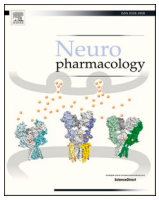
Neuropharmacology 195 (2021) 108678

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Invited review

CB1R-dependent regulation of astrocyte physiology and astrocyte-neuron interactions

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ARTICLE INFO

Keywords:
Astrocytes
Cannabinoid receptor 1
Calcium
Metabolism
Astrocyte-neuron communication

ABSTRACT

The endocannabinoid system (ECS) is involved in a variety of brain functions, mainly through the activation of the type-1 cannabinoid receptors (CB1R). CB1R are highly expressed throughout the brain at different structural, cellular and subcellular locations and its activity and expression levels have a direct impact in synaptic activity and behavior. In the last few decades, astrocytes have arisen as active players of brain physiology through their participation in the tripartite synapse and through their metabolic interaction with neurons. Here, we discuss some of the mechanisms by which astroglial CB1R at different subcellular locations, regulate astrocyte calcium signals and have an impact on gliotransmission and metabolic regulation. In addition, we discuss evidence pointing at astrocytes as potential important sources of endocannabinoid synthesis and release. Thus, we summarize recent findings that add further complexity and establish that the ECS is a fundamental effector of astrocyte functions in the brain.

This article is part of the special issue on 'Cannabinoids'.

1. Introduction

Since ancient times the extracts of marijuana (*Cannabis sativa* plant) have been associated with relieving symptoms of many diseases (Russo, 2007). Indeed, the neuroprotective effects of cannabinoid compounds have been confirmed in different models of neurodegenerative diseases like Alzheimer's Disease, multiple sclerosis, stroke, ischemic injury, Parkinson's Disease or amyotrophic lateral sclerosis (ALS) (Fernández-López et al., 2007; García et al., 2011; Kolb et al., 2019; Leussink et al., 2012; Martín-Moreno et al., 2012; Mecha et al., 2020; Rodríguez-Cueto et al., 2018; Schubert et al., 2019; Zarruk et al., 2012). However, the development of cannabinoid treatments had to face several drawbacks, mainly due to the deleterious effects that have been consistently reported including anxiety, irritability, insomnia, hyporexia, restlessness, addiction, brain structural changes or psychotic breaks (Allsop et al, 2011, 2012, 2011; Budney et al, 2004, 2008, 2004; Budney and Hughes, 2006; Chung et al., 2008; Cornelius et al., 2008; Gorelick et al., 2012; Levin et al., 2010).

The main target of these "cannabinoid" compounds are the cannabinoid receptors type 1 (CB1R) and 2 (CB2R) which, together with their endogenous ligands, forms the so-called endocannabinoid system (ECS) (Castillo et al., 2012). CB1R are one of the most abundant G-protein coupled receptors (GPCRs) in the brain and are key physiological determinants of synaptic and behavioral functions (Busquets--Garcia et al., 2018; Piomelli, 2003; Zou and Kumar, 2018). The observed pleiotropic properties of cannabinoid compounds are in part due to diverse localization of different pools of CB1R. Indeed, CB1R are present across the brain at different structural, cellular and subcellular locations, with variable expression levels and functions (Busquets-Garcia et al., 2015). Consequently, knowing how CB1R develop their functions at different locations become fundamental for the development of effective and safe cannabinoid-based treatments (Busquets-Garcia et al., 2018). Importantly, expression levels do not always correlate with the functional importance of CB1R (Busquets-Garcia et al., 2018). One example of this is the presence of the CB1R in astrocytes. Indeed, CB1R are highly expressed in neurons, whereas its presence in glial cells and astrocytes is barely detectable (Stella, 2010). However, studies during the last years have shown the crucial importance of astrocyte CB1R in the control of

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https://doi.org/10.1016/j.neuropharm.2021.108678
Received 31 March 2021; Received in revised form 24 May 2021; Accepted 17 June 2021
Available online 19 June 2021

cellular, synaptic, metabolic and behavioral functions of the brain (Bosier et al., 2013; Han et al., 2012; Jimenez-Blasco et al., 2020; Min and Nevian, 2012; Navarrete and Araque, 2008, 2010, 2008; Robin et al., 2018). In this review, we analyze these recent discoveries of CB1R-mediated regulation of astrocyte functions (calcium signals and metabolism), as well as their implications in astrocyte-neuron communications.

2. CB1R expression in astrocytes

Astrocytes represent a large proportion of brain cells, which are characterized by a close anatomical relationship with both blood vessels and synapses, and exert key metabolic, structural, synaptic and protective functions for neurons (Nortley and Attwell, 2017; Verkhratsky and Nedergaard, 2018). Indeed, by expressing in their membranes a big range of neurotransmitter receptors and transporters, astrocytes are able to detect synaptic signals coming from neurons and to modulate their activity (Araque et al., 2014).

Since the first controversies about the presence of CB1R in astrocytes, increasing number of articles have appeared in the literature in the last 20 years revealing the role of these receptors in this specific cell-type. The initial controversy of CB1R presence was due to their relatively low expression in astrocytes in comparison to neurons (Busquets-Garcia et al., 2018; Moldrich and Wenger, 2000; Salio et al., 2002; Stella, 2010), which increase the difficulty to detect astroglial CB1R by conventional immunohistochemistry or *in situ* hybridization approaches. However, despite their low levels of expression, several regions in the central nervous system (CNS) have been proven to contain astroglial CB1R, including the hippocampus (Gutierrez-Rodriguez et al., 2018), the caudate putamen (Rodriguez et al., 2001), the neocortex (Zhang et al., 2014) and the spinal cord (Hegyi et al., 2009). The use of specific deletion of CB1R in astrocytes using mutant mouse lines has demonstrated that CB1R are responsible for some of the cannabinoid-induced responses of these cells (Han et al., 2012; Jimenez-Blasco et al., 2020).

Astroglial CB1R act through specific signaling pathways that differ from the canonical neuronal ones. CB1R expressed in neurons are mainly $G_{\alpha i/o}$ coupled receptors and their activation leads to the inhibition of adenylyl cyclase (AC), of voltage-sensitive calcium channels and of inwardly rectifying potassium channels, which overall results in a presynaptic inhibition of neurotransmitter release (Castillo et al., 2012; Howlett et al., 2010; Kano et al., 2009). Conversely, astroglial CB1R have been suggested to be mainly coupled to $G_{\alpha q/11}$ proteins that activate phospholipase C (PLC) and lead to the production of inositol 1,4, 5-trisphosphate (IP_3) and calcium liberation from the internal stores (Navarrete and Araque, 2008), ultimately inducing cytosolic calcium increases in both the soma and processes of astrocytes. This is based on the observation that the CB1R-evoked calcium signal was insensitive to pertussis toxin, a toxin that blocks $G_{\alpha i/o}$ signaling pathway, but it was blocked by a PLC inhibitor and it was absent in a mouse line that lacks IP_3R2 receptors ($IP_3R2^{-/-}$ mice) (Navarrete and Araque, 2008). This study shows that the specificity of CB1R signaling is indeed cell-type dependent.

Although CB1R-evoked calcium responses cannot be induced in $IP_3R2^{-/-}$ mice, calcium analysis show that these mice still have some basal calcium activity, mostly on the fine processes (Srinivasan et al., 2015). One proposed mechanism to this IP_3-independent calcium activity has been the presence of Transient receptor potential A1 (TRPA1) channels. These proteins mediate IP_3R2-independent calcium transients in microdomains, which contribute to a reduction in synaptic GABA release (Shigetomi et al., 2011) and to D-serine release from astrocytes (Shigetomi et al., 2013). Interestingly, TRPA1 channels can be modulated by endocannabinoids (eCBs) and exogenous cannabinoids such as anandamide (AEA), Δ^9-tetrahidrocannabinol (Δ^9-THC), cannabidiol (CBD) and WIN 55,212-2 (Muller et al., 2019), opening the door for further effects of cannabinoids on astrocyte calcium regulation in a CB1R-independent manner.

At subcellular level, CB1R in astrocytes have been proven to be located not only at the plasma membrane but also associated to intracellular organelles like mitochondria (Gutierrez-Rodriguez et al., 2018; Jimenez-Blasco et al., 2020). Contrary to other pools of CB1R, astroglial mitochondrial CB1R (mtCB1R) activation has been associated with $G_{\alpha i/o}$ proteins, inhibition of mitochondrial soluble adenylyl cyclase (sAC) and reduction of mitochondrial respiration through the regulation of specific mitochondrial respiratory subunits (Hebert-Chatelain et al., 2016; Jimenez-Blasco et al., 2020). Altogether, this evidence shows that CB1R signaling and its consequent cellular responses, differ according to its cellular and subcellular localization.

In addition to the signaling pathways described above, CB1R activation also leads to the modulation of several intracellular pathways, such as the extracellular signal-regulated kinases (ERKs), protein kinase C (PKC) and others (Howlett, 2002), which also appear to be specific of certain cell types, including glial cells (Stella, 2009, 2010). These studies add further complexity to the CB1R-dependent regulation of astrocyte activity and may contribute to the diverse effects of cannabinoids in brain functions.

3. CB1R-induced release of gliotransmitters

Astrocytes actively participate in the tripartite synapse (Araque et al., 1999) by responding to neuronal activity with intracellular calcium elevations and by releasing neuroactive substances, called gliotransmitters (Volterra and Meldolesi, 2005). Gliotransmitters can then activate receptors in the pre- and/or the post-synapse to regulate neuronal excitability, synaptic transmission and, ultimately, animal behavior (Araque et al., 2014; Metna-Laurent and Marsicano, 2015; Oliveira da Cruz et al., 2016). The participation of the endocannabinoid system in the tripartite synapse and gliotransmission was first discovered in the CA1 of the hippocampal region (Navarrete and Araque, 2008), where it was shown that the activation of CB1R in astrocytes by either endogenous or exogenous cannabinoids induces intracellular signaling leading to cytosolic calcium increase. This in turn triggers glutamate release from astrocytes that activate extra-synaptic NMDA receptors in relatively far away neurons and induce depolarizing currents termed slow inward currents (SICs) (Martín et al., 2015; Navarrete and Araque, 2008). Different studies have shown that SICs are involved in neuronal synchronization (Angulo et al., 2004; Fellin et al., 2004; Pirttimaki et al., 2011), thus, through the endocannabinoid system astrocytes serve as a non-synaptic way of communication for distant non synaptically-connected neurons and may serve as a mechanism of neuronal synchronization. Additionally, as described below, astroglial CB1R have been implicated in the release of several types of gliotransmitters that exert a variety of short- and long-term synaptic effects.

3.1. Short-term synaptic regulation

Endocannabinoids are released by postsynaptic neurons during high neuronal activity and travel in a retrograde manner to bind presynaptic neuronal CB1R that inhibit voltage-gated calcium channels (VGCCs), ultimately reducing neurotransmitter release (Hoffman and Lupica, 2000; Piomelli, 2003; Szabó et al., 2014). After neuronal depolarization, this mechanism induces a synaptic depression into the depolarized neuron, a phenomenon known as depolarization-induced suppression of excitation (DSE) in glutamatergic synapses and depolarization-induced suppression of inhibition (DSI) in the case of GABAergic synapses (Kreitzer and Regehr, 2001; Maejima et al., 2001; Ohno-Shosaku et al., 2001; Piomelli, 2003; Wilson and Nicoll, 2001). Additionally, eCBs released during neuronal depolarization can activate CB1R located in surrounding astroglial processes. This activation can induce cytosolic calcium increases and gliotransmitter release that, in turn, regulates neurotransmission onto relatively far away neurons from the depolarized neuron. This phenomenon – termed lateral synaptic regulation

(Covelo and Araque, 2016)– was first described in the CA1 region of the hippocampus, where CB1R activation induces astrocyte release of glutamate that activate presynaptic type-1 metabotropic glutamate receptors ($mGluR_1$) in distant synapses, leading to an increase in glutamate release from the presynapse and eventually inducing a form of short-term lateral synaptic potentiation. Although astroglial glutamate can also regulate synaptic inputs into the depolarized neuron, these synapses could not be potentiated as the astrocyte effect was overpowered by the direct effects of the presynaptic CB1R activation (Navarrete and Araque, 2010). By this way, endocannabinoids induce a core of synaptic depression mediated by the activation of presynaptic CB1R near the source of endocannabinoids (<60 μm), and a shell of lateral synaptic potentiation induced by the activation of CB1R in astrocytes further away from the source of cannabinoids (>60 μm). Interestingly, unpublished data from our group has shown that mitochondrial calcium signaling in astrocytes may play a role in hippocampal lateral synaptic potentiation.

Lateral synaptic regulation has also been described in the dorsal striatum, a brain area critically involved in the motor system receiving dopaminergic inputs form the sustantia nigra (Gerfen, 2000; Graybiel et al., 1994). This brain region mainly contains two subtypes of GABAergic medium-spiny neurons (MSNs) that express either dopamine D_1 or D_2 receptors and that belong to two different neuronal circuits -the direct and the indirect pathways of the basal ganglia, respectively- (Kreitzer and Malenka, 2008; Surmeier et al., 2007). Striatal astrocytes respond to endocannabinoids released by MSNs with cytosolic calcium increases. These calcium responses are circuit-specific indicating that there are two different populations of striatal astrocytes that are involved in the direct or in the indirect pathway (Martín et al., 2015). Moreover, CB1R activation in striatal astrocytes can lead to the release of glutamate and presynaptic $mGluR_1$ activation inducing a lateral synaptic potentiation in MSNs of the same neural pathway far away from the origin of the endocannabinoid source (Martín et al., 2015). This suggests that the endocannabinoid system in the striatum serves as a neuron-astrocyte signaling system within specific neural circuits, inducing a lateral synaptic potentiation in a circuit-specific manner.

A form of CB1R-induced lateral synaptic regulation has also been described in the medial subdivision of the central amygdala (CeM), the main output subnucleus of the amygdala circuit. The CeM receives excitatory inputs from the basolateral amygdala (BLA) and inhibitory inputs form the lateral subdivision of the central amygdala (CeL) (Duvarci and Pare, 2014; Ehrlich et al., 2009; McDonald, 1982). Endocannabinoids released from CeM neurons activate CB1R in astrocytes leading to the release of purines that bind adenosine receptors at the presynaptic terminals and inducing a lateral synaptic regulation in relatively distant neurons. Purines released after astrocyte activation bind two types of purinergic receptors with two different functional outcomes: (i) The activation of presynaptic A_1 receptors in glutamatergic terminals impinging onto CeM deriving from BLA induces a lateral *depression* of neurotransmitter release, whereas (ii) the stimulation of presynaptic A_{2A} receptors in GABAergic terminals deriving from CeL triggers a lateral *potentiation* of neurotransmitter release. Through this mechanism, endocannabinoids regulate the excitation/inhibition ratio in the CeM, decreasing the firing frequency of the output neurons and ultimately reducing fear expression (Martin-Fernandez et al., 2017). Therefore, the endocannabinoid system differently regulates specific synapses through astrocyte activation.

A recent study performed in the suprachiasmatic nucleus (SCN) showed that CB1R in astrocytes may advance the molecular circadian clock, suggesting that endocannabinoid signaling through astrocytes is key for the timing of circadian rhythms (Hablitz et al., 2020). However, the mechanism by which this occurs is not fully understood. In this brain region, CB1R in astrocytes but not in neurons mediate the retrograde effects of endocannabinoids on GABA release, the so called DSI, by inducing adenosine release from astrocytes. This observation that astrocytes in the SCN may mediate the retrograde effects of endocannabinoids contrasts with other studies performed in other brain regions showing that while lateral synaptic regulation was mediated by astroglial CB1R (Covelo and Araque, 2018; Martín et al., 2015; Martin-Fernandez et al., 2017; Navarrete and Araque, 2010), DSE (Martín et al., 2015; Navarrete and Araque, 2010) and DSI (Covelo and Araque, 2018; Martin-Fernandez et al., 2017) were not. Therefore, it is possible that DSI is mediated by different mechanisms in different brain regions.

3.2. Long-term synaptic regulation

Accumulating evidence is showing that astroglial CB1R are not only involved in short-term synaptic regulation, but they also mediate different forms of synaptic plasticity (Heifets and Castillo, 2009). This is the case of spike timing-dependent long-term depression (tLTD), a form of synaptic plasticity that requires the synchronized firing of the pre-synaptic and post-synaptic neurons (Brzosko et al., 2019). In the neocortex tLTD induction requires the activation of astroglial CB1R (Min and Nevian, 2012) and the subsequent cytosolic calcium increases. Then, glutamate is released from astrocytes by SNARE-dependent exocytosis and activate presynaptic NMDA receptors that induce tLTD (Min and Nevian, 2012). Interestingly, in the CA1 region of the hippocampal area CB1R activation and astrocyte calcium activity are also required for inducing tLTD, possibly through astroglial D-serine release (Andrade-Talavera et al., 2016). Although a similar mechanism of action may be possible in these two brain areas, whether astroglial or neuronal CB1R are necessary for hippocampal tLTD needs to be elucidated. These findings suggest that astrocytes participate in spike timing-dependent plasticity and that the synchronization of all the elements of the tripartite synapse is necessary for the induction of tLTD.

Astroglial CB1R have been involved in other forms of endocannabinoid-mediated long-term synaptic depression (LTD). In the hippocampus, treatments with THC or other potent synthetic CB1R agonists induce hippocampal LTD in the Schaffer collaterals *in vivo* (called CB-LTD). This LTD requires the activation of astroglial but not neuronal CB1R, leading to an increase in ambient glutamate that activates extrasynaptic NMDA receptors and triggers AMPA receptor internalization. This same mechanism was found to impair spatial working memory, suggesting that *in vivo* exposure to cannabinoids induces a form of eLTD that alters spatial working memory through CB1R activation in hippocampal astrocytes (Han et al., 2012).

Although the endocannabinoid system has mainly been associated with long-term synaptic depression (LTD) (Heifets and Castillo, 2009), recent evidence shows that endocannabinoids are also necessary for long-term synaptic potentiation (LTP) by stimulating CB1R in astrocytes. This is the case of the classical hippocampal LTP that occurs in response to high frequency stimulation (HFS) of the Schaffer collaterals. Previous work had shown that astrocytes respond to the stimulation with cytosolic calcium increases (Serrano et al., 2006) and that the astrocyte calcium signal is necessary for this form of synaptic plasticity by providing the NMDA receptor co-agonist D-serine (Henneberger et al., 2010). However, the signal(s) triggering D-serine signaling during LTP induction are not fully understood. Recent work has demonstrated that astrocytes respond to endocannabinoids released during the induction protocol with calcium increases in both the soma and the processes and, in turn, they release D-serine that is necessary for LTP induction both in slices and *in vivo* and consolidation of recognition memory (Robin et al., 2018). In the neocortex, pre-activation with CB1R agonists facilitates LTP induction, which is mediated by purines released from astrocytes by a SNARE-dependent mechanism (Rasooli-Nejad et al., 2014). These findings complement previous reports showing that the CB1R activation in GABAergic synapses can facilitate LTP by inducing LTD in the GABAergic interneurons (iLTD) which reduces inhibition into glutamatergic synapses (Carlson et al., 2002; Chevaleyre and Castillo, 2003; Xu et al., 2012; Zhu and Lovinger, 2007). Therefore, it is possible that these mechanisms coexist and that endocannabinoids mediate LTD through different and complementary mechanisms. CB1R activation in

astrocytes has also been involved in a form of lateral LTP in the CA1 hippocampal region. As described above, CB1R activation in astrocytes leads to the release of astroglial glutamate and presynaptic $mGluR_1$ activation that mediate a transient lateral synaptic potentiation in relatively far away neurons. Interestingly, the simultaneous occurrence of this astrocyte-to-presynapse signaling together with retrograde signaling of nitric oxide release results in a long-term lateral potentiation. This mechanism of action indicates that the coincidence of astroglial CB1R-mediated signaling and post-synaptic activity can induce presynaptic LTP in hippocampal neurons (Gómez-Gonzalo et al., 2015).

4. CB1R-dependent modulation of astroglial glucose metabolism

Besides the aforementioned CB1R-dependent modulation of astroglial calcium dynamics and gliotransmission, recent discoveries have opened a new way by which CB1R can alter astrocyte functions, astrocyte-neuron communications and ultimately animal behavior: CB1R-mediated alterations in astrocyte metabolism.

Brain function is almost completely fueled by glucose (Attwell and Laughlin, 2001; Engl and Attwell, 2015; Yu et al., 2018). Interestingly, a mismatch between glucose and oxygen consumption occurs during increased brain activity, a phenomenon known as aerobic glycolysis (Barros et al., 2020; Fox et al., 1988), that results into a lactate surge (Hu and Wilson, 1997; Prichard et al., 1991). This production of lactate is critical for brain function by acting as an alternative energy source for neurons (Alberini et al., 2018; Barros, 2013; Magistretti and Allaman, 2018). Currently, the cellular origin and specific role of lactate in the brain is a matter of active discussion, but most of the experimental data point to astrocytes as the main producers and neurons as the main consumers (Bak and Walls, 2018; Barros and Weber, 2018; Nortley and Attwell, 2017). Moreover, lactate can modulate neurotransmission through activation of its receptor HCA1 (Bozzo et al., 2013; Herrera-López et al., 2020; Herrera-López and Galván, 2018; Lauritzen et al., 2013; Tang et al., 2014).

As glucose metabolism is tightly intermingled with brain activity, it may be expected to be sensitive to external molecules that disrupt normal brain function, such as drugs of abuse, which modulate brain glucose metabolism (Abdul Muneer et al., 2011; Berman et al., 2008; Nicolas et al., 2017; Skupio et al., 2020; Thanos et al., 2008). For instance, it has been shown that THC and synthetic cannabinoids modulate brain glucose uptake *in vivo* (Brett et al., 2001; Freedland et al., 2002; Margulies and Hammer, 1991; Miederer et al., 2017; Nguyen et al., 2012; Pontieri et al., 1999; Volkow et al., 1991, 1996; Whitlow et al., 2002). However, most of these *in vivo* studies have been phenomenological and the associated cellular/molecular mechanisms and their possible causal relationship with THC-induced behaviors remain largely unknown. Interestingly, however, it has been observed that THC alters glucose oxidation and glycogen content in astrocytes (Sanchez et al., 1998), possibly through CB1R activation.

Despite this interesting set of data and the prominent role of astrocytes in maintaining brain glucose homeostasis (Barros et al., 2017; Koepsell, 2020; Magistretti and Allaman, 2015), the modulation of astroglial metabolism by CB1R have not been fully explored, neither its possible causal relationship with CB1R-mediated effects on brain function and behavior. Recently, these questions have been tackled by our group. We have shown that, surprisingly, sustained activation of CB1R impact negatively on brain glucose metabolism by targeting astroglial mitochondrial function and resulting in altered social behavior (Jimenez-Blasco et al., 2020). More specifically, cannabinoid-induced activation of astroglial mtCB1R lead to inhibition of intra-mitochondrial cAMP/PKA signaling and to decreased phosphorylation of the complex I subunit NDUFS4. This reduces stability and function of mitochondrial complex I, affecting not only mitochondrial respiration, but also ROS production, a critical intracellular signal for astrocytes glycolysis (Vicente-Gutiérrez et al., 2021). Indeed, diminished ROS signaling promotes degradation of HIF1 alpha, a transcription factor that is considered as a master regulator of several glycolytic enzymes (Semenza et al., 1994), thereby playing a crucial role in maintaining astroglial glycolytic phenotype. The final result of astroglial mtCB1R activation is a reduced glycolytic capacity and lactate release from astrocytes which, in turn, produces neuronal bioenergetic stress and impairs mice social behavior (Jimenez-Blasco et al., 2020). This result highlights the role of astrocytes in maintaining normal brain function.

Noteworthy, as mentioned above, cannabinoids affect brain function in a time-dependent manner and THC exposure impacts glucose metabolism after hours of exposure by engaging astroglial mtCB1R. Recent unpublished data from our group suggest that a differential time-course might exist for the effects of astroglial CB1R activation on glucose metabolism. Overall, it seems that we have only started to unveil how CB1R may impact astrocytes metabolism and its relationship with brain function and behavior.

5. Endocannabinoid production by astrocytes

The canonical view of endocannabinoid signaling in the brain is that during neuronal activity eCBs are mobilized by post-synaptic neurons, thus modulating CB1R activity in pre-synaptic neurons and glial cells (Araque et al., 2017). In this model, astrocytes are seen only as "receivers" of eCBs – mainly through CB1R. However, astrocytes are also capable to produce eCBs. Studies from the beginning of 2000 demonstrated that cultured cortical astrocytes are able of producing anandamide and other acylethanolamides (Walter et al., 2002) as well as to produce and release 2-Arachydonoylglycerol (2-AG) after stimulation with ATP and endothelin-1, in a process that seems to be calcium dependent (Walter et al., 2004; Walter and Stella, 2003). These findings remained overlooked until recently, when Hegyi and colleagues described that CB1R activation in cultured spinal cord astrocytes induces a slow intracellular calcium event linked to an increased release of 2-AG. Interestingly, CB1R seem to be located in close proximity to diacylglycerol lipase alpha (DGLα), the enzyme controlling the production of 2-AG (Hegyi et al., 2018). Although astrocytes in culture are known to undergo strong phenotypic changes (Cahoy et al., 2008) and findings obtained in cultures need to be cautiously interpreted, this observation raises the possibility that astroglial eCBs production and release may be regulated by CB1R activity, which may explain some differences seen in eCBs dynamics in mouse models lacking astroglial CB1R (Belluomo et al., 2015). Altogether, these studies confirm that astrocytes from different CNS areas are able to produce and release eCBs, at least, *in vitro*.

Of note, transcriptomic analyses of *ex vivo* cortical astrocytes showed a detectable mRNA expression of the genes that drive eCBs production and metabolism, specially the production and degradation pathway of 2-AG, whose enzymes are expressed in higher levels than in neurons (Zhang et al., 2014). Moreover, a very recent work using high sensitive techniques demonstrated that astrocytes express DAGLα in the brain. Although at lower levels than in neurons, DAGLα expression was found in astrocytes from cortex, hippocampus, striatum, amygdala and hypothalamic regions; confirming that astrocytes *in vivo* can potentially produce 2-AG (Schuele et al., 2021).

The functional relevance of astroglial eCBs production and release is, however, still a matter of discussion. Cell type-specific disruption of the monoacylglycerol lipase (MAGL), the enzyme mediating the hydrolysis of 2-AG, showed that both neurons and astrocytes cooperate to terminate the 2-AG signaling (Viader et al., 2015). This interesting work found that astrocytes in culture produce and release 2-AG. However, neuron-astrocyte co-cultures and metabolic labeling experiments showed that neurons are the main producers of extracellular 2-AG while astrocytes convert this eCB to arachidonic acid that is taken up to neurons as a precursor of eCBs production (Viader et al., 2015). This study suggests that astrocytes have all the enzymes required to produce and metabolize eCBs, but their role is more implicated in a metabolic astrocyte-neuron crosstalk that contributes to the neuronal eCBs release,

similarly as it was proposed for neurotransmitters such as the glutamate-glutamine cycle (Sonnewald and Schousboe, 2016).

Two recent studies, however, brought back the idea of a signaling role of astroglial 2-AG. In the first study, genetic deletion of DAGLα specifically in a subpopulation of GLAST + astrocytes slightly changed the global amount of endocannabinoids, but showed an alteration in female mouse behaviors (Schuele et al., 2021). This study reinforces the idea that astrocyte-produced eCBs can impact on signaling and behavior. However, whether this effect is related to a disruption of the metabolic synthesis of eCBs in neurons or to the mobilization of 2-AG from astrocytes remains to be elucidated. In the second study, activation of astrocyte group II mGluRs during HFS mobilizes intracellular calcium from internal stores and induces a form of heterosynaptic depression in the hippocampus (Smith et al., 2020). This heterosynaptic depression was blocked by the CB1R antagonist AM251 and increased by JZL184, a specific inhibitor of MAGL, indicating that it is mediated by activation of CB1R by 2-AG. The authors proposed that astrocytes may release 2-AG, leading to heterosynaptic depression; however, further experiments are necessary to elucidate the source of 2-AG. For instance, it is possible that endocannabinoids mobilized upon HFS activate CB1R in astrocytes (Robin et al., 2018) leading to gliotransmitter release and to heterosynaptic depression (Covelo and Araque, 2018; Serrano et al., 2006).

Overall, the observations raised by this set of works, although preliminary, support the idea of an astroglial-mediated production and release of eCBs. Most importantly, we start to have data suggesting that these astroglial eCBs signals play a role in synaptic transmission and behavior. Although it will require further and clearer results, we may be talking of another way by which astrocytes can orchestrate neuronal activity (Kastanenka et al., 2020), as it happened with the discovery of gliotransmission 20 years ago.

6. Concluding remarks

In this review we addressed some of the mechanisms by which CB1R activity modulates astrocyte functions, astrocyte-neuron communication and, as a consequence, synaptic plasticity and animal behavior. In particular, astrocytes are implicated in some of the CB1R-dependent effects mediated by the endogenous (eCBs) and exogenous ligands (e.g. THC). Although some of these mechanisms are already well described – such as the release of gliotransmitters – we believe that the field just started to characterize other processes by which astroglial CB1R may be implicated in astrocyte-neuron communication. Moreover, the discovery that some of these effects are also mediated by mtCB1R in astrocytes, adds another layer of complexity, but also of excitement, on how the same receptor in different subcellular locations inside the same cell is involved in different functions. Since astroglial contributions to behavior in physiology and pathology are a growing field nowadays in neuroscience, we firmly believe that the study of CB1R functions in astroglial cells will continue to shed light not only in the effects mediated by cannabinoids, but also to understand the role of astrocytes in higher-brain functions.

Funding statement and acknowledgments

This paper is dedicated to the memory of our friend and colleague Federico Massa. We thank all the members of Marsicano's lab for useful discussions and for their invaluable support. This work was funded by: INSERM, European Research Council (Endofood, ERC–2010–StG–260515 and CannaPreg, ERC-2014-PoC-640923, MiCaBra, ERC-2017-AdG-786467), Fondation pour la Recherche Medicale (FRM, DRM20101220445), the Human Frontiers Science Program, Region Nouvelle Aquitaine, Agence Nationale de la Recherche (ANR, NeuroNutriSens ANR-13-BSV4-0006; ORUPS ANR-16-CE37-0010-01; CaCoVi ANR 18-CE16-0001-02; MitObesity ANR 18-CE14-0029-01; BRAIN ANR-10-LABX-0043). Graphical abstract created with biorender.com.

Declarartion of competing interest

All authors declare no conflict of interest.

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