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Endocannabinoid signaling in synaptic function

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Abstract

In the last decades, astrocytes have emerged as important regulatory cells actively involved in brain function by exchanging signaling with neurons. The endocannabinoid (eCB) signaling is widely present in many brain areas, being crucially involved in multiple brain functions and animal behaviors. The present review presents and discusses current evidence demonstrating that astrocytes sense eCBs released during neuronal activity and subsequently release gliotransmitters that regulate synaptic transmission and plasticity. The eCB signaling to astrocytes and the synaptic regulation mediated by astrocytes activated by eCBs are complex phenomena that exhibit exquisite spatial and temporal properties, a wide variety of downstream signaling mechanisms, and a large diversity of functional synaptic outcomes. Studies investigating this topic have revealed novel regulatory processes of synaptic function, like the lateral regulation of synaptic transmission and the active involvement of astrocytes in the spike-timing dependent plasticity, originally thought to be exclusively mediated by the coincident activity of pre- and postsynaptic neurons, following Hebbian rules for associative learning. Finally, the critical influence of astrocyte-mediated eCB signaling on animal behavior is also discussed.

KEYWORDS
2-AG, anandamide, astrocytes, CB1receptor, endocannabinoids, synaptic plasticity

1 | INTRODUCTION

The endocannabinoid (eCB) system is a relevant intercellular signaling system that regulates multiple physiological functions in multiple organ systems (Ahn et al., 2008; Alger & Kim, 2011; Castillo et al., 2012; di Marzo, 2009; Ohno-Shosaku & Kano, 2014; Piomelli, 2003). eCB signaling has been identified to play important roles in the peripheral and central nervous systems, including the cortex, basal ganglia, spinal cord, cerebellum, hippocampus and olfactory areas, thus being involved in a plethora of brain functions such as pain perception, food intake, learning and memory, anxiety or cognition (Navarrete et al., 2014).

The endocannabinoid system comprises mainly of two types of G-protein coupled receptors (CB1Rs and CB2Rs), two major types of endogenous neurotransmitters or endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), enzymes for the specific synthesis and degradation of these eCBs, and transporters (for reviews, see Zou & Kumar, 2018). The eCBs are lipids derived from the arachidonic acid that are released on-demand from the membrane of the postsynaptic neurons in a calcium-dependent manner regulated by neuronal activity (Castillo et al., 2012; Katona & Freund, 2012; Ohno-Shosaku & Kano, 2014; Piomelli, 2003).

The involvement of the eCB signaling in multiple brain functions is thought to be mainly mediated through the regulation of synaptic transmission and plasticity in different brain areas. The canonical cellular mechanisms underlying the eCB-induced synaptic regulation are the activity-dependent release of eCBs by the postsynaptic neuron, their action as retrograde messengers to activate presynaptic CB1Rs, and the activation of intracellular pathways that lead to the short- or

long-term depression of presynaptic neurotransmitter release (Araque et al., 2017).

In addition to this canonical process, additional cellular mechanisms have been proposed to exist. Indeed, the presence of functional CB1Rs that can be activated by endogenous and exogenous ligands has been reported in different types of glial cells (for detailed references, see other articles in the present special issue). Specifically, astrocytes, which are emerging as key neuromodulatory cells that regulate synaptic function through the so-called tripartite synapses, have been found to respond to neuronal release of eCBs and to regulate synaptic transmission.

In the present review, we will first introduce the eCB-induced synaptic regulation processes mediated by neuronal mechanisms. While this exciting topic will be succinctly introduced, the reader may find more exhaustive details in excellent recent reviews (Zou & Kumar, 2018). We will then focus on discussing the current evidence of the eCB-induced synaptic regulation by astrocytes.

2 | ECB-INDUCED SYNAPTIC REGULATION BY EXCLUSIVE NEURONAL MECHANISMS

At the end of the twentieth century, eCBs were found to regulate synaptic transmission in a form of short-term synaptic plasticity. Initial studies in the hippocampus and cerebellum described that the depolarization of postsynaptic neurons led to a transient decrease in the inhibitory synaptic efficacy, a phenomenon called depolarization-induced suppression of inhibition (DSI), and that was found to depend on eCB signaling (Llano et al., 1991; Pitler & Alger, 1992; Wilson & Nicoll, 2002). A few years later, a similar phenomenon was found to occur in excitatory synaptic terminals in the cerebellum, being named depolarization-induced suppression of excitation (DSE; Kreitzer & Regehr, 2001). Both DSE and DSI have been proposed to share similar mechanisms. First, calcium increase in the postsynaptic neuron is the initial step for the release of eCBs. Calcium enters through voltage-gated calcium channels (VGCC) with NMDA receptors also as a possible source of intracellular calcium elevations (Castillo et al., 2012). Additional mechanisms involving the neurotransmitters glutamate and acetylcholine released from presynaptic terminals have also been implicated in eCB release. The activation of group I metabotropic glutamate receptors (mGluRs) or muscarinic acetylcholine receptors (mAChRs) by their endogenous agonists induce the activation of the enzyme phospholipase C (PLC) that leads to the calcium mobilization from the internal stores (Agulhon et al., 2008; Kofuji & Araque, 2020). Then, the activation of the calcium-sensitive enzymes diacylglycerol lipase (DGL) and N-acetylphosphatidylethanolamine-hydrolysing phospholipase D (NAPE-PLD) produce 2-AG and AEA, which, after being released, act retrogradely activating CB1Rs located presynaptically (Castillo et al., 2012). Different mechanisms, not mutually exclusive, have been proposed to decrease the synaptic transmitter release, including inhibition of Ca^{2+} influx through presynaptic VGCCs and activation of presynaptic K^{+} channels (Castillo et al., 2012). Finally, eCB signaling ends by the reuptake of the eCBs and the enzymatic degradation of 2-AG by monoacylglycerol lipase (MGL) (Dinh et al., 2002) and AEA by fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996; Hillard et al., 1995; McKinney & Cravatt, 2005).

Besides mediating DSE and DSI as short-term forms of plasticity, eCBs participate in diverse forms of long-term synaptic plasticity. For example, Chevaleyre and Castillo reported a long-term depression of inhibition (iLTD) induced by eCBs release in the hippocampus. They postulated that this iLTD depends on the amount of eCBs being released and the duration of the CB1R activation. Notably, this iLTD showed spatial selectivity because it was selectively observed in the dendritic inhibitory inputs, unlike DSI that was generally manifested in dendritic and somatic inhibitory synapses. In addition, the iLTD required mGluR5 activation in postsynaptic pyramidal neurons and CB1R activation in presynaptic GABAergic terminals. By revealing that eCB-induced synaptic regulation was controlled by the magnitude and spatial–temporal properties of the eCB signaling, this study reveals the exquisiteness of eCB signaling in regulating synaptic function (Chevaleyre & Castillo, 2003).

The ECB signaling has also been shown to mediate some forms of the long-term potentiation (LTP) of synaptic transmission through network interaction. In the somatosensory cortex, the DSI induced in a subpopulation of neurons enhanced the postsynaptic Ca^{2+} spikes, which leads to the induction of the LTP, whereas subpopulation of neurons that underwent DSE instead of DSI, Ca^{2+} spikes were unaffected and LTP was absent (Maglio et al., 2018), further illustrating the spatial- and cell-specific selectivity of eCB signaling described above. Moreover, this form of LTP required the activation of the tyrosine receptor kinase B (TrkB) receptor by BDNF, in agreement with other studies showing eCB and BDNF signaling cross-talk to induce long-term synaptic plasticity in different brain areas (Gangarossa et al., 2020; Huang et al., 2008; Zhao et al., 2015). These studies also exemplify the functional relevance of the interaction between eCBs and other neurotransmitter systems, as described above for glutamatergic and cholinergic systems.

Besides the canonical mechanism of action of eCBs as retrograde signals, autocrine effects have also been reported. Activation of postsynaptic CB1Rs by eCBs released by the stimulated neuron induced a self-inhibition by the activation of inward rectifying K^{+} channels that hyperpolarized the neuron and reduced the generation of action potential (Bacci et al., 2004; Marinelli et al., 2008).

3 | ASTROCYTES SENSE ECB SIGNALING VIA CB1R ACTIVATION

Since the early 20th century, the classical view of astrocytes as passive, supportive cells has been expanded by a new concept in which astrocytes actively participate in synaptic information processing and regulation. The development of organic and genetically encoded calcium indicators (GECIs) led to the realization that astrocytes display a form of excitability reflected as calcium changes in their processes and soma. These increases in the astrocytic calcium levels can be

induced by various neurotransmitters including eCBs through activation of CB1Rs. Calcium elevations induced by eCBs in astrocytes is not only restricted to a single astrocyte but can travel to surrounding astrocytes through gap-junctions, modulating the calcium excitability in neighboring astrocytes (Figure 1) (Navarrete & Araque, 2010). The presence and functionality of CB1Rs in astrocytes has been a topic of controversy (Metna-Laurent & Marsicano, 2015; Stella, 2010). Nevertheless, in the past few years, many studies have supported the key role of astroglial CB1R in the modulation of synaptic transmission and its essential function in learning and memory processes (Han et al., 2012; Martín et al., 2015; Martin-Fernandez et al., 2017; Navarrete & Araque, 2008, 2010; Robin et al., 2018).

In neuronal cells, activation of CB1Rs usually mediate an inhibitory effect in cellular excitability. CB1Rs via Gi/o proteins suppress neurotransmitter release in presynaptic terminals. In astrocytes, CB1Rs are coupled to Gq/11 class of G-proteins (Navarrete & Araque, 2008). Gq/11 activates phospholipase C that generates the synthesis of inositol triphosphate which leads, ultimately, to release of calcium from internal stores through inositol triphosphate receptor type 2 (IP3R2) (Navarrete & Araque, 2008). The astrocytic calcium elevations induced by neuronal released eCBs have been shown to stimulate the release of neuroactive substances, called gliotransmitters, like glutamate, ATP or D-serine that can potentially influence synaptic transmission, as discussed below (Andrade-Talavera et al., 2016; Covelo & Araque, 2018; Navarrete & Araque, 2010).

The calcium signal in astrocytes, therefore, plays a key role in the release of gliotransmitters and, hence, in the regulation of synaptic function and neuronal network activity. While important progress was initially made to define the properties, mechanisms and consequences of the astrocyte calcium signal in brain slices, which provide an accessible experimental approach to study cellular activity (Perea & Araque, 2005; Porter & McCarthy, 1996; Rusakov, 2015; Volterra et al., 2014), but which present limitations in assessing normal astrocyte function in vivo. Astrocyte calcium activity in vivo has been monitored using confocal or two-photon microcopy in anesthetized or head-restrained animals (Hirase et al., 2004; Lines et al., 2020; Navarrete et al., 2012; Rusakov, 2015; Sekiguchi et al., 2016; Volterra et al., 2014), but its use is largely restricted to outer brain structures. Additional techniques, like grin lenses and fiber photometry systems, that allow monitoring calcium signal in deep brain structures, in vivo and in freely-moving behaving animals (Cobar et al., 2022; Corkrum et al., 2020; Tsunematsu et al., 2021), are expected to provide further details of the calcium dynamics in vivo while animals perform behavioral tasks. The combination of this calcium imaging techniques with the recently developed endocannabinoid fluorescent sensor (Dong et al., 2022) is expected to provide valuable information on how endocannabinoids control astrocyte calcium signaling in vivo.

4 | ECBS REGULATE SYNAPTIC TRANSMISSION THROUGH ACTIVATION OF ASTROCYTES

The participation of astrocytes in the regulation of different forms of synaptic transmission and plasticity has been demonstrated by a large number of studies in different brain areas, including the hippocampus, cortex, dorsal and ventral striatum, amygdala and cerebellum (see Kofuji & Araque, 2021). The astrocyte responsiveness with calcium elevations to different synaptically-released neurotransmitters stimulates the release of gliotransmitters that activate neuronal receptors, thus regulating neural function and synaptic activity (Araque et al., 2001; Covelo & Araque, 2016; Haydon & Carmignoto, 2006;

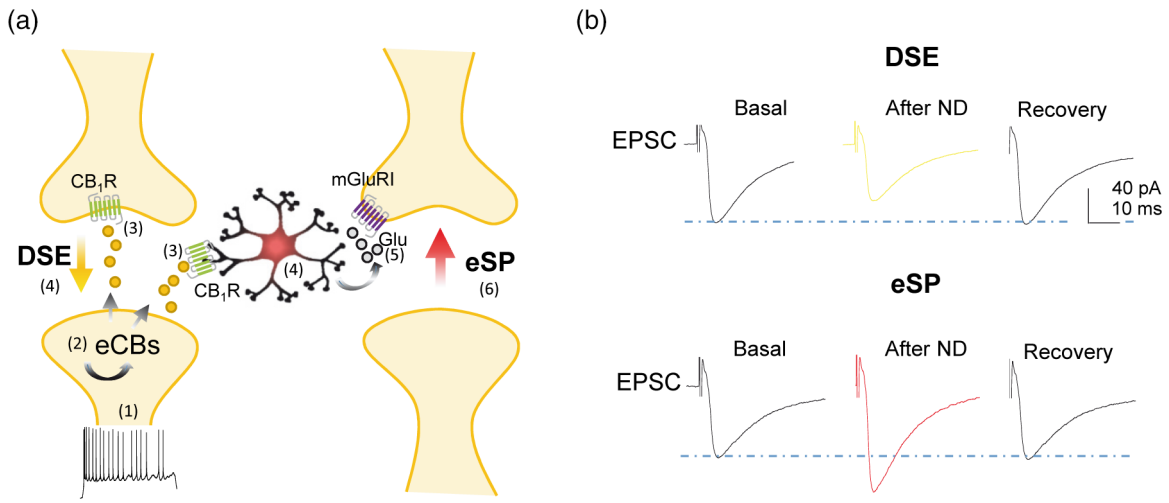

FIGURE 1 Endocannabinoids induce DSE and eSP signaling to neurons and astrocytes. (a) (1) The increase of the activity in the presynaptic terminal (2) induces the release of eCBs. (3) Binding of eCBs to the presynaptic CB_1R produces the decrease in the glutamate release inducing depolarization-induced suppression of excitation (DSE)(4). (3) Likewise, the interaction of eCBs to the astrocytic CB_1R (4) increase the mobilization of calcium from the internal stores and subsequently the exocytosis of glitransmitter glutamate and, in turn, (5) the interaction with presynaptic mGluRI in the heteroneuronal synapse generating excitatory short potentiation (eSP)(6). (b) Representative EPSC traces before, after neuronal depolarization (ND) and during recovery, showing DSE (upper traces) and eSP (bottom traces)

Navarrete et al., 2014; Nedergaard et al., 2003; Parpura & Zorec, 2010; Perea et al., 2009; Theodosis et al., 2008; Volterra & Meldolesi, 2005).

The experimental test of the idea that astrocytic calcium increases induce the release of gliotransmitters that regulate synaptic transmission and that the eCBs induced these calcium elevations, led to the description of new forms of synaptic regulatory phenomena mediated by the eCB signaling to astrocytes, such as the so-called Lateral regulation of synaptic transmission (Navarrete & Araque, 2010). Studies using the minimal stimulation technique that allows monitoring synaptic transmission at single CA1 hippocampal synapses showed that eCBs induced DSE in excitatory CA3-CA1 hippocampal synapses through the canonical mechanism of direct activation of presynaptic CB1Rs by eCBs released by the stimulated neuron. In addition, these eCBs led to the synaptic potentiation of relatively distant synapses in a neighboring neuron through the activation of astrocytic CB1Rs, which elevate the astrocyte calcium levels and stimulate the release of astrocytic glutamate that, acting on presynaptic mGluR1receptors, potentiate synaptic transmitter release (Covelo & Araque, 2018; Navarrete & Araque, 2010). This eCB-induced astrocyte-mediated lateral regulation of synaptic transmission is not restricted to the hippocampus; rather it seems to be a general phenomenon, as it has also been reported in the dorsal striatum (Martín et al., 2015) and somatosensory cortex (Baraibar et al., 2022).

Therefore, the eCB signaling, which depresses synaptic transmission when it exclusively engages neuronal processes can be transformed into a synaptic potentiating signaling when it involves astrocytes, which adds further complexity to the functional synaptic outcomes of the eCB signaling. The contrasting depressing and potentiating effects of eCBs through direct activation of neuronal processes in active synapses or indirect activation of astrocytic processes in inactive synapses, respectively, may serve as a homeostatic mechanism to maintain homogeneous synaptic function in ensembles of synapses within a circuit. Furthermore, the fact that the depressing and potentiating synaptic regulation by eCBs occurs in nearby or relatively distant synapses, respectively, further indicates the subtility of the spatial signaling by eCBs.

In addition to glutamate, the synaptic regulation by eCBs signaling to astrocytes may also involve other gliotransmitters. In the centromedial amygdala, astrocytic CB1R activation led to the release of ATP/adenosine and the consequent differential regulation of synaptic inputs. While ATP/adenosine depressed excitatory synapses from basolateral amygdala via A1 adenosine receptor activation, these gliotransmitters potentiated inhibitory synapses from the centrolateral amygdala through A2A receptor activation (Martin-Fernandez et al., 2017). Likewise, in the suprachiasmatic nucleus, which regulates the circadian rhythm, eCBs induced a decrease in the inhibitory transmission through activation of astrocytes and presynaptic A1 receptors (Hablitz et al., 2020).

Besides directly responding to eCBs, astrocytes have also been reported to be involved in the eCB-induced synaptic regulation by controlling extracellular eCB diffusion. In the hypothalamic supraoptic and paraventricular nucleus, where extensive neuronal-glial remodeling occurs in response to physiological conditions such as chronic dehydration and lactation (Hatton, 1997; Oliet et al., 2001; Theodosis & Poulain, 1999), eCB-mediated DSI was absent in control conditions but present under conditions of glial retraction or impaired astrocytic function (Di et al., 2013), suggesting that astrocytes control eCB spillover and eCB-induced synaptic regulation.

Finally, whether astrocytes are capable of releasing eCBs to regulate synaptic transmission remains largely unexplored. Initial studies reported the ability of astrocytes in culture to produce eCBs (Walter et al., 2002; Walter & Stella, 2003) upon different stimuli, like ionomycin, endothelin-1 or ATP (Walter et al., 2002, 2004; Walter & Stella, 2003). However, since these studies were performed in cultured astrocytes, which undergo strong phenotypic changes in culture, it is questionable whether such phenomenon occurs in more intact conditions. Nevertheless, a recent study in hippocampal slices has proposed that astrocytes activated by group II metabotropic glutamate receptors release eCBs that induce a transient heterosynaptic depression (tHSD) (Smith et al., 2020), although alternative astrocytic signaling independent of astrocytic eCB release may underly the observed tHSD. Further studies are required to conclusively determined whether astrocytes in situ are capable of releasing eCBs.

5 | ECBS REGULATE LONG-TERM SYNAPTIC PLASTICITY THROUGH ACTIVATION OF ASTROCYTES

Synaptic plasticity, defined as experience-dependent changes in the structure and function of the synapses is a fundamental process in brain function (Glazewski et al., 1996; Glazewski & Fox, 1996; Kuhlman et al., 2014). Long-term synaptic plasticity, which is considered the cellular mechanism underlying learning and memory (Bliss & Collingridge, 1993), can be manifested as long-term potentiation (LTP) and long-term depression (LTD) of the synaptic strength. Numerous pieces of evidence indicate that both phenomena can be regulated by astrocytes (see e.g., Adamsky et al., 2018; Cavaccini et al., 2020; Durkee et al., 2021; Henneberger et al., 2010; Navarrete et al., 2012, 2019; Noriega-Prieto et al., 2021; Pascual et al., 2005; Perea & Araque, 2007; Savtchouk et al., 2019; Suzuki et al., 2011), and specifically by astrocytes activated by eCBs.

In the hippocampus, direct activation of CB1Rs in astrocytes by exogenous cannabinoids was found to be sufficient to trigger LTD in CA3-CA1 synapses, which was associated with working memory impairments (see below; Han et al., 2012). Marsicano's group (Robin et al., 2018) also showed that high frequency stimulation of those synaptic connections induced an NMDAR-dependent LTP that required astroglial CB1Rs. Activation of these receptors elevated astrocyte calcium and supplied the necessary gliotransmitter D-serine, co-agonist of hippocampal synaptic NMDARs, to induce the LTP (Robin et al., 2018; Savtchouk et al., 2019). On the other hand, the eCB-induced astrocyte-mediated lateral synaptic regulation described above may trigger LTP in CA3-CA1 synapses when is temporally coincident with nitric oxide signaling (Gómez-Gonzalo et al., 2015). Additionally, in this brain area, the spike timing-dependent plasticity, a

synaptic plasticity paradigm based on the precise temporal coincidence of pre- and postsynaptic activity that is thought to be the cellular basis of associative learning, has been found to be controlled by eCB signaling to astrocytes. Rodriguez-Moreno's group found that the spike timing-dependent long-term depression (t-LTD) in hippocampal CA3-CA1 synapses required activation of astrocytic CB1Rs, astrocyte calcium elevations and the release of the gliotransmitter d-serine (Andrade-Talavera et al., 2016). Furthermore, this group has more recently shown that the STDP protocol that triggered the eCB-mediated t-LTD in immature (<21 days old) mice elicited a t-LTP in older (> 21 days old) mice. This t-LTP still requires astrocytic signaling (involving the release of the gliotransmitters glutamate and ATP/adenosine) but is independent of eCB signaling (Falcón-Moya et al., 2020), indicating that a developmentally regulated switch of synaptic plasticity from t-LTD to t-LTP that requires functional modification of the eCB signaling to astrocytes.

In the somatosensory barrel cortex, the t-LTD was also found to involve eCB signaling to astrocytes (Min & Nevian, 2012). In this case, the spike timing-dependent protocol induced CB1R-mediated calcium elevations in astrocytes that stimulated the release of the gliotransmitter glutamate, which activating presynaptic NMDARs induced the long-term depression of layer 2/3 synapses (Min & Nevian, 2012).

Altogether, these studies demonstrated the crucial involvement of eCB signaling to astrocytes in the induction of certain forms of synaptic plasticity. Such involvement in the spike timing-dependent plasticity has important implications. This synaptic plasticity paradigm was originally thought to be exclusively mediated by the coincident activity of the pre- and postsynaptic neuron, following Hebbian rules for associative learning (Markram et al., 2011). This idea is, however, challenged by the fact that eCB and astrocytic signaling are crucially involved in spike timing-dependent plasticity phenomena, suggesting that astrocyte activity triggered by eCB signaling is involved in associative learning and brain storage information.

6 | ECBS INFLUENCE ANIMAL BEHAVIOR THROUGH ACTIVATION OF ASTROCYTES

In addition to regulatory mechanisms of synaptic transmission and plasticity by astrocytic eCB signaling, several studies have shown that astrocytic responsiveness to endocannabinoids, as well as exogenous cannabinoids, may influence animal behavior. The use of transgenic mice in which the CB1Rs can be selectively deleted in astrocytes, e.g., crossing mice carrying the "floxed" CB1R gene ($CB1^{f/f}$) (Marsicano et al., 2003) with mice expressing the Cre recombinase under an astrocytic promoter, like GFAP (e.g., GFAP-CreERT2 mice) (Hirrlinger et al., 2006), has been instrumental in assessing the impact of astrocytic eCB signaling on behavior. Using mice lacking CB1Rs selectively in astrocytes (obtained by crossing $CB1^{f/f}$ mice with GFAP-CreERT2 mice), Han et al. showed that Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient of marijuana, induced the long-term depression of hippocampal CA3-CA1 synapses LTD that was dependent on astrocyte CB1Rs. Authors further showed that associated with these synaptic plasticity changes, the acute exposure to the exogenous cannabinoid impaired the spatial working memory in control mice, an effect that was absent in mice lacking CB1Rs in astrocytes, suggesting that the impairment of working memory by marijuana and cannabinoids was due to the activation of astroglial CB1Rs (Han et al., 2012).

Using these transgenic mice, Marsicano's group also demonstrated a key role of CB1Rs in recognition memory (Robin et al., 2018). These authors showed that mice lacking CB1Rs in astrocytes displayed reduced LTP at CA3-CA1 hippocampal synapses and impaired object recognition memory. These effects could be reverted by elevation D-serine levels, suggesting that eCB signaling stimulates the release of the gliotransmitter D-serine, which, acting as co-agonist of NMDARs, is necessary for hippocampal LTP induction (Robin et al., 2018).

The behavior output of the amygdala function has also been shown to be influenced by astrocyte activity. As described above, we found that CB1R activation of astrocytes in the centromedial amygdala, the main output nucleus of the amygdala that mediates the fear behavior, depressed excitatory transmission and potentiated inhibitory transmission in that nucleus. These effects could be mimicked by direct chemogenetic activation of astrocytes and resulted in relatively silencing the neuronal firing. Consistent with this, the fear behavior exhibited by mice with stimulated astrocytes was reduced compared to control animals, suggesting that the selective and differential regulation of excitatory and inhibitory synapses exerted by eCB-stimulated astrocytes determines animal fear responses (Martin-Fernandez et al., 2017).

7 | CONCLUDING REMARKS

For the last 20 years, astrocytes have emerged as important regulatory cells actively involved in brain function by exchanging signaling with neurons. Astrocytes can sense synaptic transmission by expressing neurotransmitter receptors that, upon activation by synaptically released neurotransmitters, elevates their intracellular calcium levels, In turn, they release gliotransmitters that, acting on neuronal receptors, regulate synaptic transmission and plasticity, which results in influencing network function and animal behavior. These astrocyte-neuron interactions, embodied in the tripartite synapse concept, have led to a paradigm shift in modern neuroscience that postulates that brain function and animal behavior result not only from neuronal activity but from the coordinated activity of astrocytes and neurons.

The demonstration of eCB-mediated neuron-astrocyte signaling has been instrumental in advancing this novel concept. As discussed in this article, evidence showing that astrocytes respond to eCBs released during neuronal activity and that they subsequently release gliotransmitters that control synaptic transmission and plasticity has not only supported this idea, but has also revealed novel synaptic regulatory phenomena with exquisite spatial and temporal properties.

The eCB signaling is widely expressed in many brain areas, being crucially involved in many brain functions and animal behaviors. While current available evidence shows that the eCB-mediated astrocytic regulation of synaptic transmission occurs in the studied paradigmatic brain regions, such as the cortex, hippocampus and amygdala, it is

feasible that it is a general phenomenon present throughout the brain. Further studies are required to test this likely hypothesis. Furthermore, studies discussed above revealed a wide variety of downstream signaling mechanisms and functional outcomes of the synaptic regulation mediated by astrocytes activated by eCBs. Additional studies in other brain areas involved in different animal behaviors may reveal novel properties and functions of this phenomenon.

AUTHOR CONTRIBUTIONS

Noriega-Prieto J, Kofuji P and Araque A designed the scope and drafted the manuscript. All authors approved the final version.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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