Cannabinoid control of hippocampal functions: the where matters

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Introduction

Higher-order brain functions depend on synchronizing a plethora of delicately balanced systems that, like an orchestra, carry out the rhythms that define our thought processes, influence our behavior, and compose what we remember. In the brain, few structures have received as much attention as the hippocampus. Indeed, the study of this multilayered brain region has revolutionized brain research [1]. Nowadays, it is considered a key part of the mnemonic systems in different species, including humans. Furthermore, several studies have proposed the hippocampal formation as a hub where the unconscious and conscious experience occurs [1,2]. Thus, the study of the molecular mechanisms regulating hippocampal circuitries is crucial in advancing brain research and understanding neural functions. In this context, molecular effectors are seen as modulators of brain networks, implying that their actions shape cognitive and behavioral

Abbreviations
2-AG, 2-arachidonoylglycerol; Ach, acetylcholine; AEA, N-arachidonoylethanolamide; BDNF, Brain-derived neurotrophic factor; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CCK, cholecystokinin; COX-2, Cyclooxygenase-2; D1R, dopamine receptor type 1; DSI, depolarization-induced suppression of inhibition; ECS, endocannabinoid system; EtOH, ethanol; GCs, granule cells; GPCR, G protein-coupled receptor; I-LTD, inhibitory long-term depression; JNK, c-Jun N-terminal kinases; LTD, long-term depression; LTP, long-term potentiation; MAP/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinase; MCs, Mossy hiliar cells; mtCB1, mitochondrial cannabinoid receptor type 1; mTOR, mammalian target of rapamycin; NMDAr, N-Methyl-D-Asperate receptor; NOR, Novel object recognition; PGE2, prostaglandin E2; PI3K/Akt, phosphatidylinositol 3-kinases; PKA, protein kinase A; PV, parvalbumin; SWM, spatial working memory; SWR, sharp wave ripples; THC, Δ9- tetrahydrocannabinol; VHPC, ventral hippocampus.
outcomes. Indeed, brain circuits under the control of cellular and subcellular systems can underlie specific behaviors. The endocannabinoid system (ECS) is a widely distributed neuromodulatory system whose endogenous activation occurs in a precise temporal and spatial manner throughout the body and brain [3]. By achieving this specificity, it fine-tunes many physiological processes that are of most interest to current neuroscience research, such as neuronal excitation, neuroplasticity, adult neurogenesis, and cognitive performance.

The endocannabinoid system

The ECS is comprised of at least two G protein-coupled receptors (GPCR), their endogenous ligands, and the enzymes needed for their synthesis and degradation [4]. The cannabinoid receptor type 1 (CB1) is considered the most abundant GPCR in the brain [3]. The CB1 receptor is expressed in a wide range of brain regions, including the prefrontal cortex, basal ganglia, and hippocampus, the latter, which will be the topic of this review. On the other hand, the cannabinoid receptor type 2 (CB2) is mainly localized in peripheral tissue and immune cells [4], making it an attractive therapeutic target [5]. Interestingly, it was recently proven that the CB2 receptor participates in neuromodulation [6,7], but whether or not CB2 receptors are anatomically present in neurons is still under constant scrutiny [6,8,9]. The most studied receptor is the CB1 receptor, and further work is needed to clarify CB2 receptor’s location and mechanisms. In this review, we will focus mainly on the CB1 receptor modulation of hippocampal function.

The endogenous ligands that activate cannabinoid receptors are two lipid compounds known as anandamide (N-arachidonoyl ethanolamide, AEA) and 2-arachidonoylglycerol (2-AG) [3]. Endocannabinoids act as retrograde messengers; they are synthesized in a postsynaptic, activity-dependent manner, and stimulate Gα/o proteins coupled to presynaptic CB1 receptors. The activation of these receptors results in a reduction in neurotransmitter release [10]. The discovery of CB1 receptors in perisomatic and dendritic areas of neurons, glial cells (namely astrocytes), and mitochondria of both neurons and astrocytes suggests a wider collection of noncanonical mechanisms of action [3,11]. Additionally, CB1 receptors are known to activate different signaling pathways, most importantly the mammalian target of rapamycin (mTOR), the mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK), c-Jun N-terminal kinases (JNK), and phosphatidylinositol 3-kinases (PI3K/Akt) pathways [12]. The location-dependent modulation of cannabinoid signaling is reinforced by the fact that CB1 receptors form homodimers and heterodimers with other GPCRs, including CB2 receptors and dopamine, opioid, serotonergic, and orexin receptors [3,13–17]. Indeed, several heterodimers have been described as specific modulators of hippocampal function (e.g., adenosine receptor A2A-R-CB1 and orexin receptor OX1-CB1) [18,19]. Interestingly, activations of these heterodimers exert opposing effects to solitary CB1 receptor activation. The existence of these dimers could explain, at least in part, the heterogeneity in CB1 receptor’s action, depending on its location and interactions with nearby proteins [3].

The phytocannabinoids commonly found in marijuana, including its main psychoactive component Δ9-tetrahydrocannabinol (THC), and synthetic cannabinoid compounds, compose the exogenous ligands that activate cannabinoid receptors [4,20,21]. Unlike the endogenous ligands, exogenous cannabinoid agonists do not display the specificity and coordination of physiological activation. Consequently, the use of exogenous ligands leads to an unclear distinction that underlies current research between the endogenous functions of the ECS and the effects that result from a systemic pharmacological activation [22].

Cannabinoid action in hippocampal circuits

The ECS is widely distributed in the peripheral and central nervous systems and acts on different cell types and cellular compartments. Some of the most relevant characteristics of the ECS result from its presence in the hippocampus. As mentioned above, the hippocampus is a forebrain structure that participates in cognitive functions such as learning, memory, and sensory integration [7,20,23]. Additionally, it is a center of adult neurogenesis and is implicated in several neurological and psychiatric diseases [24–27]. Furthermore, it is particularly rich in CB1 receptors, whose activation is key to regulating pathophysiological processes [20,23]. In the hippocampus, the CB1 receptor is primarily localized in GABAergic neurons, but it can also be found in glutamatergic neurons and astrocytes as well as in subcellular compartments [3,28–30]. To ascertain the functions carried out by this extensive system, we need to distinguish its various roles at its different sites of action in cellular and subcellular levels. In this review, we examine the role of the CB1 receptor in hippocampal circuits (Fig. 1), discussing the findings that are shaping our current understanding of this relevant and complex system.
**Canonical action: GABAergic transmission**

CB1 receptors in the hippocampus are more densely expressed in GABAergic interneurons than in principal glutamatergic cells [31]. GABAergic inhibitory interneurons are widely distributed throughout the different hippocampal subregions. Although they represent only 10–15% of the neuronal population, they provide the inhibitory input necessary to regulate excitation and facilitate oscillatory activity. GABAergic cells are classified by their neuroanatomical characteristics, molecular expression profiles (parvalbumin (PV) or cholecystokinin (CCK) expressing cells), developmental origins, or their electrical activity (for an extensive review, see Pelkey et al.) [32]. Notably, most CCK-positive interneurons express CB1 receptors (approximately 90%), whereas only about 4% of PV interneurons do [33].

The reduction in GABA transmission has been signaled as the primary cause of the amnesic effects produced by cannabinoids. The result of the inhibition of GABAergic transmission leads to an imbalance of neurotransmitter release and an increase in excitatory firing rates. Subsequently, the mTOR signaling pathway is activated due to the increased excitation via an NMDA receptor (NMDAr)-mediated mechanism. The activation of mTOR then provokes an upregulation of translation rates and an aberrant increase in protein synthesis, which has been associated with memory deficits [34].

In the dentate gyrus, exogenous cannabinoids acting on CB1 receptors present in GABAergic neurons could also result in a disruption of short-term memory [23]. In contrast, there is evidence that physiological activation of CB1 receptors in GABAergic neurons is essential for certain types of memory [20,35,36]. The inhibition produced by endocannabinoid signaling in hippocampal GABAergic neurons is necessary for complex learning processes such as incidental associations [35]. Incidental associations are those produced when low salience stimuli are associated with other stimuli paired with a meaningful event. In other words, these initially ‘nonmeaningful’ stimuli mediate behavior through their associations with other conditioned stimuli. Mice lacking CB1 receptors from GABAergic cells display deficits in mediated aversion while maintaining normal expression of direct learning [35]. Furthermore, a specific sub-population of hippocampal GABAergic interneurons that expresses both the dopamine receptor type 1 (D1R) and CB1 receptors is necessary for hippocampal long-term episodic memory. These neurons control the late stages of novel object recognition (NOR) memory by facilitating learning-induced long-term potentiation (LTP) [36]. The dopaminergic system participates in memory consolidation [37], and particularly, in the coding of novel experiences [38]. Intriguingly, the study of these neurons also suggests that there is a dopaminergic regulation that underlies cannabimimetic signaling and memory consolidation. The exact phenotype of this subset of neurons also remains to be determined (e.g., PV or CCK). As stated above, most of the CB1 receptor-positive GABAergic neurons are also CCK-positive interneurons [39]. The ECS regulates working memory and aversive conditioning by influencing the communication between the ventral hippocampus (vHPC) and the prefrontal cortex by acting on CCK-positive GABAergic interneurons. By doing so, the ECS modulates excitation through a process of

![Cannabinoid receptors localization in the hippocampus](image)
synaptic plasticity known as depolarization-induced suppression of inhibition (DSI). CCK-positive interneurons hence mediate feedforward inhibition [40]. Thus, this subset of neurons is crucial in forming memory-relevant functional networks between hippocampal circuits and prefrontal cortex.

The cellular basis of memory relies on experience-dependent changes of synaptic transmission known as neuroplasticity. These changes can result in long-lasting effects that impact synaptic strength. The changes induced by experience can potentiate synaptic transmission through long-term potentiation (LTP) or weaken it through long-term depression (LTD). LTD is especially linked to novelty acquisition [41]. Hippocampal GABAergic regulation by the ECS has an important impact in different forms of neuroplasticity [7,35,36,42–44]. The ECS participates in controlling activity-dependent forms of plasticity by inducing long-term changes in GABAergic release. Excitatory activity in the hippocampus can induce the synthesis of 2-AG that then acts upon presynaptic GABAergic synapses, modulating excitability by regulating the inhibitory tone of hippocampal circuits [32]. Plasticity occurs as a result of an intracellular rise of calcium at the postsynaptic neuron and is mediated primarily by NMDAr [45]. Nevertheless, the ECS and CB1 receptor can modify inhibitory tone in a retrograde manner and provoke LTD through an NMDAr-independent mechanism. This LTD is observed in electrophysiological studies after applying a high frequency stimulation protocol to dendritic inhibitory synaptic terminals (I-LTD) on CA1 pyramidal neurons. Additionally, this type of LTD relies on the activation of the mGluR 1/5 [46].

The effects of the exogenous cannabinoid application on synaptic plasticity [21,45] depend on the dosage, procedure, and type of plasticity studied. The changes in synaptic plasticity that occur in the hippocampus can be further explained by the high sensitivity of the CB1 receptor [47]. The over-stimulation of CB1 receptors by even low doses of THC creates a functional tolerance that abolishes LTD [47]. Other observations indicate that the expression and function of hippocampal CB1 receptors are dynamically regulated. For example, several studies demonstrated phasic changes in CB1 receptor expression depending on the light-dark cycle, as well as a result of food ingestion, and physical activity [20,48–50]. Repeated administration of cannabinoid agents also produced changes in CB1 receptor efficacy in hippocampal GABAergic neurons [3]. Moreover, GABAergic CB1 receptors regulate inflammatory processes in the hippocampus, specifically through the regulation of hippocampal microglia. Although the mechanisms that underlie this regulation are unknown, the genetic deletion of CB1 receptors from GABAergic neurons resulted in a proinflammatory microglial phenotype and altered reactivity to bacterial infections in mice [51]. Thus, immunological regulation by hippocampal CB1 receptors represents a novel target for future research.

**Glutamatergic transmission**

In the hippocampus, there exist distinct types of excitatory neurons, including pyramidal neurons and granular and mossy cells present in the dentate gyrus and the hilus, respectively. All three types of neurons have been extensively studied given their implications in epilepsy, dementia, and neuroplasticity [52]. Considering that cannabinoids weaken the synaptic connections they act upon [3], CB1 receptors on glutamatergic terminals protect postsynaptic neurons from over-excitation. The correct balance of neuronal activation is necessary for normal brain function and to avoid the harsh effects of excitotoxicity. Indeed, the ECS is a neuromodulatory system that has been proposed as neuroprotective [53–55]. For example, following epileptiform producing injections of kainic acid, mice that did not express CB1 receptors in principal glutamatergic neurons (Glu-CB1-KO mice) suffered from more severe seizures than wild-type mice [53,54]. Furthermore, activation of the ECS alleviates disturbances in oscillatory activity, hippocampal alterations, and neuron loss in a kainic acid-induced excitotoxicity model in Guinea pigs [55]. The activation of CB1 receptors in principal glutamatergic neurons also induced intracellular signaling pathways that led to ERK phosphorylation and an increase in the transcription factor c-Fos and the brain-derived neurotrophic factor (BDNF). These changes, among others, underlie the neuroprotective shield against excessive neuronal activation [54,56,57].

The ECS also mediates neuroplastic changes in glutamatergic neurons. A cannabinoid-dependent form of LTD has been identified in the medial perforant path synapses of the dentate gyrus [58,59]. Interestingly, the expression and efficacy of these receptors could be altered by alcohol intake. Alcohol (EtOH) consumption has effects on glutamatergic CB1 receptors in the hippocampus. EtOH intake, both chronic and adolescent ‘binge drinking’, decreases the expression of CB1 receptors and endogenous cannabinoid levels. These changes result in a disruption of endocannabinoid-mediated LTD that entail long-lasting alterations of neuroplasticity and memory deficits [60]. It has also been demonstrated that the cognitive and motor...
deficits provoked by EtOH during adolescence can be reversed by an enriched environment after alcohol withdrawal [61]. It is still to be determined whether the behavioral changes correlate with functional or structural changes in the CB1 receptor.

Recent data indicate that CB1 receptor control of glutamate release in the dentate gyrus mediates the communication between the entorhinal cortex and the hippocampus [62]. In particular, by regulating the synaptic connectivity between mossy (MC) and granular cells (GC). MCs are highly active and extensive excitatory cells that have the potential to elicit LTP. CB1 receptors stabilize MC-to-GC synaptic transmission by a tonic and phasic activation that suppresses glutamate release. The tonic CB1 receptor-dependent inhibition of glutamate release negatively regulates LTP in the absence of endocannabinoids. However, phasic activity is dependent on endocannabinoid release and causes a further suppression of LTP. The phasic activity observed in these receptors could serve a protective function to avoid runaway activity that could lead to epilepsy. This study sheds light on the differential activations of CB1 receptors and their specificity and functional outcomes.

Exogenous cannabinoids also activate CB1 receptors in glutamatergic neurons. This activation, which causes an imbalance in neurotransmitters, is yet another explanation for the hippocampal-dependent memory deficits related to cannabinoid use. The imbalance of neurotransmission that results from THC exposure is also provoked by an alteration of CB1 receptors in glutamatergic cells. THC causes a reduction in CB1 receptors and alterations in hippocampal CA1 morphology that affect not only GABAergic neurons but also glutamatergic neurons, astrocytes, and mitochondria [63]. It is also worth mentioning that some of the effects observed post-THC administration might not be specific to the CB1 receptor. THC, 2-AG, and AEA can all activate both CB1 and CB2 receptors. Activation of CB2 receptors in hippocampal slices increased both dendritic spine density in CA1 neurons and miniature excitatory postsynaptic currents. Consequently, CB2 receptors influence excitatory transmission. Curiously, these effects were only observed after chronic activation of CB2 receptors and were absent in acute activations [64].

**Cholinergic and dopaminergic transmission**

Besides the classic excitatory/inhibitory transmission regulation by CB1 receptors, cannabinoid signaling also controls cholinergic and dopaminergic neurotransmitter release [54,65]. In particular, the cholinergic terminals in the hippocampus establish mixed GABAergic synapses, where both acetylcholine (ACh) and GABA are released [66]. However, the potential functional impact of cannabinoid signaling on those synapses is still unknown. In this context, cognitive and emotional processes could be regulated by CB1 receptor-dependent modulation of dopaminergic and cholinergic transmission in the hippocampus. The use of cannabinoid antagonists has been related to enhanced cognitive functions [67]. This can be explained by elevated acetylcholine levels in the hippocampus that result from cholinergic disinhibition. THC has a dose-dependent biphasic effect on ACh neurotransmission. Thus, only high doses of THC (but not low or moderate) suppress ACh levels which are mediated by dopamine receptor activation. Hence, hippocampal D2 receptor activity leads to ACh suppression induced by high doses of THC, while septal D1 receptor signaling causes an increase in ACh efflux [68]. Intrahippocampal CB1 receptor activation produces an increase in ventral tegmental area dopaminergic terminal activity (firing frequency and bursting rates). A well-balanced regulation of these systems is crucial for optimal hippocampal function, especially under periods of stress, when variations in the levels of neurotransmitters could lead to maladaptive changes associated with neuropsychiatric diseases [7,65,69]. For example, dysregulation of the hippocampal ECS and overdrive of mesolimbic dopaminergic activity could be related to the pathogenesis of schizophrenia [70].

**Beyond neurons: astrocytes**

The importance of the role that astrocytes play in information processing has become increasingly clear during the past years. Previous research has highlighted some of the mechanisms by which astrocytes participate in synaptic signaling and defined the so-called ‘tripartite synapse’ [71]. With the ECS as one of the mediators in the neuron-astrocyte relationship [72], the CB1 receptor can modulate glutamatergic transmission indirectly through astrocyte-dependent mechanisms such as the release of gliotransmitters like glutamate and D-serine [42,71,73]. The release of glutamate by astrocytes has been described as a way that astrocytic CB1 receptor activation can potentiate synaptic transmission. This effect opposes synaptic CB1 receptor activation which depresses synaptic transmission. The latter has been proposed as a short-range effect of endocannabinoid release, whereas astrocytic CB1 receptor activation has a long-range effect that targets synapses further away from the...
endocannabinoid releasing location [73]. Furthermore, the gliotransmitter D-serine is also modulated by CB1 receptor activation [42]. The release of D-serine involves a biochemical pathway known as the phosphorylated pathway which is defined as the cytosolic de novo synthesis of L-serine that stems from aerobic glycolysis and takes place primarily in astrocytes [74]. The product of this pathway allows the formation of D-serine, a coagonist of the NMDAr. The activation of astroglial CB1 receptors gives rise to an intracellular calcium increase that in turn activates the phosphorylated pathway and leads to the release of D-serine. Interestingly, recognition memory is dependent on astroglial CB1 receptor modulation of astrocytic D-Serine production [42]. Furthermore, astrocytic cannabinoid signaling is sensitive to environmental factors proven to impair memory performance. In particular, alcohol consumption during adolescence provokes a reduction in hippocampal astroglial CB1 receptors as well as astrocytic swelling [75].

Although the use of exogenous cannabinoids has been suggested as a potential therapeutic agent for certain forms of epilepsy, astroglial CB1 receptors might play an important role in the maintenance of epileptic form activity [76]. They react to glutamate and ATP produced during neuronal excitation by producing more glutamate and creating a positive feedback loop. The rise of glutamate provoked by astrocytes is also responsible for the impairment of spatial working memory (SWM) that results from cannabinoid exposure. The SWM deficits are generated by an astrocyte-dependent mechanism that is defined as hippocampal CB1-LTD (LTD induced by cannabinoid exposure) [77]. Cannabinoids induce in vivo LTD of CA3-CA1 synapses as a result of an increase in glutamate following CB1 receptor activation. The excessive glutamate release activates NMDAr and provokes the internalization of AMPA receptors that lead to LTD.

There are differences in the signaling pathways activated by endogenous cannabinoids versus exogenous ones, in this case, THC. Depending on the ligand, CB1 receptor activation could lead to stimulation or inhibition of cyclooxygenase-2 (COX-2), an enzyme that converts arachidonic acid to prostanoids. The endogenous ligand 2-AG induces the suppression of COX-2 in response to inflammation or excitotoxicity. This differential cannabinoid modulation is determined by the activation of either the G-βγ subunit (by THC) or the G-α1 subunit (by 2-AG) of the CB1 receptor-coupled G protein. The THC-induced rise in expression and activity of COX-2 is also accompanied by an increase in prostaglandin E2 (PGE2) levels. PGE2 in turn stimulates glutamate release and elevates extracellular glutamate levels. Notably, the THC-induced expression of COX-2 is particularly elevated in astrocytes. Persistent elevation of COX-2 will have a detrimental effect on synaptic integrity and plasticity and is associated with a reduced expression of glutamate receptor subunits GluA1, GluN2A, and GluN2B and a lower density of dendritic spines [78]. These observations reflect the main idea proposed by this review: Hippocampal CB1 receptor activity has complex consequences and sometimes opposing effects depending on its location [3,20] (Fig. 2).

**Inside the cell: mitochondria**

Mitochondrial CB1 receptor (mtCB1) activity has been connected to changes in bioenergetics and mitochondrial respiration that condition hippocampal synaptic transmission, and subsequently, memory consolidation [20,29,79]. The mtCB1 receptor reduces mitochondrial respiration by activating a subset of mitochondrial G proteins, namely Gsi proteins, forming a synaptic-phosphorylation of proteins involved in oxidative phosphorylation (OXPHOS). OXPHOS is the biochemical process in which ATP is formed in the mitochondria by the transfer of electrons obtained from the citric acid cycle through the mitochondrial respiratory chain [3,80,81]. Considering that synaptic transmission has drastic energetic costs, any interruptions of mitochondrial respiration directly affect this activity. Activation of the mtCB1 receptor produces a reduction in ATP and interrupts excitatory synaptic transmission in the CA1-CA3 circuit, resulting in a disruption of long-term memory [29]. CB1 receptors have recently been described in hippocampal astroglial mitochondria [28], but their implications on astrocytic activity and potential modulation of hippocampal networks are only just starting to emerge. A recent study linked astroglial mtCB1 receptor activation to a disruption of glucose metabolism and lactate production [30]. The application of THC to cultured astrocytes leads to reduced phosphorylation of mitochondrial proteins, which in turn affects reactive oxygen species (ROS) levels, resulting in the downregulation of the transcription factor hypoxia-inducible factor 1 (HIF-1). Given that the HIF-1 pathway stimulates glycolysis, its downregulation has negative effects on glucose metabolism and lactate production. The authors link these metabolic changes to changes in social-associated behavioral responses in mice. In future studies, it would be interesting to see what impact these metabolic changes have in hippocampal astrocytes. Furthermore, other organelles such as endosomes have also
been shown to express CB1 receptors [3]. Their presence in endosomal and lysosomal compartments has been related to the internalization postactivation of these receptors in the rat forebrain (including the hippocampus) [82]. Considering that there is limited data regarding this subclass of CB1 receptors, other studies must be done to fully characterize CB1 receptor expression in intracellular compartments.

**Neurogenesis: neuronal stem cells**

The subgranular zone of the dentate gyrus and the sub-ventricular area of the lateral ventricle are described as neurogenic niches in the adult mouse brain [25]. The newborn neurons produced in the dentate gyrus migrate to the granule cell layer. There, they are incorporated into local hippocampal circuitry, where they contribute to synaptic plasticity and hippocampal functions, like learning and memory. The ECS, particularly the CB1 receptor and its endogenous ligands have been involved in this process [24,83].

Previous studies demonstrate the presence of the CB1 receptor in neural stem cells (NSCs) and neural progenitor cells. Additionally, CB1 receptor deletion and inhibition of endocannabinoid synthesis result in a reduction in adult neurogenesis. The deletion of CB1 receptor from NSCs reduces the pool of astrocytes, neuroblasts, and neurons due to an altered proliferative capacity. CB1 receptor is also involved in the integration of adult-born neurons in hippocampal circuitry; mice lacking this receptor have altered neuronal growth and dendritic morphology. These morphological changes translate to physiological alterations that affect LTP in the hippocampus, potentially leading to deficits in spatial memory and an enhancement of behavioral despair [83].

**System-wide regulations: cannabinoid control of network oscillations**

Brain functions are maintained by synchronous oscillatory activity of neuronal networks. Specifically,
hippocampal-dependent memories are supported by three types of network activity that aid the process of memory formation and consolidation. These are hippocampal theta (4–12 Hz), gamma (30–80 Hz), and ripple oscillations (100–200 Hz). The first two are hypothesized to be essential for the encoding of episodic memory, whereas ripple oscillations are associated with long-term memory consolidation [84]. By provoking variations in the firing patterns of hippocampal neurons, CB1 receptor agonists reduce cell assembly organization, and spike synchrony leading to changes in network oscillations. The lack of firing coordination as well as the reduction in power of local field potentials (especially theta power) correlated with memory impairments [20,84]. Apart from decreasing overall synchrony, the synergistic effects of systemic cannabinoid activation decrease the amplitude of the three types of network activity mentioned above, as well as reduce spiking correlation of the hippocampus and prefrontal cortex [85]. At a behavioral level, the activation of CB1 receptors by endogenous cannabinoids is thought to play a role in the downregulation of aversive memories and this could explain the physiological role for these changes [11,29,46].

The role of the hippocampus in the coding of spatial information is well characterized. Additionally, it also participates in the process of nonspatial information, like time [1]. In humans, a recent study concluded that THC administration leads to time overestimation, only in infrequent cannabis users [86]. Although the concept of specific time cells is in dispute, the neural substrate of the spatiotemporal construction probably lies within the hippocampus [1,87]. Regardless of whether it is time cells or more complex network activation patterns that dictate our perception of time, it is likely that these events are mediated by the ECS. Altogether, considering the well-known effect that THC has on the perception of time [86,88], the study of CB1 receptor activation and its impact on time perception is a complex, yet fascinating area of future research.

The lack of highly selective antibodies for CB2 as well as of a full CB2 knockout mouse have hindered the study of this receptor and led to controversy. Notwithstanding, evidence of a physiological role for CB2 receptors in neurons begins to emerge [4]. Stempel et al. have provided an in-depth description of CB2 receptor expression and characterized the effects of CB2 activation in hippocampal pyramidal neurons. Although the hyperpolarizing effects they observed in these neurons post-CB2 receptor activation were restricted to CA2/3, they acknowledge the possibility of similar effects extending to the whole of the hippocampal formation. The hyperpolarization of postsynaptic pyramidal neurons could serve a neuroprotective role complementary to that of CB1 and fine-tune hippocampal excitability. The modulation of excitability exerted by CB2 could also facilitate slow gamma oscillations in CA3 thus modifying local network rhythms and memory. Additionally, it is precisely in CA3 where the encoding of episodic memories proposed as the neural representation of consciousness takes place [2,89]. How, when, where, and to what extent CB2 activation modifies normal brain function will be a compelling topic in endocannabinoid research.

Sleep

Sleep can be described as a natural recurrent and reversible state of reduced wakefulness and responsiveness to external stimuli. It is composed by alternating transitions between rapid eye movement (REM) sleep and non-REM sleep. The latter includes slow wave sleep (SWS) and light sleep. REM sleep is more abundant in later parts of the night and is characterized by the desynchronization of neuronal networks, pontogeniculo-occipital (PGO) waves, and theta activity. REM sleep has been associated with both hippocampus-dependent and independent forms of memory consolidation. Additionally, REM sleep is characterized by a high cholinergic activity that has been proposed to support memory consolidation [90]. As reported by Rueda-Orozco et al., an injection of AEA directly in the hippocampus leads to an increased frequency (not duration) of REM sleep when administered in the dark phase (active phase) of a 12 h light/dark cycle. Given that they had previously found that the concentrations of endocannabinoids and the density of CB1 receptor varied depending on the light-dark cycle [48], they also studied the effect that endocannabinoids had on sleep at different times of the day. They hypothesize that the CB1 receptor could play a role in the generation of REM sleep and that the administration of endocannabinoids could favor REM sleep in an unfavorable context such as insomnia [91]. An overall reduction in REM sleep has also been observed after administration of various types of CB1 receptor agonists. The reduction in time spent in REM sleep can also be explained by reduced cholinergic activity provoked by high doses of CB1 receptor agonists. CB1 receptor activation also leads to an increase in total time spent sleeping. On the contrary, CB1 receptor antagonists have the opposite effect and lead to an increase in wakefulness [49].

The ECS is considered to act as a homeostatic modulator of plasticity and has the capacity to promote not
only potentiation of synaptic strength but also downscaling or inhibition of certain synapses [44,92]. Intriguingly, these processes also occur during REM sleep states [93,94]. Endocannabinoids have also been shown to disrupt sharp wave ripples (SWR). SWRs are fast oscillations (120–250 Hz) that occur during slow wave sleep and are associated with memory consolidation. The reduction in neurotransmitter release provoked by AEA in hippocampal slices reduced the frequency of SWRs and reorganizes spiking patterns [95]. This finding could be linked to the memory deficits associated with the use of exogenous cannabinoids. Additionally, the ECS has also been proposed as an influence over the content of dreams, given its ability to modulate cognitive, emotional, and memory-related processes as well as consciousness and wakefulness [96].

Pathophysiology

ECS dysfunction is associated with a significant number of pathologies. As mentioned before, the ECS mediates inflammatory responses via GABAergic neurons and astrocytes and neuroprotective functions via glutamatergic neurons. Furthermore, alterations in the ECS could underlie age-related neurodegeneration [97]. A reduced expression of CB1 receptors in the hippocampus is linked to age-related cognitive decline and the deletion of CB1 receptors from GABAergic hippocampal neurons led to neuronal loss and increased inflammation [98]. Additionally, disrupted endocannabinoid signaling between GABAergic neurons and microglia is linked to age-related dysfunction and development of neurodegenerative disorders [99]. Given that the CB1 receptor is also involved in sleep regulation, these changes have also been proposed to contribute to sleep disturbances in the elderly [100]. Alterations in CB1 receptor signaling specific to glutamatergic neurons could also play a role in age-related cognitive decline and reduced synaptic integrity and plasticity. Given that CB1 receptor activation increased BDNF expression, a reduction in levels of this neurotrophic factor could contribute to age-related pathologies and excitotoxicity [97].

Interestingly, abnormalities in the ECS have been found in both animal models of Alzheimer’s disease (AD) and human brain samples. As explained by Thompson 2020, these alterations depend on the stage of the disease. Early AD is characterized by an increase in CB1 receptor expression and activity while the opposite occurs in later stages of the disease. Accordingly, the deletion of CB1 receptors worsened AD progression and synaptic dysfunction [101]. On the other hand, components of the ECS have been proposed as biomarkers for mood and neuropsychiatric disorders [102]. Decreased endocannabinoid tone has been reported in rat models of chronic stress as well as in women with major depression [103]. Moreover, The ECS is also consistently disrupted in schizophrenia [104,105]. Animal models of schizophrenia have shown decreased levels of CB1 receptors in the hippocampus, and human postmortem brain samples have shown altered levels of endocannabinoids AEA and 2-AG [105,106].

Recent data seem to support the possibility that CB2 receptor signaling mediates microglial gene expression, influencing the fluctuations between proinflammatory (M1), neuroprotective (M2), and homeostatic (Mo) activations [87]. Considering that alterations in microglial activation have been associated with AD, schizophrenia, stress, and autism, further studies regarding these interactions could shed light on the involvement of the hippocampal ECS in these pathologies [99,107–109]. Preliminary data from our laboratory support CB1 receptor localization in microglial cells (Grandes et al., personal communication). However, the precise role of both CB1 and CB2 receptors on microglia and the related inflammatory impact on hippocampal functions is still to be determined.

Alterations in endocannabinoid signaling and neuroinflammation are strongly linked to epileptic seizures. The ECS’s role of maintaining a neuroprotective, anti-inflammatory environment and preventing excitotoxicity make it a major player in the pathophysiology of epilepsy [110]. Thus, cannabinoid activity acts as a break for recurrent excitatory signaling [62], making it an important drug target for epilepsy [111]. Despite this fact, the multiphasic cannabinoid action raises some issues, as we have also stated before in this review. A decreased activation of the ECS at inhibitory synapses will potentiate network excitation whereas the same decrease in excitatory synapses will have the opposite effect. The role of astrocytic CB1 receptors in maintaining epileptiform activity must also be considered (see section on astrocytes). Lastly, potentiating the ECS’s anti-inflammatory actions requires a careful study of downstream signaling cascades and interactions. In summary, the functional dissection of hippocampal CB1 receptors is crucial to further understand brain disorders and age-related pathologies.

Conclusions

It is more and more evident that ‘the where matters’ when studying the influence of CB1 receptor activity in
Cannabinoid control of hippocampal functions

pathophysiological processes. In the hippocampus, canonical activation of CB1 receptors in GABAergic cells participates in the consolidation of memories and downscaling of possibly aversive memories [11,35,36,46]. On the other hand, cannabinoid action on glutamatergic cells regulates LTP and serves a neuroprotective function by suppressing glutamate release and favoring the secretion of neurotrophic factors [53,54,62]. Meanwhile, actions in astrocytes stand out because they ‘contradict’ previously stated effects. CB1 receptors in astrocytes participate in a positive feedback loop activated by glutamate and produce the NMDAr coagonist D-Serine thus favoring glutamatergic activity [42,73,76]. Furthermore, mCB1 receptors regulate mitochondrial respiration and neuronal energy metabolism, resulting in modulation of memory processes and social recognition [29,79]. Finally, CB1 receptors present in neural stem cells enhance adult neurogenesis and facilitate the integration of new neurons into hippocampal circuitry [12,24]. Thus, hippocampal cannabinoid signaling forms a key molecular mechanism that composes the cellular basis of cognitive functions and related pathological conditions.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to the writing of the manuscript.

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