 or 6 g/kg, i.g.; 3 days/week for 4 weeks). Moreover, URB597 reduced the levels of IL-4, IL-10 and BDNF in the PFC. Thus, the amplification of the ECS seems to exert neuroprotective functions against alcohol-induced neuronal damage, albeit the exact underlying mechanism needs to be further clarified. It is known that URB597 increases AEA (also PEA and OEA) availability, which interacts with PPAR family receptors, known for their anti-inflammatory and antioxidant activities.

In this context, the role of OEA, a structural analogue of AEA, has been investigated to counteract the alcohol-induced damage. Using a 5-week pharmacological administration of OEA (10 mg/kg/day; i.p.; 5 days/week) in a rat model of binge-like alcohol consumption (3 g/kg, i.g.; weekly) combined with acute administrations of THC (5 mg/kg; i.p) during adolescence, Silva-Peña et al. (2019) demonstrated that OEA was capable of preventing the short-term spatial memory impairments induced by alcohol and THC. Furthermore, combined administration of OEA and THC restored the alcohol-induced BDNF deficiency in plasma. However, OEA reduced mRNA expression of BDNF in the HPC, even though it increased the expression of its receptor tropomyosin receptor kinase B (TrkB). In addition, repeated administration of OEA rescued the

reduction of neural stem cell proliferation and newborn cell survival in the subgranular zone of the dentate gyrus induced by alcohol and THC exposure and increased the hippocampal levels of phospho-AKT and phospho-ERK1, key signalling regulators of neurogenesis and cell survival. Also, both treatments (THC and OEA) alone or in combination diminished the mRNA levels of the pro-apoptotic protease caspase-3 in the HPC. Hence, OEA and other putative PPAR-α activators seem to display a protective role in response to cognitive and brain dysfunctions related to alcohol exposure.

Recently, another approach by which memory deficits induced by adolescent alcohol exposure can be rescued through the modulation of the ECS in mice has been described (Peñasco et al., 2020). Repeated binge alcohol drinking (20% (v/v); 4 days/week for 4 weeks) during adolescence leads to long-term deficits in CB1 receptor expression and distribution in the brain and consequently, it disrupts a form of excitatory long-term depression that is dependent on CB1 receptors (eCB-eLTD) in the hippocampal dentate gyrus. These alterations were associated with an impairment of recognition memory in alcohol-exposed mice 2 weeks after the cessation of alcohol consumption, which could be rescued by inhibiting the MAGL with JZL184 (8 mg/kg). Therefore, increasing the availability of the endogenous 2-AG restored the functional deficits induced by adolescent binge alcohol exposure.

However, co-exposure of WIN-55,212-2 (3 mg/kg; s.c.) with alcohol (increasing concentrations of alcohol solution; 3-8% (v/v) alcohol) during early adolescence (PD 21-30) increased anxiety-like behaviour (PD 35) and enhanced alcohol intake and preference (6% (v/v) alcohol) in mice (up to PD 75) (Frontera et al., 2018). In addition, WIN-55,212-2 treatment increased the number of dendritic ramifications in neurons of the substantia nigra but lowered the number of dendritic spines in alcohol-exposed mice. These results demonstrated that exposure to a cannabinoid receptor agonist during adolescence could interfere with neural development affecting the neuronal morphology in key brain areas that ultimately lead to functional and behavioural changes.

To summarize, extensive evidence has been focused on the interaction between alcohol and cannabinoids along adolescence (see *Table 1*). Co-exposure of alcohol and potent CB1 agonist drugs, such as THC or WIN-55,212-2, enhances alcohol-induced brain damage, in addition to accentuating functional deficits regarding behavioural domains like cognition. Interestingly, several studies have already reported the advantage of

implementing other cannabinoid-based approaches. Again, the data discussed above suggests that preventing CB1 activation while acting through other targets, which are part of the expanded endocannabinoid system, such as N-acylethanolamines/PPARs pathways, could be a beneficial strategy to avoid alcohol-induced brain damage in this developmental period.

435 **Table 1. Summary of *in vivo* preclinical evidences on the role of cannabinoid's modulation in alcohol-induced neuroinflammation, oxidative stress or**
436 **neurodegeneration during the adolescence.**

Reference	Animal model	Alcohol administration	Cannabinoid treatment	EtOH molecular effects	Cannabinoid molecular effects	Synergic effects	Behavioural improvement/ impairment
Bellozi *et al.*, (2019)	Male Wistar rats	**Acute binge** alcohol (3 or 6 g/kg; i.g.) for 3 consecutive days **Chronic binge** 3 binge cycles over 4 weeks (PD30)	**URB597** 0.3 mg/kg; i.p., 40 min before the alcohol administration	**Chronic binge** ↑ IFN-γ and TNF-α in PFC and HPC. ↑ IL-10 and BDNF in PFC.	No effects	↓ IFN-γ and TNF-α in PFC and HPC (*vs.* chronic alcohol binge group). ↓ IL-4, IL-10 and BDNF in PFC (*vs.* chronic alcohol binge group).	↑ long-term memory in novel object recognition (*vs.* acute 3 g/kg alcohol binge group).
Peliçao *et al.*, (2016)	Male Wistar rats	**Acute binge** alcohol (3 or 6 g/kg; i.g.) for 3 consecutive days **Chronic binge** 3 binge cycles over 4 weeks (PD30)	**URB597** 0.3 mg/kg, i.p., 40 min before the alcohol administration	**Acute (3 and 6 g/kg) and chronic (6 g/kg) binge** ↑ production of superoxide anions (oxidative stress) in PFC.	No effects	↓ oxidative stress in PFC (*vs.* acute and chronic 6 g/kg alcohol binge).	Not applicable

Silva-Peña *et al.*, (2019)	Male Wistar rats	**EtOH** 3 g/kg; i.g. once per week for 5 consecutive weeks (PD34-69)	**OEA** 10 mg/kg; i.p; 5 days/week, for 5 weeks **Δ^9-THC** 5 mg/kg; i.p.; 1 day/week for 5 weeks **Combination of both**	↑ ERK1 and ERK2 in HPC ↓ pERK1/ERK1 and pERK2/ERK2 in HPC	Not applicable	**OEA** ↑ pAKT/AKT and pERK1/ERK1 protein levels in HPC **THC + OEA** ↓ Casp-3 mRNA	**OEA** blocks the short-term spatial-memory impairment (Y-maze) in rats induced by THC+alcohol.
Frontera *et al.*, (2018)	Male CD1 mice	**Forced EtOH consumption** alcohol 3% (PD21-24), alcohol 6% (PD25-27), alcohol 8% (PD 28-29).	**WIN55-212,2** 3mg/kg, s.c. daily administered (P30-P35)	Not applicable.	Not applicable.	↑ dendritic ramifications in neurons of the substantia nigra ↓ number of dendritic spines	↑ alcohol preference (two-bottle choice). ↑ anxiety-like behaviour in the open field.
Peñasco *et al.*, (2020)	Male C57BL/6 mice	**DID test** Limited access to 20% (v/v) alcohol for 4 days/week over 4 weeks (PD32-56)	**JZL184** 8 mg/kg, i.p. (PD 67-71)	↓ CB1 receptor-mediated excitatory transmission ↓ eCB-eLTD at medial perforant path synapses.	Not applicable.	↑ eCB-eLTD	JZL184 rescued alcohol-induced deficits in recognition memory

437

Alcohol molecular effects (alcohol group vs vehicle control group); Cannabinoid molecular effects (cannabinoid group vs vehicle control group); Synergic effect (alcohol + cannabinoid group vs alcohol group). **Abbreviations:** Δ9-Tetrahydrocannabinol (Δ9-THC); Brain-derived neurotrophic factor (BDNF); Hippocampus (HPC); Interferon-γ (IFN-γ); Interleukin (IL); intragastrical (i.g.); intraperitoneal (i.p.); Oleoylethanolamide (OEA); Postnatal day (PD); Prefrontal cortex (PFC); subcutaneous (s.c.); Tumour necrosis factor-α (TNF-α).

4.2. Adult alcohol exposure

Several studies have shown that cannabinoid treatment could mitigate neuroinflammation and damage produced by alcohol exposure during adulthood (see *Table 3*). In this sense, OEA could prevent the neuroimmune response not only in rodent models (Antón et al., 2017; Orio et al., 2019) but also in humans (Antón et al., 2018; Orio et al., 2019). Preclinical studies suggest that OEA not only prevents alcohol self-administration relapse and reduces withdrawal signs of alcohol (Bilbao et al., 2016) but it also inhibits the expression of proinflammatory markers in brain (Antón et al., 2017). Authors applied an intragastric alcohol (3g/kg) treatment to male Wistar adult rats, followed by a repeated 4-day binge paradigm until they reached an intoxicating blood alcohol levels (Antón et al., 2017). Consistent with this result, pre-treatment with OEA (5 mg/kg, i.p.) prevented the expression of inflammatory mediators induced by alcohol exposure in the frontal cortex, such as HMGB1, TLR4, the myeloid differentiation protein-2 (MD2), and MyD88. Additionally, they found that OEA pre-treatment blocked the HMGB1/TLR4/MyD88 danger cascade associated with NF-κB-mediated pro-inflammatory pathway and the MCP-1 in frontal cortex in alcohol-binged rats (Antón et al., 2017), when the animals were sacrificed 2-4h after last alcohol administration. In parallel, OEA (5mg/kg, i.p.) could ameliorate alcohol-induced damage due to its neuroprotectant activity, reducing caspase-3 activity, the expression of caspase 8, COX-2 and the iNOS (Antón et al., 2017), molecules intimately involved with cell death and neurotoxicity associated with alcohol (Liu et al., 2020; Pascual et al., 2007).

By contrast, other studies showed contradictory results regarding neuroinflammation depending on both the dose and brain area studied. Whereas the OEA (10mg/kg, i.p.) treatment *per se* increases the number of Iba1-positive cells in the HPC (Rivera et al., 2018), it decreases this cell population in the striatum (Rivera et al., 2019). Additionally, OEA increases the Iba1- and iNOS-positive cells but decreases the vimentin immunoreactivity in the striatum of alcohol-intoxicated and control rats, indicating a reduction of astrogliosis (Rivera et al., 2019). Surprisingly, their results in the striatum showed a reduced reactive astroglia despite the increased number of GFAP-positive cells. Authors then hypothesized that these discrepancies either could be explained due to the U-shape partial and dose-dependent OEA effects or due to the OEA-induced glial recruitment and/or proliferation in these specific areas (Rivera et al., 2019). When the

cannabinoid is co-administered with a 2 weeks of 10% alcohol liquid diet, both increase the Iba1-positive cells in the striatum (Rivera et al., 2019) and HPC (Rivera et al., 2018), promoting also an increasing of GFAP-positive and iNOS-positive cells in the striatum (Rivera et al., 2019).

Moreover, OEA (5mg/kg; i.p.) is able to reduce the pro-inflammatory markers in blood. Antón et al., (2017) found that this molecule could also reduce levels of TNF-α in blood and IL-1β in blood and frontal cortex of alcohol-exposed rats, after a binge alcohol exposure (3g/kg; i.g.; 3 times/day for 4 days). Interestingly, a recent study in young adult alcohol binge drinkers during abstinence found that these inflammatory markers (TLR4, IL-1β, COX-2, IL-6) positively correlated with the OEA levels in plasma, especially in females (Antón et al., 2018). Possible discrepancies could be due to the impossibility to establish which is the cause or the consequence in the relationship between inflammatory markers and alcohol consumption (María Antón et al., 2018). Noteworthy, patients were in abstinence and, probably, the upregulation of these biomarkers could be reflecting an anti-inflammatory response.

In the same line of OEA, the AEA (10mg/kg; i.p.) treatment increased both astrocytes iNOS-positive cells in the CA1 of HPC (Rivera et al., 2018) and GFAP- and Iba1-immunoreactive cells in the striatum (Rivera et al., 2019) of alcohol-exposed rats. In fact, URB597 treatment also increased the number of Iba1-postive cell in HPC and induced minor morphological changes. However, the URB597 (0.3mg/kg; i.p.) treatment could restore the effects of alcohol-induced inflammatory and neurodegenerative process, since it was able to reduce mRNA levels of Iba1, TNF-α, IL-6 and the MCP-1 and reduce iNOs-positive cells, thus improving memory function in these rats (Rivera et al., 2018). Even though they found increased mRNA levels of TLR4, GFAP cells and the SDF-1α/CXCL1, they found an increasing hippocampal cell population expressing chemokine receptors CX3CR1, CCR2 and CCR4. These receptors have been associated with recruitment processes of immune cells. Therefore, authors hypothesized that URB597 (0.3mg/kg; i.p.) induced an anti-inflammatory microglial activation that might counteract the alcohol-induced pro-inflammatory response (Rivera et al., 2018). These observations run in parallel with the protective role of URB597 against alcohol intoxication. This FAAH inhibitor might prevent the alcohol-induced neuroinflammation, since it reduces alcohol consumption in the drinking in the dark paradigm, and preference after early

withdrawal in mice (Zhou et al., 2017). Indeed, these results are supported by an increased alcohol intake and preference in mice modified with the FAAH human single-nucleotide polymorphism insertion (C385A) (Zhou et al., 2016), associated with a reduction of the FAAH activity and an enhancement of AEA levels in humans and mice (Dincheva et al., 2015). Additionally, these effects could be blocked by a pre-treatment of a selective CB1 antagonist AM251 (Zhou et al., 2017, 2016). Despite its role in neuroinflammation, URB597 failed to attenuate the number of necrotic cells within both dentate gyrus and entorhinal cortex (Liput et al., 2017) in a rat binge model.

Phytocannabinoids are also important in the reduction of binge alcohol-induced brain damage. Recently, Karoly et al., (2018) reported an association between circulating proinflammatory cytokine IL-6 marker and alcohol consumption in alcohol regular drinkers. Although variations in IL-1β were not found due to the low severity of the consumers, alcohol dependent patients have shown an association between circulating IL-1β and alcohol consumption (Leclercq et al., 2014). Extended studies revealed a different pattern of cytokines expression comparing alcohol and cannabis abusing patients. Among others, they observed a higher level of MCP-1, some interleukins (IL-16, IL-10, IL-309, IL-12-p40, IL-15), TNF-α, tissue inhibitor of metalloproteinases 2 (TIMP-2), macrophage colony-stimulating factor (MCSF) and macrophage inflammatory protein 1α (MIP-1α) (Nair et al., 2015) obtained by array profiles from monocyte-derived dendritic cells. Moreover, there is a negative association between cannabis and IL-1β in cannabis users (Karoly et al., 2018), suggesting that the phytocannabinoids contained in cannabis could reduce inflammatory signals in users.

One of the phytocannabinoids that could have a neuroprotective action is CBD, reducing apoptosis in both the entorhinal cortex and HPC of rats exposed to a binge-drinking alcohol model (Hamelink et al., 2005; Liput et al., 2013). In fact, the CBD neuroprotectant action observed in entorhinal cortex was similar when using a transdermal or i.p. delivery (Liput et al., 2013). However, the mechanisms that could mediate CBD neuroprotective effects still remain unknown due to the number of targets that CBD uses to exert its action.

Thus, eCBs and phytocannabinoids could promote their beneficial effects reducing neuroinflammatory, neurodegenerative and apoptotic signalling. Although OEA could increase some specific proinflammatory markers in a dose- and brain area-dependent manner, in general, this substance seems to procamote a proliferative and/or recruitment

process in these areas, triggering an anti-inflammatory response. Additionally, we could not discard opposite roles of cannabinoids due to different time-course in the experiments or time-point in animals sacrifice. Moreover, it is necessary to consider possible different sexual responses in the cannabinoid anti-inflammatory effect due to the fact that all studies reported in the present section have been performed in male rats. To do so, it should be mandatory performed parallel studies that asses the role of cannabinoids in alcohol-induced neuroinflammatory processes in females.

Altogether, the results recruited above suggest that the activation of the expanded endocannabinoid system could prevent alcohol-induced neurotoxic damage during adulthood (see *Table 2*).

548 **Table 2. Summary of *in vivo* preclinical evidences on the role of cannabinoid's modulation in alcohol-induced neuroinflammation, oxidative stress or**
549 **neurodegeneration at adulthood.**

Reference	Animal model	Alcohol administration	Cannabinoid treatment	Alcohol molecular effects	Cannabinoid molecular effects	Synergic effects	Behavioural improvement/ impairment
Antón *et al.* (2017)	Male Wistar rats	**Majchrowicz binge model** Binge alcohol (3 g/kg; i.g.) 3 times/day for 4 days. Control group isocaloric 5% dextrose (equivalent to 3 g/kg alcohol) 3 times/day for 4 days.	**OEA** 5 mg/kg, i.p. previous each alcohol gavage	**1h after** alcohol **administration** ↑ TNF-α, IκBα **6h after EtOH administration** ↑p65, I κB α, COX-2 **24h after** alcohol **administration** ↓ TNF-α, p65, IκBα **2-4h after** alcohol **administration** ↑ HMGB1, TLR4, MD2, MyD88, TNF-α, IL1b and MCP1 protein levels	No effects	**2-4h after** alcohol **administration** ↓ HMGB1, TLR4, MD2, MyD88, IL1b, MCP1 and HNE protein levels ↓ TLR4, p65, iNOS, COX-2, Caspase-8 and Caspase-3 mRNA ↓ Caspase 3 and p65 activity	OEA exerted antidepressant-like effects during acute alcohol withdrawal (forced swimming and elevated plus maze).

				↑ TLR4, IκB α, iNOS, HNE, Caspase-8 and Caspase 3 mRNA ↑ Caspase 3 activity			
Liput *et al.*, (2017)	Male Sprague Dawley rats	**Majchrowicz binge model:** alcohol 0-5 g/kg; i.g., 3 times/day for 4 days. Control group isocaloric dextrose; 3 times/day for 4 days.	**URB597** 0.3 mg/kg, i.p. Twice daily after the third intubation of alcohol /control diet and continued for the duration of binge treatment.	↑ FJB+ positive cells in both DG and entorhinal cortex	No effects	No effects	Not applicable
Liput *et al.*, (2013)	Male Sprague Dawley rats	**Majchrowicz binge model:** alcohol 0-5 g/kg; i.g., 3 times/day for 4 days. Control group isocaloric	**CBD** 20 mg/kg i.p. or 2.5% (w/w) transdermal gel application.	↑ FJB+ positive cells in entorhinal cortex	Not applicable	↓ FJB+ positive cells	Not applicable

		dextrose; 3 times/day for 4 days.					
Rivera *et al.*, (2018)	Male Wistar rats	*Ad libitum* access to 11% alcohol (v/v) liquid diet for 2 weeks Control group isocaloric 14.7% (w/v) sucrose liquid diet	**URB597** 0.3 mg/kg; i.p. **OEA** 10 mg/kg; i.p. **AEA** 10 mg/kg; i.p. **ACEA** 3 mg/ kg; i.p. **JWH133** 0.2 mg/kg; i.p.	↓ iNOS+ cells in DG, CA3 and CA1 ↑ Iba1, Tnfα, IL-6 and MCP-1 mRNA ↓ CX3CR1+ cells in the DG, CA3 and the whole HPC ↑ CCR4+ cells	**All treatments:** ↓ iNOS+cells within the HPC **OEA, AEA, ACEA, JWH133:** ↑ GFAP+cells within the HPC **OEA, JWH133:** ↓ Iba1+cells within the HPC **URB597, AEA:** ↑ Iba1+cells within the HPC **URB597** ↓ GFAP+cells within the HPC ↓ *Tnfα* mRNA	**OEA, JWH133:** ↑ Iba1+cells within the HPC **ACEA, JWH133:** ↑ GFAP+cells in DG **URB597** ↓ iNOS+cells in CA3 and CA1 and whole HPC ↓ *Iba1, Tnfα, IL-6* and *MCP-1* mRNA ↑ *Tlr4, Gfap, Sdf-1α/Cxcl12* mRNA ↑ CX3CR1+, CCR2+ and CCR4+ cells in the HPC ↑ CX3CR1+ cells in the DG, CA3, CA1	URB597 improves memory (novel object recognition) vs alcohol group.

					↑ CX3CR1+ cells population in CA1 ↑ the CCR2+ cells population in the DG, CA3, CA1 ↑ CCR4+ cells in CA1 ↓ CXCR4+cells in DG	**AEA** ↑ iNOS+cells in CA1	
Rivera *et al.*, (2019)	Male Wistar rats	*Ad libitum* access to 10% alcohol (v/v) liquid diet for 2 weeks Control group isocaloric 14.7% (w/v) sucrose liquid diet	**OEA** 10 mg/kg, i.p. **AEA** 10 mg/kg, i.p. Daily treatment the last 5 days of EtOH exposure	In striatum: ↑ *Nape-pld* mRNA ↓ iNOS+ cells ↑ Caspase- 3 ↓caspase 3 + cells expressing Iba1	In striatum: **OEA** ↓ vimentin+ cells ↑ Iba1+ and iNOS+ cells ↓ GFAP+/cleaved caspase 3 + cells **AEA** ↑ GFAP+ cells ↑ Iba1+ and iNOS+ cells ↑ Caspase-3	In striatum: **OEA** ↑ GFAP+, Iba1+ and iNOS+ cells ↑ Caspase 3 ↓ Caspase 3 + cells expressing Iba-1 ↓ GFAP+/cleaved caspase 3 + cells **AEA** ↑ GFAP+ and Iba1+ cells	**OEA and AEA** ↑ sucrose intake **AEA** ↑ EtOH intake. **OEA** ↑ alcohol -induced hypolocomotion

						↓ caspase 3 + cells expressing Iba1	

Alcohol molecular effects (alcohol group vs vehicle control group); Cannabinoid molecular effects (cannabinoid group vs vehicle control group); Synergic effect (alcohol + cannabinoid group vs alcohol group). **Abbreviations:** Arachidonyl-2-chloroethylamide (ACEA); Anandamide (AEA); Cannabidiol (CBD); Cyclooxigenase-2(COX-2);Chemokine receptor (CCR); CX3C chemokine receptor 1 (CX3CR1); Dentate gyrus (DG); Frontal Cortex (FC); Fluoro-Jade B (FJB); Glial fibrillary acidic protein (GFAP); Glutathione (GSH); High mobility group box 1 (HMGB1); Hippocampus (HPC); Inducible nitric oxide synthase (iNOS); Ionized calcium binding adaptor molecule 1 (Iba1); Inhibitory kappa Bα (IκBα); Interleukin (IL); intragastrical (i.g.); intraperitoneal (i.p.); Monocyte chemoattractant protein 1 (MCP-1); Myeloid differentiation factor (MyD88); Oleoylamide (OEA); Chemokine stromal cell-derived factor 1 (SDF-1α/CXCL1); Toll-like receptor (TLR); Tumour necrosis factor-α (TNF-α).

To conclude this section, it is crucial to highlight the controversial evidence regarding the cannabinoid-induced harmful/therapeutic effects on the modulation of damaging consequences associated with alcohol exposure. This lack of consistency among studies is due to the breadth of the term "cannabinoid", including a lot of endogenous and exogenous compounds. As we mentioned before, usage of CB1 agonists commonly induce detrimental outcomes, whereas non-CB1 agonist could promote desirable anti-inflammatory and neuroprotective effects. Thus, further preclinical studies are needed to fully clarify the mechanisms of action underlying these promising cannabinoid-based drugs.

5. Putative mechanisms underlying cannabinoid modulation of alcohol-induced neuroinflammation

Cannabinoids are able to modulate neuroinflammatory responses due to alcohol exposure. However, the mechanisms by which cannabinoids interfere with alcohol-induced intracellular signalling to counterbalance the inflammatory phenotype are complex and remain poorly understood.

5.1. Inhibition of pro-inflammatory signalling

The cannabinoid-induced interruption of the neuroinflammatory signalling can be mediated by cannabinoid receptor-dependent or -independent mechanisms as showed in Figure 1A.

5.1.1. Cannabinoid receptors-dependent mechanisms

Despite the extensive research regarding intracellular events triggered by cannabinoid receptor activation, the available information regarding putative interactions with pathways regulating immune response is often contradictory and solid conclusions are difficult to draw. Yang et al. (2013) found that activation of CB1 inhibits the TRPV1-induced inflammatory response in corneal epithelial cells. Upon CB1 agonism, inhibition of cyclic adenosine monophosphate (cAMP) formation decreases the cAMP-dependent activation of protein kinase A (PKA). This decline translates in a reduction of the TRPV1 phosphorylation and activation, leading to a blunting in the inflammatory response. Ehrhart et al. (2005) demonstrated that the agonism of CB2 inhibits the IFN-γ-induced

phosphorylation of JAK/STAT1 and decreases microglial production of proinflammatory mediators, such as TNF-α and nitric oxide. JAK/STAT signalling is the main molecular pathway activated by ILs (Murray, 2007), promoting the expression of either pro-inflammatory or anti-inflammatory genes. Noteworthy, the most documented STAT upon the inflammatory signalling are the subtype STAT1 and STAT3. STAT1 induces the expression of pro-inflammatory molecules, whereas STAT3 mostly activates the expression of suppressors of cytokine signalling (SOCS) (Carey et al., 2012; Murray, 2006). However, the role of STAT3 in inflammation is still controversial, as the activation of this transcriptional factor has been shown to both repress the transcription of pro-inflammatory genes and promote cell apoptosis (Nabavi et al., 2019). Another study revealed that AEA-dependent microglial CB2 activation inhibits the phosphorylation of inhibitory kappa Bα (IκBα), preventing the translocation of NF-κB to the nucleus (Correa et al., 2010). In the same line, the activation of cannabinoid receptors, specially CB2, is related to the drive of activated microglia to more homeostatic phenotypes (Mecha et al., 2016). Therefore, cannabinoid receptors, through the inhibition of different components of the inflammatory signalling, might ameliorate the immune response caused by alcohol exposure.

5.1.2. Cannabinoid receptors-independent mechanisms

PPARα and PPARγ are involved in the inhibition of the NF-κB and AP-1 pro-inflammatory pathways, which are highly involved in the alcohol-induced inflammatory response. When activated, these nuclear receptors are able to translocate to the nucleus and bind to transcription factors to prevent their activity through a mechanism called transrepression. Another form of transrepression is the binding of PPARs to the repressor complex located on the promoter of inflammatory genes, therefore preventing their transcription by NF-κB or AP-1 (Varga et al., 2011b). Du et al. (2011) inhibited the phosphorylation of NF-κB and further COX-2 expression through the activation of PPARγ by 2-AG and other PPARγ synthetic agonists in hippocampal neurons *in vitro*. Another study by Yang et al. (2016) revealed that the activation of PPARα by OEA inhibits phosphorylation of IκBα, preventing the activation of NF-κB, in THP-1 monocytic cells. In the same study, activation of PPARα by OEA was also found to inhibit the ERK1/2/AP-1/STAT3 pathway, leading to the suppression of the inflammatory response.

On the other side of the balance, TRPV1 stimulation leads to the activation of pro-inflammatory signalling pathways and a potential increase of alcohol-induce neuroinflammation. Therefore, the modulation of this receptor could be of therapeutic interest. When activated, intracellular Ca2+ rises in a TRPV-1 dependent manner leading to the phosphorylation of ERK1/2 and the activation of the AP-1 transcription factor (Backes et al., 2018) in H2C1 cell line. Furthermore, the TRPV1 stimulation-induced increase in intracellular Ca2+ is thought to activate the transforming growth factor beta-activated kinase 1 (TAK1) in human corneal epithelial cells, which will ultimately lead to the activation of NF-κB and AP-1 (Wang et al., 2011; Yang et al., 2013), although this mechanism needs to be further explored. Nevertheless, some studies have found activation of TRPV1 to play neuroprotective and anti-inflammatory roles, although the mechanism of action are not clear (Kong et al., 2017).

Microglial GPR55 stimulation has also been shown to activate ERK1/2 and NF-κB, leading to the transcription of pro-inflammatory mediators (Liu et al., 2015; Pietr et al., 2009). Therefore, the antagonism of GPR55 by cannabinoids, such as CBD (Kaplan et al., 2017), could lead to more protective and homeostatic phenotypes to counterbalance the alcohol-induced neuroinflammation.

In the CNS, alcohol-induced release of HMGB1 and other DAMPs activates TLR4, which triggers different intracellular pathways leading to the activation of the main pro-inflammatory transcription factors, NF-κB, AP-1 and IRF3, as well as STAT1. As we have reviewed in this section, cannabinoids are able to interfere with the proper course of this signalling in order to inhibit the pro-inflammatory response.

5.2. Activation of anti-inflammatory signalling

Despite a broad body of research that has focused on the pro-inflammatory signalling inhibition, molecular mechanisms that regulate the transition of microglia from detrimental states to phenotypes associated with CNS homeostasis are currently being investigated. Modulation of the ECS has been proposed as a promising strategy against pro-inflammatory microglial activation (Cristino et al., 2020; Franco and Fernández-Suárez, 2015), as represented in Figure 1B.

5.2.1. Upregulation of anti-inflammatory molecules

Evidence reveals that many cannabinoids can induce the expression of anti-inflammatory cytokines, such as IL-4, IL-10 or TFG-β, in a chronic inflammatory context (Al-Ghezi et al., 2019; Smith et al., 2000), which might be partially mediated by CB2 (Correa et al., 2010; Robinson et al., 2015). Although depending on different factors like the inflammatory context, generally anti-inflammatory ILs bring balance toward STAT3 or STAT6 activation, enhancing the function of suppressors of cytokine signalling (SOCS) (Busch-Dienstfertig and González-Rodríguez, 2013; Carey et al., 2012). SOCS expression mainly leads to the inhibition of the cytokine-JAK/STAT signalling, as a negative feedback mechanism (Liau et al., 2018). In this respect, one study displayed that CBD was able to strengthen the STAT3 activation in a LPS-induced pro-inflammatory response, thereby promoting anti-inflammatory signalling in BV-2 microglia cells (Kozela et al., 2010).

In addition, other authors have suggested non-canonical pathways by which the anti-inflammatory IL-4 could directly activate the PPARγ (Li et al., 2014), which then translocates to the nucleus to accomplish its biological function. In turn, some studies revealed that the activation of these nuclear receptors by a specific agonist enhanced some anti-inflammatory IL, such as IL-10, in microglia (Choi et al., 2017a, 2017b). Nonetheless, other molecular pathways in which PPARγ is a key modulator could be exploited.

5.2.2. Activation of PPARγ

The PPARγ activation increases the expression of Arginase-1, which is a pro-regenerative microglial marker (Fumagalli et al., 2018). Besides, a positive loop exists between PPARγ and nuclear factor erythroid 2-related factor 2 (Nrf2). Therefore, PPARγ can upregulate Nrf2 and vice versa. Nrf2 is a transcriptional factor that activates the expression of numerous genes critical for the maintenance of redox homeostasis (Zhang et al., 2013). These proteins are necessary to inhibit the generation of reactive oxygen species (ROS) and mitigate neuroinflammation (Cai et al., 2018; Rojo et al., 2018). Moreover, CD36 microglial marker, which is under the regulation of both PPARγ and Nrf2 (Yamanaka et al., 2012; Zhao et al., 2015), has been shown to facilitate the resolution of oxidative stress and neuroinflammation (Ballesteros et al., 2014; Huang et al., 2014). Interestingly, a recent study has demonstrated that the expression of CB2 in

679 microglia is Nrf2-dependent (Galán-Ganga et al., 2020). As we mentioned above, CB2
680 agonism has also been proved to enhance anti-inflammatory IL expression (Correa et al.,
681 2010; Robinson et al., 2015). In this context, it is established that both the exogenous
682 cannabinoids and the expanded endocannabinoid molecules can activate the PPARγ
683 (O'Sullivan, 2016) as well as the CB2. Furthermore, the modulation of these two
684 receptors has been proposed to exert neuroprotective and anti-inflammatory effects in the
685 alcohol context (Cippitelli et al., 2017; Nair et al., 2015). Thus, distinct cannabinoids
686 might be underpinning a promising mechanism involving PPARγ-Nrf2-CB2 and anti-
687 inflammatory cytokines, to switch to alternative and pro-regenerative microglial
688 activation.

689 In the last decades, an epigenetic mechanism which involved the link between
690 microRNAs (miRNA) expression and alcohol-related disorders has been explored
691 (Ignacio et al., 2015; Mandal et al., 2018). Some studies have suggested that the
692 modulation of miRNAs expression plays a key role in the pathophysiologic inflammation
693 induced by alcohol exposure (Lippai et al., 2014, 2013). In regard to the inflammatory
694 response, other authors have proposed the implication of several miRNAs in promoting
695 pro-regenerative microglia phenotypes (Fumagalli et al., 2018; Guo et al., 2019). In fact,
696 a mechanistic study has confirmed that inhibition of pro-inflammatory cytokines
697 expression by the upregulation of miRNA-124 is mediated by the activation of PPARγ
698 (Wang et al., 2017). More evidence reported the effect of distinct miRNAs on the
699 microglia polarization, highlighting that miRNA-124 could promote the anti-
700 inflammatory phenotype (Guo et al., 2019). Interestingly, a recently reported mechanism
701 shows that cannabinoids can interfere with neuroinflammation through the modulation of
702 several miRNAs (Dinu et al., 2020). Another research group has identified a repertoire of
703 miRNAs that are regulated by cannabinoids in resting and LPS-activated microglia
704 (Juknat et al., 2019). Their results revealed that the modulated miRNAs are linked to
705 inflammatory pathways and Nrf2-mediated cellular stress.

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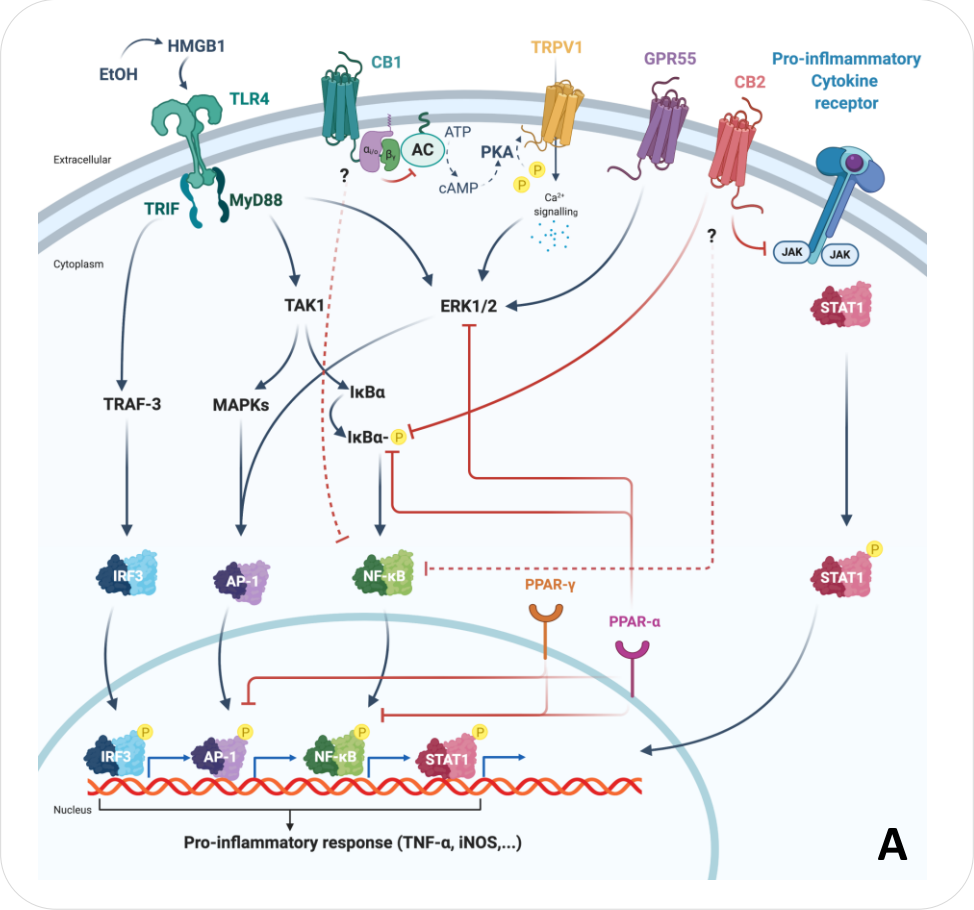
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CB1
TRPV1
GPR55
CB2
Pro-inflmammatory
Cytokine
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Ca2+
signalling
TRIF
MyD88
Cytoplasm
JAK
JAK
STAT1
TAK1
ERK1/2
TRAF-3
MAPKs
IκBα
IκBα-
IRF3
AP-1
NF-κB
PPAR-γ
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Pro-inflammatory response (TNF-α, iNOS,...)
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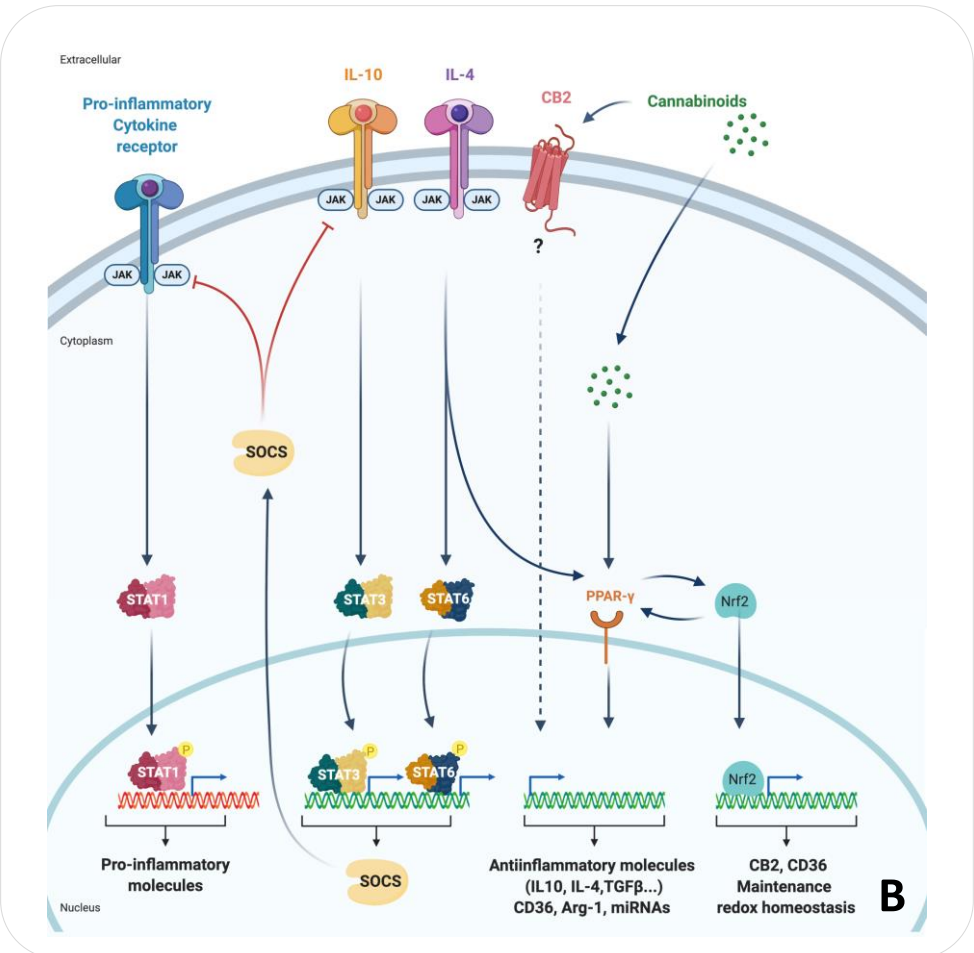
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SOCS
STAT1
STAT3
STAT6
PPAR-γ
Nrf2
STAT1
STAT3
STAT6
Nrf2
Pro-inflammatory
molecules
SOCS
Antiinflammatory molecules
(IL10, IL-4,TGFβ...)
CD36, Arg-1, miRNAs
CB2, CD36
Maintenance
redox homeostasis
Nucleus
B

Figure 1. Cannabinoid modulation of alcohol-induced neuroinflammation in microglia. A) Inhibition of pro-inflammatory signalling. Cannabinoid binding to different receptors from the expanded endocannabinoid system is able to interrupt pro-inflammatory signalling pathways. CB1 and CB2 activation leads to the inhibition of NF-κB. Besides, CB1 inhibits the TRPV1 and CB2 inhibits the JAK/STAT1 pro-inflammatory signalling pathways. PPARα and PPARγ directly inhibit NF-κB and AP-1. PPARα also blocks the phosphorylation of ERK1/2. **B) Anti-inflammatory signalling activated by cannabinoids.** Several endocannabinoids and exogenous cannabinoids can increase the expression of anti-inflammatory cytokines (IL-10, IL-4, etc.) mainly through the activation of CB2 and PPARγ. These cytokines activate JAK/STAT toward an anti-inflammatory signalling, inducing the inhibition of pro-inflammatory cytokines owing to the rising SOCS expression. PPARγ is able to activate Nrf2 and vice versa, promoting a positive anti-inflammatory feedback that allows an increasing expression of pro-regenerative mediators (CD36, Arg-1, redox-related enzymes, miRNAs, among some anti-inflammatory cytokines). Abbreviations: activator protein 1 (AP-1); arginase-1 (Arg-1); cannabinoid receptor 1 (CB1); cannabinoid receptor 2 (CB2); extracellular signal-regulated kinase (ERK); interleukin (IL); interferon regulatory factor 3 (IRF3); Janus kinase (JAK); nuclear factor erythroid 2-related factor 2 (Nrf2); nuclear factor kappa B (NF-κB); microRNA (miRNA); peroxisome proliferator-activated receptor (PPAR); suppressor cytokine signalling (SOCS); signal transducer and activator transcription proteins (STAT); transforming growth factor beta (TFGβ); transient receptor potential vanilloid 1 (TRPV1). Figure created with Biorender.com

In this section, we have hypothesised diverse mechanisms by which cannabinoid modulation may exert its anti-inflammatory effects in an alcohol context. On the one hand, we focused our research on the convergent molecules between pro-inflammatory pathways activated by alcohol in which cannabinoids might interfere, such as NF-κB. On the other hand, we discussed complementary mechanisms based on the activation of anti-inflammatory signalling which might cooperate to resolve the chronic deleterious neuroinflammation caused by alcohol exposure. The studies mentioned above indicate that cannabinoids are generally able to inhibit several components of pro-inflammatory pathways that are activated after different insults. Furthermore, a number of studies have shown the transition from detrimental microglial activation toward a regenerative phenotype instigated by cannabinoid modulation. Yet, the majority of these studies have been carried out upon common inflammatory insults and the factor that induces the neuroinflammation is noteworthy for the type of pro-inflammatory pathways, which will be activated. In this sense, further research is required to clarify the role of cannabinoids in the field of alcohol-induced neuroinflammation, because there is scarce scientific literature concerning mechanistic studies of how cannabinoids might act within alcohol-dependent pro-inflammatory context.

6. Conclusions

Alcohol exposure might trigger a series of pro-inflammatory and neurodegenerative signalling pathways that drives the CNS to chronic and non-physiological stages. The ECS is known to play a crucial role in the modulation of neuroinflammatory processes, trending towards the resolution of the immune response. Although many studies have focused on the anti-inflammatory properties of cannabinoids, only a few have used alcohol as the etiological factor. Despite the fact that alcohol exposure derived effects vary depending on the developmental state, we have found some consistencies across adolescent and adult exposures to alcohol. Evidence suggests that direct agonism to CB1 is related to a worsening of the alcohol-induced detrimental effects. However, other therapeutic approaches based on other components of the expanded endocannabinoid system, such as PPARγ or the usage of OEA, have been shown to exert more promising outcomes. The mechanisms through which cannabinoids are able to ameliorate the alcohol-induced neuroinflammation are poorly understood. In this review, we propose a model where cannabinoids might counterbalance the immune response in alcohol contexts through the inhibition of pro-inflammatory and the stimulation of anti-inflammatory signalling pathways. Therefore, cannabinoids act through multiple and complementary mechanisms in order to achieve a wider and more potent effect. Cannabinoid modulation represents an extremely interesting therapeutic target in alcohol-induced chronic neuroinflammation.

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