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REVIEW

Type-1 cannabinoid receptors and their ever-expanding roles in brain energy processes

Ignacio Fernández-Moncada | Rui S. Rodrigues | Unai B. Fundazuri | Luigi Bellocchio | Giovanni Marsicano

Université de Bordeaux, INSERM, Neurocentre Magendie, Bordeaux, France

Correspondence
Ignacio Fernández-Moncada and Giovanni Marsicano, Université de Bordeaux, INSERM, Neurocentre Magendie, U1215, F-33000 Bordeaux, France.
Email: ignacio.fernandez-moncada@inserm.fr and giovanni.marsicano@inserm.fr

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Abstract

The brain requires large quantities of energy to sustain its functions. At the same time, the brain is isolated from the rest of the body, forcing this organ to develop strategies to control and fulfill its own energy needs. Likely based on these constraints, several brain-specific mechanisms emerged during evolution. For example, metabolically specialized cells are present in the brain, where intercellular metabolic cycles are organized to separate workload and optimize the use of energy. To orchestrate these strategies across time and space, several signaling pathways control the metabolism of brain cells. One of such controlling systems is the endocannabinoid system, whose main signaling hub in the brain is the type-1 cannabinoid (CB_1) receptor. CB_1 receptors govern a plethora of different processes in the brain, including cognitive function, emotional responses, or feeding behaviors. Classically, the mechanisms of action of CB_1 receptors on brain function had been explained by its direct targeting of neuronal synaptic function. However, new discoveries have challenged this view. In this review, we will present and discuss recent data about how a small fraction of CB_1 receptors associated to mitochondrial membranes ($mtCB_1$), are able to exert a powerful control on brain functions and behavior. $mtCB_1$ receptors impair mitochondrial functions both in neurons and astrocytes. In the latter cells, this effect is linked to an impairment of astrocyte glycolytic function, resulting in specific behavioral outputs. Finally, we will discuss the potential implications of (mt)CB_1 expression on oligodendrocytes and microglia metabolic functions, with the aim to encourage interdisciplinary approaches to better understand the role of (mt)CB_1 receptors in brain function and behavior.

KEYWORDS
astrocytes, CB_1 receptors, glucose, lactate, mitochondria, neurons

Abbreviations: AC, Adenylyl cyclase; AD, Alzheimer's disease; Akt, Protein kinase B; ATP, Adenosine triphosphate; cAMP, Cyclic adenylate monophosphate; CB_1, Type-1 cannabinoid receptor; CB_1-KO, Type-1 cannabinoid receptor knockout; CB_2, Type-2 cannabinoid receptor; CX3CR1, CX3C motif chemokine receptor 1; eCBs, Endocannabinoids; ECS, Endocannabinoid system; GABA, γ-Aminobutyric acid; GFAP, Glial fibrillary acidic protein; GPCRs, G protein-coupled receptors; HIF1, Hypoxia-inducible factor 1; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; $mtCB_1$, Mitochondrial type-1 cannabinoid receptor; mTORC1, Mechanistic target of rapamycin complex 1; NADH, Nicotinamide adenine dinucleotide bonded with a hydrogen ion; NDUFS2, NADH dehydrogenase (ubiquinone) iron–sulfur protein 2; NDUFS4, NADH dehydrogenase (ubiquinone) iron–sulfur protein 4; ObR, Leptin receptor; OPC, Oligodendrocyte precursor cells; PI3K, Phosphoinositide 3-kinase; PKA, Protein kinase A; POMC, Pro-opiomelanocortin; RNA, Ribonucleic acid; ROS, Reactive oxygen species; sAC, soluble adenylyl cyclase; TBI, Traumatic brain injury; THC, Δ9-tetrahydrocannabinol; WT, Wild-type.

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1 | CB_1 RECEPTOR SIGNALING IN THE BRAIN

The brain performs several molecular and cellular processes necessary for life. For the precise spatio-temporal control of such processes, diverse stimuli activate specific signaling pathways that control intracellular and intercellular processes, ultimately promoting and controlling brain functions. One example of such signaling systems is the endocannabinoid system (ECS) (Martinez Ramirez et al., 2023; Zou & Kumar, 2018), which is known for being targeted by Δ^9-tetrahydrocannabinol (THC), the main psychoactive component of the plant *Cannabis sativa* (Stella, 2023). The molecular target of THC is the G protein-coupled receptor (GPCR) type-1 (CB_1) and type-2 (CB_2) cannabinoid receptors, that together with their endogenous ligands called endocannabinoids (eCBs), and the enzymatic machinery for eCB synthesis and degradation, are the principal components that conform the ECS (Martinez Ramirez et al., 2023; Zou & Kumar, 2018). By engaging CB_1 receptors as the main signaling hub, the ECS governs brain physiological functions such as cognitive functions, feeding, emotional states, or energy balance, among others. Consistently, its involvement in pathophysiological conditions such as psychiatric and neurological disorders has also been extensively described (Araque et al., 2017; Busquets-García et al., 2022). Interestingly, the large spectrum of functions carried out by CB_1 receptors can be explained not only by their cellular distribution across the entire central nervous system, but also by their subcellular signaling compartmentalization (Busquets-Garcia et al., 2018; Hebert-Chatelain et al., 2016; Jimenez-Blasco et al., 2020; Soria-Gomez et al., 2021). Even though CB_1 receptors are present in many brain areas, their expression magnitude is not equal in all cell types. For example, certain cortical GABAergic interneurons express very high amounts of CB_1 receptors when compared to glutamatergic neurons (Bellocchio et al., 2010). Steindel et al. (2013) provided a quantification of the differential expression and function of CB_1 receptors in GABAergic versus glutamatergic hippocampal cells. Thus, immunohistochemistry and ligand binding assays indicated that roughly 80% of hippocampal CB_1 receptors are on GABAergic neurons, whereas glutamatergic ones account for approximately 10–20%. However, functional GTPγ assays showed that, whereas "glutamatergic" CB_1 receptors account for about 50% of hippocampal cannabinoid signaling, the much more abundant "GABAergic" CB_1 receptors provide no more than 20%–25% of G protein activation by different types of cannabinoid agonists (Steindel et al., 2013). Another striking example of this disconnection between levels of receptor expression and functional relevance is astrocytes, which express almost undetectable levels of CB_1, but whose role in determining brain functions is preponderant (Busquets-García et al., 2022; Eraso-Pichot et al., 2023; Han et al., 2012; Jimenez-Blasco et al., 2020; Robin et al., 2018; Serrat et al., 2021). Notably, CB_1 receptors aside from the classical functional plasma membrane localization typical of GPCRs, these receptors can be associated to mitochondrial membranes ($mtCB_1$ receptor), and their engagement directly impact mitochondrial activity, brain function and behavior (Benard et al., 2012; Hebert-Chatelain et al., 2016; Jimenez-Blasco et al., 2020; Soria-Gomez et al., 2021).

The engagement of CB_1 receptors results in the activation of intracellular signaling cascades that are cell-type specific. In neurons, the activation of CB_1 receptors triggers $G_{i/o}$ signaling and inhibits neuronal function (Alger, 2002; Araque et al., 2017; Howlett, 2002). Similarly, $mtCB_1$ receptor signaling activates intramitochondrial $G_{i/o}$ proteins and reduces intramitochondrial protein kinase A (PKA) signaling, thereby reducing mitochondrial respiration (Hebert-Chatelain et al., 2016; Soria-Gomez et al., 2021). Conversely, activation of CB_1 receptors in astrocytes results in intracellular calcium increases that are mediated by G_q signaling, which in turn modulates astrocyte function (Covelo et al., 2021; Martin-Fernandez et al., 2017; Navarrete & Araque, 2008, 2010; Serrat et al., 2021). Alongside G protein signaling, engagement of CB_1 receptors activates diverse kinase cascades, such as mitogen-activated protein kinase (MAPK) or protein kinase B/AKT pathways (Howlett, 2002). Furthermore, CB_1 receptor activation also initiates beta-arrestin 1 and 2 signaling (Raehal & Bohn, 2014), further increasing the complexity of CB_1 receptor-mediated intracellular activity.

Taken as a whole, CB_1 receptors are key controllers of brain activity and behavior, but how they exert these diverse functions is far from being completely understood. Remarkably, in recent years it has been unveiled that the control of brain function and behavior by CB_1 receptors can occur via a direct control of cellular bioenergetics. In the next sections, we will present the most recent research on the impact of CB_1 receptors on brain bioenergetics and discuss how these observations pave the way to better understanding how CB_1 receptors put forth a fine control of brain functions and behavior.

2 | CB_1 RECEPTORS IMPACT NEURONAL ACTIVITY VIA CONTROL OF BRAIN MITOCHONDRIAL FUNCTION

The expression pattern of CB_1 receptors in different tissues, including brain, liver, skeletal muscle, and adipose tissue, highlights their contribution to the regulation of multiple functions needed for the control of whole-body energy homeostasis (Busquets-García et al., 2022). Indeed, accumulating evidence shows that brain CB_1 receptors control different processes related to this energy homeostasis, as for example appetite, energy substrate accumulation, and feeding behavior (Busquets-García et al., 2022). This regulatory oversight of energy balance and food intake may greatly vary depending on the brain regions and/or cell types where CB_1 receptors are expressed (Bellocchio et al., 2010, 2013; Koch et al., 2015; Quarta et al., 2010; Soria-Gómez et al., 2014). Accordingly, taking the hypothalamus as an example, the localization of CB_1 receptors in different hypothalamic subregions has been found to differentially control distinct energy homeostasis processes. For instance, CB_1 receptor-mediated modulation of the target of rapamycin complex 1 (mTORC1) signaling was shown to regulate glutamatergic inputs from pro-opiomelanocortin (POMC) neurons onto the hypothalamic

paraventricular nucleus (Mazier et al., 2019; Saucisse et al., 2021). Importantly, this structure plays a crucial role in metabolic responses dependent on energy availability. Similarly, the activation of CB_1 receptors in POMC neurons has been found to increase food intake through the modulation of POMC cell activity (Koch et al., 2015) and downstream effectors (Morello et al., 2016).

As metabolic signal transducers, and classically viewed as plasma membrane elements, CB_1 receptors were found to mediate cannabinoid actions by prompting a series of intracellular cascades that inhibit synaptic neurotransmitter release and/or modulate gliotransmission (Alger, 2002; Araque et al., 2017; Busquets-Garcia et al., 2018). The cytosolic signal transduction in neurons typically involves the sequential inhibition of adenylyl cyclase (AC), decreased cyclic adenylate monophosphate (cAMP), and diminished PKA signaling. However, given that functional GPCRs can also be located in intracellular compartments, such as endosomes and mitochondria (Belous et al., 2006; Irannejad & von Zastrow, 2014), interest arose as to whether CB_1 receptors could be found in other intracellular organelles besides the plasma membrane. Interestingly, seminal studies in the 70s have hinted at this possibility by showing that plant-derived cannabinoids can impact mitochondrial activity by affecting NADH oxidase activity and ATP synthesis (Bartova & Birmingham, 1976; Chari-Bitron & Bino, 1971). Nevertheless, solid evidence demonstrating the subcellular localization of CB_1 receptors in mitochondria only emerged when immunogold electron microscopy was used to observe the brains of wild-type (WT) and CB_1 receptor knockout (CB_1-KO) mice. These experiments confirmed the presence of CB_1 receptors associated with mitochondrial outer membranes in hippocampal tissue (Benard et al., 2012; Koch et al., 2015), which were christened by the authors as $mtCB_1$ receptors. Noteworthy, approximately 30% of WT hippocampal mitochondria were found to contain CB_1 receptors whereas only 3% of mitochondria showed non-specific immunoreactivity in CB_1-KO mice. Follow-up experiments focused on signal transduction that, together with intracellular readout analyses, revealed that $mtCB_1$ receptor activation promotes a decrease in cAMP concentrations and reduction of PKA and complex I activities, which ultimately lead to diminished mitochondrial respiration (Benard et al., 2012; Hebert-Chatelain et al., 2014). Moreover, diverse exogenous agonists of CB_1 receptors (such as THC, WIN55,212–2, and HU210) or JZL195 (an inhibitor of the enzymatic degradation of endocannabinoids) were found to decrease, in a dose-dependent manner, the respiration rates of purified brain mitochondria from WT mice, but not from CB_1-KO mice (Benard et al., 2012; Fišar et al., 2014). In other words, exogenous and endogenous cannabinoids activate $mtCB_1$ receptors, down-regulate mitochondrial respiration, and subsequent ATP production. Importantly, key experiments using cell-impermeant CB_1 receptor ligands, together with mice selectively lacking $mtCB_1$ receptors, showed that endocannabinoid-dependent control of synaptic plasticity is partially controlled by this subcellular receptor pool. Thus, the lack of $mtCB_1$ receptor signaling reduces the amplitude of depolarization-induced suppression of inhibition (DSI) in the hippocampus, a prototypical retrograde synaptic function of the ECS. This suggests that the participation of this subcellular receptor pools in the control of both energy availability and synaptic function (Benard et al., 2012; Hebert-Chatelain et al., 2016; Soria-Gomez et al., 2021). Moreover, $mtCB_1$ receptors present have been recently shown to promote calcium uptake by astrocyte mitochondria, thereby regulating lateral synaptic potentiation, another form of synaptic plasticity determined by astroglial CB_1 receptors (Gómez-Gonzalo et al., 2015; Martin-Fernandez et al., 2017; Navarrete & Araque, 2008, 2010; Serrat et al., 2021). Altogether, these data provided the first pieces of evidence demonstrating the functional readout of CB_1 receptors in mitochondria, most notably highlighting the $mtCB_1$ receptor pool as regulator of synaptic functions (Figure 1). Strikingly, others have not only showed that CB_1 receptors can be localized in other intracellular compartments (Delgado-Peraza et al., 2016; Grimsey et al., 2010) but also validated the presence of $mtCB_1$ receptors in other cell types and tissues, namely in sperm, ovarian cells, muscles, and white adipose tissue (Kamnate et al., 2022; Mendizabal-Zubiaga et al., 2016; Pagano Zottola et al., 2022; Rossato et al., 2005), illustrating their potential importance in shaping peripheral metabolism.

In the brain, advancements regarding $mtCB_1$ receptors and their role in the control of cannabinoid-induced modulation of brain function, allowed the establishment of $mtCB_1$ receptors as gatekeepers of bioenergetic pathways whose activity is essential for controlling different behavioral functions. Specifically, Hebert-Chatelain and colleagues have shown that acute cannabinoid-induced memory impairments in mice require the activation of hippocampal $mtCB_1$ receptors (Hebert-Chatelain et al., 2016). Importantly, genetic exclusion of the receptors from mitochondria prevented the cannabinoid-induced reduction of mitochondrial mobility, decreased synaptic transmission, and impaired memory formation. Rescue experiments with full-length versus N-terminally truncated CB_1 receptors (which block their mitochondrial localization) in CB_1-KO mice, resulted in striking differences in brain mitochondria respiration upon cannabinoid exposure. Moreover, in a series of mechanistically driven experiments, $mtCB_1$ receptors were found to signal through intramitochondrial $G_{i/o}$ protein activation, causing the inhibition of soluble AC (sAC) and reduction of PKA-dependent phosphorylation of the complex I-specific subunit NDUFS2. This cascade of intramitochondrial events was shown to lead to decreased cellular respiration and subsequent amnesic effects evoked by cannabinoids, establishing a mechanistic link between brain mitochondrial function and memory formation (Hebert-Chatelain et al., 2016).

Of note, while much effort has been made to understand the signaling cascades and the intracellular dynamics of the known CB_1 receptor subcellular pools (plasma membrane CB_1 receptors, $mtCB_1$ receptors), the complexity of this signaling system is still far from being understood. Moreover, the mechanisms that dictate the trafficking of CB_1 receptors to either plasma or mitochondrial membranes, the turn-over rate by which they occur or whether these depend on cellular activity, metabolic state, or pathological condition, remains to be elucidated.

The discovery of $mtCB_1$ receptors shed some light onto the intertwined connection between cannabinoid signaling and brain

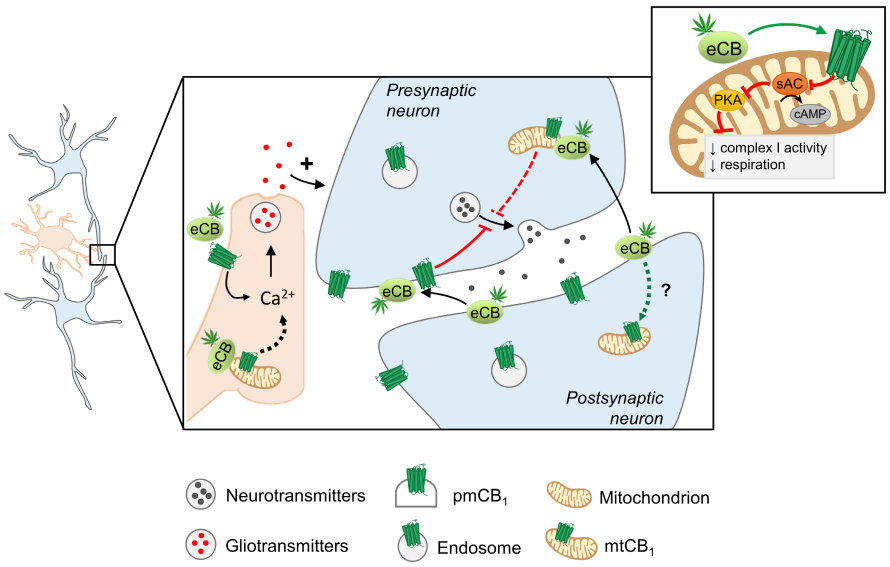

FIGURE 1 Mitochondria-associated CB_1 receptor control synaptic function. During synaptic transmission, postsynaptic neurons release endocannabinoids (eCBs) that bind to plasma membrane CB_1 receptors in presynaptic neurons and trigger a cascade of events that reduce neurotransmitter release. Alternatively, eCBs can activate the mitochondria-associated CB_1 receptors, thereby inhibiting the soluble adenyl cyclase (sAC) and reducing the intramitochondrial cAMP levels. This impairs the PKA function, and reduces the complex I activity, thereby inhibiting the mitochondrial respiration ultimately reducing energy production and inhibiting neurotransmitter release. In parallel, the activation of (mt)CB_1 receptors in neighboring astrocytes modulate the intracellular Ca^{2+} level, thereby promoting the release of gliotransmitters to trigger a lateral synaptic modulation.

bioenergetics. While the link between energy homeostasis and CB_1 receptor signaling has been known for some time now (Silvestri & Di Marzo, 2013), the presence of $mtCB_1$ in different tissues and their participation in the control of several organ functions, particularly in the brain, triggered an endless number of possibilities related to the CB_1-mediated control of metabolic processes. Indeed, $mtCB_1$ receptors have been increasingly recognized as key players in the regulation of brain metabolism and rewiring of certain behavioral responses. Amidst the repertoire of behaviors in which the activity of $mtCB_1$ receptors may play a crucial role, these include the regulation of food intake (Koch et al., 2015), hippocampal memory (Hebert-Chatelain et al., 2016), social behavior (Jimenez-Blasco et al., 2020), nociception, and motor control (Soria-Gomez et al., 2021).

The behavioral fine-tuning arises from the ability of CB_1 receptors to mediate, often in a biphasic manner, the homeostatic equilibrium of different neural circuits that underly distinct behavioral responses because of their presence in different cell types and/or intracellular compartments (Busquets-Garcia et al., 2018). In line with this rationale, the activation of CB_1 receptors at different subcellular locations in the same neuronal circuit was found to originate multimodal behavior (Soria-Gomez et al., 2021). For instance, while striatonigral $mtCB_1$ receptors were shown to drive cannabinoid-induced catalepsy, striatonigral plasma membrane CB_1 receptors were found to enable the antinociception triggered by the same drug administration. Specifically, activation of plasma membrane CB_1 receptors led to inhibition of cytosolic PKA activity and substance P release, and subsequently, to a decrease in nociception. In contrast, $mtCB_1$ receptors mediated cannabinoid-induced catalepsy through the decrease in intramitochondrial PKA-dependent cellular respiration and synaptic transmission (Soria-Gomez et al., 2021). In other words, although PKA is required for both cannabinoid inhibition of nociception and motor activity, the specific behavioral responses are determined by the differential subcellular localization of CB_1 receptors. Interestingly, mtCB1 receptors were also suggested to be important mediators in pathological conditions, particularly in the context of traumatic brain injury (TBI) (Xu et al., 2016). Briefly, $mtCB_1$ receptors were found to be quickly up-regulated after TBI and to induce the inhibition of mitochondrial cAMP, PKA, and complex I activities that consequently exacerbated metabolic defects, energy insufficiency, and neuronal apoptosis evoked by TBI (Xu et al., 2016).

Altogether, these data support $mtCB_1$ receptors as significant players in the control of brain metabolic functions, and fine-tuning modulation of synaptic function and behavioral responses mediated by cannabinoids. Nevertheless, the direct impact of $mtCB_1$ receptors on brain bioenergetics is not only ascribed to changes in mitochondrial function but also by its control of the cannabinoid-mediated modulation of astrocyte glucose metabolism.

3 | ASTROGLIAL $mtCB_1$ RECEPTORS GOVERN BRAIN GLUCOSE METABOLISM

Glucose is the obligatory energy substrate of the brain, whose consumption is controlled by workload (Hyder et al., 2013; Shulman et al., 2009). Exogenous psychoactive compounds that modify neural function, as for example cannabinoids, can also alter brain glucose metabolism. Exposure to THC results in a biphasic, dose-dependent effect on glucose metabolism, in which low doses increase glucose

consumption and high doses result in a decrease (Brett et al., 2001; Freedland et al., 2002; Margulies & Hammer, 1991; Miederer et al., 2017; Pontieri et al., 1999). Interestingly, time-dependent effects have been also observed for cannabinoid treatments. In particular, THC exposure decreases glucose consumption in specific brain areas after 1 h of treatment, and this alteration reverts to control levels after 6 h of exposure in most brain structures, but not in mesolimbic and amygdala structures. In these brain regions, glucose consumption remains low for 24 h after exposure to THC (Whitlow et al., 2002). Conversely, a high dose of the synthetic cannabinoid HU210 causes a general increase in brain glucose consumption after 1 h of treatment, which reverts to control levels after 24 h of cannabinoid exposure (Nguyen et al., 2012). These observations suggest that time-dependent effects of exogenous cannabinoids on brain glucose metabolism might accompany the diverse repertoire of behavioral alterations induced by cannabinoids. Nevertheless, the underpinnings that explain these observations are scantly known, neither it has been tested if these metabolic changes may be partially responsible for the cannabinoid-mediated alteration of brain function and behavior. However, recent data have tackled this paucity of knowledge, by demonstrating that astroglial CB_1 receptors control brain glucose metabolism and the cannabinoid-induced impairment of social behavior (Jimenez-Blasco et al., 2020). However, this is not the only observation that demonstrates the impact of cannabinoids on astrocyte energy metabolism, as early findings showed that cannabinoids modulate specific astrocyte metabolic functions (Blazquez et al., 1999; Sanchez et al., 1998). In particular, exposure to THC (6 h) caused stimulation of glucose oxidation and increased glycogen content in cultured astrocytes (Sanchez et al., 1998), thus providing evidence for a metabolic shift from glycolytic to oxidative metabolism triggered by cannabinoids. Nonetheless, the molecular target of THC in astrocytes was not clear at the moment. Ten years later, Araque and collaborators demonstrated the functional expression of CB_1 receptors in hippocampal astrocytes (Navarrete & Araque, 2008, 2010). Later on, the expression of CB_1 receptors in hippocampal astrocytes was confirmed by electron microscopy and specific deletion of the receptor in glial fibrillary acidic protein (GFAP)-positive cells (Han et al., 2012). In the light of these findings, the observations of cannabinoid-induced modulation of astrocyte energy metabolism by Guzman and collaborators, might be explained by the activation of CB_1 receptors. Consistent with this rationale, pharmacological inhibition of CB_1 receptors with AM-251 blocks the cannabinoid-mediated reduction of [U–^{13}C]glucose and [2-^{13}C]acetate oxidation in brain slices (Duarte et al., 2012), indicating that activation of CB_1 receptors causes the inhibition both neuronal and astrocyte metabolic function. Worthy of note, the expression of CB_1 receptors in hypothalamic astrocytes is necessary for expression of the leptin receptor (ObR) and the leptin-mediated increase in astroglial glycogen content (Bosier et al., 2013). Still, despite mounting evidence pointing to CB_1 receptors as controller of astrocyte energy metabolism, the involvement of astrocyte functions in the cannabinoid-mediated modulation of brain glucose metabolism was not clear, until not long ago.

Recently, it had been observed that persistent activation (24 h) of $mtCB_1$ receptors in astrocytes causes inhibition of glycolysis, which negatively impact brain function and social behavior (Jimenez-Blasco et al., 2020). The long-term effects of astroglial $mtCB_1$ receptor engagement are explained by the inhibition of sAC and PKA signaling, thereby reducing the phosphorylation of the complex I NDUFS4 subunit. This brings about a reduction in complex I activity and stability and diminished ROS production. This decreased mitochondrial function resulted in the loss of HIF1 transcriptional activity, which is critical for expression of several glycolytic enzymes (Semenza et al., 1994). Ultimately, this $mtCB_1$ receptor-mediated mitochondrial failure led to decreased astrocyte lactate synthesis, neuronal energetic stress, and impaired social behavior after 24 h of exposure to THC (Figure 2). By taking into consideration these

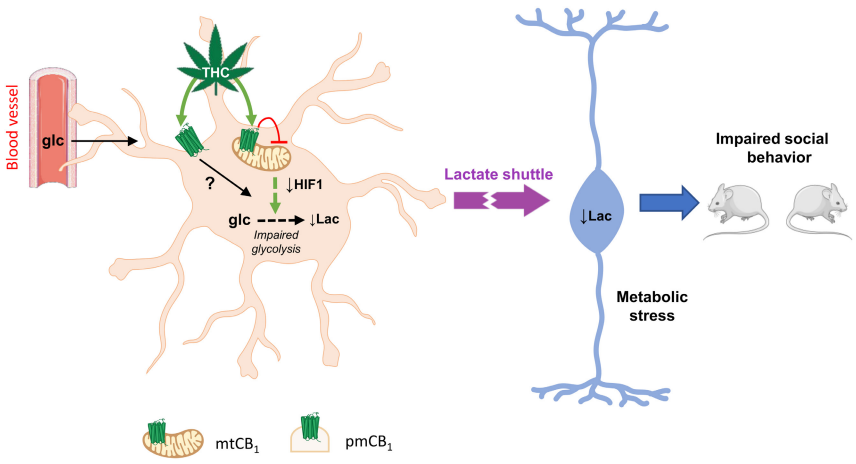

FIGURE 2 The activation of astroglial $mtCB_1$ receptors reduces lactate production and impairs social behavior. Persistent activation of $mtCB_1$ receptors inhibits the mitochondrial function in astrocytes, which in turn causes a decrease in HIF1 levels. This results in the impairment of glycolytic activity and lactate production. The primary consequence of this astrocyte metabolic failure is a decrease in lactate availability for neurons, which causes a metabolic stress that ultimately impairs mouse social behavior. Of note, the impact of plasma membrane CB_1 activation on astrocyte glucose metabolism remains to be elucidated.

results, it is plausible that the decreased brain glucose metabolism induced by high doses of THC is explained by activation of astroglial $mtCB_1$ receptors and impairment of their glycolytic function. Nevertheless, the molecular and cellular mechanisms explaining the increase in brain glucose metabolism by low doses of cannabinoids, or the time-dependent effects remains to be elucidated. Worthy of note, our knowledge about the exact effect of cannabinoids on brain glucose metabolism is still narrow, thus further studies focusing on glycogen synthesis and storage, the pentose phosphate pathway, the phosphorylated pathway, and other minor branches of the glucose metabolism will be required to fully unveil the role of the (endo)cannabinoid signaling and CB_1 receptors on the control of brain glucose metabolism.

4 | COULD CB_1 RECEPTORS CONTROL THE ENERGY METABOLISM IN OTHER BRAIN CELLS?

CB_1 receptors are widely expressed across the brain parenchyma (Kano et al., 2009). A similar observation holds true when searching for the cell types that express CB_1 receptors in brain tissue, because not only neurons and astrocytes express this GPCR, but also other glia cells as oligodendrocytes and microglia (Marinelli et al., 2023; Molina-Holgado et al., 2023), whose activity exert an important role in brain physiology and pathophysiology (Parpura et al., 2012).

Oligodendrocytes are the myelinating cells of the central nervous system (Boullerne, 2016), and they contribute, together with astrocytes, to the bioenergetic support of neuronal function (Narine & Colognato, 2022; Rosko et al., 2019; Simons & Nave, 2015). The expression of CB_1 receptors in oligodendrocyte precursor cells (OPCs) and mature oligodendrocytes had been demonstrated at the transcript, protein, and functional level (Gomez et al., 2010; Mato et al., 2009; Molina-Holgado et al., 2002; Moreno-Luna et al., 2021; Sánchez-de la Torre et al., 2022; Sanchez-Rodriguez et al., 2018; Sim et al., 2006). In spite of this, there is not much information about the subcellular distribution of CB_1 receptors in these cells. However, it had been observed with immunofluorescence detection that CB_1 receptors signal co-localizes with the fluorescence of the mitochondrial marker Mito Tracker in OPC, hence suggesting the presence of $mtCB_1$ receptors in these cells (Molina-Holgado et al., 2023). Nevertheless, the presence of CB_1 receptors associated with mitochondrial membranes in mature oligodendrocytes is still pending.

Interestingly, cannabinoids wield a neuroprotective effect that had been observed in different models of demyelination (Arevalo-Martin et al., 2012; Huerga-Gómez et al., 2021; Tomas-Roig et al., 2020). One parsimonious explanation for these observations is the modulation of OPC survival and differentiation via PI3K/Akt and mTORC1 signaling mediated by both CB_1 and CB_2 receptors (Molina-Holgado et al., 2023). Noteworthy, these molecular pathways are well known controllers of cellular energy metabolism (Manning & Toker, 2017; Saxton & Sabatini, 2017), and importantly, the synthesis of myelin is a heavy energy burden for oligodendrocytes during development, thus requiring both the engagement of glycolysis and mitochondrial function (Narine & Colognato, 2022; Rosko et al., 2019). Noteworthy, it will be interesting to determine if engagement of CB_1 receptors modulates OPC and/or oligodendrocyte metabolism to promote the synthesis of myelin. Nevertheless, fully mature oligodendrocytes sustain their energy needs mainly via glycolysis (Fünfschilling et al., 2012; Rao et al., 2017), thus a potential effect of cannabinoids on the energy metabolism of OPC and oligodendrocytes might possess a differential effect depending on the cellular state and maturity of these cells. Finally, the potential expression of $mtCB_1$ receptors might add another complex layer for the role of cannabinoids on OPC and oligodendrocyte functions. As described before, $mtCB_1$ receptors are negative regulators of glia cell metabolic function (Jimenez-Blasco et al., 2020), thus it is possible that activation of $mtCB_1$ receptors might cause a deleterious effect on myelin synthesis. Indeed, a cuprizone-induced demyelination insult is much worse in the presence of high doses of the cannabinoid WIN55,212–2 (Tomas-Roig et al., 2020), suggesting that in certain conditions this cannabinoid-mediated effect might be partially explained by inhibition of OPC and/or oligodendrocyte metabolic function. Furthermore, as the oligodendrocyte lactate production has been proposed to be necessary for axonal health (Fünfschilling et al., 2012; Lee et al., 2012; Simons & Nave, 2015), a potential oligodendrocyte metabolic malfunction alongside a demyelination insult might accelerate axonal death, and loss of neuronal function. Overall, the role of CB_1 receptors on oligodendrocyte seems complex and warrants much more studies to fully understand both its protective and potential deleterious effects.

Microglia are so far the least studied glia cells of the brain. These cells are most known for their immune-related tasks in the brain (Sierra et al., 2019), however, microglia also play a pivotal role in the maintenance of synapses and neuronal plasticity (Cornell et al., 2022; Crapser et al., 2021; Sierra et al., 2019). The expression of CB_1 receptors in microglia is controversial, as contradictory results had been obtained at the level of RNA expression (Moreno-García et al., 2020; Thion et al., 2018). Nonetheless, functional expression of CB_1 receptors was demonstrated by Najdar and collaborators just recently (De Meij et al., 2021). Whereas conditional deletion of CB_1 receptors in CX3CR1-positive cells, which correspond to the majority of brain microglia, but also macrophages (Goldmann et al., 2013), did not caused changes in mice behavior, the genetic ablation of CB_1 receptors in these cells altered the lipopolysaccharide (LPS)-induced sickness development in male mice (De Meij et al., 2021), suggesting a role for CB_1 receptors in the microglia-dependent control of inflammatory processes. Interestingly, the energy metabolism of microglia is critical for its adequate function (Kaushik & Yong, 2021; Lauro & Limatola, 2020). In physiological conditions, microglia metabolism is flexible and can support the energy required for immune surveillance either via glycolytic or mitochondrial activity (Bernier et al., 2020). However, upon microglia activation and transition toward an inflammatory phenotype, glycolysis is up regulated and mitochondria activity suppressed (Kaushik & Yong, 2021; Lauro & Limatola, 2020). Importantly, this glycolytic phenotype and

ensuing increase in lactate production may provide a mechanistic ground for the increased production of pro-inflammatory cytokines such as tumor necrosis factor alpha or interleukin-6 (Andersson et al., 2005). Moreover and interestingly, microglia isolated from the 5XFAD Alzheimer's disease (AD) mice model possess increased lactate levels, which in turn promotes the lactylation of histones (Zhang et al., 2019) and the expression of glycolytic genes that in turn reinforce the microglia glycolytic phenotype, thereby causing microglia malfunction and worsening of the AD pathology (Pan et al., 2022). All in all, these results underscore the critical role of the energy metabolism in the control of microglia function (Kaushik & Yong, 2021; Monsorno et al., 2022). Thus, by considering the emerging role of CB_1 receptors as key modulator of brain energy metabolism, it will be appealing to understand if these receptors might exert a functional control of microglia metabolism and function. For this purpose, further studies will be necessary to unveil if microglia possess $mtCB_1$ receptors and the intramitochondrial machinery necessary to trigger the inhibition of complex I activity and reduction of glycolytic flux. This effort might be of interest, as the persistent activation $mtCB_1$ receptor with cannabinoids could be a potential therapeutic target to inhibit the aberrant microglia lactate metabolism observed in AD (Pan et al., 2022), or to target the lactate-stimulated production of pro-inflammatory cytokines (Andersson et al., 2005).

5 | CONCLUSION

As we learn more about the role of CB_1 receptors in governing brain function and behavior, it is becoming apparent that their expression is not only prominent across brain structures and cell types, but also at the level of the intracellular processes controlled by CB_1 receptors. One recently described role of CB_1 receptors is the direct control of energy-related metabolic pathways in the brain. By tapping onto the mitochondrial function and glucose metabolism in neurons and astrocytes, CB_1 receptor signaling governs brain functions and behavior. However, our knowledge about the relationship between CB_1 receptors and the brain metabolic function is still limited, both at the level of the metabolic pathways engaged, and the cell types involved. On top of this, dose- and time-dependent effects of cannabinoids might exert differential outcomes on brain cell metabolism and function. Therefore, much more work is needed to fill the gaps in the ever-growing relationship between CB_1 receptor signaling, cellular energy metabolism, brain function, and behavior.

AUTHOR CONTRIBUTIONS

I.F-M., L.B. and G.M. contributed to the conceptualization and writing of the review. R.S.R and U.B.F. contributed by writing specific sections of the review. All authors read and approved the manuscript version.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no competing interests associated with the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Ignacio Fernández-Moncada https://orcid.org/0000-0002-8733-0031

Giovanni Marsicano https://orcid.org/0000-0003-3804-1951

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