Progress in Lipid Research 91 (2023) 101239

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Endocannabinoid signaling in adult hippocampal neurogenesis: A mechanistic and integrated perspective

Sergio Oddi [a,b,*], Maria Teresa Fiorenza [b,c], Mauro Maccarrone [b,d]

[a] Department of Veterinary Medicine, University of Teramo, Via R. Balzarini 1, 64100 Teramo, Italy
[b] European Center for Brain Research/IRCCS Santa Lucia Foundation, Via del Fosso di Fiorano 64, 00143 Rome, Italy
[c] Department of Psychology, Division of Neuroscience and "Daniel Bovet" Neurobiology Research Center, Sapienza University of Rome, Via dei Sardi 70, 00185 Rome, Italy
[d] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Via Vetoio Snc, 67100 L'Aquila, Italy

A B S T R A C T

Dentate gyrus of the hippocampus continuously gives rise to new neurons, namely, adult-born granule cells, which contribute to conferring plasticity to the mature brain throughout life. Within this neurogenic region, the fate and behavior of neural stem cells (NSCs) and their progeny result from a complex balance and integration of a variety of cell-autonomous and cell-to-cell-interaction signals and underlying pathways. Among these structurally and functionally diverse signals, there are endocannabinoids (eCBs), the main brain retrograde messengers. These pleiotropic bioactive lipids can directly and/or indirectly influence adult hippocampal neurogenesis (AHN) by modulating, both positively and negatively, multiple molecular and cellular processes in the hippocampal niche, depending on the cell type or stage of differentiation. Firstly, eCBs act directly as cell-intrinsic factors, cell-autonomously produced by NSCs following their stimulation. Secondly, in many, if not all, niche-associated cells, including some local neuronal and nonneuronal elements, the eCB system indirectly modulates the neurogenesis, linking neuronal and glial activity to regulating distinct stages of AHN. Herein, we discuss the crosstalk of the eCB system with other neurogenesis-relevant signal pathways and speculate how the hippocampus-dependent neurobehavioral effects elicited by (endo)cannabinergic medications are interpretable in light of the key regulatory role that eCBs play on AHN.

1. Introduction

N-Arachidonoylethanolamine (AEA, also known as "anandamide") and 2-arachidonoylglycerol (2-AG) represent the up-to-date best-characterized endocannabinoids (eCBs), namely the endogenous ligands for CB_1 and CB_2 receptors [1,2]. Despite their structural simplicity, these bioactive lipids highlight an unexpected organizational complexity in terms of mechanisms of synthesis, transport, degradation, and signaling, which collectively constitute the so-called "eCB system" (ECS), an evolutionary ancient lipid signaling system widely expressed throughout the body and involved in many aspects of human health and disease. Within the central nervous system (CNS), the ECS is activated by

Abbreviations: 2-AG, 2-arachidonoylglycerol; abGC, adult-born granule cell; AC, adenylyl cyclase; AEA, *N*-arachidonoylethanolamine; AHN, adult hippocampal neurogenesis; AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; BDNF, brain derived neurotrophic factor; CA1/2/3, *cornu ammonis* subfield 1, 2 and 3; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; $CB_{1/2}$, cannabinoid receptor type 1 and 2; CCK, cholecystokinin; CCK-INs, cholecystokinin-expressing interneurons; CNS, central nervous system; CREB, cAMP response element-binding protein; DAGL, diacylglycerol lipase; DG, dentate gyrus; DSI, depolarization-induced suppression of inhibition; DSE, depolarization-induced suppression of excitation; EC, entorhinal cortex; eCB, endocannabinoid; ECS, endocannabinoid system; EMT, endocannabinoid membrane transporter; ERK, extracellular-signaling regulated protein kinase; FAAH, fatty acid amide hydrolase; FGF2, fibroblast growth factor 2; GABA, gamma-aminobutyric acid; GAD, glutamate decarboxylase; GC, granule cell; GCL, granule cell layer; GIRK, $G_{i/o}$ coupled inwardly rectifying K^+ channel; GPCR, G protein-coupled receptor; GSK3β, glycogen synthase kinase 3 beta; IML, inner molecular layer; LPP, lateral perforant pathway; LTD, long-term depression; LTP, long-term potentiation; KO, knock-out; MAGL, monoacylglycerol lipase; MC, mossy cell; ML, molecular layer; MML, middle molecular layer; MPP, medial perforant pathway; $mtCB_1$, mitochondrial CB_1; mGluR1/5, metabotropic glutamate receptors 1 and 5; mTORC1, mammalian target of rapamycin complex 1; NArPE, *N*-arachidonoyl phosphatidylethanolamine; NAT, *N*-acyltransferase; NCAM, neural cell adhesion molecule; NGF, nerve growth factor; NMDAR, *N*-methyl-D-aspartate receptor; NPC, neural progenitor cell; NSCs, neural stem cells; OML, outer molecular layer; PC, principal cell; PI3K, phosphatidylinositol-3-kinase; PKA, protein kinase A; PKC, protein kinase C; PP, perforant pathway; PPAR, peroxisome proliferator activated receptor; PV-INs, parvalbumin-expressing interneurons; ROCK, Rho-associated kinase; SGZ, subgranular zone; SSI, slow self-inhibition; TRPV1, transient receptor potential vanilloid type-1 channel; VGCC, voltage-gated Ca^{2+} channel; vGlut, vesicular glutamate transporter.

* Corresponding author at: Department of Veterinary Medicine, University of Teramo, Via R. Balzarini 1, 64100 Teramo, Italy.
E-mail address: soddi@unite.it (S. Oddi).

https://doi.org/10.1016/j.plipres.2023.101239
Received 4 January 2023; Received in revised form 1 June 2023; Accepted 25 June 2023
Available online 27 June 2023

several internal and/or external stimuli, eliciting multiple adaptive responses, such as anti-excitotoxic and antioxidant defenses, as well as neuromodulatory and immunomodulatory responses, which altogether help to maintain and/or reestablish brain homeostasis in the face of a challenging environment [3,4].

During the embryonic development of the central nervous system (CNS), eCB signaling plays a crucial role in regulating neuronal identity acquisition [5–7]. In the adult brain, the ECS maintains its role in regulating neural cell fate decisions in two main areas: the subventricular zone lining the lateral ventricles and the hippocampal dentate gyrus (DG). In the last few years, the regulatory role of the brain ECS in adult neurogenesis has been extensively investigated in rodents and recently discussed in comprehensive reviews [6,8–10]. Given the topic's inherent vastness and complexity, we decided to focus our attention on adult hippocampal neurogenesis (AHN).

AHN is the process whereby neural stem cells (NSCs) — self-renewing, multipotent progenitor cells — in the subgranular zone (SGZ) of the DG of the hippocampus give rise to adult-born granule cells (abGCs) and astrocytes throughout adulthood [11]. These new neurons impose substantial remodeling in the pre-existing hippocampal neural circuitry, thus influencing several functions that rely on the hippocampus, including the discrimination of spatial contexts associated with positive or negative rewards, detection of novel features in a familiar environment, resilience to stress and depression, and the ability to forget old and aversive memories [12].

Here, we aim to review relevant information available so far that supports a prominent role of eCB signaling in controlling AHN, both under normal and pathological conditions. To meet this objective, we have divided the review into 5 parts, the first of which provides a brief introduction to the topics covered. Part 2 includes a brief description of the gross anatomy of the DG and the cytoarchitectonics of the hippocampal neurogenic niche, introducing the reader to the nature of the neurogenic process and the special morphological and molecular features of stem cells, neural progenitors, and new neurons generated in the adult hippocampus. The description of the anatomical distribution of the molecular components of the eCB signaling, either at the cellular or subcellular level, is instrumental for understanding its physiological role within the hippocampal neurogenic niche. Therefore, in Part 3, we will briefly describe the molecular organization of this lipid signaling system, with a particular focus on its expression and functions within the brain and, more specifically, in the DG, emphasizing the active presence of its key components, as well as of its main signaling pathways in the context of the different cell types of the neurogenic niche. Part 4 is devoted to highlighting the complexity of the role played by ECS in regulating several biological processes that could directly or indirectly influence the fate and behavior of NSCs and their descendants. In Part 5, we provide a brief overview of the mechanisms governing the neurogenic process in the adult brain and describe how the ECS, acting at several molecular and cellular levels, can be part of the complex network of signaling pathways that translate pro- and antineurogenic stimuli — such as enriched environment, physical activity and chronic stress — into specific modulation of the rate of AHN.

2. Overview of the adult hippocampal neurogenesis

The hippocampus is an essential part of the brain's limbic system, responsible for encoding and retrieving memories formed continuously throughout an individual's life. For this peculiar function, the hippocampus must remain plastic past prenatal and early postnatal life and into adulthood. Such plasticity seems to be essentially ensured by the uninterrupted birth and functional integration of adult-born neurons in an integral region of the hippocampal formation: the DG.

The neurogenic process in the adult hippocampus, along with its pathophysiological implications, has been extensively described by some excellent reviews [11–13]. Here, we will give only a brief overview of the anatomical organization of the DG and the cytoarchitecture of its neurogenic niche, the specialized microenvironment within which AHN occurs.

2.1. Neuroanatomy of the dentate gyrus

Within the hippocampus formation, the DG forms a V-shaped structure embedded into the curved *cornu ammonis* (CA), which itself is composed of three major subfields, namely CA1, CA2 and CA3 (Fig. 1B). Histologically, the DG is divided into three layers, or strata (sing. stratum): (*i*) the molecular layer (ML), (*ii*) the GC layer (GCL), and (*iii*) the *hilus* (Fig. 1B).

The ML, also known as *stratum moleculare*, is the most superficial layer of the DG and is divided into three sublayers with approximately the same width: inner, middle, and outer ML (IML, MML, and OML). It is a relatively cell-free layer, mainly occupied by the dendrites of the GCs and the axons of the perforant pathway (PP) that originate from the entorhinal cortex (EC) and form synaptic contacts with dendrites of GCs. More specifically, EC projections are the major source of cortical input to the hippocampus and can be divided into the lateral and medial PPs (LPP and MPP), arising from the lateral and medial EC, respectively (Fig. 1C).

The GCL, or *stratum granulosum*, is formed by four to eight layers of densely packed cell bodies of GCs, the principal neurons of the DG. It also contains sparse gamma-aminobutyric acid-containing (GABAergic) interneurons and afferent fibers of inputs extrinsic to the DG. GCs have a round-to-oval cell body measuring about 25 μm in diameter. Mature GCs generally have only one primary apical dendrite emerging from the soma and which is vertically oriented toward the ML. This dendrite remains poorly bifurcated until it reaches the ML, where it branches extensively (Fig. 1C).

The hilus, or polymorphic layer, is the innermost layer of the DG and contains the unmyelinated axons of GCs, called mossy fibers, which project into CA3 to make excitatory synapses on the dendrites of pyramidal cells (PCs) of this hippocampal area. In addition, this layer contains mossy cells (MCs), the other major glutamatergic neurons of the DG, and two classes of perisomatic GABAergic neurons, the parvalbumin-expressing and the cholecystokinin-expressing interneurons (PV-INs and CCK-INs) (Fig. 1C). The hilus contains a third population of interneurons expressing somatostatin, which inhibit distal dendrites of GCs and other interneuron types near their PP input synapses [14].

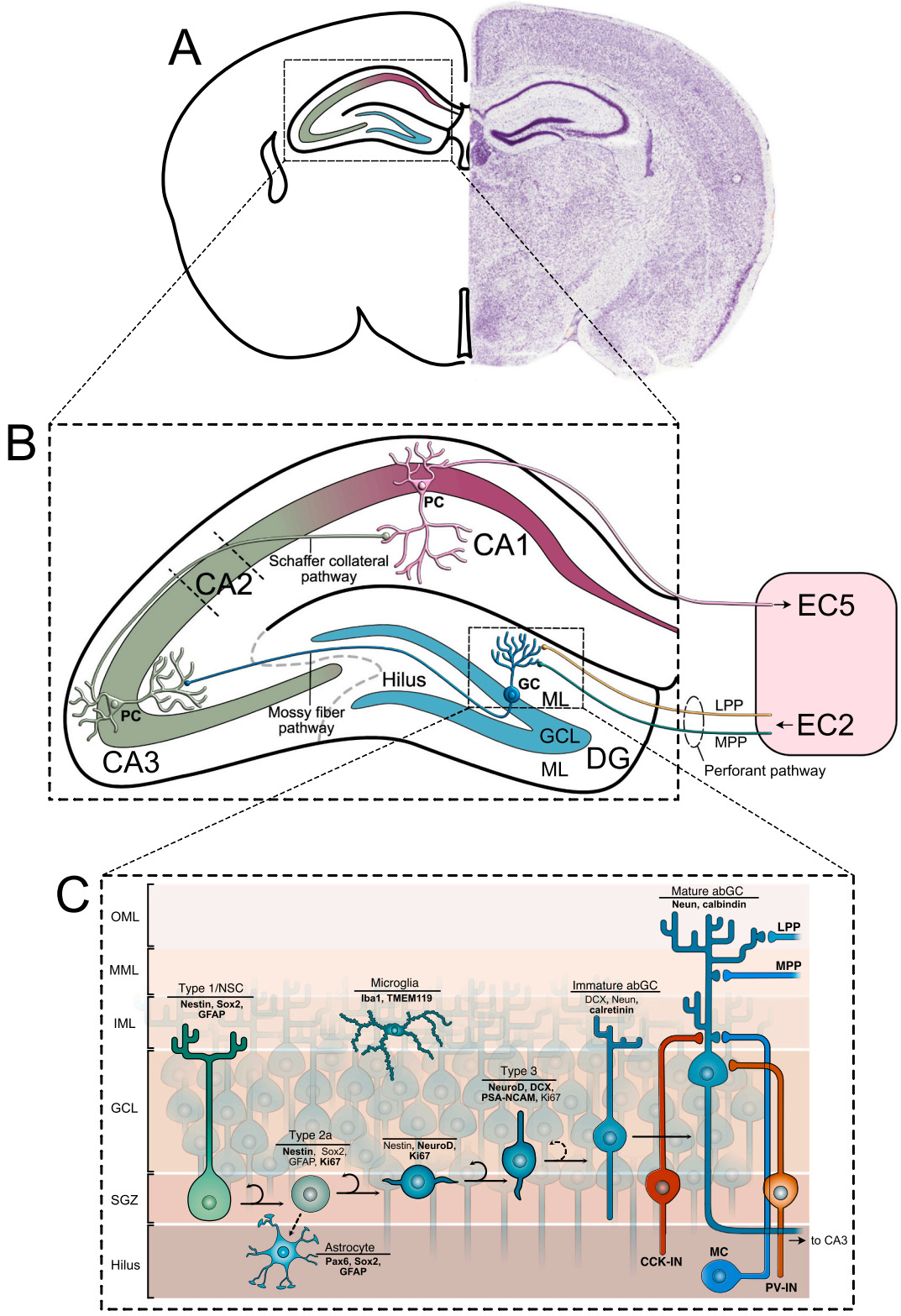
2.2. The hippocampal neurogenic niche

The SGZ — the hippocampal neurogenic niche — is a thin germinal layer between the hilus and the GCL that hosts the NSCs. These cells are characterized by a unique, tree-like morphology with the soma located in the SGZ and a main shaft extending through the adjacent GCL and ramifying into the IML in a dense network of fine cytoplasmic processes. Within DG, NSCs are in close contact with their direct descendants, along with diverse local cell types, including microglia, astrocytes, excitatory (e.g., GCs, and MCs) and inhibitory neurons (e.g., CCK-INs and PV-INs), endothelial cells, and terminal axons of subcortical neurons that project to the DG (Fig. 1C). Concerning distal afferences, MPP and LPP excitatory projections onto older and newborn GCs make synapses in the OML and MML, respectively, and convey spatial (MPP) and semantic (LPP) information from EC to the hippocampus.

NSCs, named also type 1 cells, are predominantly in a mitotically dormant, quiescent state and are activated in response to environmental inputs. Upon activation, NSCs proliferate in two different modes of division: (*i*) symmetric division, generating two NSCs that return to quiescence for the maintenance of NSC pools, and (*ii*) asymmetric division, which produces one NSC and one neural progenitor cell (NPC) or type 2 cell (Fig. 1C). NPCs, have a high proliferative capability that allows their expansion to type 2a, type 2b cells and finally to neuroblast-like cells, also named type 3 cells. Then, these neural lineage-committed

cells exit the cell cycle and enter a maturation stage, during which they extend their dendrites into the ML and their axon to CA3. These abGCs undertake a maturation process lasting several weeks, during which they show increased synaptic plasticity, before finally becoming indistinguishable from the older GCs.

AHN is a very complex biological process consisting of distinct phases that are tightly regulated — both temporally and spatially — including cell quiescence and proliferation, neuronal differentiation, survival, apoptosis, migration, and positioning, as well as maturation and integration of newborn neurons (extensively reviewed in [11,15–18]). Fate choices made by NSCs, and their progeny, depend on both local cell-cell interactions and a plethora of electrical and chemical



(caption on next page)

Fig. 1. Adult hippocampal neurogenesis. (A) Schematic of a coronal section of adult mouse brain showing the dorsal part of the hippocampus. A higher magnification view of the boxed region is shown in B. (B) Schematic illustration of the three-layered appearance of the dentate gyrus and its main connectivity. The dentate gyrus (DG) serves as the primary gateway, receiving most of the afferent multimodal sensory and spatial information from the superficial layers of the nearby entorhinal cortex (EC). The classic trisynaptic circuit of the hippocampus describes the relay of signals from the EC to the DG, then to CA3 and to CA1: neurons in layer II of the EC (EC2) send their axons through the perforant path to make excitatory synapses onto dendrites of the granule cells (GCs) in the molecular layer (ML) of the DG. The GCs extend their axons, passing through the hilus, to pyramidal cells (PCs) in CA3, forming the mossy fiber tract. CA3 PCs project to the CA1 region, forming the Schaffer collateral pathway. Finally, PCs in CA1 extend axons back to layer 5 of EC (EC5). GCL, granular cell layer; CA1/2/3, *cornu ammonis* subfield 1, 2 and 3; MPP/LPP, medial and lateral perforant path. (C) Cytoarchitectonics of the hippocampal neurogenic niche. Adult neurogenesis in the hippocampus implies the coordinate control of proliferation, migration, and differentiation of neural stem cells (NSCs, aka type 1 cells) and their direct descendants. The cell body of quiescent radial glial-like NSCs resides in the subgranular zone (SGZ), a narrow band of tissue lying between the GCL and the hilus. Upon activation, NSCs undergo asymmetric division, self-renewing themselves and generating rapidly amplifying type 2 cells (type 2a and type 2b) that subsequently differentiate into neuroblasts (type 3), immature neurons, and finally give rise to mature adult-born GCs (abGCs), or, to a lesser extent, to astrocytes. During their functional integration with the pre-existing neural circuitry, new abGCs receive excitatory inputs from MCs and MPP and LPP axons, while receiving inhibitory inputs from hilar interneurons, primarily parvalbumin- and cholecystokinin-expressing interneurons (PV-INs and CCK-INs). These constant supply of new neurons and synapses provides a substantial degree of structural and functional plasticity in the tri-synaptic hippocampal circuit. NSCs and their progeny can be distinguished based on morphology and expression of specific proteins (some of which are indicated over the cell). DCX, doublecortin; GFAP, glial fibrillary acid protein; Iba1, ionized calcium binding adaptor molecule 1; Ki67, cellular marker for proliferation; NeuN, neuronal nuclear protein; Pax6, paired box 6 protein; Sox2, SRY-box 2 transcription factor; TMEM119, transmembrane protein 119.

factors converging in the hippocampal stem cell niche. Each of these activities needs to be controlled and integrated by several different signal transduction systems that allow NSCs to appropriately face and respond to various internal and external stimuli, ultimately producing the appropriate number of new neurons and new circuitries.

Within this specialized microenvironment, eCB signaling is critically involved in regulating several biological processes, including neuronal and glial activation/proliferation, migration, and differentiation, which directly or indirectly influence the fate and behavior of NSCs and their progeny [8–10]. In the next section, we will briefly describe the

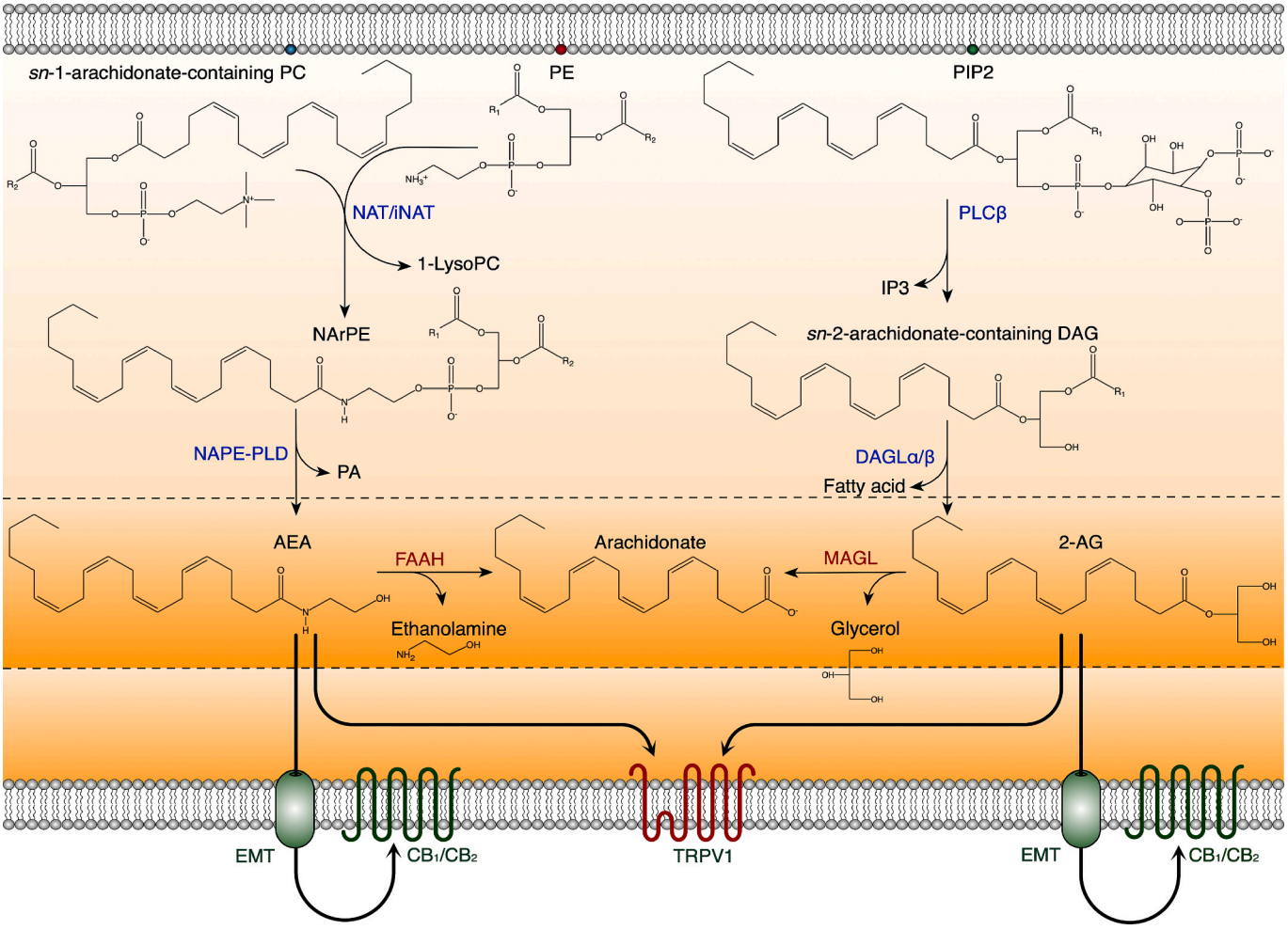


Fig. 2. Biosynthesis, hydrolysis, and the primary molecular targets of the main endocannabinoids. The biosynthetic pathways for *N*-arachidonoylethanolamide (AEA) and 2-arachidonoylglycerol (2-AG) are shown on the upper side, the degradative pathways on the middle side, and the main signaling targets on the lower side. CB_1/CB_2, cannabinoid receptors 1 and 2; DAG, diacylglycerol; DAGLα/β, diacylglycerol lipase α/β; EMT, endocannabinoid membrane transporter; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-selective phosphodiesterase; NATs, *N*-acyltransferases; PA, phosphatidic acid; PLCβ, phospholipase Cβ; R1-R2, long chain alkyl group; TRPV1, transient receptor potential vanilloid type 1 receptor. Thin arrows indicate enzymatic process, thick arrows denote movement or action.

molecular components of the ECS and review how they are widely and dynamically expressed in every cell type of the neurogenic niche, influencing every stage of their differentiation and functional activation.

3. The endocannabinoid system in the hippocampal neurogenic niche

3.1. Endocannabinoid synthesis

AEA and 2-AG are prototype members of fatty acid amides and monoacylglycerols, respectively (Fig. 2). Because of their high hydrophobicity, neuronal and glial cells do not pre-synthesize eCBs nor store them in secretory vesicles, unlike classical neurotransmitters and neuropeptides. Indeed, these signaling lipids are produced "on-demand" (i.e., when and where needed) by Ca^{2+}-dependent and/or receptor-stimulated cleavage of precursor membrane phosphoglycerides by several hydrolases and released from cells immediately afterward. Available evidence indicates that the synthesis of both AEA and 2-AG occurs through several alternative routes, which can also co-exist in the same cell and contribute to their production in a time-, space- and activity-dependent manner.

This section will focus on the main synthetic pathways for AEA and 2-AG, given the large amount of data supporting their role in forming these eCBs in the brain and particularly in the DG of the hippocampus.

3.1.1. Biosynthesis of AEA

In the brain, the primary synthetic route of AEA begins with the transfer of the arachidonic residue from *sn*-1-arachidonate-containing phosphatidylcholine to phosphatidylethanolamine via both Ca^{2+}-sensitive and Ca^{2+}-insensitive *N*-acyltransferases (NATs and iNATs) [19–21], to form a precursor *N*-arachidonoyl phosphatidylethanolamine (NArPE) (Fig. 2). NArPE is then transformed into AEA by several alternative pathways, the most direct of which is catalyzed by a Mg^{2+}/Ca^{2+}-sensitive *N*-acylphosphatidylethanolamine-selective phospholipase with a D-type activity called NAPE-PLD [22]. However, it is important to point out that the AEA synthesis mechanism is not yet fully characterized and that different NAPE-PLD-independent routes for the AEA formation have been proposed, involving the phospholipase C (PLC) and protein-tyrosine phosphatase enzyme nonreceptor type 22, or the α/β-hydrolase domain 4 and glycerophosphodiester phosphodiesterase

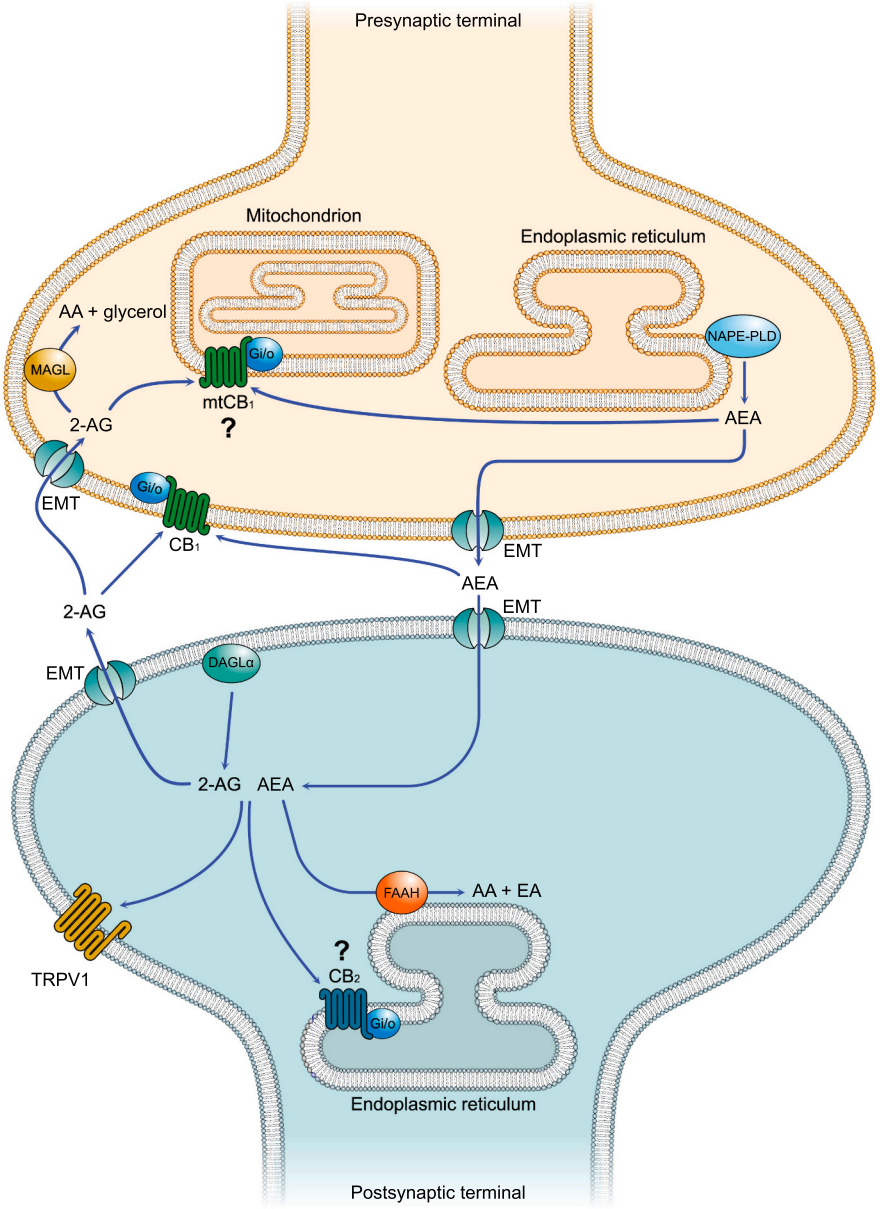


Fig. 3. Schematic view representing the specialized molecular architecture of the endocannabinoid system in the chemical synapse. The endocannabinoids (eCBs) are normally produced from postsynaptic terminals upon neuronal activation: AEA and 2-AG are synthesized from membrane precursors by NAPE-specific phospholipase D (NAPE-PLD (1)) and diacylglycerol lipase-α and β (DAGLα/β), respectively. Once produced, eCBs readily cross the membrane, possibly facilitated by a putative eCB membrane transporter (EMT), and retrogradely travel to activate cannabinoid 1 (CB_1) receptors located in the presynaptic terminals leading to the inhibition of neurotransmitter release (not shown). The presence of CB_1 receptors associated with the outer mitochondrial membrane ($mtCB_1$) further increases the complexity of the eCB-dependent neuromodulatory mechanisms. Although eCBs, as retrograde messengers, are typically active on presynaptic terminals, accumulating evidence indicates that these lipids can regulate synaptic transmission also acting as autocrine factors, by activating eCB-binding receptors at the postsynaptic site where they are produced. Indeed, both AEA and 2-AG synthesized in the postsynaptic terminal may activate transient receptor potential vanilloid type 1 (TRPV1) channel and cannabinoid 2 (CB_2) receptor located in the plasma membrane and endoplasmic reticulum, respectively. 2-AG and AEA are degraded in arachidonate acid (AA), glycerol and ethanolamine (EA) by two main intracellular hydrolases: monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively. Interestingly, these enzymes often displayed complementary expression in the synapse, with MAGL located presynaptically and FAAH postsynaptically. Notably, since NAPE-PLD (2) could also be expressed presynaptically, such a distribution of the enzymes responsible for the synthesis and degradation of AEA enables it to function also as an anterograde signal. For the sake of simplicity, the downstream elements of the eCB signaling are not depicted.

1 and lyso-*N*-arachidonoyl phosphatidyl ethanolamine [23].

Although the expression patterns of NATs and iNATs in the CNS are not known in detail, their activity is relatively high in the rodent brain [21,24].

Compared to other brain areas, the DG of the hippocampus contains the highest amount of NAPE-PLD, which is concentrated presynaptically in several types of excitatory axon terminals [25]. In particular, this enzyme is highly expressed in axon terminals of GCs, where it is intracellularly located on the external surface of the smooth endoplasmic reticulum [26] (Fig. 3). Dense NAPE-PLD immunoreactivity is also present in the IML, likely in the axon terminals of MCs. The high expression of the transcript of this enzyme both in the GCs and in the MCs of the DG is confirmed by next-generation RNA sequencing (RNA-seq) data (https://hipposeq.janelia.org). Finally, expression of NAPE-PLD has also been documented in nonneuronal cells, such as microglia [27] (Fig. 4). No studies have been conducted to verify the expression of (i)NATs and NAPE-PLD in NSCs and their progeny.

3.1.2. Biosynthesis of 2-AG

Much like AEA, 2-AG is produced on-demand by receptor-stimulated cleavage of a phospholipid precursor through several routes. Among these, the main pathway operating in the CNS is a 2-step process involving the removal of the inositol triphosphate from arachidonate-containing phosphatidylinositol bisphosphate (PIP2) by phospholipases C β (PLCβ) [28], followed by removal of the acyl group in the *sn*-1 position by diacylglycerol lipases α and β (α/β) [29,30] (Fig. 2).

PLCβ is typically activated by $G_{q/11}$-coupled metabotropic receptors, such as group I metabotropic glutamate receptors 1 and 5, mGluR1 and mGluR5, thereby explaining the influence of synaptically released glutamate on 2-AG synthesis [31–33]. In the hippocampal formation, PLCβ mRNA is present mainly in CA1 and CA3 pyramidal neurons, as well as in GCs, MCs, and glial cells [34,35]. Instead, GABAergic interneurons seem devoid of this enzyme [34].

DAGLα is highly expressed by glutamatergic neurons of the adult hippocampus, particularly by GCs, where its subcellular location is mainly restricted to the head and neck of dendritic spines [36–38] (Fig. 3). Much lower levels of DAGLα expression are present in

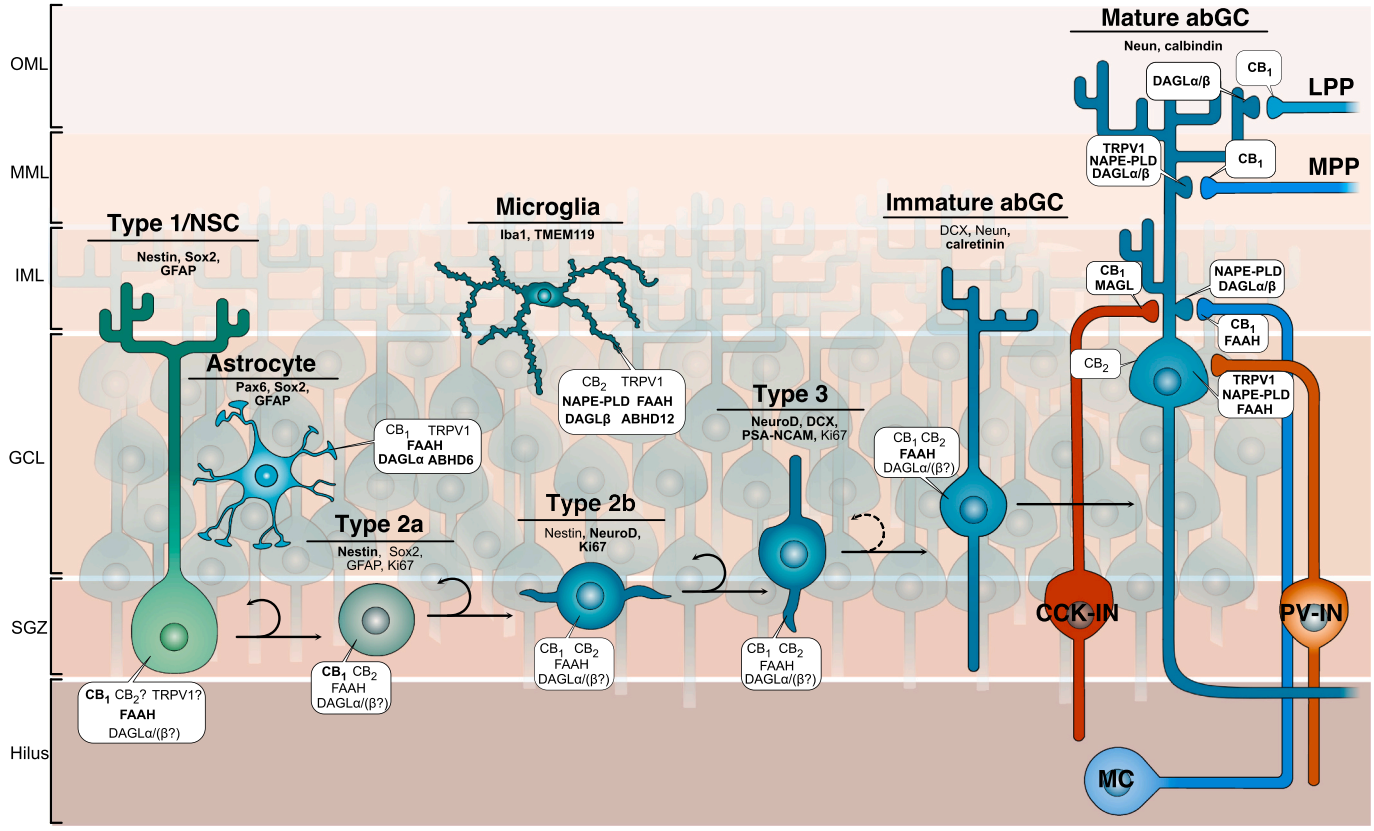


Fig. 4. Spatial and temporal organization of the endocannabinoid system in the cells of hippocampal neurogenic niche. The cytoarchitecture of the hippocampal niche is displayed, including neuronal and nonneuronal cells. The 2-AG-biosynthesizing enzyme DAGLα and possibly its isoform DAGLβ are expressed throughout the entire neurogenic process. Starting from neural stem cells (NSCs), their expression along with that of CB_1 and CB_2 receptors landmarks the various intermediate precursor cells – Type 2a, Type 2b, Type 3 – and immature calretinin-expressing adult-born granule cells (abGCs). A similar expression pattern is observed for the main AEA-degrading enzyme, FAAH, although a decrease of its abundance during the development of intermediate precursors and an upraise of its expression in abGCs have been reported (see text for details). Interestingly, CB_1 receptors are not expressed by mature GCs and parvalbumin-expressing interneurons (PV-INs) while are predominantly expressed by cholecystokinin-expressing interneurons (CCK-INs) and to lower extent by mossy cells (MCs), as well as by medial and lateral perforant path (MPP and LPP) terminals. TRPV1 receptors are only transiently expressed by NSCs within 1–39 days of post-natal life, while they are stably expressed by mature abGCs at the level of soma and at dendritic spines that receive inputs from MPP. Among neuronal cells, only mature abGCs express the AEA biosynthetic enzyme NAPE-PLD, whereas the expression of the 2-AG-degrading enzyme MAGL has been detected in axon terminals of CCK-INs only. In astrocytes and microglia MAGL activity appears to be replaced by α/β-hydrolases domain containing proteins, such as ABHD6 and ABHD12. Both astrocytes and microglia express TRPV1 receptors, whereas the expression of CB_1 and CB_2 receptors seems more restricted to astrocytes and microglia, respectively. Astrocytes and microglia express DAGLα and DAGLβ, respectively, indicating that both glial cells can produce 2-AG. Conversely, between these cell types, only microglia appear to be the source of AEA, as indicated by the expression of NAPE-PLD enzyme. AEA, *N*-arachidonoylethanolamide; 2-AG, 2-arachidonoylglycerol; CB_1/CB_2, cannabinoid receptors 1 and 2; DAGLα/β, diacylglycerol lipase α/β; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-selective phosphodiesterase; TRPV1, transient receptor potential vanilloid type 1 receptor.

hippocampal interneurons, particularly in PV-INs [39]. Although the β isoform is considered an embryonic isotype, DAGLβ mRNA was recently detected by RNAscope in GCs [40].

Within the neurogenic niche, DAGLα transcript has been identified in NSCs and their neuronal progeny, where it is found to be upregulated during the differentiation process, with NSCs having 3-fold less DAGLα mRNA than type 3 cells (neuroblasts) [41]. The presence of DAGLα in NSCs and in immature abGCs was also confirmed at a protein level [40,42]. Interestingly, NSCs co-express DAGLα and DAGLβ, suggesting that these cells can produce 2-AG autonomously by both DAGL isoforms [40] (Fig. 4).

Functional expression of DAGLα and DAGLβ has been documented in astrocytes and microglial cells, respectively, indicating that distinct DAGL isoforms are responsible for controlling 2-AG synthesis in these glial elements [40,43].

3.2. Endocannabinoid degradation

The enzymatic pathways mediating the degradation of eCBs are much better known than those involved in their synthesis. Indeed, in the brain, eCBs are essentially hydrolyzed by two distinct intracellular serine hydrolases: fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MAGL), which degrade AEA and 2-AG, respectively, to yield inactive breakdown products [44–46] (Fig. 2). In the hippocampus, neuronal FAAH and MAGL displayed distinct, often complementary, expression patterns in cell types and subcellular compartmentalization, which is suggestive for potential distinct roles of AEA and 2-AG in regulating neuronal physiology [47] (Fig. 3).

3.2.1. Degradation of AEA

FAAH is primarily confined to glutamatergic neurons, i.e., CA1/CA3 PCs, MCs, and GCs, but not in interneurons [47–50]. Subcellularly, FAAH is located postsynaptically, integrated into the endoplasmic reticulum of soma or dendrites, often juxtaposed to CB_1-containing fibers [47,49,50] (Fig. 3). In nonneuronal cells, FAAH is also expressed at low levels by microglial cells and astrocytes (Fig. 4).

The expression of FAAH in the cells of the neurogenic niche appears to change dynamically with the maturation process: FAAH immunoreactivity is detectable in NSCs and decreases in rapidly amplifying type 2 NPCs, then returns to be expressed in mature abGCs [51] (Fig. 4).

3.2.2. Degradation of 2-AG

MAGL is expressed in glutamatergic CA3 PCs but not in GCs and MCs, while it is weakly expressed in GABAergic interneurons (mainly CCK-INs) [38,47] (Fig. 4). MAGL is presynaptically associated with axon terminals in these cells, primarily located on the cytoplasmic surface of the plasma membrane, whereas cell bodies and dendrites do not appear to contain the enzyme [38,47,48] (Fig. 3). In nonneuronal cells, MAGL seems to be replaced by other hydrolases, such as α/β-hydrolases domain containing 6 (ABHD6) and 12 (ABHD12) [43] (Fig. 4). No systematic study has been conducted yet to evaluate MAGL expression in the cells of the hippocampal SGZ niche.

3.2.3. Oxidation of AEA and 2-AG

As an alternative to hydrolytic pathways, AEA and 2-AG may be oxidized by either cyclooxygenase-2, 12- and 15-lypoxigenase, or cytochromes P450, into a variety of eicosanoids such as prostaglandin-ethanolamides and glycerol esters, hydroxy-AEA and hydroxy-eicosatetraenoyl-glycerols, respectively [52,53]. Although these oxidative derivatives of eCBs have limited or no affinity toward cannabinoid receptors, evidence is emerging that they could be provided with novel biological activities, probably mediated by non-cannabinoid receptors, thus further expanding the complexity of signaling pathways through which eCBs and their congeners can control cellular functions, including those relevant in the adult neurogenesis [53].

3.3. Endocannabinoid molecular targets

Once produced, eCBs act as autocrine and/or paracrine ligands binding their target receptors, which can be expressed either on the same cell that made them or a neighboring cell, respectively. These lipids act primarily as endogenous agonists of metabotropic CB_1 and CB_2 receptors. In addition, they can also interact with non-metabotropic receptors, further increasing the complexity of the ECS and the signaling pathways triggered thereof. In particular, the best known of these targets is the transient receptor potential vanilloid type 1 (TRPV1) channel, an ionotropic eCB-receptor, which can be activated both by AEA and 2-AG, although with less potency than CB_1/CB_2 [54–56]. Finally, other potential targets modulated by eCBs are nuclear peroxisome proliferator-activated receptors α and γ, and $Ca_v3.2$ low-voltage activated T-type calcium channel [57,58]. However, eCBs bind these additional receptors with a lower affinity, requiring micromolar concentrations, which are only rarely achieved under physiological conditions.

In the remainder of the review, we will focus on CB_1/CB_2 receptors and TRPV1, given the large amount of data supporting their role in AHN.

3.3.1. Cannabinoid receptors

CB_1 and CB_2 receptors are members of the superfamily A of the heptahelical transmembrane-spanning G protein-coupled receptors (GPCRs) encoded by *CNR1* and *CNR2* genes and exhibit 44% and 68% amino acid identity throughout the whole protein and within the seven transmembrane helices, respectively. AEA and 2-AG bind to the CB_1 and CB_2 receptors with similar affinities in the mid- to the high-nanomolar range. AEA binds a little more readily to CB_1 than to CB_2, behaving as a partial agonist, while 2-AG is a full agonist of both receptors, on which it displays higher efficacy than AEA [59].

3.3.1.1. Expression of CB_1. The CB_1 receptor is considered the GPCR with the highest expression in the CNS and is especially abundant in the adult hippocampus. More specifically, in the DG, this receptor is predominantly expressed in some GABAergic interneurons (primarily, CCK-INs) and, in smaller quantities, in specific subpopulations of glutamatergic neurons (i.e., MCs) [35,49,60–62] (Fig. 4). Contrarily, CB_1 was virtually absent from other interneuronal subtypes (for example, calretinin- and PV-INs), as well as from mature GCs [35,36,61,63].

The functional expression of CB_1 was documented in NSCs and NPCs, as well as in their descendants [41,51,62,64,65]. Like what happens during embryonic neurogenesis, in which CB_1 level progressively decreases as glutamatergic neuron precursors differentiate, the expression of the receptor is gradually reduced during the maturation of newborn GCs [66], until being completely absent in terminally differentiated GCs [35]. CB_1 is expressed in NSCs and persists at the stage of calretinin expression in developing newborn neurons (immature GCs), whereas it is absent on terminally differentiated calbindin-positive GCs in the SGZ [41] (Fig. 4).

Finally, there is evidence that CB_1 is also expressed, albeit at a lower level, by nonneuronal cells in the brain, including astrocytes [67,68], oligodendrocytes [69], endothelial [70] but not in microglial cells [71] (Fig. 4).

3.3.1.2. Expression of CB_2. Based on its broad expression in immune cells, the type-2 cannabinoid (CB_2) receptor was traditionally thought to act as the "peripheral receptor" or non-psychotropic receptor with almost exclusively immunomodulatory functions [72]. However, anatomical, behavioral, and electrophysiological evidence support its functional expression in different neuronal and glial cells [73–76], thus opening the way to a reconsideration of CB_2 signaling in the context of brain pathophysiology, synaptic plasticity, and neuroprotection [77].

Within the brain, the expression of the CB_2 receptor was described for the first time in resting microglial cells at constitutively low levels

[74,78] (Fig. 4). Although these findings have been questioned by assessing CB_2 mRNA levels via RNAscope [79], it is well ascertained that, upon activation, microglia significantly overexpress their CB_2, likely as a part of a neuroprotective response (for a more recent review on this topic, see [80]).

In the hippocampus, appreciable expression of CB_2 was documented in microglia in the hilus of DG [81,82] (Fig. 4). Using neuron-specific CB_2-knockout (KO), in combination with electrophysiological and molecular biology techniques, Stempel and colleagues produced convincing evidence for the functional expression of neuronal CB_2 in hippocampal glutamatergic neurons (i.e., CA3 PCs), as well as in adult GCs [75]. A further study, conducted on inducible systems for overexpressing and disrupting the CB_2 gene in adult hippocampal neurons, demonstrated the functional expression of CB_2 in the CA1 PCs, where it appeared to be involved in the regulation of memory and anxiety [82].

Compared to CB_1, the expression of CB_2 in the NSCs seems to be more reduced and circumscribed. Indeed, the CB_2 receptor is present in nestin-positive cells (i.e., in NSC/NPCs) but not in committed neuroblasts (NeuN-positive cells) [83]. Moreover, in neurospheres generated from DG of the mouse hippocampus, CB_2 mRNA is expressed at almost two orders of magnitude less than CB_1 [41]. Notably, in primary neurosphere cultures, obtained by conditional KO mice in which CB_1 has been specifically removed from NSCs, even more reduced levels of CB_2 mRNA were observed, suggesting that CB_2 expression in the NSC/NPC is a downstream target of CB_1 signaling [41] (Fig. 4).

More importantly, the presence of a low, but appreciable, level of CB_2 mRNA was documented by RNAscope in situ hybridization in GCs and corroborated by comparing the transcript expression level in neuron-specific CB_2-KO mice and their wild-type littermates [75]. The presence of CB_2 within GCs of DG was recently ascertained by immunohistochemistry labeling of mouse hippocampus [84]. These findings suggest that the two eCB-binding receptors follow a complementary expression trend during neuronal differentiation, with CB_1 more abundant in NSCs and absent in mature abGCs, and vice versa for CB_2.

3.3.2. Transient receptor potential vanilloid type-1 (TRPV1)

The best-established ionotropic receptor for eCBs is the TRPV1 channel, previously discovered as the receptor for capsaicin, the pungent ingredient in hot chili peppers [85]. TRPV1 is an integral plasma membrane protein with a transmembrane region consisting of six helical segments, a short extracellular pore-forming hydrophobic stretch, and intracellular N- and C-terminal domains [86,87]. TRPV1 functions as a nonselective tetrameric cation channel with a high permeability to Ca^{2+}. TRPV1 is characterized by remarkable gating promiscuity, acting as a molecular integrator of a wide range of cellular and environmental signals, including noxious temperature, mild acidification, local mediators of inflammation, and eCBs [88]. AEA and 2-AG bind to TRPV1 with similar affinities in the low micromolar range and act as physiologically relevant activators of this channel [89–91].

3.3.2.1. Expression of TRPV1. Long regarded as exclusively confined to sensory neurons of the peripheral nervous system, TRPV1 is now recognized to have a broader distribution and function in the CNS, and increasing evidence suggests its active presence in the brain, both on neuronal and nonneuronal cells [92, 93].

Although some seminal reports showed no, or weak, expression of this channel in CNS [94], accumulating immunohistochemical, pharmacological, and electrophysiological evidence proves the functional presence of TRPV1 in hippocampal pyramidal and glial cells, although absent from most, but not all, interneurons. Specifically, TRPV1 is present in the somas of CA1 and CA3 PCs, in the dendritic spines and soma of GCs [95–99], in the endfeet of astrocytes [100,101], as well as in the cellular and intracellular membranes of microglial cells [102] (Fig. 4). The expression of TRPV1 has been ascertained during post-natal neurogenesis (from 1 day of age until 39 days of age) in NSCs, NPCs, and immature abGCs [103]. However, after that period, in the adult mice under normal conditions, TRPV1 expression in NSCs and their progeny was below the detection level [103]. Noteworthy, within the GCs, TRPV1 displays a specific subcellular expression, being confined on the plasma membrane of cell soma [98] and in the postsynaptic dendritic spines receiving PP inputs (in the OML) [97], while its expression is absent, or very weak, at more proximal excitatory hilar MC synapses (in the IML) [96,104].

3.4. Endocannabinoid signaling

3.4.1. Endocannabinoid signaling: An overview

Like many other GPCRs, CB_1 and CB_2 receptors exert a multifaceted and very complex signaling activity (for more recent comprehensive reviews, see [4,105,106]). CB_1 and CB_2 receptors are primarily coupled with heterotrimeric G_i or G_o proteins and then act negatively to adenylyl cyclase (AC) and subsequent protein kinase A (PKA) signaling [107]. Moreover, they stimulate extracellular signal-regulated kinase (ERK)1/2, primarily via $G\alpha_{i/o}$, and phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin complex 1 (mTORC1), via $G\beta\gamma$-subunit (Fig. 5). Finally, both receptors regulate the membrane potential of neurons and other excitable cells by modulating the opening of specific K^+ and Ca^{2+} ion channels, thus further expanding the versatility of the signaling by which both receptors control cellular functions.

As for most GPCRs, CB_1 receptor also can couple, in a cell-context dependent manner, to other than $G_{i/o}$ proteins, thus eliciting various downstream signaling cascades. For example, it can couple to G_s protein in striatal neurons to activate AC and PKA, when it is co-expressed and co-stimulated with dopamine D2 receptors [108]. In the plasma membrane of astrocytes, CB_1 receptor was reported to couple to $G_{q/11}$, thus activating phospholipase C (PLC) and inducing intracellular Ca^{2+} rise through inositol 1,4,5-triphosphate-sensitive endoplasmic reticulum stores [67]. To add a further level of complexity, astrocytes and neurons confine a pool of CB_1 in the outer mitochondrial membrane, referred to as $mtCB_1$ [68,109]. Unlike plasmalemmal CB_1, $mtCB_1$ is coupled to mitochondrial $G_{i/o}$ proteins, thus its stimulation leads to inhibition of mitochondrial soluble AC and reduction of oxidative phosphorylation through the regulation of specific respiratory components [109]. Finally, atypical coupling of CB_1 receptor to $G_{12/13}$ proteins in cultured hippocampal neurons was reported to shape neuronal morphology and growth via Rho-GTPase and Rho-associated kinase (ROCK) pathways [110]. Apart from having a higher affinity for G_i than G_o, less is known about additional G proteins interacting with CB_2 [111].

The activation of TRPV1 mainly permits an influx of extracellular cations (Na^+ but primarily Ca^{2+}), resulting in plasma membrane depolarization and increased intracellular Ca^{2+} concentration, whose effects depend on the specific cell type [88,93] (Fig. 5). Given its role in modulating the intracellular concentration of Ca^{2+}, TRPV1 may also trigger several Ca^{2+}-dependent signal pathways, including those associated with PKA, protein kinase C (PKC), and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), thereby influencing the balance among proliferation, quiescence, resistance to oxidative stress, and apoptosis, depending on the concentration, timing, and duration of the signal (Fig. 5). TRPV1-mediated apoptosis involves aberrant Ca^{2+} influx and efflux among cytosol, mitochondria, and endoplasmic reticulum, resulting in c-Jun N-terminal kinase (JNK) and caspase activation, mitochondrial transmembrane potential dissipation, production of reactive species of oxygen, and oligonucleosomal DNA fragmentation [112,113].

These metabotropic and ionotropic receptors offer different access points to their ligands, with their binding sites for the eCBs located on opposite sides of the plasma membrane: extracellular for cannabinoid receptors and intracellular for TRPV1 (Fig. 2). Furthermore, within the same cell, these receptors can display a regional specialization, being located in different membrane compartments; for example, in the plasma membrane of neurons, they can be restricted to axonal (CB_1),

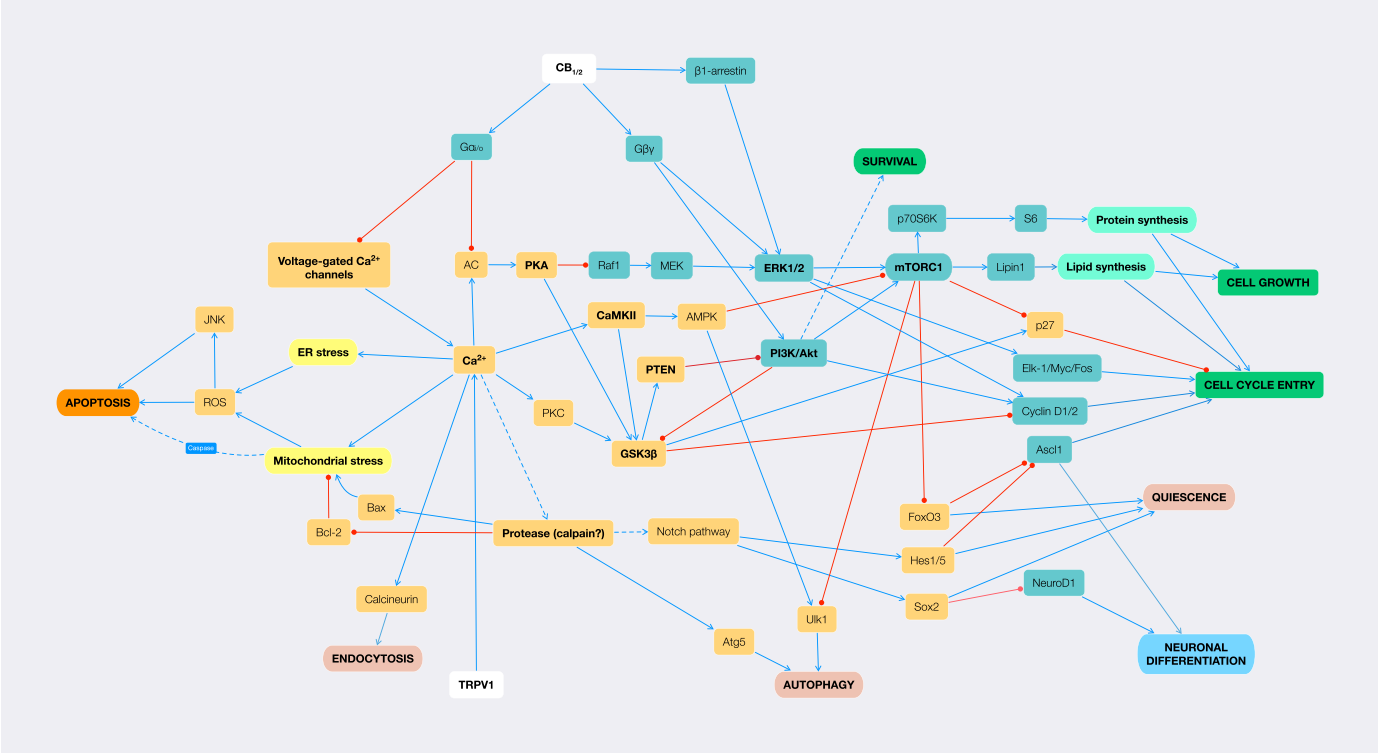


Fig. 5. Main endocannabinoid signaling cascades.
The schematic shows how endocannabinoid (eCB) receptors can give rise to complex signaling activity within the neural stem cell, with multiple nodes of interaction and cross-regulation with respect to major cellular signaling pathways. All pathways of cell physiology are virtually influenced by eCB signaling. Among pathways that are turned on (blue lines) upon activation of $CB_{1/2}$ receptors are the ERK1/2 and PI3K/Akt ones, which through mTORC1 stimulate cell survival, cell growth and cell cycle entry. Opposite effects are determined by the activation of the TRPV1 receptor, which allows the influx of Ca^{2+} causing membrane depolarization and intracellular Ca^{2+} concentration upraise. The latter activates PKA, PKC and CaMKII, thereby influencing the balance between proliferation and quiescence. In fact, among pathways downstream from the increase of intracellular Ca^{2+} concentration is the activation of Notch signaling that is presumably activated by calpain-dependent proteolytic cleavage (dashed blue lines) and associates with cell quiescence. The activation of calpain-dependent proteases also triggers autophagy, while endoplasmic reticulum (ER) and mitochondrial stress drive cell to apoptosis, through an increase of the oxidative stress. AC, adenylyl cyclase; AMPK, AMP kinase; Ascl1, Achaete-scute homolog 1; ATG5, autophagy related 5; Bax, Bcl-2-associated X; Bcl-2, B-cell lymphoma protein 2; Ca^{2+}, calcium; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CB_1/CB_2, cannabinoid receptors 1 and 2; Elk-1/Myc/Fos, ETS like-1 protein/oncogene with sequence similarity to Myelocytomatosis virus; Fos proto-oncogene; ERK1/2, extracellular-signal-regulated kinase 1/2; FoxO3, forkhead transcription factor 3; GSK3β, glycogen synthase kinase-3β; Hes1/5, hairy and enhancer of split-1/5 transcription factors; JNK, Jun N-terminal kinase MEK, mitogen-activated protein kinase (MAPK) kinase; mTORC1, mammalian target of rapamycin complex 1; NeuroD1, neurogenic differentiation 1; Notch, neurogenic locus notch homolog protein; p70S6K, 70-kDa ribosomal protein S6 kinase; PI3K/Akt, phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene homolog; PKA, protein kinase A; PKC, protein kinase C; PTEN, phosphatase and tensin homolog; Raf1, rapidly accelerated fibrosarcoma 1; ROS, reactive oxygen species; S6, ribosomal protein S6; SOX2, sex determining region Y-box 2 transcription factor; TRPV1, transient receptor potential vanilloid type 1 receptor; ULK1, Unc-51 like autophagy activating kinase 1. Blue lines indicate an activating effect, red lines indicate an inactivating effect; dashed lines indicate an indirect action.

dendritic or somatic domains (TRPV1). Besides the cell membrane, they could also be expressed in other organelles, such as endosomes (CB_2 and TRPV1) or the outer membrane of mitochondria ($mtCB_1$) (Fig. 3).

3.4.2. *Neuromodulatory role of the endocannabinoid signaling*

Within the brain, eCBs act as neuromodulators crucially involved in neuronal communication by fine-tuning the synaptic efficacy and plasticity. Depending on the type and the localization of the receptor involved, these messengers trigger a variety of pre- or postsynaptic mechanisms capable of modifying synaptic transmission at both excitatory and inhibitory synapses — normally attenuating them — on timescales that are either transient (on a scale of seconds) or long-lasting (on a scale of minutes or more).

Once postsynaptically produced, in response to short depolarization of the neuronal membrane, intracellular Ca^{2+} elevation, and/or activation of some $G_{q/11}$-coupled metabotropic receptors, eCBs travel across the synaptic cleft and activate presynaptic CB_1 receptors to suppress the release of inhibitory or excitatory neurotransmitters (i.e., GABA or glutamate) (Fig. 6A). This type of activity is referred to as "retrograde signaling" since the signal travels backward from the postsynaptic to the presynaptic neuron. Notably, due to their relatively high diffusivity, eCBs produced in a postsynaptic neuron can spread into the local environment and affect not only the presynaptic neuron but also the neighboring neurons in the region of the active synapse (Fig. 6B).

The activation of CB_1 receptor generally leads to the hyperpolarization of the presynaptic membrane via inhibition of presynaptic voltage-gated Ca^{2+} channels (VGCCs), along with the activation of $G_{i/o}$ coupled inwardly rectifying K^+ (GIRK) channels, thus inducing two activity-dependent forms of short-term plasticity, named depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE), at the GABAergic and glutamatergic synapse, respectively [114,115] (Figs. 6A, B). Yet, depending on the duration and the mode of activation of both postsynaptic and presynaptic neurons, eCBs can suppress neurotransmitter release in a more persistent manner, inducing long-term depression (LTD) of inhibitory (iLTD) and excitatory transmission (eLTD), possibly by interfering with PKA-dependent cascades [116–118] (Fig. 6B). Finally, in certain hippocampal synapses, 2-AG may also induce a form of long-term potentiation of excitatory transmission (eLTP) by presynaptic CB_1-dependent stimulation of integrin-associated focal adhesion kinase (FAK) and

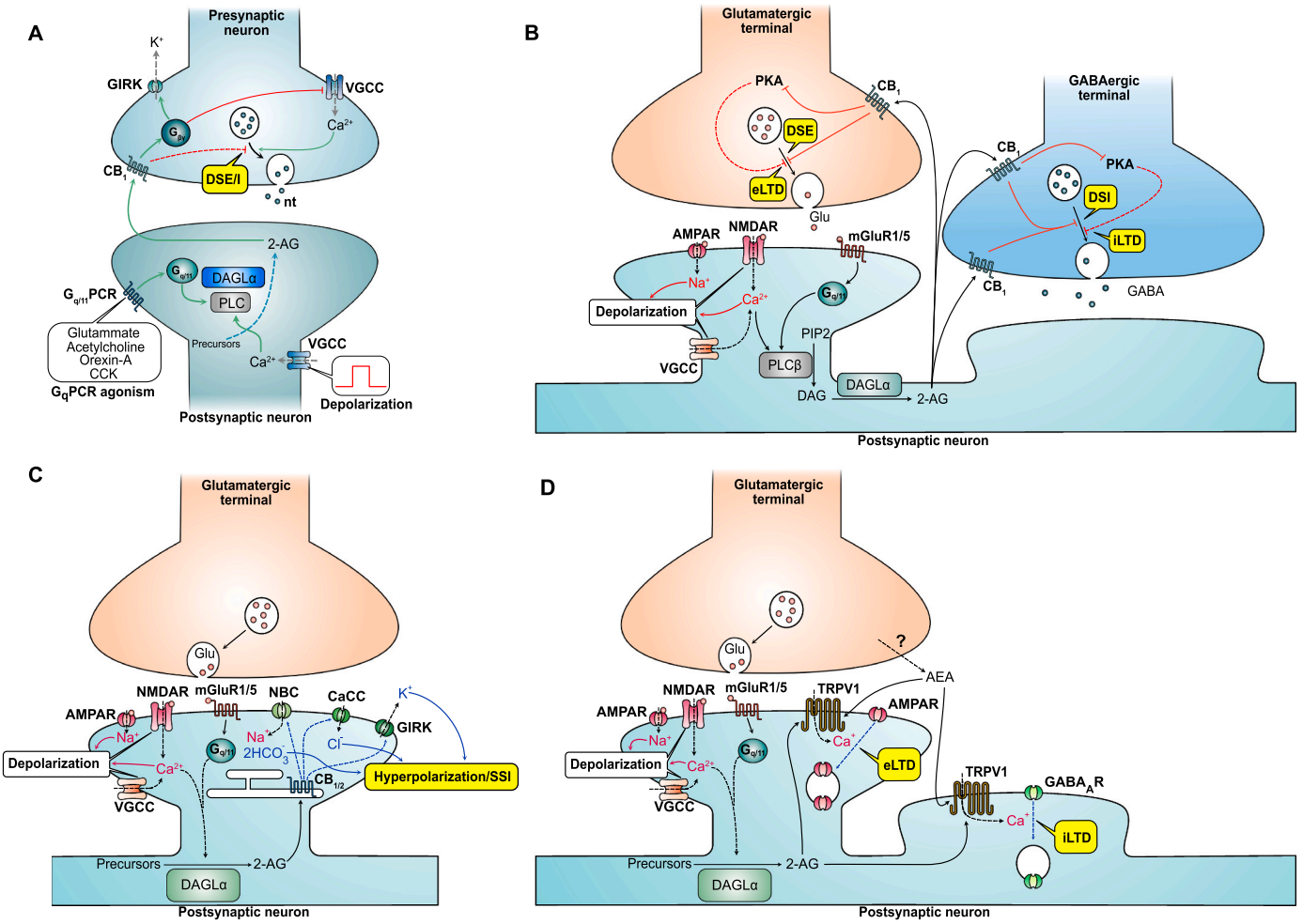


Fig. 6. Mechanisms of endocannabinoid-dependent short- and long-term depression. (A) Schematic representation of endocannabinoid (eCB)-dependent short-term depression by retrograde signaling. Activation of Gq/11-coupled metabotropic receptors (Gq11/PCR) and/or voltage-gated Ca^{2+} channels (VGCCs) on the postsynaptic neuron promotes the synthesis of 2-arachidonoylglycerol (2-AG) through the hydrolysis of membrane phospholipids via Ca^{2+}-dependent and Ca^{2+}-independent mechanisms. Once produced, eCBs retrogradely traverse the synaptic cleft and activate the presynaptic cannabinoid 1 (CB_1) receptor, thereby regulating ion channels (i.e., positively G protein-coupled inwardly rectifying potassium (GIRK) channels and negatively VGCCs) and ultimately suppressing neurotransmitter (nt) release. According to the type of synapse regulated, this transient form of synaptic plasticity is denoted depolarization-stimulated suppression of excitation (DSE) (if glutamatergic transmission is suppressed) or depolarization-stimulated suppression of inhibition (DSI) (if GABAergic transmission is suppressed). (B) Schematic representation of eCB-dependent homosynaptic (i.e., target afferent) and heterosynaptic (i.e., nearby afferent) mechanisms for short- and long-term depression (LTD). The eCB-mediated suppression of nt release can occur at the same synapse that generated the eCBs (homosynaptic regulation) or at immediately adjacent synapses (heterosynaptic regulation), thus modulating multiple targets than typical retrograde transmission. (The scheme shows a glutamatergic synapse in close proximity to a GABAergic synapse.) At the excitatory synapse, afferent stimulation evokes increased glutamate release and subsequent activation of the glutamate receptors at the postsynaptic terminal, resulting in the release of eCBs from the same membrane. Given their diffusivity, eCBs can activate CB_1 receptors present on the presynaptic membrane of the same synapse, as well as those of nearby synapses. In the first case, the CB_1 signaling leads to DSE, in the second one, to DSI. Although presynaptic mechanisms of eCB-LTD have not been fully elucidated, inhibition of the cAMP/PKA pathway seems to be crucial to determine eLTD and iLTD at the excitatory and inhibitory synapse, respectively. (C) Schematic representation of $CB_{1/2}$-mediated slow self-inhibition (SSI) of neurotransmission by 2-AG autocrine signaling. In addition to its well-established function as retrograde messenger, 2-AG might also behave as autocrine modulator of synaptic strength by acting on postsynaptic $CB_{1/2}$ receptors. Prolonged depolarization by repetitive action potential firing triggers the production of 2-AG, which in turn induce an autocrine $CB_{1/2}$-mediated long-lasting hyperpolarization of the membrane potential, rendering the cells less excitable, a phenomenon termed SSI. The $CB_{1/2}$-dependent cell-intrinsic hyperpolarization of the postsynaptic neuron has been described to be mediated by activation of GIRK channels, VGCCs and/or sodium bicarbonate cotransporter. (D) Schematic representation of TRPV1-mediated long-term inhibition of neurotransmission by eCB autocrine signaling. Those shown are two examples of long-lasting TRPV1-dependent neuromodulation that have been described in specific glutamatergic and GABAergic synapses on dentate granule cells (GCs). In these synapses, TRPV1 is located postsynaptically, and its stimulation by produced eCBs (AEA mainly released from presynaptic neuron and 2-AG from postsynaptic neuron) leads to eLTD and iLTD at the level of excitatory and inhibitory synapses, respectively. These postsynaptic forms of LTD involve long-lasting, clathrin- and dynamin-dependent endocytosis of AMPA and $GABA_A$ receptors from the postsynaptic membrane. For clarity, the transport and inactivation of eCBs have been omitted.

ROCK-mediated reorganization of presynaptic cytoskeleton [119,120].

As an example of cell-type-specific differences in the eCB-dependent neuromodulatory mechanisms, efficiency by which neuronal CB_1 couples with G proteins depends on the cell type where they are expressed. Indeed, it has been found that, within the hippocampus, the G_i protein activation by CB_1 receptors expressed in glutamatergic neurons is much stronger than the one induced in GABAergic interneurons [121], suggesting that the signaling activity of CB_1 is not directly related to its level of expression. This unusual feature can be due to several non-mutually exclusive mechanisms influencing the coupling of CB_1 with its effector G proteins, including (*i*) the interaction with GPCR-accessory proteins [122,123], (*ii*) the post-translational modifications [124–126], (*iii*) the ability to heterodimerize with other GPCRs [127,128], and (*iv*) the precise intracellular distribution of the receptor within the different

microdomains of cellular membranes and organelles [129,130]. Concerning the latter mechanism, low but functional expression of CB_1 was reported in the outer membrane of mitochondria ($mtCB_1$, Fig. 3), where it would act to inhibit the electron transport chain, thereby attenuating the mitochondrial respiration and energy production by inhibiting soluble PKA via mitochondrial G_i proteins [130]. Since $mtCB_1$ is present in both GABAergic and glutamatergic CA1 hippocampal neurons [130], it could also be involved in modulating eCB-dependent synaptic plasticity in neurogenic niche neurons.

In addition to their well-established functions as retrograde messengers, AEA and 2-AG might also behave as fast autocrine modulators of synaptic strength by acting on postsynaptic CB_1, CB_2 and TRPV1 receptors. Indeed, neuronal CB_2 has been found to display a postsynaptic intracellular localization and, once activated by autocrine-synthesized eCBs, to mediate a long-lasting, cell-intrinsic hyperpolarization, termed slow self-inhibition (SSI) via stimulation of Ca^{2+}-activated Cl^- channels and Na^+ bicarbonate cotransporter [73,75,131] (Fig. 6C). Similarly, some neuronal populations expressing CB_1 receptors on somatodendritic membranes display a specific form of SSI, which involves a 2-AG/CB_1-dependent activation of GIRK channels in the stimulated cell [132–134] (Fig. 6C). When located at postsynaptic compartments, TRPV1 activation, primarily by AEA, promotes eLTD and iLTD involving long-lasting, Ca^{2+}/calcineurin- and clathrin/dynamin-dependent endocytosis of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and $GABA_A$ receptors, respectively (Fig. 6D) [97,98]. Finally, astroglial, but not neuronal, CB_1 activation, by stimulating Ca^{2+}-dependent release of glutamate, promotes eLTD of CA3-CA1 excitatory synapses in vivo [135].

3.5. Endocannabinoid transport system

The process whereby eCBs are transported across the plasma membrane and within the cell is considered a hot topic because it constitutes a crucial step involved both in the control of signaling (i.e., autocrine versus paracrine action, CB versus TRPV1 receptors) and inactivation of these lipid signals, thus representing a potential target for the treatment of several pathologies associated with ECS dysfunctions [136–138] (Fig. 3).

During their activity as retrograde messengers, eCBs are produced on the inner side of the postsynaptic neuron membrane, and they need to cross the synaptic cleft and reach the outer side of the presynaptic membrane to activate the $CB_{1/2}$ receptors. As an additional stage of their signaling, eCBs must penetrate the postsynaptic membrane, or immediately surrounding cells, to reach their specific hydrolases (mainly FAAH and MAGL), as well as the intracellular binding site of TRPV1.

Given their highly lipophilic nature, with partition coefficients (i.e., XlogP values) of 5.5 and 5.4 for AEA and 2-AG, respectively, eCBs can diffuse passively through lipid membranes. Still, this process could be accelerated by a rapid and selective carrier system (eCB membrane transporter, EMT) postulated to be expressed in both neurons and glial cells (Figs. 2 and 3).

Despite indirect solid evidence for this transmembrane transport system, the molecular identity of the protein(s) involved in the cellular (re-)uptake of eCBs remains to be characterized. However, some extracellular and intracellular lipid-carrier proteins that assist the trafficking of AEA within (i.e., fatty acid-binding proteins and heat shock proteins) and outside (i.e., albumin) the cells have been identified, confirming that, despite the current controversy, an eCB transport system is indeed an actual biological entity that deserves to be further investigated and understood in the next years [136,139].

4. Role of the endocannabinoid-mediated signaling in adult hippocampal neurogenesis

Several preclinical studies, carried out either by genetic depleting or pharmacological targeting the different elements of the eCB signaling, outlined the pivotal relevance of the ECS in the AHN. These studies revealed that under "normal conditions," CB_1-deficient mice (i.e., $CB_1^{-/-}$ or CB_1-KO mice) display reduced adult hippocampal NSC proliferation, as well as decreased differentiation and survival of their progeny [51,64–66,140].

However, these genetical manipulations have, in some cases, produced conflicting, if not contradictory, results with those obtained by pharmacological approaches, highlighting the complexity of the role played by this lipid signaling system in the regulation of every step of adult neurogenesis (reviewed in [8–10]). For example, several studies have described that pharmacological blockade of the CB_1 leads to increased, rather than decreased, cell proliferation in the SGZ [66,141–143]. To make the cause-and-effect relationship between CB_1 and AHN even more complicated, CB_1 agonism, obtained by natural and synthetic cannabinoids, often, but not always, produced mitogenic effects on hippocampal NSCs [64,66,144–147].

Although these apparent discrepancies may be variously interpreted (e.g., by compensatory mechanisms, subtle differences in models, cannabinergic drugs, time and dosage, methodology for assessing NSC/NPC biology), they seem instead to be related to the differential impact of these manipulations on the widespread expression and multimodal activity of the ECS within the SGZ. In fact, due to its functional expression in every cell component of the hippocampal niche (Fig. 4), the ECS can influence directly and/or indirectly adult neurogenesis by modulating, both positively and negatively, multiple molecular and cellular processes, depending on the cell type (e.g., stem cell, neuron, and glial cell), stage of differentiation (e.g., type 1, type 2, type 3 and immature abGC), or subcellular localization (e.g., plasma membrane, mitochondria, and endoplasmic reticulum). Thus, it is not surprising that the traditional approaches exploited up to now to elucidate the role of ECS in the AHN (e.g., constitutive KO, receptor agonists and antagonists, and enzyme inhibitors) have often produced puzzling results that are hardly interpretable since they fail in keeping intact the cell-specificity and the on-demand feature, namely, the "where" and the "when" of the eCB signaling.

In the following sections, we will briefly summarize current knowledge on the functional involvement of the ECS in the AHN and how the eCB signaling is critically involved in regulating several biological processes that directly or indirectly influence the fate and behavior of NSCs and their progeny.

4.1. Direct mechanisms

As discussed above, deciphering the molecular and cellular mechanisms through which the ECS participates in adult neurogenesis is a really challenging task, requiring recourse to novel technologies with a greater power of spatial and temporal resolution (including single-cell RNA sequencing, cell- and stage-specific KO and knockin). Fortunately, the recent development of inducible Cre-deleter mouse lines, two new mouse strains, where CB_1 and DAGLα are conditionally KO in adult NSCs, provided powerful tools for addressing — in an exact temporal and spatial manner — the influence of the ECS on NSC physiology [40,41].

4.1.1. Role of CB_1

As already described in complete CB_1-KO animals [51,65,140,148,149], the lack of CB_1 in NSCs is sufficient to reduce NSC/NPC proliferation without affecting the survival and/or apoptosis of newly generated cells [41]. These mice also showed an altered neuronal differentiation in terms of dendritic maturation but had no defect in axonal growth, indicating that CB_1 is required for proper dendritogenesis of adult-born neurons originating from NSCs in the SGZ. Consistently, defects in the neurogenic-dependent form of LTP at MPP to immature granule neuron (i.e., MPP-GC, Fig. 1) synapses were also observed, providing evidence for the functional relevance of CB_1 in determining the plasticity of the progeny of NSCs (i.e., immature

abGCs).

Importantly, at a behavioral level, deteriorated neurogenesis induced by NSC-specific CB_1-KO was associated with decreased short-term spatial memory and increased depression-like phenotype, providing a strong link between eCB signaling in NSCs and behavioral outputs of AHN [41].

4.1.2. Role of CB_2 and TRPV1

To date, no NSC-specific KO models for TRPV1 and CB_2 have been developed for testing the direct impact of these receptors on adult NSC functions. However, in vitro studies performed on hippocampal neurospheres suggested the functional presence of both receptors in NSC/NPCs [93,103,150,151] (see 4.1.6).

4.1.3. Role of DAGLα and additional endocannabinoid metabolic enzymes

Using distinct rodent strains in which DAGLα is genetically removed from either neurons or NSCs and astrocytes of adult mice (i.e., Syn-Cre-DAGLα$^{-/-}$ and GLAST-Cre-ERT2-DAGLα$^{-/-}$ mice), NSCs, and possibly niche astrocytes, were identified as the main cellular source of "neurogenically active" 2-AG [40]. Indeed, hippocampal neurogenesis was markedly reduced only in mice lacking DAGLα in NSCs (and in astrocytes), while it was unaffected in those lacking the same enzyme in neurons of the DG, suggesting that 2-AG is an autocrine neurogenic factor in the AHN.

Notably, the removal of DAGLα from NSC/astrocytes determines a large reduction (60%) in the expression of the DAGLβ in adult GCs. This fact implies that the transcription of the DAGLβ gene in GCs is dynamically regulated through signaling cascade(s) stimulated by 2-AG primarily produced by NSCs and their direct progeny. Given that the genetic deletion of DAGLβ also leads to impaired hippocampal neurogenesis in the DG like that of DAGLα [29], such a co-regulated expression of the two isoforms of DAGL could represent a feedback mechanism involved in regulating neurogenesis.

To date, the lack of similar approaches does not allow us to interrogate the direct involvement of the other eCB metabolic enzymes in the physiology of NSCs. Nevertheless, the current evidence supports the notion that NSCs can dynamically synthesize and degrade eCBs, using them as autocrine neurotrophic factors [42,51,152,153].

4.1.4. Synthesis of endocannabinoids by NSCs

It is worth noting that the synthesis of eCBs can be triggered by several neurogenic factors, including BDNF [154,155], FGF2 [156], CCK [157], orexin-A [42], and glutamate [31], released closely to the NSCs by the different cells that constitute the neurogenic niche. Given that NSCs possess the receptors for many, if not all, these signals, including (*i*) BDNF (i.e., tropomyosin receptor kinase B (TrkB)) [158]; (*ii*) glutamate (ionotropic glutamate receptors, AMPAR and *N*-methyl-D-aspartate receptor (NMDAR); and metabotropic glutamate receptors mGluR1 and mGluR5)) [159–161]; and (*iii*) orexin-A (Ox1-R) [42], it is plausible that a part of the proneurogenic message of these molecules consists precisely in promoting the autocrine synthesis of eCBs by NSCs.

4.1.5. Endocannabinoid signaling in NSC/NPCs

Although there are still few mechanistic studies on this topic, the stimulation of $CB_{1/2}$ in NSCs may promote their entry into the cell cycle by activating ERK1/2 and PI3K/Akt pathways which, in turn, stimulate mTORC1, an important positive regulator of NSC activation and proliferation, as well as the subsequent differentiation of their offspring [11,162] (Fig. 5). The downstream signaling from these receptors promotes the switch that commits NPCs to mature GCs by regulating the expression of genes that determine neural identity. During GC maturation, CB_1, and possibly CB_2, may control migration and neuritogenesis, acting on neuronal cytoskeleton via their atypical coupling to $G_{12/13}$ proteins and then Rho-GTPase and Rho-associated coiled- coil containing kinase (ROCK) pathways [110]. Incidentally, this potential pro-differentiative role of CB_1 could explain the alterations in the synaptic plasticity of young GCs observed in nestin-CB1$^{-/-}$ mice [41].

In adult mice, it has been described that, although the cells in the SGZ do not express TRPV1 at an appreciable level, NSC/NPCs (nestin^{+}) and immature GCs (DCX^{+}) re-express the receptor following stimulation of neurogenesis by physical exercise and performance of spatial learning and memory tasks [103]. In this context, TRPV1 seems to mitigate (or put a break to) adult neurogenesis. In fact, TRPV1-KO mice show a greater physical exercise-induced neurogenesis than wild-type mice that performed the same activity [103]. Considering its downstream signaling, it is conceivable that TRPV1 can favor NSC quiescence through Ca^{2+}-dependent cascades, including activation of Notch signaling, possibly by calpain-dependent proteolytic cleavage (Fig. 5). TRPV1 may also control the proliferation of NSCs influencing their excitability by removing $GABA_A$ and/or AMPA receptors from the plasma membrane of NSCs via Ca^{2+}/calcineurin-dependent endocytosis, as documented in specific synapses of adult GCs [97,98]. In this regard, eCB metabotropic and ionotropic targets, by directly promoting or attenuating NSC activation respectively, seem to play antagonistic roles in the physiology of NSCs.

In vitro studies performed on NPC cells of TRPV1$^{-/-}$ mice grown under differentiating conditions have shown that the presence of this receptor is also important for directing astrocytic and neuronal differentiation [103].

Overall, $CB_{1/2}$ receptors and TRPV1 perform pleiotropic actions during AHN, participating in the complex and dynamic integration of the multiple signaling pathways involved in NSC physiology.

4.2. Indirect mechanisms

The presence of several components of the ECS in many, if not all, cells of the hippocampal neurogenic niche, including some local neurons (e.g., MCs and CCK-INs) and glia cells (e.g., astrocytes and microglial cells), suggests that this system can also indirectly modulate the neurogenesis, linking together neuronal and glial activity to the regulation of distinct stages of AHN. The current evidence leads to considering the ECS as a multi-distributed integrator system of various internal and external signals reaching the NSCs. In this sense, the eCB signaling may act as a sensor of circuit and cellular activity and exert pro- and anti-neurogenic actions, depending on which pattern of activity emerges in the stem cell niche.

4.2.1. Impact of endocannabinoids in neuronal activity-dependent control of neurogenesis

The choice of NSCs to remain quiescent or to proliferate is in part determined by the state of electric polarization of their plasma membrane, which is in turn regulated by the tonic concentration of the neurotransmitters GABA and glutamate in the SGZ, which derives from the spillover of the synapses immediately surrounding NSC soma and radial processes [159,163]. In this context, the synapses formed onto the GCs from proximal and distal neurons in the GCL, as well as in the IML, appear particularly relevant for regulating neurogenesis (Fig. 7). For example, ultrastructural studies showed that the bushy processes of NSCs wrap around glutamatergic synapses likely formed between MCs and mature GCs in the IML (i.e., MC-GC) [159,164]. On the other hand, the soma of NSCs in the SGZ is near terminals of PV-INs and respond tonically to GABA released from the synapses that these neurons form with mature GCs (i.e., PV-GCs) [163,165].

Given the crucial importance of the activity level of GCs (both under physiological and pathological conditions) in the control of NSC quiescence and neurogenesis [166], in this section, we will focus on the impact exerted by eCB signaling on the synapses that these cells establish with the surrounding hippocampal neural network. In particular, we will examine the possible implications of the neuromodulatory role of the ECS on neural network activity-dependent spillover of GABA and glutamate from the primary excitatory and inhibitory synapses to GCs.

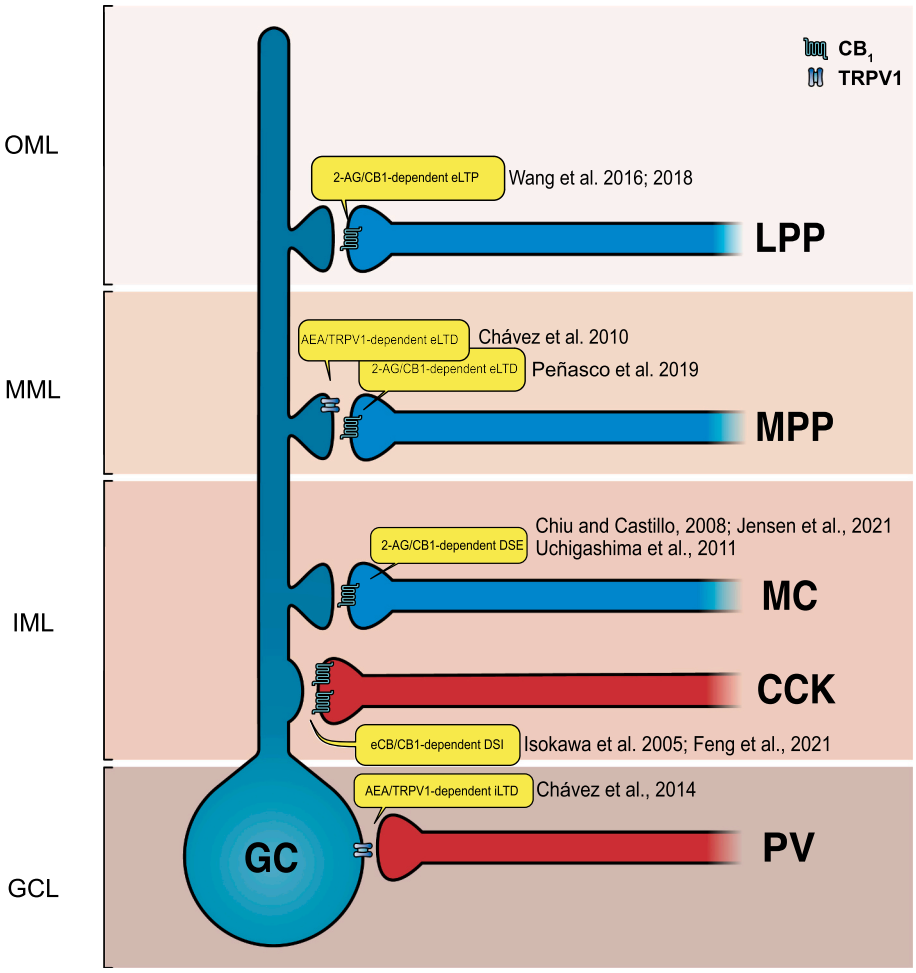


Fig. 7. Endocannabinoid-mediated plasticity on granule cell synapses. A scheme of the complex neuromodulatory control exerted by the endocannabinoid system on granule cell (GC) activity through multiple afferents, either GABAergic (PV-GC and CCK-GC) or glutamatergic (MC-GC, MPP-GC, LPP-GC) synapses. Postsynaptic TPRV1 receptors mainly localizing in either soma or dendritic spines of GCs, and CB_1 receptors localizing at the presynaptic terminals of CCK-GC, MC-GC, MPP-GC and LPP-GC synapses are displayed. In detail, PV inputs target the GC soma and mediate long-term depression of inhibitory transmission (iLTD); CCK inputs target the somatodendritic area encompassing the IML zone, and mediate depolarization-stimulated suppression of inhibition (DSI); MC inputs target proximal dendrites encompassing the IML zone, and mediate depolarization-stimulated suppression of excitation (DSE); MPP and LPP inputs target distal dendrites of GCs and mediate long-term depression of excitatory transmission (eLTD) and long-term potentiation of excitatory transmission (eLTP), respectively. See text for further details and abbreviations.

4.2.1.1. Synaptic inputs and outputs of immature granule cells. As stated in section 3, CB_1 is present during the various stages of maturation of adult-born GCs, where it is involved in regulating axon outgrowth, navigation, and synaptogenesis by modulating cytoskeleton stability and levels of axon guidance/adhesion molecules. Moreover, the enhanced synaptic plasticity of immature abGCs could, in part, be due to the presence of CB_1, which is lacking in functionally mature abGCs. The expression of CB_2 and TRPV1 is not yet well characterized, although it seems that the expression of these receptors increases with the degree of differentiation from type 2b cells onwards.

Compared to their adult counterpart, immature abGCs change their primary inputs dynamically. Initially, they are not at all responsive to neuronal activity [167] and gradually receive only GABAergic inputs from local interneurons, primarily PV-INs and CCK-INs [168,169]. Like immature neurons in the developing brain, abGCs initially become depolarized in response to GABA because of their higher intracellular concentration of chloride ions. The response to GABA switches from depolarization to hyperpolarization at 2–4 weeks after neuronal birth, which coincides with the growth of dendritic spines and the onset of glutamatergic MPP and LPP inputs from the EC. Starting from the third week from the birth, as newborn GCs differentiate, they receive most of their excitatory input from mature GCs, hilar MCs, CA3 PCs, and cholinergic cells of the septum. By one-month, newborn GCs receive comparatively less input from mature GCs, while input from EC begins to strengthen, and by 2–3 months, input from mature GCs progressively disappears. Within this time window, immature abGCs display a lower threshold for the induction of LTP upon stimulation from the MPP [170,171]. This AHN-dependent form of LTP can be elicited without $GABA_A$ receptor blockade and requires the activation of NR2b subunit-containing NMDARs [167]. Regarding their outputs, by one week of age, newborn abGCs begin to extend an axon through the hilus to reach the CA3, forming fully functional synapses onto MCs and CA3 PCs by 4–8 weeks [172]. These changes do not occur uniformly for all cells born at a similar time but rather show heterogeneity among cells of the same age. From approximately 8 weeks of age, the electrophysiological properties of abGCs become highly similar to those of GCs born embryonically or early postnatally.

4.2.1.2. Synaptic inputs and outputs of mature granule cells. CB_1 and TRPV1 receptors are present at the pre- and postsynaptic level, respectively, in the synapses that adult GCs form with at least five different afferents (Fig. 7), suggesting a prominent role for the ECS in regulating neurotransmission through these synapses. In particular, the CB_1 receptor is expressed at the highest density in the axon terminals of CCK+ GABAergic interneurons (i.e., CCK-INs), which mostly target the somatodendritic area of GCs in the IML. Furthermore, dentate GCs receive CB_1-positive glutamatergic synaptic inputs in distinct subdomains: (*i*) their proximal dendrites in the IML are primarily innervated by axon terminals of hilar MCs [173]; (*ii*) their most distal dendritic regions, between the MML and OML of the DG, are innervated by MPP and LPP [38,119,120,174]. In the adult GCs, the presence of TRPV1 receptor has been reported in postsynaptic dendritic spines receiving MPP excitatory inputs, as well as in their soma receiving inhibitory inputs from PV-INs. Finally, CB_2 has been described to be present within GCs, but there is no experimental evidence that it is functionally active [75]. It is, however, possible that, once activated by autocrine-synthesized eCBs, the CB_2 could mediate SSI, a long-lasting, cell-intrinsic hyperpolarization that

may contribute to keeping the GCs silenced [75].

4.2.1.3. Endocannabinoid-mediated plasticity onto granule cells. CB_1, TRPV1 and, possibly, CB_2 seem strategically placed to control synaptic plasticity of either adult or immature GCs at the level of their critical GABAergic (CCK-GC and PV-GC) and glutamatergic (MC-GC, MPP-GC and LPP-GC) synapses. Indeed, their activation selectively depresses both excitatory and inhibitory transmission onto GCs, reducing in a compartment-specific manner the synaptic strength by means of either short- (i.e., DSE and DSI) or long-lasting (i.e., eLTD, iLTD) forms of plasticity [38,97,98,175–179] (Fig. 7). Interestingly, at the glutamatergic synapse formed by the LPP with GCs, CB_1 signaling mediates long-term potentiation (eLTP), rather than inhibition [119,120]. On the other, given that TRPV1 is responsible for the eLTD at the MPP-GC synapse, its action seems to put a brake on glutamatergic signaling on this neurogenesis-relevant input.

Notably, it is very likely that the presence of CB_1 in immature GCs contributes to the hyperexcitability of these cells that enable them to regulate adult GCs. Indeed, CB_1 deletion from adult-born neurons resulted in alterations in the AHN-dependent LTP at the MPP-immature GC synapse [41], indicating a functional role of CB_1 signaling in regulating neuroplasticity of new hippocampal neurons and linking its impaired activity to altered mood-related behavior.

In accordance with a key role of the eCB signaling in the neuromodulatory control of neurogenesis, interfering with the influence that the hippocampal ECS exerts on both GABAergic and glutamatergic transmission has been widely described to have profound impact on memory formation and consolidation [35,149,180,181], as well as to produce anxiogenic and depressive-like phenotype [82,148,182–187].

From a mechanistic point of view, neuronal ECS may influence AHN in many ways. Firstly, as described in section 3.4.2, eCBs, acting through CB_1, TRPV1, and, possibly, CB_2 receptors, are critical retrograde/autocrine modulators of neurotransmitter release from these neurogenesis-relevant synapses. Therefore, through such neuromodulatory functions, the ECS may dynamically control the balance between the tonic levels of GABA and glutamate derived from the synaptic spillover in the neurogenic niche, thus linking neuronal activity to the fate of NSCs. Secondly, by fine-tuning the plasticity of these synapses, the ECS can also dynamically regulate the excitation state of GCs, which in turn control NSC activation via direct GC-NSC contacts [166]. Thirdly, eCBs released by neurons in addition of being neuromodulators can also act as neurogenic factors. For example, the peculiar subcellular localization of the different ECS components in the MC-GC synapses, makes possible a certain diffusive capacity of 2-AG: within short-range distances, 2-AG released from a given GC dendritic spine in the IML could readily escape from enzymatic degradation by MAGL (neither the axon terminals of MC nor the dendritic spines of the GC express MAGL) and reach neighboring structures expressing CB_1, such as other MC-GC synapses and CCK-GC synapses, but also the radial processes of NSCs [38] (Fig. 4). However, this possibility seems to be excluded, at least as far as 2-AG is concerned, by the results obtained from Syn-Cre-DAGL$\alpha^{-/-}$, in which the removal of DAGLα from DG neurons did not alter the basal rate of hippocampal neurogenesis [40]. Finally, the neuroprotective activity from hyperexcitation or other insults exerted by eCBs through multiple mechanisms, including anti-excitotoxicity, anti-oxidative, anti-apoptotic and neurotrophic actions (Fig. 5), should not be underestimated, as it could represent another pertinent role through which neuronal ECS may influence hippocampal neurogenesis.

Overall, the impact of the ECS on the excitability of the GCs, and then on their outcomes onto the neurogenesis, depends on which synapse is functionally active, resulting from a complex spatiotemporal integration of the different internal and environmental inputs that converge on these important components of the hippocampal neurogenic niche (Fig. 8).

4.2.2. Impact of the endocannabinoid system in glial activity-dependent control of neurogenesis

The role of astrocytes and microglia in AHN is rather complicated, having both positive and negative impacts on it, which depend on the functional phenotype (namely, homeostatic/surveillant state versus reactive/inflammatory state) acquired by these cells in response to different stimuli. Indeed, niche glia can rapidly react to subtle microenvironmental alterations by changing morphology and developing an array of functions relevant to promoting or attenuating neurogenesis, including the secretion of soluble factors (neurotrophic factors, gliotransmitters, and cytokines) and specific juxtacrine (i.e., cell-cell contact-dependent) signaling cascades.

4.2.2.1. Endocannabinoid-dependent regulation of niche astrocytes. Astrocytes express a fully functional ECS, being able to autonomously produce eCBs and respond to them via CB_1 and TRPV1. Autocrine and/or paracrine activated eCB signaling within these cells has a profound impact on their functions, including gliotransmitter release (glutamate and D-serin), glucose metabolism, and the release of neurotrophic (FGF-2 and eCBs) and inflammatory mediators (IL-1β and IL-6), all of which play an important role in the indirect regulation of AHN. For example, the stimulation of astroglial CB_1 leads to release of glutamate and D-serin via $G_{q/11}$-mediated Ca^{2+} signaling, exerting appreciable effects on hippocampal synaptic plasticity and long-term memory [67,135,188]. Indeed, these two gliotransmitters, apart from regulating synaptic plasticity or neuronal circuitry, act also as neurogenic factors promoting NSC proliferation and dendritogenesis of newborn neurons [189–191]. In this regard, the critical importance of astrocyte-mediated glutamatergic signaling cascade in AHN was highlighted by a study in which the release of astrocyte-derived glutamate, in response to stimulation of the CCK receptor (i.e., CCK2R), has a dominant proneurogenic action by promoting the activation and proliferation of NSCs [160]. It is tempting to speculate that the astroglial CCK2R, in addition to determine glutamate release [160], could also mediate the synthesis of eCBs, thus having a possible synergistic effect on the activity of astrocytes and NSCs [40,67,135] (Fig. 9). Moreover, it is also worth noting that the main producers of CCK in the neurogenic niche, namely CCK-INs, are highly modulated by environmental stimuli and neurotransmitter systems associated with memory and mood, including the serotonergic, cholinergic, and cannabinergic systems. Indeed, environmental enrichment increases the number of GABAergic CCK^+ synapses that these hilar interneurons form with mature GCs in the DG, thus causing an increase in the number of synapses expressing CB_1 and its downstream signaling [179]. Incidentally, the increase in CB_1 receptor density in the DG induced by environmental enrichment [66,192] may be primarily due to the rise of CB_1-enriched GABAergic terminals of CCK-INs, which make new neurogenic-relevant synaptic contacts with GCs, in proximity with radial processes of niche astrocytes (Fig. 9).

Although astrocytes produce several factors that, in physiological conditions, positively regulate adult neurogenesis, the changes in the astrocyte secretome and metabolism that occur under pathological conditions may generate opposite effects. For example, chronic ethanol exposure acts on astrocytes polarizing them toward a proinflammatory phenotype (i.e., reactive astrocytosis) that is detrimental to AHN. In this context, chronic alcohol intake during adolescence leads to a long-lasting decrease in astroglial CB_1 receptor expression that may compromise its proneurogenic signaling [193]. Furthermore, the sustained activation of astroglial mtCB_1 has been described to produce behavioral effects, by reducing the energy support that astrocytes ensure to neurons [109,194]. In fact, the stimulation of mtCB_1 slows the rate of glycolysis in astrocytes, leading to a lower release of lactate, thus causing a reduced supply of this critical metabolite to neurons. Therefore, by controlling the astrocyte-neuron crosstalk, the mitochondrial-associated CB_1 receptor could have a critical role in the metabolic support of DG niche neurons, including neuroblasts and immature GCs.

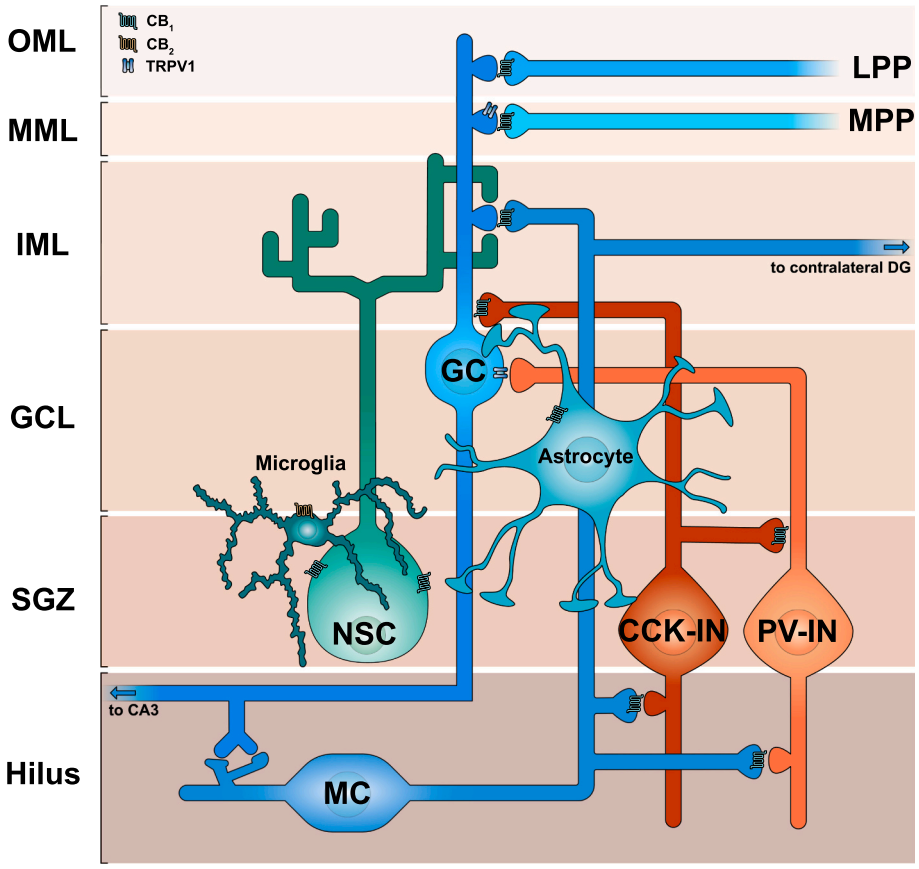


Fig. 8. Functional inter-relationships among cellular components of the hippocampal neurogenic niche. In the neurogenic niche of the hippocampus, the expression of the various elements of the endocannabinoid system (here, for simplicity, only cannabinoid receptors 1 and 2 (CB_1 and CB_2) and transient receptor potential vanilloid type 1 (TRPV1) receptors are indicated) is both cell- and synapse-specific. Therefore, distinct patterns of niche cell activity may trigger different endocannabinoid signaling cascades that, by regulating the relative weight of excitatory and inhibitory inputs in the whole network, determine the overall output response of neural stem cells (NSCs). See text for further details. CA3, *cornu ammonis* subfield 3; CCK-IN, cholecystokinin-expressing interneuron; DG, dentate gyrus; IML, inner molecular layer; LPP, lateral perforant pathway; MC, mossy cell; MML, middle molecular layer; MPP, medial perforant pathway; OML, outer molecular layer; PV-IN, parvalbumin-expressing interneuron.

The impact of eCBs on astroglial functions through TRPV1 is still to be established. It is noteworthy that astroglial TRPV1 is more permeable to Na^+ than Ca^{2+}, as opposed to neuronal TRPV1, which is mainly permeable to Ca^{2+} [195]. From the few studies conducted on the role played by this receptor on astrocytes, it emerged that by increasing Ca^{2+} levels and stimulating Janus kinase 2 (JAK2)-signal transducer and activator of transcription protein 3 (STAT3) signaling, TRPV1 promotes astrocyte reactivity, characterized by hypertrophy, reduced release of neurotrophic factors and enhanced production of pro-inflammatory cytokines and reactive oxygen species [196,197]. These findings suggest that, by polarizing astrocytes toward a neurotoxic phenotype, the stimulation of astroglial TRPV1 may create an unfavorable milieu for neurogenesis.

4.2.2.2. Endocannabinoid-dependent regulation of niche microglia. Microglial cells dynamically metabolize eCBs and are indeed considered the primary cellular source of these bioactive lipids under normal and pathological conditions [198,199]. They seem devoid of CB_1 while expressing low amounts of CB_2 and TRPV1, both of which increase upon microglia activation [200–202]. As much like for astrocytes and NSC (Fig. 5), the stimulation of these two eCB receptors triggers multiple, mainly antagonizing, signaling cascades that profoundly influence the activity of microglial cells, including proliferation, migration, phagocytosis, and secretion of pro- and anti-inflammatory mediators [80,203], that in turn may indirectly impact the AHN.

The role of microglial CB_2 in neuronal function and hippocampal homeostasis was explored in transgenic mice, where the expression of the CB_2 receptor was either abolished or enhanced in adult microglia in the CA1 area [82]. This cell-specific and inducible genome-editing approach revealed that the elevation and disruption of *Cnr2* expression in postnatal microglia increased and decreased, respectively, contextual fear memory, implicating a pivotal role of microglial CB_2 in modulating cognitive behaviors related to AHN [82]. Moreover, it is well ascertained that the activation of CB_2 signaling in microglia polarizes these cells toward an anti-inflammatory/pro-homeostatic phenotype [80,204] that may favor the establishment of a neurogenic milieu in the niche. In particular, CB_2 agonism not only suppresses the expression of pro-inflammatory cytokines and enzymes in LPS/INFγ-activated microglial cells but, at the same time, can promote an anti-inflammatory switching of these cells by stimulating phagocytosis and increasing the expression of arginase 1, IL-10, and critical neurotrophic factors, such as BDNF and GDNF [202,205–209].

Conversely, the role of TRPV1 on microglial functions appears to be diametrically opposite to that of CB_2. In fact, stimulation of microglial TRPV1, through Ca^{2+}-dependent pathways, generally induces a pro-inflammatory phenotype, consisting in hypertrophy, enhanced migration/autophagy, and increased production of reactive oxygen species, IL-6, IL-1β, and TNFα [102,210–215]. By mounting the microglial response to inflammatory insults, such as LPS and β-amyloid peptides, microglial TRPV1 may act as a sensor of brain inflammation [102,210]. Remarkably, TRPV1 can also influence the crosstalk between microglia and neurons. Indeed, TRPV1 activation in cerebral microglia can indirectly increase spontaneous glutamatergic synaptic activity by promoting the shedding of membrane microvesicles, which in turn, possibly by fostering sphingosine metabolism in neurons, enhances presynaptic release probability [102].

5. Physiopathological relevance of the endocannabinoid signaling in adult hippocampal neurogenesis

The literature has consistently established that AHN is essential for several hippocampal-dependent functions, including memory formation, pattern separation (the ability to separate distinct experiences), forgetting, stress buffering, and regulating affective states [11,12]. This

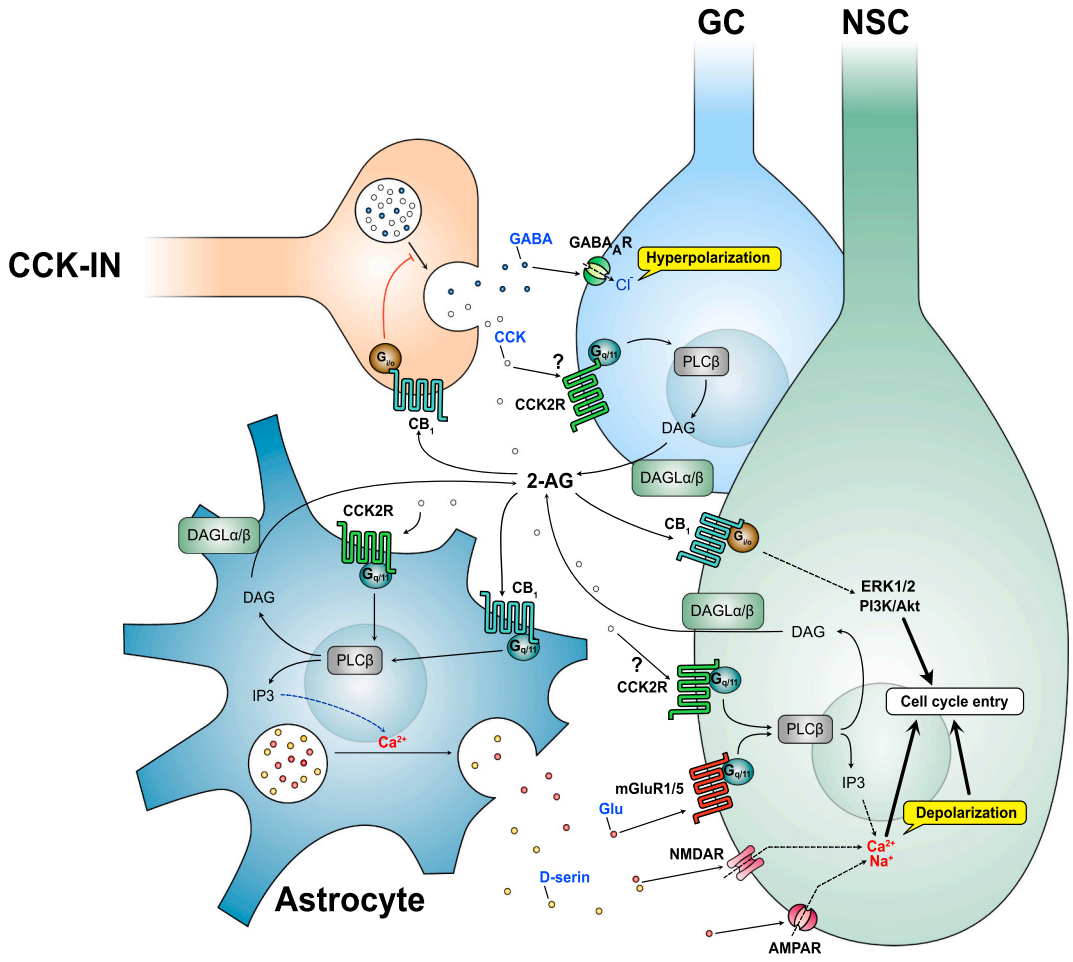


Fig. 9. Endocannabinoid-mediated crosstalk among astrocytes, cholecystokinin-expressing interneurons, granule cells and neural stem cells in the hippocampal niche. The scheme depicts autocrine and/or paracrine mechanisms of endocannabinoid (eCB) signaling among astrocytes, cholecystokinin-expressing interneurons (CCK-INs), granule cells (GCs) and neural stem cells (NSCs). The key player in this context is CCK released by CCK-INs. CCK2 receptor (CCK2R) activation increases the release of both glutamate and D-serine by astrocytes, which acting on mGluR1/5, NMDA and AMPA receptors, promote NSC proliferation. Meanwhile, the activation of CCK2R may also stimulate the synthesis and release of 2-AG by astrocytes, and, possibly, also by GCs and NSCs (the functional presence of CCK2R in GCs and NSCs has yet to be ascertained), thus synergizing with a variety of long-distance stimuli that converge on these cells (see text for details). The consequent accumulation of 2-AG in this hippocampal niche leads to the activation of CB_1 receptors expressed by NSCs and may contribute at stimulating their proliferation. Note also that activation by 2-AG of CB_1 receptors of CCK-INs helps to attenuate the synaptic activity that these GABAergic neurons establish with GCs. AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; mGluR1/5, metabotropic glutamate receptors 1 and 5; NMDAR, *N*-methyl-D-aspartate receptor.

surprising form of neural plasticity is highly regulated by several extrinsic and cell-intrinsic factors and contributes to the organism's adaptation to environmental changes/challenges. The evidence examined here shows how the ECS, acting at different molecular and cellular levels, may be an integral part of the specialized mechanisms by which all these factors integrate with each other, influencing the birth and the integration of abGCs within pre-existing circuits. Therefore, it is tempting to ask whether, and to what extent, the hippocampus-dependent neurobehavioral effects elicited by (endo)cannabinergic drugs and treatments, including anxiolytic and antidepressant actions, are interpretable in the light of the critical regulatory role of the ECS on AHN. Furthermore, another question that arises spontaneously is whether the changes that the ECS undergoes in response to physiological or pathological stimuli may represent the molecular basis through which experience- and environmental-dependent activity is reliably translated into specific patterns of neurogenesis.

AHN can be influenced by a plethora of apparently heterogeneous extrinsic factors, including alcohol abuse, sleep deprivation, obesity, acute and chronic stress, caloric restriction, learning and physical exercise. Given the vastness and complexity of the topic related to pro- and anti-neurogenic effects of these conditions, here we will focus on a small number of them, namely learning, physical exercise and chronic stress, as examples of how the experience of "favorable" or stressful environments may regulate the ECS, converging into distinct forms of local neuronal and glial activity that ultimately impinge on mechanisms regulating neurogenesis.

5.1. Relevance of the endocannabinoid system in the impact of learning and voluntary exercise on hippocampal neurogenesis

Physiological experiences such as learning and physical exercise have been associated with an increase of survival and proliferation of adult-born hippocampal cells, respectively. Intriguingly, under these circumstances, enhanced neurogenesis is invariably associated with an elevated ECS tone, as reviewed in [216]. For example, environmental enrichment housing, a non-invasive intervention used to improve learning in mice, increases CB_1 expression in the hippocampus, specifically in the DG [66]. As reported above, this increase could be associated with an augmented number of CB_1-enriched synapses that CCK-INs establish with GCs in the IML [179]. Notably, the magnitude of CB_1-mediated DSI has a twofold increase in mice exposed to preweaning enrichment, demonstrating that early experience enhances the

contribution of CB_1-mediated inhibition of GABA transmission in the DG, possibly impacting the rate of neurogenesis [179]. Further substantiating the functional role of the CB_1 in mediating experience-driven neurogenesis, a seminal study showed that its genetic ablation abolishes the prosurvival effects of enriched environment on newborn GCs [66].

Furthermore, voluntary wheel running increases the expression and signaling activity of CB_1 receptor in the hippocampus [66,217,218]. The same paradigm of physical activity increases the concentration in the hippocampus (but not in the PFC) of AEA and, to a lesser extent, of 2-AG [217], indicating that voluntary physical activity stimulates eCB signaling in this brain area. Importantly, also in this case, the total absence of CB_1 jeopardizes the proliferative effects of physical exercise on NSC/NPCs [66] and prevents the physical-mediated overexpression of hippocampal BDNF [218,219]. Similarly, chronic antagonism of CB_1 abrogates exercise-induced increase in cell proliferation in the GCL [217], indicating that exercise-induced AHN requires CB_1 receptor activity. More recently, a study showed that CB_1 signaling in glutamatergic, but not in GABAergic, neurons, mediates the enhancement of learning and memory by exercise, which involves increased BDNF production and dendritic spine density in the hippocampus [219]. Finally, the expression of TRPV1 in adult NSCs is induced by pro-neurogenic stimuli, such as physical exercise and spatial learning, but, in this case, its action seems to mitigate (or put a stop to) adult neurogenesis [103], as previously mentioned.

In summary, the hippocampal ECS is influenced by exercise and learning and in turn it influences the effects of these physiological experiences on mood and cognition, at least in part, by regulating AHN.

5.2. Relevance of the endocannabinoid system in the impact of chronic stress on hippocampal neurogenesis

The generation of abGCs in the ventral DG is particularly compromised by stressful environmental challenges such as chronic unpredictable stress, chronic restraint stress, chronic social defeat, early life stress, and glucocorticoid administration. Intriguingly, eCB signaling is dampened in the hippocampus of several murine models of such stressors that negatively impact the rate of AHN [182,220]. For example, exposure of animals to chronic unpredictable stress, a regimen which elicits both adrenal hypertrophy and basal hypersecretion of glucocorticoids, results in a robust and selective reduction in expression of the CB_1 receptor in the hippocampus [221–224], that is accompanied by concomitant increase of hippocampal FAAH level [222] and reduction of hippocampal AEA concentrations [225].

Similarly, repeated exposure to restraint stress, a homotypic stress paradigm that is known to induce dendritic atrophy in the hippocampus, evokes a reduction in the hippocampal AEA, but not of 2-AG [226], accompanied with a downregulation and desensitization of CB_1 in the DG [225]. Importantly, chronic restraint stress impairs the short-term suppression of GABA transmission (DSI) that is mediated via CB_1 receptors expressed in the CCK-INs [227]. In this context, it is worth underlining how, symmetrically to the effects of environmental enrichment paradigm, restraint stress negatively impacts the expression and function of CB_1 in CCK-INs, suggesting that the stress-induced impairment of CB_1-mediated neuroplasticity, at the level of these critical GABAergic synapses, may underlie neurogenesis-dependent cognitive deficits and emotional changes, which are commonly observed in this animal model of chronic stress.

Interestingly, early maternal deprivation, a model for neurodevelopmental stress, differentially affects the two hippocampal cannabinoid receptors, inducing a significant decrease of CB_1 immunoreactivity (more marked in males than in females) while increasing CB_2 expression in the various subdomains of the hippocampus, indicating a functional diversification for these receptors, and their downstream signaling cascades, in the context of stress response [228].

The relevance of the eCB signaling in the stress-related effects on AHN is supported by several preclinical studies using pharmacological and genetical approaches to target different components of the ECS. For example, CB_1-KO mice express higher anxiogenic-like behavior and have enhanced vulnerability to the depressive effects of chronic stressors compared to wild-type littermates [229–232]. Chronic agonism of CB_1 and CB_2 in mice exposed to chronic unpredictable stress exerts anxiolytic effects and reverts stress-induced impairment in cell proliferation and differentiation in the SGZ [143,233]. Conversely, chronic blockade of CB_1 in chronically stressed rats prevents the antidepressant/anxiolytic effects of repetitive transmagnetic stimulation, also abolishing its pro-neurogenic effects, including the increase in NSC/NPC proliferation, BDNF, and B-cell lymphoma 2 (Bcl-2) expression, and decrease in Bcl-2 associated X (Bax) protein expression in the DG [223]. In addition, facilitation of eCB signaling, obtained via inhibition of either eCB reuptake or degrading enzymes, FAAH and MAGL, reverses the stress-induced alterations in AHN, mood and cognition [142,147,234–238]. Interestingly, chronic inhibition of MAGL, possibly by reversing a defective 2-AG signaling and stimulating CB_1 mediated-activation of mTOR-dependent signal transduction in the hippocampus, prevented neurogenesis impairment in SGZ, restored neurogenesis-dependent LTP, and attenuated depressive-like behaviors on mice that were subjected to chronic unpredictable stress [239,240]. Consistently, reduced levels of hippocampal eCBs found in mice lacking DAGLα compromises adult neurogenesis and adversely affects the emotional state of animals, resulting in enhanced anxiety, stress, and fear responses [241].

Even considering the limitations associated with these investigations, which lack the necessary level of cellular and temporal resolution, current experimental evidence reveals the existence of a close relationship between ECS, stress, and AHN. Forthcoming studies will have to ascertain whether the complex interplay that eCB and glucocorticoids play in stress response and resilience [220] takes place in the context of their antagonistic effects on the hippocampal neurogenesis.

5.3. Conclusions and perspectives

AHN is the process by which new functional neurons are continuously generated and integrated into the DG of the hippocampus, after embryonic development and throughout adulthood. Postnatally born GCs impose a substantial remodeling of pre-existing circuits, involving the formation, competition and elimination of synaptic inputs and outputs in the DG, thus profoundly affecting different hippocampus-mediated functions. In particular, it is believed that the activity and experience-dependent rewiring ensured by the daily addition of new neurons constitutes the causal basis of the discrimination of spatial contexts associated with positive or negative rewards, the identification of new characteristics in a family environment, resilience to stress and depression, along with the ability to forget old memories, making significant contributions to learning, memory and emotional behavior.

Within the brain, the ECS is part of the complex biochemical machinery through which neurons and glial cells react to different perturbations/insults that come from the external and internal environment, mutually integrating their activities for (*i*) plastically adapting to them; (plasticity), (*ii*) restoring physiological conditions (homeostasis), and/or (*iii*) repairing and coping damages (resilience). The continuous generation of new neurons and new synapses into the DG is a prominent example of structural and functional plasticity in the adult mammalian brain and is a process in which the regulatory role of the ECS on glial and neural network activity seems to be particularly relevant. Indeed, being dynamically and functionally expressed in every cell component of the hippocampal niche, ECS acts as a multi-distributed integrator system of various internal and external signals converging to NSCs (Fig. 4). Following its stimulation, it can directly and/or indirectly influence the AHN by modulating multiple molecular and cellular processes, depending on the cell type, stage of differentiation, or even subcellular localization.

In NSCs, CB_1, CB_2 and TRPV1 receptors perform pleiotropic actions,

yet largely to be characterized, that participate in the complex and dynamic integration of the multiple signaling pathways operating in these cells (Fig. 5). Upon appropriate stimulation (for example, by BDNF, FGF2, CCK, and glutamate), NSCs can autonomously produce eCBs that, acting as autocrine factors, trigger relevant intracellular signaling pathways, such as PI3K/Akt/mTORC1 and ERK, thus favoring the cell cycle entry of NSCs and influencing their survival, proliferation and lineage differentiation (Figs. 5 and 9). In the other cell components of the neurogenic niche, namely, local neurons and glial cells, the ECS seems to be strategically placed to sense any perturbation of the internal and external environment, eliciting multiple adaptive responses, such as neuromodulatory, immunomodulatory and neuroprotective responses, ultimately linking together neuronal and glial activity to the regulation of distinct stages of AHN (Fig. 8).

However, the organizational complexity of this multi-distributed, redundant, and highly interconnected lipid signaling makes extremely challenging to decipher the molecular and cellular mechanisms through which eCBs, and eCB-based drugs, participate in generating new postnatal neurons and then to predict the final outcomes of the ECS manipulation on AHN (Fig. 8).

From a physiopathological point of view, the critical role of the ECS in adult neurogenesis leads to consider the intriguing possibility that the anxiolytic and anti-depressant effects of (endo)cannabinergic drugs can be partly attributable to their counterbalancing actions on chronic stress-induced changes in the AHN. We are confident that the advent of modern techniques, capable of manipulating individual elements of this complex signaling system with greater spatial and temporal precision, will allow verifying this hypothesis, thus providing a proof-of-concept that targeting eCB signaling may be the basis of new protocols of neurogenesis-based treatments against chronic stress and its related psychopathologic consequences.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors apologize to colleagues whose work we could not include due to space constraints. This investigation was supported by the Italian Ministry of University and Research under the competitive grants (PRIN) n. 2017BTHJ4R_001 to MM and 2017BTHJ4R_005 to SO.

References

[1] Baggelaar MP, Maccarrone M, van der Stelt M. 2-Arachidonoylglycerol: a signaling lipid with manifold actions in the brain. Prog Lipid Res 2018;71:1–17. https://doi.org/10.1016/J.PLIPRES.2018.05.002.

[2] Maccarrone M, Bab I, Bíró T, Cabral GA, Dey SK, di Marzo V, et al. Endocannabinoid signaling at the periphery: 50 years after THC. Trends Pharmacol Sci 2015;36:277–96. https://doi.org/10.1016/J.TIPS.2015.02.008.

[3] Galve-Roperh I, Chiurchiù V, Díaz-Alonso J, Bari M, Guzmán M, Maccarrone M. Cannabinoid receptor signaling in progenitor/stem cell proliferation and differentiation. Prog Lipid Res 2013;52:633–50. https://doi.org/10.1016/J.PLIPRES.2013.05.004.

[4] Lutz B. Neurobiology of cannabinoid receptor signaling. Dialogues Clin Neurosci 2020;22:207–22. https://doi.org/10.31887/DCNS.2020.22.3/BLUTZ.

[5] Harkany T, Guzmán M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol Sci 2007;28:83–92. https://doi.org/10.1016/j.tips.2006.12.004.

[6] Maccarrone M, Guzmán M, Mackie K, Doherty P, Harkany T. Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies. Nat Publ Group 2014;15. https://doi.org/10.1038/nrn3846.

[7] Harkany T, Mackie K, Doherty P. Wiring and firing neuronal networks: endocannabinoids take center stage. Curr Opin Neurobiol 2008;18:338–45. https://doi.org/10.1016/j.conb.2008.08.007.

[8] de Oliveira RW, Oliveira CL, Guimarães FS, Campos AC. Cannabinoid signalling in embryonic and adult neurogenesis: possible implications for psychiatric and neurological disorders. Acta Neuropsychiatr 2018:1–16. https://doi.org/10.1017/neu.2018.11.

[9] Oddi S, Scipioni L, Maccarrone M. Endocannabinoid system and adult neurogenesis: a focused review. Curr Opin Pharmacol 2020;50:25–32. https://doi.org/10.1016/j.coph.2019.11.002.

[10] Prenderville JA, Kelly ÁM, Downer EJ. The role of cannabinoids in adult neurogenesis. Br J Pharmacol 2015;172:3950–63. https://doi.org/10.1111/bph.13186.

[11] Denoth-Lippuner A, Jessberger S. Formation and integration of new neurons in the adult hippocampus. Nat Rev Neurosci 2021;22:223–36. https://doi.org/10.1038/s41583-021-00433-z.

[12] Anacker C, Hen R. Adult hippocampal neurogenesis and cognitive flexibility-linking memory and mood. Nat Rev Neurosci 2017;18:335–46. https://doi.org/10.1038/nrn.2017.45.

[13] Vicidomini C, Guo N, Sahay A. Communication, cross talk, and signal integration in the adult hippocampal neurogenic niche. Neuron 2020;105:220–35. https://doi.org/10.1016/j.neuron.2019.11.029.

[14] Houser CR. Interneurons of the dentate gyrus: an overview of cell types, terminal fields and neurochemical identity. Prog Brain Res 2007:163. https://doi.org/10.1016/S0079-6123(07)63013-1.

[15] Cope EC. Adult neurogenesis, glia, and the extracellular matrix. Cell Stem Cell 2019;24:690–705. https://doi.org/10.1016/j.stem.2019.03.023.Adult.

[16] Delgado-Garcia LM. Adult brain neurogenesis, neural stem cells and neurogenic niches. Int J Stem Cell Res Ther 2017:3. https://doi.org/10.23937/2469-570x/1410039.

[17] Abbott LC, Nigussie F. Adult neurogenesis in the mammalian dentate gyrus. Anat Histol Embryol 2020;49:3–16. https://doi.org/10.1111/AHE.12496.

[18] Li Y, Guo W. Neural stem cell niche and adult neurogenesis. Neuroscientist 2021;27:235–45. https://doi.org/10.1177/1073858420939034.

[19] Ueda N, Tsuboi K, Uyama T. Metabolism of endocannabinoids and related N-acylethanolamines: canonical and alternative pathways. FEBS J 2013;280:1874–94. https://doi.org/10.1111/FEBS.12152.

[20] Ogura Y, Parsons WH, Kamat SS, Cravatt BF. A calcium-dependent acyltransferase that produces N-acyl phosphatidylethanolamines. Nat Chem Biol 2016;12:669–71. https://doi.org/10.1038/NCHEMBIO.2127.

[21] Cadas H, di Tomaso E, Piomelli D. Occurrence and biosynthesis of endogenous cannabinoid precursor, N-arachidonoyl phosphatidylethanolamine, in rat brain. J Neurosci 1997;17:1226–42. https://doi.org/10.1523/JNEUROSCI.17-04-01226.1997.

[22] Ueda N, Okamoto Y, Morishita J. N-acylphosphatidylethanolamine-hydrolyzing phospholipase D: a novel enzyme of the beta-lactamase fold family releasing anandamide and other N-acylethanolamines. Life Sci 2005;77:1750–8. https://doi.org/10.1016/J.LFS.2005.05.018.

[23] Fezza F, Bari M, Florio R, Talamonti E, Feole M, Maccarrone M. Endocannabinoids, related compounds and their metabolic routes. Molecules 2014;19:17078–106. https://doi.org/10.3390/molecules191117078.

[24] Shinohara N, Uyama T, Jin XH, Tsuboi K, Tonai T, Houchi H, et al. Enzymological analysis of the tumor suppressor A-C1 reveals a novel group of phospholipid-metabolizing enzymes. J Lipid Res 2011;52:1927–35. https://doi.org/10.1194/JLR.M015081.

[25] Egertová M, Simon GM, Cravatt BF, Elphick MR. Localization of N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) expression in mouse brain: a new perspective on N-acylethanolamines as neural signaling molecules. J Comp Neurol 2008;506:604–15. https://doi.org/10.1002/CNE.21568.

[26] Nyilas R, Dudok B, Urbán GM, Mackie K, Watanabe M, Cravatt BF, et al. Enzymatic machinery for endocannabinoid biosynthesis associated with calcium stores in glutamatergic axon terminals. J Neurosci 2008;28:1058–63. https://doi.org/10.1523/JNEUROSCI.5102-07.2008.

[27] Hegyi Z, Holló K, Kis G, Mackie K, Antal M. Differential distribution of diacylglycerol lipase-alpha and N-acylphosphatidylethanolamine-specific phospholipase d immunoreactivity in the superficial spinal dorsal horn of rats. Glia 2012;60:1316–29. https://doi.org/10.1002/GLIA.22351.

[28] Hashimotodani Y, Ohno-Shosaku T, Tsubokawa H, Ogata H, Emoto K, Maejima T, et al. Phospholipase Cβ serves as a coincidence detector through its Ca 2+ dependency for triggering retrograde endocannabinoid signal. Neuron 2005;45:257–68. https://doi.org/10.1016/j.neuron.2005.01.004.

[29] Gao Y, Vasilyev DV, Goncalves MB, Howell FV, Hobbs C, Reisenberg M, et al. Loss of retrograde endocannabinoid signaling and reduced adult neurogenesis in diacylglycerol lipase knock-out mice. J Neurosci 2010;30:2017–24. https://doi.org/10.1523/JNEUROSCI.5693-09.2010.

[30] Tanimura A, Yamazaki M, Hashimotodani Y, Uchigashima M, Kawata S, Abe M, et al. The endocannabinoid 2-arachidonoylglycerol produced by diacylglycerol lipase alpha mediates retrograde suppression of synaptic transmission. Neuron 2010;65:320–7. https://doi.org/10.1016/J.NEURON.2010.01.021.

[31] Varma N, Carlson GC, Ledent C, Alger BE. Metabotropic glutamate receptors drive the endocannabinoid system in hippocampus. J Neurosci 2001:21. https://doi.org/10.1523/JNEUROSCI.21-24-J0003.2001.

[32] Maejima T, Hashimoto K, Yoshida T, Aiba A, Kano M. Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. Neuron 2001;31:463–75. https://doi.org/10.1016/S0896-6273(01)00375-0.

[33] Ohno-Shosaku T, Shosaku J, Tsubokawa H, Kano M. Cooperative endocannabinoid production by neuronal depolarization and group I metabotropic glutamate receptor activation. Eur J Neurosci 2002;15:953–61. https://doi.org/10.1046/J.1460-9568.2002.01929.X.

[34] Watanabe M, Nakamura N, Sato K, Kano M, Simon M, Inoue Y. Patterns of expression for the mRNA corresponding to the four isoforms of phospholipase

Cbeta in mouse brain. Eur J Neurosci 1998;10:2016–25. https://doi.org/10.1046/J.1460-9568.1998.00213.X.
[35] Monory K, Massa F, Egertová M, Eder M, Blaudzun H, Westenbroek R, et al. The endocannabinoid system controls key epileptogenic circuits in the hippocampus. Neuron 2006;51:455–66. https://doi.org/10.1016/J.NEURON.2006.07.006.
[36] Katona I, Urbán GM, Wallace M, Ledent C, Jung KM, Piomelli D, et al. Molecular composition of the endocannabinoid system at glutamatergic synapses. J Neurosci 2006;26:5628–37. https://doi.org/10.1523/JNEUROSCI.0309-06.2006.
[37] Yoshida T, Fukaya M, Uchigashima M, Miura E, Kamiya H, Kano M, et al. Localization of diacylglycerol lipase-alpha around postsynaptic spine suggests close proximity between production site of an endocannabinoid, 2-arachidonoylglycerol, and presynaptic cannabinoid CB1 receptor. J Neurosci 2006;26:4740–51. https://doi.org/10.1523/JNEUROSCI.0054-06.2006.
[38] Uchigashima M, Yamazaki M, Yamasaki M, Tanimura A, Sakimura K, Kano M, et al. Molecular and morphological configuration for 2-arachidonoylglycerol-mediated retrograde signaling at mossy cell–granule cell synapses in the dentate gyrus. J Neurosci 2011;31:7700–14. https://doi.org/10.1523/JNEUROSCI.5665-10.2011.
[39] Péterfi Z, Urbán GM, Papp OI, Németh B, Monyer H, Szabó G, et al. Endocannabinoid-mediated long-term depression of afferent excitatory synapses in hippocampal pyramidal cells and GABAergic interneurons. J Neurosci 2012;32:14448–63. https://doi.org/10.1523/JNEUROSCI.1676-12.2012.
[40] Schuele L-L, Schuermann B, Bilkei-Gorzo A, Gorgzadeh S, Zimmer A, Leidmaa E. Regulation of adult neurogenesis by the endocannabinoid-producing enzyme diacylglycerol lipase alpha (DAGLa). Sci Rep 2022;12:1–12. https://doi.org/10.1038/s41598-021-04600-1.
[41] Zimmermann T, Maroso M, Beer A, Baddenhausen S, Ludewig S, Fan W, et al. Neural stem cell lineage-specific cannabinoid type-1 receptor regulates neurogenesis and plasticity in the adult mouse hippocampus. Original Article 2018;28:4454–71. https://doi.org/10.1093/cercor/bhy258.
[42] Forte N, Boccella S, Tunisi L, Fernández-Rilo AC, Imperatore R, Iannotti FA, et al. Orexin-a and endocannabinoids are involved in obesity-associated alteration of hippocampal neurogenesis, plasticity, and episodic memory in mice. Nat Commun 2021;12:1–20. https://doi.org/10.1038/s41467-021-26388-4.
[43] Viader A, Ogasawara D, Joslyn CM, Sanchez-Alavez M, Mori S, Nguyen W, et al. A chemical proteomic atlas of brain serine hydrolases identifies cell type-specific pathways regulating neuroinflammation. Elife 2016;5:1–24. https://doi.org/10.7554/eLife.12345.
[44] Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 1996;384:83–7. https://doi.org/10.1038/384083a0.
[45] Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci U S A 2002;99:10819–24. https://doi.org/10.1073/pnas.152334899.
[46] Goparaju SK, Ueda N, Taniguchi K, Yamamoto S. Enzymes of porcine brain hydrolyzing 2-arachidonoylglycerol, an endogenous ligand of cannabinoid receptors. Biochem Pharmacol 1999;57:417–23. https://doi.org/10.1016/S0006-2952(98)00314-1.
[47] Gulyas AI, Cravatt BF, Bracey MH, Dinh TP, Piomelli D, Boscia F, et al. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. Eur J Neurosci 2004;20:441–58. https://doi.org/10.1111/j.1460-9568.2004.03428.x.
[48] Rivera P, Arrabal S, Cifuentes M, Grondona JM, Pérez-Martín M, Rubio L, et al. Localization of the cannabinoid CB1 receptor and the 2-AG synthesizing (DAGLα) and degrading (MAGL, FAAH) enzymes in cells expressing the Ca2+−binding proteins calbindin, calretinin, and parvalbumin in the adult rat hippocampus. Front Neuroanat 2014;8:1–16. https://doi.org/10.3389/fnana.2014.00056.
[49] Tsou K, Nogueron MI, Muthian S, Sañudo-Peña MC, Hillard CJ, Deutsch DG, et al. Fatty acid amide hydrolase is located preferentially in large neurons in the rat central nervous system as revealed by immunohistochemistry. Neurosci Lett 1998;254:137–40. https://doi.org/10.1016/S0304-3940(98)00700-9.
[50] Egertová M, Cravatt BF, Elphick MR. Comparative analysis of fatty acid amide hydrolase and CB1 cannabinoid receptor expression in the mouse brain: evidence of a widespread role for fatty acid amide hydrolase in regulation of endocannabinoid signaling. Neuroscience 2003;119:481–96. https://doi.org/10.1016/S0306-4522(03)00145-3.
[51] Aguado T, Palazuelos J, Monory K, Stella N, Cravatt B, Lutz B, et al. The endocannabinoid system promotes astroglial differentiation by acting on neural progenitor cells. J Neurosci 2006;26:1551–61. https://doi.org/10.1523/JNEUROSCI.3101-05.2006.
[52] Kozak KR, Crews BC, Morrow JD, Wang LH, Ma YH, Weinander R, et al. Metabolism of the endocannabinoids, 2-arachidonylglycerol and anandamide, into prostaglandin, thromboxane, and prostacyclin glycerol esters and ethanolamides. J Biol Chem 2002;277:44877–85. https://doi.org/10.1074/JBC.M206788200.
[53] Kingsley PJ, Rouzer CA, Morgan AJ, Patel S, Marnett LJ. Aspects of prostaglandin glycerol Ester biology. Adv Exp Med Biol 2019;1161:77–88. https://doi.org/10.1007/978-3-030-21735-8_8.
[54] Di Marzo V, Bisogno T, Melck D, Ross R, Brockie H, Stevenson L, et al. Interactions between synthetic vanilloids and the endogenous cannabinoid system. FEBS Lett 1998;436:449–54. https://doi.org/10.1016/S0014-5793(98)01175-2.
[55] Zygmunt PM, Ermund A, Movahed P, Andersson DA, Simonsen C, Jönsson BAG, et al. Monoacylglycerols activate TRPV1–a link between phospholipase C and TRPV1. PloS One 2013:8. https://doi.org/10.1371/JOURNAL.PONE.0081618.
[56] Iwasaki Y, Saito O, Tanabe M, Inayoshi K, Kobata K, Uno S, et al. Monoacylglycerols activate capsaicin receptor, TRPV1. Lipids 2008;43:471–83. https://doi.org/10.1007/S11745-008-3182-5.
[57] Pistis M, O'Sullivan SE. The role of nuclear hormone receptors in cannabinoid function. Adv Pharmacol 2017;80:291–328. https://doi.org/10.1016/BS.APHA.2017.03.008.
[58] De Petrocellis L, Nabissi M, Santoni G, Ligresti A. Actions and regulation of ionotropic cannabinoid receptors. 1st ed.vol. 80. Elsevier Inc.; 2017. https://doi.org/10.1016/bs.apha.2017.04.001.
[59] Hillard CJ. Biochemistry and pharmacology of the endocannabinoids arachidonylethanolamide and 2-arachidonylglycerol. Prostaglandins Other Lipid Mediat 2000;61:3–18. https://doi.org/10.1016/S0090-6980(00)00051-4.
[60] Marsicano G, Lutz B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 1999;11:4213–25. https://doi.org/10.1046/j.1460-9568.1999.00847.x.
[61] Kawamura Y, Fukaya M, Maejima T, Yoshida T, Miura E, Watanabe M, et al. The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum. J Neurosci 2006;26:2991–3001. https://doi.org/10.1523/JNEUROSCI.4872-05.2006.
[62] Tsou K, Mackie K, Sañudo-Peña MC, Walker JM. Cannabinoid CB1 receptors are localized primarily on cholecystokinin-containing GABAergic interneurons in the rat hippocampal formation. Neuroscience 1999;93:969–75. https://doi.org/10.1016/S0306-4522(99)00086-X.
[63] Katona I, Sperlágh B, Sík A, Käfalvi A, Vizi ES, Mackie K, et al. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci 1999;19:4544–58. https://doi.org/10.1523/jneurosci.19-11-04544.1999.
[64] Jiang W, Zhang Y, Xiao L, van Cleemput J, Ji SP, Bai G, et al. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J Clin Investig 2005;115:3104–16. https://doi.org/10.1172/JCI25509.
[65] Jin K, Xie L, Kim SH, Parmentier-Batteur S, Sun Y, Mao XO, et al. Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice. Mol Pharmacol 2004;66:204–8. https://doi.org/10.1124/mol.66.2.204.
[66] Wolf SA, Bick-Sander A, Fabel K, Leal-Galicia P, Tauber S, Ramirez-Rodriguez G, et al. Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis. Cell Commun Signal 2010:8. https://doi.org/10.1186/1478-811X-8-12.
[67] Navarrete M, Araque A. Endocannabinoids potentiate synaptic transmission through stimulation of astrocytes. Neuron 2010;68:113–26. https://doi.org/10.1016/j.neuron.2010.08.043.
[68] Gutiérrez-Rodríguez A, Bonilla-Del Río I, Puente N, Gómez-Urquijo SM, Fontaine CJ, Egaña-Huguet J, et al. Localization of the cannabinoid type-1 receptor in subcellular astrocyte compartments of mutant mouse hippocampus. Glia 2018;66:1417–31. https://doi.org/10.1002/GLIA.23314.
[69] Molina-Holgado E, Vela JM, Arévalo-Martín A, Almazán G, Molina-Holgado F, Borrell J, et al. Cannabinoids promote oligodendrocyte progenitor survival: involvement of cannabinoid receptors and phosphatidylinositol-3 kinase/Akt signaling. J Neurosci 2002;22:9742–53. https://doi.org/10.1523/JNEUROSCI.22-22-09742.2002.
[70] Golech SA, McCarron RM, Chen Y, Bembry J, Lenz F, Mechoulam R, et al. Human brain endothelium: coexpression and function of vanilloid and endocannabinoid receptors. Brain Res Mol Brain Res 2004;132:87–92. https://doi.org/10.1016/J.MOLBRAINRES.2004.08.025.
[71] Moreno-García Á, Bernal-Chico A, Colomer T, Rodríguez-Antigüedad A, Matute C, Mato S. Gene expression analysis of astrocyte and microglia endocannabinoid signaling during autoimmune demyelination. Biomolecules 2020;10:1–19. https://doi.org/10.3390/biom10091228.
[72] Chiurchiù V, Battistini L, Maccarrone M, Chiurchiù V, Battistini L, Maccarrone M. Endocannabinoid signalling in innate and adaptive immunity. Immunology 2015;144:352–64. https://doi.org/10.1111/imm.12441.
[73] den Boon FS, Chameau P, Schaafsma-Zhao Q, van Aken W, Bari M, Oddi S, et al. Excitability of prefrontal cortical pyramidal neurons is modulated by activation of intracellular type-2 cannabinoid receptors. Proc Natl Acad Sci 2012;109:3534–9. https://doi.org/10.1073/pnas.1118167109.
[74] Brusco A, Tagliaferro P, Saez T, Onaivi ES. Postsynaptic localization of CB2 cannabinoid receptors in the rat hippocampus. Synapse 2008;62:944–9. https://doi.org/10.1002/SYN.20569.
[75] Stempel AV, Stumpf A, Zhang HY, Özdoğan T, Pannasch U, Theis AK, et al. Cannabinoid type 2 receptors mediate a cell type-specific plasticity in the hippocampus. Neuron 2016;90:795–809. https://doi.org/10.1016/j.neuron.2016.03.034.
[76] Viscomi MT, Oddi S, Latini L, Pasquariello N, Florenzano F, Bernardi G, et al. Selective CB2 receptor agonism protects central neurons from remote axotomy-induced apoptosis through the PI3K/Akt pathway. J Neurosci 2009;29:4564–70. https://doi.org/10.1523/JNEUROSCI.0786-09.2009.
[77] Visvanathar R, Papanikolaou M, Nôga DA, Pádua-reis M. Hippocampal Cb 2 receptors : An untold story. 2021.
[78] Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, et al. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res 2006;1071:10–23. https://doi.org/10.1016/J.BRAINRES.2005.11.035.

[79] Li Y, Kim J. Neuronal expression of CB2 cannabinoid receptor mRNAs in the mouse hippocampus. Neuroscience 2015;311:253–67. https://doi.org/10.1016/j.neuroscience.2015.10.041.Neuronal.
[80] Scipioni L, Ciaramellano F, Carnicelli V, Leuti A, Lizzi AR, de Dominicis N, et al. Microglial endocannabinoid signalling in AD. Cells 2022:11. https://doi.org/10.3390/CELLS11071237.
[81] Schmöle AC, Lundt R, Gennequin B, Schrage H, Beins E, Krämer A, et al. Expression analysis of CB2-GFP BAC transgenic mice. PloS One 2015;10:1–16. https://doi.org/10.1371/journal.pone.0138986.
[82] Li Y, Kim J. Distinct roles of neuronal and microglial CB2 cannabinoid receptors in the mouse hippocampus. Neuroscience 2017;363:11–25. https://doi.org/10.1016/j.neuroscience.2017.08.053.
[83] Palazuelos J, Aguado T, Egia A, Mechoulam R, Guzmán M, Galve-Roperh I. Non-psychoactive CB2 cannabinoid agonists stimulate neural progenitor proliferation. FASEB J Off Publ Feder Am Soc Exp Biol 2006; 20(13):2405-7. doi: 10.1096/fj.06-6164fje..
[84] Cao Q, Yang F, Wang H. CB2R induces a protective response against epileptic seizures through ERK and p38 signaling pathways. Int J Neurosci 2021;131:735–44. https://doi.org/10.1080/00207454.2020.1796661.
[85] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816–24. https://doi.org/10.1038/39807.
[86] Kwon DH, Zhang F, Fedor JG, Suo Y, Lee S-Y. Vanilloid-dependent TRPV1 opening trajectory from cryoEM ensemble analysis. Nat Commun 2022:13. https://doi.org/10.1038/S41467-022-30602-2.
[87] Zhang K, Julius D, Cheng Y. Structural snapshots of TRPV1 reveal mechanism of polymodal functionality. Cell 2021;184:5138–5150.e12. https://doi.org/10.1016/j.cell.2021.08.012.
[88] Storozhuk MV, Moroz OF, Zholos AV. Multifunctional TRPV1 ion channels in physiology and pathology with focus on the brain, vasculature, and some visceral systems. Biomed Res Int 2019;2019. https://doi.org/10.1155/2019/5806321.
[89] Iwasaki Y, Saito O, Tanabe M, Inayoshi K, Kobata K, Uno S, et al. Monoacylglycerols activate capsaicin receptor, TRPV1. Lipids 2008;43:471–83. https://doi.org/10.1007/S11745-008-3182-5/FIGURES/8.
[90] Zygmunt PM, Petersson J, Andersson DA, Chuang HH, Sørgård M, di Marzo V, et al. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 1999;400:452–7. https://doi.org/10.1038/22761.
[91] Zygmunt PM, Ermund A, Movahed P, Andersson DA, Simonsen C, Jönsson BAG, et al. Monoacylglycerols activate TRPV1–a link between phospholipase C and TRPV1. PloS One 2013:8. https://doi.org/10.1371/JOURNAL.PONE.0081618.
[92] Meza RC, Ancatén-González C, Chiu CQ, Chávez AE. Transient receptor potential vanilloid 1 function at central synapses in health and disease. Front Cell Neurosci 2022;16:864828. https://doi.org/10.3389/fncel.2022.864828.
[93] Ramírez-Barrantes R, Cordova C, Poblete H, Muñoz P, Marchant I, Wianny F, et al. Perspectives of TRPV1 function on the neurogenesis and neural plasticity. Neural Plast 2016;2016. https://doi.org/10.1155/2016/1568145.
[94] Cavanaugh DJ, Chesler AT, Jackson AC, Sigal YM, Yamanaka H, Grant R, et al. Trpv1 reporter mice reveal highly restricted brain distribution and functional expression in arteriolar smooth muscle cells. J Neurosci 2011;31:5067–77. https://doi.org/10.1523/JNEUROSCI.6451-10.2011.
[95] Cristino L, de Petrocellis L, Pryce G, Baker D, Guglielmotti V, di Marzo V. Immunohistochemical localization of cannabinoid type 1 and vanilloid transient receptor potential vanilloid type 1 receptors in the mouse brain. Neuroscience 2006;139:1405–15. https://doi.org/10.1016/J.NEUROSCIENCE.2006.02.074.
[96] Puente N, Reguero L, Elezgarai I, Canduela M-J, Mendizabal-Zubiaga J, Ramos-Uriarte A, et al. The transient receptor potential vanilloid-1 is localized at excitatory synapses in the mouse dentate gyrus. Brain Struct Funct 2015. https://doi.org/10.1007/s00429-014-0711-2.
[97] Chávez AE, Chiu CQ, Castillo PE. TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. Nat Neurosci 2010;13:1511–9. https://doi.org/10.1038/nn.2684.
[98] Chávez AE, Hernández VM, Rodenas-Ruano A, Savio Chan C, Castillo PE. Compartment-specific modulation of GABAergic synaptic transmission by TRPV1 channels in the dentate gyrus. J Neurosci 2014;34:16621–9. https://doi.org/10.1523/JNEUROSCI.3635-14.2014.
[99] Wang SE, Ko SY, Jo S, Choi M, Lee SH, Jo HR, et al. TRPV1 regulates stress responses through HDAC2. Cell Rep 2017;19:401–12. https://doi.org/10.1016/j.celrep.2017.03.050.
[100] Tóth A, Boczán J, Kedei N, Lizanecz E, Bagi Z, Papp Z, et al. Expression and distribution of vanilloid receptor 1 (TRPV1) in the adult rat brain. Mol Brain Res 2005;135:162–8. https://doi.org/10.1016/j.molbrainres.2004.12.003.
[101] Sun FJ, Guo W, Zheng DH, Zhang CQ, Li S, Liu SY, et al. Increased expression of TRPV1 in the cortex and hippocampus from patients with mesial temporal lobe epilepsy. J Mol Neurosci 2013;49:182–93. https://doi.org/10.1007/S12031-012-9878-2/FIGURES/5.
[102] Marrone MC, Morabito A, Giustizieri M, Chiurchiù V, Leuti A, Mattioli M, et al. TRPV1 channels are critical brain inflammation detectors and neuropathic pain biomarkers in mice. Nat Commun 2017;8:15292. https://doi.org/10.1038/ncomms15292.
[103] Stock K, Garthe A, de Almeida Sassi F, Glass R, Wolf SA, Kettenmann H. The capsaicin receptor TRPV1 as a novel modulator of neural precursor cell proliferation. Stem Cells 2014;32:3183–95. https://doi.org/10.1002/stem.1805.
[104] Canduela MJ, Mendizabal-Zubiaga J, Puente N, Reguero L, Elezgarai I, Ramos-Uriarte A, et al. Visualization by high resolution immunoelectron microscopy of the transient receptor potential vanilloid-1 at inhibitory synapses of the mouse dentate gyrus. PloS One 2015;10:15–20. https://doi.org/10.1371/journal.pone.0119401.
[105] Ibsen MS, Connor M, Glass M. Cannabinoid CB 1 and CB 2 receptor Signaling and bias. Cannabis Cannabinoid Res 2017;2:48–60. https://doi.org/10.1089/can.2016.0037.
[106] Busquets-Garcia A, Bains J, Marsicano G. CB 1 receptor Signaling in the brain: extracting specificity from ubiquity. Neuropsychopharmacology 2018;43:4–20. https://doi.org/10.1038/npp.2017.206.
[107] Howlett AC, Abood ME. CB1 and CB2 Receptor Pharmacology. 2017. p. 169–206. https://doi.org/10.1016/bs.apha.2017.03.007.
[108] Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. J Neurosci 1997;17:5327–33. https://doi.org/10.1523/JNEUROSCI.17-14-05327.1997.
[109] Jimenez-Blasco D, Busquets-Garcia A, Hebert-Chatelain E, Serrat R, Vicente-Gutierrez C, Ioannidou C, et al. Glucose metabolism links astroglial mitochondria to cannabinoid effects. Nature 2020;583:603–8. https://doi.org/10.1038/S41586-020-2470-Y.
[110] Roland AB, Ricobaraza A, Carrel D, Jordan BM, Rico F, Simon A, et al. Cannabinoid-induced actomyosin contractility shapes neuronal morphology and growth. Elife 2014;3:e03159. https://doi.org/10.7554/ELIFE.03159.
[111] Glass M, Northup JK. Agonist selective regulation of G proteins by cannabinoid CB(1) and CB(2) receptors. Mol Pharmacol 1999;56:1362–9. https://doi.org/10.1124/MOL.56.6.1362.
[112] Shirakawa H, Yamaoka T, Sanpei K, Sasaoka H, Nakagawa T, Kaneko S. TRPV1 stimulation triggers apoptotic cell death of rat cortical neurons. Biochem Biophys Res Commun 2008;377:1211–5. https://doi.org/10.1016/J.BBRC.2008.10.152.
[113] Ramírez-Barrantes R, Córdova C, Gatica S, Rodriguez B, Lozano C, Marchant I, et al. Transient receptor potential Vanilloid 1 expression mediates capsaicin-induced cell death. Front Physiol 2018:9. https://doi.org/10.3389/FPHYS.2018.00682.
[114] Castillo PE, Younts TJ, Chávez AE, Hashimotodani Y. Endocannabinoid signaling and synaptic function. Neuron 2012;76:70–81. https://doi.org/10.1016/j.neuron.2012.09.020.
[115] Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science 2002;296:678–82. https://doi.org/10.1126/SCIENCE.1063545.
[116] Chevaleyre V, Takahashi KA, Castillo PE. Endocannabinoid-mediated synaptic plasticity in the CNS. Annu Rev Neurosci 2006;29:37–76. https://doi.org/10.1146/annurev.neuro.29.051605.112834.
[117] Ohno-Shosaku T, Kano M. Endocannabinoid-mediated retrograde modulation of synaptic transmission. Curr Opin Neurobiol 2014;29:1–8. https://doi.org/10.1016/j.conb.2014.03.017.
[118] Cachope R. Functional diversity on synaptic plasticity mediated by endocannabinoids. Philos Trans R Soc Lond B Biol Sci 2012;367:3242–53. https://doi.org/10.1098/rstb.2011.0386.
[119] Wang W, Trieu BH, Palmer LC, Jia Y, Pham DT, Jung KM, et al. A primary cortical input to hippocampus expresses a pathway-specific and endocannabinoid-dependent form of long-term potentiation. ENeuro 2016;3:10049–53. https://doi.org/10.1523/ENEURO.0160-16.2016.
[120] Wang W, Jia Y, Pham DT, Palmer LC, Jung KM, Cox CD, et al. Atypical endocannabinoid signaling initiates a new form of memory-related plasticity at a cortical input to hippocampus. Cereb Cortex 2018;28:2253–66. https://doi.org/10.1093/cercor/bhx126.
[121] Steindel F, Lerner R, Häring M, Ruehle S, Marsicano G, Lutz B, et al. Neuron-type specific cannabinoid-mediated G protein signalling in mouse hippocampus. J Neurochem 2013;124:795–807. https://doi.org/10.1111/JNC.12137.
[122] Guggenhuber S, Alpar A, Chen R, Schmitz N, Wickert M, Mattheus T, et al. Cannabinoid receptor-interacting protein Crip1a modulates CB1 receptor signaling in mouse hippocampus. Brain Struct Funct 2016;221:2061–74. https://doi.org/10.1007/S00429-015-1027-6.
[123] Smith TH, Blume LC, Straiker A, Cox JO, David BG, Secor McVoy JR, et al. Cannabinoid receptor-interacting protein 1a modulates CB1 receptor signaling and regulation. Mol Pharmacol 2015;87:747–65. https://doi.org/10.1124/mol.114.096495.
[124] Oddi S, Stepniewski TM, Totaro A, Selent J, Scipioni L, Dufrusine B, et al. Palmitoylation of cysteine 415 of CB1receptor affects ligand-stimulated internalization and selective interaction with membrane cholesterol and caveolin 1. Biochim Biophys Acta Mol Cell Biol Lipids 2017;1862:523–32. https://doi.org/10.1016/j.bbalip.2017.02.004.
[125] Oddi S, Totaro A, Scipioni L, Dufrusine B, Stepniewski TM, Selent J, et al. Role of palmitoylation of cysteine 415 in functional coupling CB1 receptor to Gαi2 protein. Biotechnol Appl Biochem 2018;65:16–20. https://doi.org/10.1002/bab.1575.
[126] Eldeeb K, Ganjiwale AD, Chandrashekaran IR, Padgett LW, Burgess JP, Howlett AC, et al. CB1 cannabinoid receptor-phosphorylated fourth intracellular loop structure-function relationships. Pept Sci (Hoboken) 2019:111. https://doi.org/10.1002/PEP2.24104.
[127] Callén L, Moreno E, Barroso-Chinea P, Moreno-Delgado D, Cortés A, Mallol J, et al. Cannabinoid receptors CB1 and CB2 form functional heteromers in brain. J Biol Chem 2012;287:20851–65. https://doi.org/10.1074/JBC.M111.335273.
[128] Viñals X, Moreno E, Lanfumey L, Cordomí A, Pastor A, de La Torre R, et al. Cognitive impairment induced by delta9- tetrahydrocannabinol occurs through heteromers between cannabinoid CB1 and serotonin 5-HT2A receptors. PLoS Biol 2015;13:1–40. https://doi.org/10.1371/journal.pbio.1002194.
[129] Saumell-Esnaola M, Barrondo S, García Del Caño G, Goicolea MA, Sallés J, Lutz B, et al. Subsynaptic distribution, lipid raft targeting and G protein-dependent

signalling of the type 1 cannabinoid receptor in Synaptosomes from the mouse hippocampus and frontal cortex. Molecules 2021:26. https://doi.org/10.3390/molecules26226897.
[130] Bénard G, Massa F, Puente N, Lourenço J, Bellocchio L, Soria-Gómez E, et al. Mitochondrial CB 1 receptors regulate neuronal energy metabolism. Nat Neurosci 2012;15:558–64. https://doi.org/10.1038/nn.3053.
[131] Stumpf A, Parthier D, Sammons RP, Stempel AV, Breustedt J, Rost BR, et al. Cannabinoid type 2 receptors mediate a cell type-specific self-inhibition in cortical neurons. Neuropharmacology 2018;139:217–25. https://doi.org/10.1016/j.neuropharm.2018.07.020.
[132] Bacci A, Huguenard JR, Prince DA. Long-lasting self-inhibition of neocortical interneurons mediated by endocannabinoids. Nature 2004;431:312–6. https://doi.org/10.1038/NATURE02913.
[133] Marinelli S, Pacioni S, Bisogno T, Di Marzo V, Prince DA, Huguenard JR, et al. The endocannabinoid 2-arachidonoylglycerol is responsible for the slow self-inhibition in neocortical interneurons. J Neurosci 2008;28:13532–41. https://doi.org/10.1523/JNEUROSCI.0847-08.2008.
[134] Marinelli S, Pacioni S, Cannich A, Marsicano G, Bacci A. Self-modulation of neocortical pyramidal neurons by endocannabinoids. Nat Neurosci 2009;12:1488–90. https://doi.org/10.1038/NN.2430.
[135] Han J, Kesner P, Metna-Laurent M, Duan T, Xu L, Georges F, et al. Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal LTD. Cell 2012;148:1039–50. https://doi.org/10.1016/j.cell.2012.01.037.
[136] Maccarrone M, Dainese E, Oddi S. Intracellular trafficking of anandamide: new concepts for signaling. Trends Biochem Sci 2010;35:601–8. https://doi.org/10.1016/j.tibs.2010.05.008.
[137] Nicolussi S, Gertsch J. Endocannabinoid transport revisited. Vitam Horm 2015;98:441–85. https://doi.org/10.1016/BS.VH.2014.12.011.
[138] Fowler CJ. Transport of endocannabinoids across the plasma membrane and within the cell. FEBS J 2013;280:1895–904. https://doi.org/10.1111/febs.12212.
[139] Kaczocha M, Haj-Dahmane S. Mechanisms of endocannabinoid transport in the brain. Br J Pharmacol 2021. https://doi.org/10.1111/BPH.15469.
[140] Kim SH, Won SJ, Mao XO, Ledent C, Jin K, Greenberg DA. Role for neuronal nitric-oxide synthase in cannabinoid-induced neurogenesis. J Pharmacol Exp Ther 2006;319:150–4. https://doi.org/10.1124/jpet.106.107698.
[141] Rueda D, Navarro B, Martínez-Serrano A, Guzmán M, Galve-Roperh I. The endocannabinoid anandamide inhibits neuronal progenitor cell differentiation through attenuation of the Rap1/B-Raf/ERK pathway. J Biol Chem 2002;277:46645–50. https://doi.org/10.1074/jbc.M206590200.
[142] Hill MN, Kambo JS, Sun JC, Gorzalka BB, Galea LAM. Endocannabinoids modulate stress-induced suppression of hippocampal cell proliferation and activation of defensive behaviours. Eur J Neurosci 2006;24:1845–9. https://doi.org/10.1111/j.1460-9568.2006.05061.x.
[143] Fogaça MV, Campos AC, Coelho LD, Duman RS, Guimarães FS. The anxiolytic effects of cannabidiol in chronically stressed mice are mediated by the endocannabinoid system: role of neurogenesis and dendritic remodeling. Neuropharmacology 2018;135:22–33. https://doi.org/10.1016/j.neuropharm.2018.03.001.
[144] Andres-Mach M, Haratym-Maj A, Zagaja M, Rola R, Maj M, Chrościńska-Krawczyk M, et al. ACEA (a highly selective cannabinoid CB1 receptor agonist) stimulates hippocampal neurogenesis in mice treated with antiepileptic drugs. Brain Res 2015;1624:86–94. https://doi.org/10.1016/j.brainres.2015.07.028.
[145] Andres-Mach M, Zagaja M, Haratym-Maj A, Rola R, Maj M, Haratym J, et al. A long-term treatment with arachidonyl-2′-chloroethylamide combined with valproate increases neurogenesis in a mouse pilocarpine model of epilepsy. Int J Mol Sci 2017;18:900. https://doi.org/10.3390/ijms18050900.
[146] Rivera P, Blanco E, Bindila L, Alen F, Vargas A, Rubio L, et al. Pharmacological activation of CB2 receptors counteracts the deleterious effect of ethanol on cell proliferation in the main neurogenic zones of the adult rat brain. Front Cell Neurosci 2015;9:1–14. https://doi.org/10.3389/fncel.2015.00379.
[147] Realini N, Vigano D, Guidali C, Zamberletti E, Rubino T, Parolaro D. Chronic URB597 treatment at adulthood reverted most depressive-like symptoms induced by adolescent exposure to THC in female rats. Neuropharmacology 2011;60:235–43. https://doi.org/10.1016/j.neuropharm.2010.09.003.
[148] Dubreucq S, Koehl M, Abrous DN, Marsicano G, Chaouloff F. CB1 receptor deficiency decreases wheel-running activity: consequences on emotional behaviours and hippocampal neurogenesis. Exp Neurol 2010;224:106–13. https://doi.org/10.1016/j.expneurol.2010.01.017.
[149] Albayram O, Alferink J, Pitsch J, Piyanova A, Neitzert K, Poppensieker K, et al. Role of CB1 cannabinoid receptors on GABAergic neurons in brain aging. Proc Natl Acad Sci U S A 2011;108:11256–61. https://doi.org/10.1073/pnas.1016442108.
[150] Molina-Holgado F, Rubio-Araiz A, García-Ovejero D, Williams RJ, Moore JD, Arévalo-Martín Á, et al. CB2 cannabinoid receptors promote mouse neural stem cell proliferation. Eur J Neurosci 2007;25:629–34. https://doi.org/10.1111/j.1460-9568.2007.05322.x.
[151] Palazuelos J, Ortega Z, Díaz-Alonso J, Guzmán M, Galve-Roperh I. CB2 cannabinoid receptors promote neural progenitor cell proliferation via mTORC1 Signaling. J Biol Chem 2012;287:1198–209. https://doi.org/10.1074/JBC.M111.291294.
[152] Aguado T, Monory K, Palazuelos J, Stella N, Cravatt B, Lutz B, et al. The endocannabinoid system drives neural progenitor proliferation. FASEB J 2005;19:1704–6. https://doi.org/10.1096/fj.05-3995fje.
[153] Avraham HK, Jiang S, Fu Y, Rockenstein E, Makriyannis A, Zvonok A, et al. The cannabinoid CB $_2$ receptor agonist AM1241 enhances neurogenesis in GFAP/Gp120 transgenic mice displaying deficits in neurogenesis. Br J Pharmacol 2014;171:468–79. https://doi.org/10.1111/bph.12478.
[154] Lemtiri-Chlieh F, Levine ES. BDNF evokes release of endogenous cannabinoids at layer 2/3 inhibitory synapses in the neocortex. J Neurophysiol 2010;104:1923–32. https://doi.org/10.1152/jn.00472.2010.
[155] Yeh ML, Selvam R, Levine ES. BDNF-induced endocannabinoid release modulates neocortical glutamatergic neurotransmission. Synapse 2017:71. https://doi.org/10.1002/SYN.21962.
[156] Williams EJ, Walsh FS, Doherty P. The FGF receptor uses the endocannabinoid signaling system to couple to an axonal growth response. J Cell Biol 2003;160:481–6. https://doi.org/10.1083/jcb.200210164.
[157] Földy C, Lee SY, Szabadics J, Neu A, Soltesz I. Cell type–specific gating of perisomatic inhibition by cholecystokinin. Nat Neurosci 2007;10(9):1128–30. https://doi.org/10.1038/nn1952.
[158] Vilar M, Mira H. Regulation of neurogenesis by neurotrophins during adulthood: expected and unexpected roles. Front Neurosci 2016;10:26. https://doi.org/10.3389/FNINS.2016.00026/BIBTEX.
[159] Yeh CY, Asrican B, Moss J, Quintanilla LJ, He T, Mao X, et al. Mossy cells control adult neural stem cell quiescence and maintenance through a dynamic balance between direct and indirect pathways. Neuron 2018;99:493–510.e4. https://doi.org/10.1016/j.neuron.2018.07.010.
[160] Asrican B, Wooten J, Li YD, Quintanilla L, Zhang F, Wander C, et al. Neuropeptides modulate local astrocytes to regulate adult hippocampal neural stem cells. Neuron 2020;108:349–366.e6. https://doi.org/10.1016/j.neuron.2020.07.039.
[161] Shin J, Berg DA, Zhu Y, Shin JY, Song J, Bonaguidi MA, et al. Single-cell RNA-Seq with waterfall reveals molecular cascades underlying adult neurogenesis. Cell Stem Cell 2015;17:360–72. https://doi.org/10.1016/J.STEM.2015.07.013.
[162] Matsubara S, Matsuda T, Nakashima K. Regulation of adult mammalian neural stem cells and neurogenesis by cell extrinsic and intrinsic factors. Cells 2021:10. https://doi.org/10.3390/cells10051145.
[163] Song J, Zhong C, Bonaguidi MA, Sun GJ, Hsu D, Gu Y, et al. Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. Nature 2012;489:150–4. https://doi.org/10.1038/nature11306.
[164] Moss J, Gebara E, Bushong EA, Sánchez-Pascual I, O'Laoi R, el M'Gharia I, et al. Fine processes of nestin-GFP-positive radial glia-like stem cells in the adult dentate gyrus ensheathe local synapses and vasculature. Proc Natl Acad Sci U S A 2016;113:E2536–45. https://doi.org/10.1073/PNAS.1514652113.
[165] Moss J, Toni N. A circuit-based gatekeeper for adult neural stem cell proliferation: Parvalbumin-expressing interneurons of the dentate gyrus control the activation and proliferation of quiescent adult neural stem cells. Bioessays 2013;35:28–33. https://doi.org/10.1002/BIES.201200136.
[166] Dong J, Pan YB, Wu XR, He LN, Liu XD, Feng DF, et al. A neuronal molecular switch through cell-cell contact that regulates quiescent neural stem cells. Sci Adv 2019:5. https://doi.org/10.1126/SCIADV.AAV4416.
[167] Snyder JS, Kee N, Wojtowicz JM. Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol 2001;85:2423–31. https://doi.org/10.1152/JN.2001.85.6.2423.
[168] Espósito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, et al. Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci 2005;25:10074–86. https://doi.org/10.1523/JNEUROSCI.3114-05.2005.
[169] Ge S, Goh ELK, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 2006;439:589–93. https://doi.org/10.1038/NATURE04404.
[170] Ge S, Yang C, hao, Hsu K sen, Ming G li, Song H.. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 2007;54:559–66. https://doi.org/10.1016/J.NEURON.2007.05.002.
[171] Schmidt-Hieber C, Jones P, Bischofberger J. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 2004;429:184–7. https://doi.org/10.1038/NATURE02553.
[172] Hastings NB, Gould E. Rapid extension of axons into the CA3 region by adult-generated granule cells. J Comp Neurol 1999;413:146–54. https://doi.org/10.1002/(sici)1096-9861(19991011)413:1<146::aid-cne10>3.0.co;2-b.
[173] Johnston D, Amaral DG. Hippocampus. In: The Synaptic Organization of the Brain; 2004. https://doi.org/10.1093/ACPROF:OSO/9780195159561.003.0011.
[174] Witter MP. The perforant path: projections from the entorhinal cortex to the dentate gyrus. Prog Brain Res 2007;163:43–61. https://doi.org/10.1016/S0079-6123(07)63003-9.
[175] Peñasco S, Rico-Barrio I, Puente N, Gómez-Urquijo SM, Fontaine CJ, Egaña-Huguet J, et al. Endocannabinoid long-term depression revealed at medial perforant path excitatory synapses in the dentate gyrus. Neuropharmacology 2019;153:32–40. https://doi.org/10.1016/j.neuropharm.2019.04.020.
[176] Chiu CQ, Castillo PE. Input-specific plasticity at excitatory synapses mediated by endocannabinoids in the dentate gyrus. Neuropharmacology 2008;54:68–78. https://doi.org/10.1016/j.neuropharm.2007.06.026.
[177] Jensen KR, Berthoux C, Nasrallah K, Castillo PE. Multiple cannabinoid signaling cascades powerfully suppress recurrent excitation in the hippocampus. Proc Natl Acad Sci U S A 2021:118. https://doi.org/10.1073/pnas.2017590118.
[178] Isokawa M, Alger BE. Retrograde endocannabinoid regulation of GABAergic inhibition in the rat dentate gyrus granule cell. J Physiol 2005;567:1001–10. https://doi.org/10.1113/jphysiol.2005.094219.
[179] Feng T, Alicea C, Pham V, Kirk A, Pieraut S. Experience-dependent inhibitory plasticity is mediated by CCK+ basket cells in the developing dentate gyrus. 2021. https://doi.org/10.1101/2020.04.30.071126.

[180] Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. Life Sci 1999;65:715–23. https://doi.org/10.1016/S0024-3205(99)00294-5.
[181] Puighermanal E, Marsicano G, Busquets-Garcia A, Lutz B, Maldonado R, Ozaita A. Cannabinoid modulation of hippocampal long-term memory is mediated by mTOR signaling. Nat Neurosci 2009;12:1152–8. https://doi.org/10.1038/NN.2369.
[182] Lutz B, Marsicano G, Maldonado R, Hillard CJ. The endocannabinoid system in guarding against fear, anxiety and stress. Nat Rev Neurosci 2015;16:705–18. https://doi.org/10.1038/nrn4036.
[183] Martín-García E, Bourgoin L, Cathala A, Kasanetz F, Mondesir M, Gutiérrez-Rodriguez A, et al. Differential control of cocaine self-administration by GABAergic and glutamatergic CB1 cannabinoid receptors. Neuropsychopharmacology 2016;41:2192–205. https://doi.org/10.1038/npp.2015.351.
[184] Moreira FA, Kaiser N, Monory K, Lutz B. Reduced anxiety-like behaviour induced by genetic and pharmacological inhibition of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) is mediated by CB1 receptors. Neuropharmacology 2008;54:141–50. https://doi.org/10.1016/j.neuropharm.2007.07.005.
[185] Zimmermann T, Bartsch JC, Beer A, Lomazzo E, Guggenhuber S, Lange MD, et al. Impaired anandamide/palmitoylethanolamide signaling in hippocampal glutamatergic neurons alters synaptic plasticity, learning, and emotional responses. Neuropsychopharmacology 2019;44:1377–88. https://doi.org/10.1038/S41386-018-0274-7.
[186] Ortega-Alvaro A, Aracil-Fernández A, García-Gutiérrez MS, Navarrete F, Manzanares J. Deletion of CB2 cannabinoid receptor induces schizophrenia-related behaviors in mice. Neuropsychopharmacology 2011;36:1489–504. https://doi.org/10.1038/npp.2011.34.
[187] Navarrete F, Pérez-Ortiz JM, Manzanares J. Cannabinoid CB_2 receptor-mediated regulation of impulsive-like behaviour in DBA/2 mice. Br J Pharmacol 2012;165:260–73. https://doi.org/10.1111/j.1476-5381.2011.01542.x.
[188] Robin LM, Oliveira da Cruz JF, Langlais VC, Martin-Fernandez M, Metna-Laurent M, Busquets-Garcia A, et al. Astroglial CB1 receptors determine synaptic D-serine availability to enable recognition memory. Neuron 2018;98:935–944.e5. https://doi.org/10.1016/j.neuron.2018.04.034.
[189] Sultan S, Li L, Moss J, Petrelli F, Cassé F, Gebara E, et al. Synaptic integration of adult-born hippocampal neurons is locally controlled by astrocytes. Neuron 2015;88:957–72. https://doi.org/10.1016/j.neuron.2015.10.037.
[190] Sultan S, Gebara EG, Moullec K, Toni N. D-serine increases adult hippocampal neurogenesis. Front Neurosci 2013:7. https://doi.org/10.3389/FNINS.2013.00155.
[191] Uemura M, Blankvoort S, Shui S, Tok L, Yuan L, Cobar LF, et al. A neurogenic microenvironment defined by excitatory-inhibitory neuronal circuits in adult dentate gyrus. Cell Rep 2021;36:109324. https://doi.org/10.1016/j.celrep.2021.109324.
[192] el Rawas R, Thiriet N, Nader J, Lardeux V, Jaber M, Solinas M. Early exposure to environmental enrichment alters the expression of genes of the endocannabinoid system. Brain Res 2011;1390:80–9. https://doi.org/10.1016/j.brainres.2011.03.025.
[193] Bonilla-Del Río I, Puente N, Peñasco S, Rico I, Gutiérrez-Rodríguez A, Elezgarai I, et al. Adolescent ethanol intake alters cannabinoid type-1 receptor localization in astrocytes of the adult mouse hippocampus. Addict Biol 2019;24:182–92. https://doi.org/10.1111/ADB.12585.
[194] Serrat R, Covelo A, Kouskoff V, Delcasso S, Ruiz-Calvo A, Chenouard N, et al. Astroglial ER-mitochondria calcium transfer mediates endocannabinoid-dependent synaptic integration. Cell Rep 2021:37. https://doi.org/10.1016/J.CELREP.2021.110133.
[195] Huang C, Hu ZL, Wu WN, Yu DF, Xiong QJ, Song JR, et al. Existence and distinction of acid-evoked currents in rat astrocytes. Glia 2010;58:1415–24. https://doi.org/10.1002/GLIA.21017.
[196] Yang XL, Wang X, Shao L, Jiang GT, Min JW, Mei XY, et al. TRPV1 mediates astrocyte activation and interleukin-1β release induced by hypoxic ischemia (HI). J Neuroinflammation 2019;16. https://doi.org/10.1186/S12974-019-1487-3.
[197] Ho KW, Lambert WS, Calkins DJ. Activation of the TRPV1 cation channel contributes to stress-induced astrocyte migration. Glia 2014;62:1435–51. https://doi.org/10.1002/GLIA.22691.
[198] Walter L, Franklin A, Witting A, Wade C, Xie Y, Kunos G, et al. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. J Neurosci 2003;23:1398–405. https://doi.org/10.1523/JNEUROSCI.23-04-01398.2003.
[199] Mecha M, Feliú A, Carrillo-Salinas FJ, Rueda-Zubiaurre A, Ortega-Gutiérrez S, de Sola RG, et al. Endocannabinoids drive the acquisition of an alternative phenotype in microglia. Brain Behav Immun 2015;49:233–45. https://doi.org/10.1016/J.BBI.2015.06.002.
[200] Maresz K, Carrier EJ, Ponomarev ED, Hillard CJ, Dittel BN. Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli. J Neurochem 2005;95:437–45. https://doi.org/10.1111/J.1471-4159.2005.03380.X.
[201] Kong W, Wang X, Yang X, Huang W, Han S, Yin J, et al. Activation of TRPV1 contributes to recurrent febrile seizures via inhibiting the microglial M2 phenotype in the immature brain. Front Cell Neurosci 2019:13. https://doi.org/10.3389/FNCEL.2019.00442.
[202] de Martín Ruiz, Esteban S, Benito-Cuesta I, Terradillos I, Martínez-Relimpio AM, Arnanz MA, et al. Cannabinoid CB 2 receptors modulate microglia function and amyloid dynamics in a mouse model of Alzheimer's disease. Front Pharmacol 2022:13. https://doi.org/10.3389/FPHAR.2022.841766.
[203] Duffy SS, Hayes JP, Fiore NT, Moalem-Taylor G. The cannabinoid system and microglia in health and disease. Neuropharmacology 2021;190:108555. https://doi.org/10.1016/j.neuropharm.2021.108555.
[204] Young AP, Denovan-Wright EM. The dynamic role of microglia and the endocannabinoid system in neuroinflammation. Front Pharmacol 2022;12:4069. https://doi.org/10.3389/FPHAR.2021.806417/BIBTEX.
[205] Hernangómez M, Mestre L, Correa FG, Loría F, Mecha M, Iñigo PM, et al. CD200-CD200R1 interaction contributes to neuroprotective effects of anandamide on experimentally induced inflammation. Glia 2012;60:1437–50. https://doi.org/10.1002/GLIA.22366.
[206] Correa F, Hernangómez M, Mestre L, Loría F, Spagnolo A, Docagne F, et al. Anandamide enhances IL-10 production in activated microglia by targeting CB(2) receptors: roles of ERK1/2, JNK, and NF-kappaB. Glia 2010;58:135–47. https://doi.org/10.1002/GLIA.20907.
[207] Malek N, Popiolek-Barczyk K, Mika J, Przewlocka B, Starowicz K. Anandamide, acting via CB2 receptors, alleviates LPS-induced Neuroinflammation in rat primary microglial cultures. Neural Plast 2015;2015. https://doi.org/10.1155/2015/130639.
[208] Ehrhart J, Obregon D, Mori T, Hou H, Sun N, Bai Y, et al. Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. J Neuroinflammation 2005:2. https://doi.org/10.1186/1742-2094-2-29.
[209] Ma L, Jia J, Liu X, Bai F, Wang Q, Xiong L. Activation of murine microglial N9 cells is attenuated through cannabinoid receptor CB2 signaling. Biochem Biophys Res Commun 2015;458:92–7. https://doi.org/10.1016/J.BBRC.2015.01.073.
[210] Lu J, Zhou W, Dou F, Wang C, Yu Z. TRPV1 sustains microglial metabolic reprogramming in Alzheimer's disease. EMBO Rep 2021:22. https://doi.org/10.15252/EMBR.202052013.
[211] Sappington RM, Calkins DJ. Contribution of TRPV1 to microglia-derived IL-6 and NFkappaB translocation with elevated hydrostatic pressure. Invest Ophthalmol Vis Sci 2008;49:3004–17. https://doi.org/10.1167/IOVS.07-1355.
[212] Schilling T, Eder C. Importance of the non-selective cation channel TRPV1 for microglial reactive oxygen species generation. J Neuroimmunol 2009;216:118–21. https://doi.org/10.1016/J.JNEUROIM.2009.07.008.
[213] Miyake T, Shirakawa H, Nakagawa T, Kaneko S. Activation of mitochondrial transient receptor potential vanilloid 1 channel contributes to microglial migration. Glia 2015;63:1870–82. https://doi.org/10.1002/GLIA.22854.
[214] Huang WX, Yu F, Sanchez RM, Liu YQ, Min JW, Hu JJ, et al. TRPV1 promotes repetitive febrile seizures by pro-inflammatory cytokines in immature brain. Brain Behav Immun 2015;48:68–77. https://doi.org/10.1016/J.BBI.2015.01.017.
[215] Kim SR, Kim SU, Oh U, Jin BK. Transient receptor potential vanilloid subtype 1 mediates microglial cell death in vivo and in vitro via Ca2+−mediated mitochondrial damage and cytochrome c release. J Immunol 2006;177:4322–9. https://doi.org/10.4049/JIMMUNOL.177.7.4322.
[216] Charytoniuk T, Zywno H, Konstantynowicz-Nowicka K, Berk K, Bzdega W, Chabowski A. Can physical activity support the endocannabinoid system in the preventive and therapeutic approach to neurological disorders? Int J Mol Sci 2020;21:1–16. https://doi.org/10.3390/ijms21124221.
[217] Hill MN, Titterness AK, Morrish AC, Carrier EJ, Lee TT-Y, Gil-Mohapel J, et al. Endogenous cannabinoid Signaling is required for voluntary exercise-induced enhancement of progenitor cell proliferation in the hippocampus. Hippocampus 2010;20:513. https://doi.org/10.1002/HIPO.20647.
[218] Ferreira-Vieira TH, Bastos CP, Pereira GS, Moreira FA, Massensini AR. A role for the endocannabinoid system in exercise-induced spatial memory enhancement in mice. Hippocampus 2014;24:79–88. https://doi.org/10.1002/hipo.22206.
[219] Wang H, Han J. The endocannabinoid system regulates the moderate exercise-induced enhancement of learning and memory in mice. J Sports Med Phys Fitness 2020;60:320–8. https://doi.org/10.23736/S0022-4707.19.10235-6.
[220] Maldonado R, Cabañero D, Martín-García E. The endocannabinoid system in modulating fear, anxiety, and stress. Dialogues Clin Neurosci 2020;22:229–39. https://doi.org/10.31887/DCNS.2020.22.3/RMALDONADO.
[221] Hill MN, Patel S, Carrier EJ, Rademacher DJ, Ormerod BK, Hillard CJ, et al. Downregulation of endocannabinoid signaling in the hippocampus following chronic unpredictable stress. Neuropsychopharmacology 2005;30:508–15. https://doi.org/10.1038/SJ.NPP.1300601.
[222] Reich CG, Taylor ME, McCarthy MM. Differential effects of chronic unpredictable stress on hippocampal CB1 receptors in male and female rats. Behav Brain Res 2009;203:264–9. https://doi.org/10.1016/J.BBR.2009.05.013.
[223] Ning Wang H, Wang L, Guo Zhang R, Chun Chen Y, Liu L, Gao F, et al. Anti-depressive mechanism of repetitive transcranial magnetic stimulation in rat: the role of the endocannabinoid system. J Psychiatr Res 2014;51:79–87. https://doi.org/10.1016/J.JPSYCHIRES.2014.01.004.
[224] Reich CG, Mihalik GR, Iskander AN, Seckler JC, Weiss MS. Adolescent chronic mild stress alters hippocampal CB1 receptor-mediated excitatory neurotransmission and plasticity. Neuroscience 2013;253:444–54. https://doi.org/10.1016/J.NEUROSCIENCE.2013.08.066.
[225] Hill MN, Carrier EJ, McLaughlin RJ, Morrish AC, Meier SE, Hillard CJ, et al. Regional alterations in the endocannabinoid system in an animal model of depression: effects of concurrent antidepressant treatment. J Neurochem 2008;106:2322–36. https://doi.org/10.1111/j.1471-4159.2008.05567.x.
[226] Hill MN, McLaughlin RJ, Bingham B, Shrestha L, Lee TTY, Gray JM, et al. Endogenous cannabinoid signaling is essential for stress adaptation. Proc Natl Acad Sci U S A 2010;107:9406–11. https://doi.org/10.1073/PNAS.0914661107/-/DCSUPPLEMENTAL.
[227] Hu W, Zhang M, Czéh B, Zhang W, Flügge G. Chronic restraint stress impairs endocannabinoid mediated suppression of GABAergic signaling in the

hippocampus of adult male rats. Brain Res Bull 2011;85:374–9. https://doi.org/10.1016/J.BRAINRESBULL.2011.04.005.
[228] Suárez J, Llorente R, Romero-Zerbo SY, Mateos B, Bermúdez-Silva FJ, de Fonseca FR, et al. Early maternal deprivation induces gender-dependent changes on the expression of hippocampal CB1 and CB2 cannabinoid receptors of neonatal rats. Hippocampus 2009;19:623–32. https://doi.org/10.1002/HIPO.20537.
[229] Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O. Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology 2002; 159:379–87. https://doi.org/10.1007/S00213-001-0946-5.
[230] Urigüen L, Pérez-Rial S, Ledent C, Palomo T, Manzanares J. Impaired action of anxiolytic drugs in mice deficient in cannabinoid CB1 receptors. Neuropharmacology 2004;46:966–73. https://doi.org/10.1016/J.NEUROPHARM.2004.01.003.
[231] Valverde O, Torrens M. CB1 receptor-deficient mice as a model for depression. Neuroscience 2012;204:193–206. https://doi.org/10.1016/J.NEUROSCIENCE.2011.09.031.
[232] Fride E, Suris R, Weidenfeld J, Mechoulam R. Differential response to acute and repeated stress in cannabinoid CB1 receptor knockout newborn and adult mice. Behav Pharmacol 2005;16:431–40. https://doi.org/10.1097/00008877-200509000-00016.
[233] Campos AC, Ortega Z, Palazuelos J, Fogaça MV, Aguiar DC, Díaz-Alonso J, et al. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: Involvement of the endocannabinoid system. 2013. https://doi.org/10.1017/S1461145712001502.
[234] Fidelman S, Mizrachi Zer-Aviv T, Lange R, Hillard CJ, Akirav I. Chronic treatment with URB597 ameliorates post-stress symptoms in a rat model of PTSD. Eur Neuropsychopharmacol 2018;28:630–42. https://doi.org/10.1016/J.EURONEURO.2018.02.004.
[235] Shoshan N, Segev A, Abush H, Mizrachi Zer-Aviv T, Akirav I. Cannabinoids prevent the differential long-term effects of exposure to severe stress on hippocampal- and amygdala-dependent memory and plasticity. Hippocampus 2017;27:1093–109. https://doi.org/10.1002/hipo.22755.
[236] Wang Y, Gu N, Duan T, Kesner P, Blaskovits F, Liu J, et al. Monoacylglycerol lipase inhibitors produce pro- or antidepressant responses via hippocampal CA1 GABAergic synapses. Mol Psychiatry 2017;22:215–26. https://doi.org/10.1038/MP.2016.22.
[237] Jiang HX, Ke BW, Liu J, Ma G, Hai KR, Gong DY, et al. Inhibition of fatty acid amide hydrolase improves depressive-like behaviors independent of its peripheral antinociceptive effects in a rat model of neuropathic pain. Anesth Analg 2019; 129:587–97. https://doi.org/10.1213/ANE.0000000000003563.
[238] Cuccurazzu B, Zamberletti E, Nazzaro C, Prini P, Trusel M, Grilli M, et al. Adult cellular Neuroadaptations induced by adolescent THC exposure in female rats are rescued by enhancing anandamide Signaling. Int J Neuropsychopharmacol 2018; 21:1014–24. https://doi.org/10.1093/ijnp/pyy057.
[239] Zhang Z, Wang W, Zhong P, Liu SJ, Long JZ, Zhao L, et al. Blockade of 2-arachidonoylglycerol hydrolysis produces antidepressant-like effects and enhances adult hippocampal neurogenesis and synaptic plasticity. Hippocampus 2015;25: 16–26. https://doi.org/10.1002/hipo.22344.
[240] Zhong P, Wang W, Pan B, Liu X, Zhang Z, Long JZ, et al. Monoacylglycerol lipase inhibition blocks chronic stress-induced depressive-like behaviors via activation of mTOR signaling. Neuropsychopharmacology 2014;39:1763–76. https://doi.org/10.1038/npp.2014.24.
[241] Jenniches I, Ternes S, Albayram O, Otte DM, Bach K, Bindila L, et al. Anxiety, stress, and fear response in mice with reduced endocannabinoid levels. Biol Psychiatry 2016;79:858–68. https://doi.org/10.1016/j.biopsych.2015.03.033.