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Endocannabinoid system and adult neurogenesis: a focused review

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The endocannabinoid system (eCB) is a ubiquitous lipid signaling system composed of at least two receptors, their endogenous ligands, and the enzymes responsible for their synthesis and degradation. Within the brain, the eCB system is highly expressed in the hippocampus and controls basic biological processes, including neuronal proliferation, migration and differentiation, which are intimately linked with embryonal neurogenesis. Accumulated preclinical evidence has indicated that eCBs play a major role also in regulating adult neurogenesis. Increased cannabinoid receptor activity, either by increased eCB content or by pharmacological blockade of their degradation, produces neurogenic effects alongside rescue of phenotypes in animal models of different psychiatric and neurological disorders. Therefore, in the light of the higher therapeutic potential of adult neurogenesis compared to the embryonic one, here we sought to summarize the most recent evidence pointing towards a neurogenic role for eCBs in the adult brain, both under normal and pathological conditions.

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Introduction

Adult neurogenesis is the process by which functional neurons are continuously generated in the nervous system, after embryonal development and throughout the animal life [1]. Such a process has been well documented in rodents, where neural stem cells (NSCs) — self-renewing, multipotent progenitor cells — were identified within specific niches of the central nervous system, in particular the subventricular zone (SVZ), along the lateral ventricular wall, and in the subgranular zone (SGZ) of dentate gyrus of the hippocampus [2]. At present, conclusive evidence that also human brain can generate new neurons post-developmentally and throughout adulthood is lacking [3]. In this context, two studies have recently reported conflicting results on the actual presence of adult neurogenesis in humans, highlighting the methodological pitfalls inherent to human brain research [4,5].

Although the biological role of adult neurogenesis is far from being fully elucidated, there is now solid evidence that adult-born neurons from SVZ and SGZ are functionally incorporated into the olfactory bulb and hippocampus, respectively, where they can participate in the control of olfactory inputs and memory processing throughout the life of the organism [2]. From a pharmacological point of view, the possibility of generating new functional neurons for the replacement of those lost during neurodegenerative disorders or age-related cognitive decline, could be the basis for the development of future potential therapies for many neurological and psychiatric conditions [6,7].

The research on the mechanistic aspects of adult neurogenesis has revealed that generation of functional neurons is a very complex and coordinated process, that involves survival, proliferation, differentiation and migration of NSCs, as well as synaptic integration of the newborn neurons into the existing circuitry [2]. Thus, a number of intrinsic and extrinsic factors have been identified that play essential roles in various aspects of adult neurogenesis. Among them endocannabinoids (eCBs), a specialized class of bioactive lipids, have emerged as key regulators of neurogenesis, eliciting cell signaling cascades such as mitogen-activated protein kinases (MAPKs) and mammalian target of rapamycin (mTOR), that are primarily involved in deciding stem cell fate [8•].

In the last few years, the regulatory role of the eCB signaling in embryonic and adult neurogenesis has been extensively investigated in rodents, and recently discussed in comprehensive reviews [9,10]. Here, in the light of the higher therapeutic potential of adult neurogenesis compared to the embryonic one, we sought to summarize the most recent evidence pointing towards a neurogenic role for eCBs in the adult brain, both under normal and pathological conditions. To this aim, we give also a brief overview of the key components of the eCB

system, as well as of its main signaling pathways that can impact post-developmental neurogenesis. Then, we describe preclinical research conducted over the last five years supporting the notion that targeted manipulation of eCB signaling may represent a valuable strategy for developing new adult neurogenesis-based treatments to improve brain health (Table 1).

The eCB system

The eCB system is a pro-homeostatic modulator of basic biological processes, including cell choice between survival and death, immune response, neuronal maturation, neurotransmission, energy homeostasis and reproduction [11•]. Widely distributed throughout the body and highly expressed within the central nervous system, the eCB system comprises a group of phospholipid-derived neuromodulatory lipids, also known as eCBs that mainly include *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), in addition to at least two G protein-coupled receptors (GPCRs), named type 1 (CB_1) and type 2 (CB_2) cannabinoid receptors; in addition, the eCB system includes two main biosynthetic enzymes, *N*-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL), for AEA and 2-AG respectively, and two main degradative enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), for AEA and 2-AG respectively (Figure 1). Unlike classical neurotransmitters, within neurons AEA and 2-AG are formed 'on demand' from membrane precursors, rather than being stored in synaptic vesicles [11•]. The mechanisms by which cells release and take up these bioactive lipids, have not been fully understood yet, but it is likely to involve putative eCB membrane transporters, intracellular carriers and/or passive diffusion (Figure 1).

CB_1 receptor is the most abundant GPCR in the central nervous system, and is highly expressed in brain areas associated with emotionality, cognition and memory like brain cortex, limbic system, *substantia nigra* and hippocampus [11•]. Of note, CB_1 is also responsible for the pharmacological and psychotropic effects of natural and synthetic cannabinoids, such as the main ingredient of cannabis (*Cannabis sativa*) extracts, Δ^9-tetrahydrocannabinol. Instead, CB_2 receptor is mainly located in immune cells, where it exerts various immunosuppressive actions [12], but there is growing evidence that it is also expressed by some neurons, both under physiological conditions and upon acute and chronic stress [13,14]. Notably, even though to a minor extent CB_1 is also co-expressed with CB_2 in glial elements, such as astrocytes and microglial cells [11•,12–15], thus further confirming essential and pleiotropic roles of eCB signaling in brain neuroimmune physiology and pathology.

Emerging evidence has revealed the eCB system as a key player in controlling NSC biology in the adult brain [9,10]. In NSCs and their descendant neurons, the expression of CB_1 and CB_2 receptors changes during the different stages of neuronal differentiation, with CB_1 increasing along neural maturation and CB_2 being more abundant in less committed cells [8•]. Moreover, NSCs possess all the enzymes involved in eCB metabolism and produce AEA and 2-AG in response to increased intracellular Ca^{2+} concentration [8•]. Furthermore, *in vitro* studies demonstrated that the eCB tone contributes to basal and stimulus-induced neuronal proliferation, primarily via CB_1 and CB_2 [8•].

In NSCs, CB_1 and CB_2 receptors display an extremely intricate signaling activity through which they modulate a variety of cellular processes that include survival, proliferation, lineage differentiation, migration, maturation of NSCs and their descendants (Figure 2). In particular, both cannabinoid receptors are coupled to heterotrimeric $G_{i/o}$ proteins through which they modulate multiple signal transduction pathways, including (*i*) inhibition of adenylyl cyclase and cyclic AMP-protein kinase A (PKA); (*ii*) activation of extracellular signal-regulated kinase 1 (ERK1) and ERK2; (*iii*) activation of p38 MAPK and JUN N-terminal kinases (JNKs); and (*iv*) activation of phosphatidylinositol 3-kinase-Akt-mTOR (PI3K/Akt/mTOR) [8•]. Moreover CB_1, but also CB_2, were shown to regulate membrane potential of neurons and other excitable cells, by modulating the opening of specific Ca^{2+} and K^+ ion channels [14,15], thus further expanding the complexity of the signaling pathways by which both receptors control cellular functions.

Role of the eCB system in adult neurogenesis

CB_1-dependent effects

The evidence from the latest research confirmed the pro-neurogenic role of CB_1 in the two germinal areas of adult rodents, both under normal and pathological conditions. The chronic stimulation of CB_1 by arachidonyl-2-chloroethylamide (ACEA), a highly selective CB_1 agonist, produced a robust neural proliferation in the SGZ [16,17] and an increased neuroblast migration along the rostral migratory stream towards the olfactory bulb [18]. Similarly, chronic administration of 2-AG ether, another selective CB_1 agonist, promoted neurogenesis in mouse olfactory epithelium [19], an effect that was blocked by the specific CB_1 antagonist AM251 and was absent in CB_1/CB_2 double knockout mice [19].

In a more pathological context, Andres-Mach *et al.* found that CB_1 chronic stimulation by ACEA had a strong impact on proliferation, migration and differentiation of newly born cells in the hippocampus of a mouse model of epilepsy [16]. Interestingly, they described that administration of valproate, an anti-epileptic drug, had no significant impact on neurogenesis on this model; instead, combination of valproate with ACEA markedly enhanced neurogenesis in the SGZ [16]. In keeping with these observations, studies

Table 1

Effects of manipulating the eCB system on adult neurogenesis

Target	Model	Treatment	Biological activity	Effect	Ref.
CB_1	Mouse model of epilepsy (pilocarpine)	ACEA, 10 mg/kg, i.p., 10 days		Alone or co-treated with an anti-epileptic drug (valproate) enhances neurogenesis in the SGZ	[16]
	Rat model of ethanol-induced neurotoxicity	ACEA, 3 mg/kg, i.p., 5 days	Agonist	Reverts ethanol-induced anti-proliferative effects on NSCs in the SGZ, but not in SVZ	[20]
	Adolescent CB57/BL male mice	ACEA, 10 mg/kg, i.p., 10 days		Compared to control mice, increases neurogenesis in the SGZ	[30]
	Mouse brain slice cultures, and rostral migratory stream explants	ACEA, 0.5 μM, 2 hour		Stimulates neuroblasts migration towards the olfactory bulb	[18]
		AM251, 1 μM, 2 hour	Antagonist/ inverse agonist	Interferes with neuroblasts migration (reduce the motility and the percentage of cells migrating towards the olfactory bulb)	
	Cultures of human and murine NSCs	ACEA, 1 μM, 2 days	Agonist	Reduces cell death of human NSCs mediated by Gp120	[21•]
	Rat SVZ and DG neurospheres	ACEA, 0.1, 0.3 and 1 μM, 24 hour	Agonist	Promotes neurogenesis in SVZ cells	[22••]
		WIN55,212-2, 0.1, 0.3 and 1 μM, 24 hour	Non-selective CB_1/CB_2 agonist	Promotes neurogenesis in SGZ, but not in SVZ stem/progenitor cells	
		AM251, 1 μM, 24 hour	Antagonist/ inverse agonist	Reverts the neurogenic effects of ACEA in SVZ cells	
	Swiss Webster and C57BL/6 mice	2-AG ether, 1, 5 and 10 μM, i.n., 2 days	Agonist	Promotes neurogenesis in the olfactory epithelium in a dose-dependent manner	[19]
		WIN55, 212-2, 10 μM, i.n., 2 days	Non-selective CB_1/CB_2 agonist	Promotes neurogenesis in the olfactory epithelium	
		AM251, 10 μM, i.n., 2 days	Antagonist/ inverse agonist	Decreases the neurogenesis in the olfactory epithelium compared to vehicle-treated Swiss Webster mice; reverses the neurogenic effects of WIN55,212-2	
	CB_1/CB_2 double knock-out mice			Show no change in neurogenic levels in response to any cannabinoid pharmacological manipulation	
CB_2	Mouse model of Parkinson's disease (MPTP mice)	AM1241, 0.75–12 mg/kg, i.p., 12 days	Agonist	Dose-dependently increases survival of neurotoxin-damaged neurons in the substantia nigra	[25••]
	Mouse model of HIV-associated encephalitis	AM1241, 10 mg/kg, i.p., 20 days, analyzed at 9 months of age	Agonist	Prevents deficits in neurogenesis in SGZ and reduces neuroinflammation	
	Cultures of human and murine NSCs	AM1241, 100 nM, 7–21 days	Agonist	Inhibits Gp120-mediated neurotoxicity and apoptosis of NSCs and increased their survival and differentiation	[21•]
		AM630, 1 mM, 7–21 days	Antagonist	Reverts the effects of AM1241 in mouse NSCs treated with Gp120	
	CB_2 knock-out mice and wildtype littermates			Compared to wildtype genotype, CB_2 deficiency does not influence basal adult neurogenesis in SGZ	[23]
	Mouse model of Alzheimer's disease (APP/PS1)	MDA7	Agonist	Restores Sox2 expression and increases neurogenesis in hippocampal DG	[26]
	Mouse model of stroke (middle cerebral artery occlusion)	JWH133, 1.5 mg/kg, i.p., 7, 14, 28 days	Agonist	Does not affect neurogenesis *in vivo*, but increases the migration of NPCs *in vitro*	[27]
		SR144528, 5 mg/kg, i.p., 7, 14, 28 days	Antagonist/ inverse agonist	Decreases the migration of neuroblasts towards the boundary of the infarct region	
		CB_2 knock-out mice		Compared to wild-type mice, display lower number of new neurons (NeuN+/BrdU + cells) in peri-infarct cortex 28 days after stroke	
	Rat SVZ and DG neurospheres	HU-308, 1 μM, 24 hour	Agonist	Promotes SVZ neuronal differentiation; in co-treatment with ACEA, results in DG cell proliferation	[22••]
		AM630	Antagonist/ inverse agonist	Blocks the HU-308-mediated SVZ neuronal differentiation; reverts the neurogenic effects of CB_1/CB_2 co-activation in the DG cells	
	Rat model of ethanol-induced neurotoxicity	JWH133, 0.2 mg/kg, i.p., 5 days	Agonist	Counteracts the anti-neurogenic effects of ethanol in the SVZ and SGZ	[20]

Table 1 (*Continued*)

Target	Model	Treatment	Biological activity	Effect	Ref.
Metabolic enzymes	Cultures of human NSCs	URB597, 100 nM, 2 weeks	Inhibitor of FAAH	Increases differentiation of human NSCs	[21•]
	Rat model of ethanol-induced neurotoxicity	URB597, 0.3 mg/kg, i.p., 5 days		Does not revert the toxic effects of alcohol on neurogenesis	[20]
	Rats	URB597, 0.3 mg/kg, i.p., 5 days	Inhibitor of FAAH	Acute treatment increases neurogenesis in SVZ, but not in SGZ. Chronic treatment reduces neurogenesis in SGZ and lowers the expression of CB_1 gene	[30]
	Swiss Webster and C57BL/6 mice	URB597, 100 μM, i.n., 2 days JZL184, 10 μM, i.n., 2 days		Co-administered with JZL184 increases neurogenesis in olfactory epithelium	[19]
	Mouse model of chronic unpredictable stress-induced depression	JZL184, 8 mg/kg, i.p., 21 days	Inhibitor of MAGL	Prevents the chronic stress-induced impairment of neurogenesis in the SGZ and ameliorates the depressive-like behaviors	[31•]

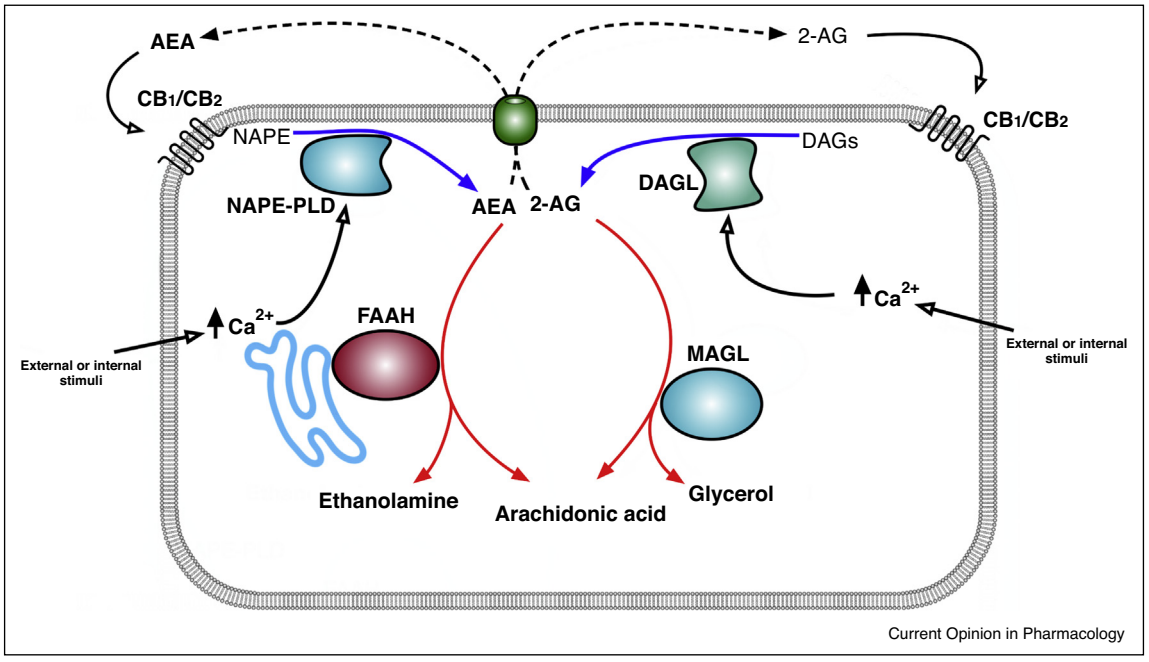
conducted on a rat model of alcohol intoxication demonstrated that ACEA reversed impairment of neurogenesis induced by ethanol in the SGZ, but not in SVZ [20].

In vitro, ACEA inhibited HIV-1/Gp120-mediated apoptosis, and enhanced the survival of human NSCs [21•], while in primary cultures of rat neurospheres it promoted proliferation of SVZ-derived NSCs [22••]. By contrast, ACEA alone was not sufficient to stimulate proliferation of SGZ-derived NSCs, an effect that was reached only upon co-administered with HU-308, a selective CB_2 agonist. Notably, in the same experimental paradigm co-activation of CB_1 and CB_2 by WIN 55,212-2, a synthetic CB_1/CB_2 agonist, exerted a mitogenic effect in SGZ, but not in SVZ cells, indicating the presence of a context-dependent interplay between these two cannabinoid receptors [22••]. Taken together, these results confirm the multifaceted role of eCB signaling in neurogenesis, and suggest that some conflicting results could be due, at least in part, to the crosstalk between CB_1 and CB_2 receptors.

CB_2-dependent effects

Recent studies suggest a more complex role in adult neurogenesis for CB_2 than for CB_1. In particular,

Figure 1



Schematic representation of the main elements of the eCB system within the cell. See text for details. 2-AG, 2-arachidonoylglycerol; AEA, *N*-arachidonoylethanolamine; CB_1/CB_2, type 1 and type 2 cannabinoid receptors; DAGs, diacylglycerols; DAGL, diacylglycerol lipase; EMT, purported "eCB membrane transporter"; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAPE, *N*-acyl-phosphatidylethanolamine; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D.

Mensching *et al.* have recently found that genetic ablation of CB_2 in four-month-old healthy mice did not significantly alter SGZ neurogenesis compared to wild-type animals [23]. These findings are at variance with previous studies showing reduced basal levels of cell proliferation in the SGZ of CB_2 knockout mice at embryonic day 17.5, and at two-months of age [24]. Although this discrepancy could be due to the different age of the animals, it is also possible that in adults CB_2 might be more physiologically relevant in coping with brain injury than in maintaining basal neurogenesis. Indeed, in the last few years it has been clearly documented that CB_2 agonism promotes neurogenesis in different models of neuropathological conditions, primarily by normalizing key-processes known to compromise neuronal homeostasis and survival, like apoptosis, oxidative stress and inflammation (Figure 2).

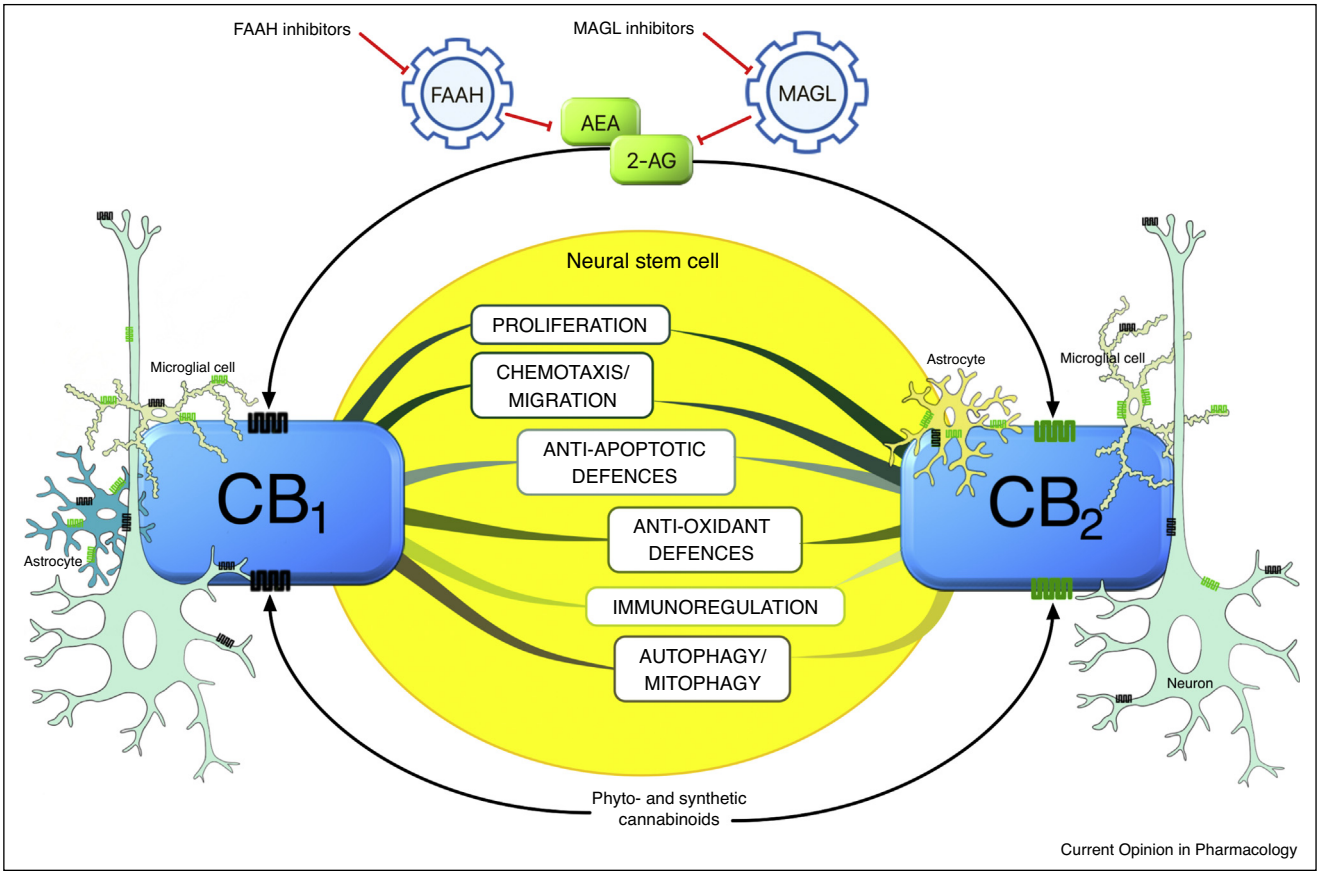
Specifically, in a mouse model of HIV-1-associated encephalitis, where mice exhibit decreased adult neurogenesis in the hippocampus, chronic treatment with AM1241, a selective CB_2 agonist, prevented deficits in SGZ neurogenesis [21•]. In the same study, Avraham *et al.* found that, *in vitro*, AM1241 inhibited HIV-1/Gp120-mediated apoptosis and promoted proliferation and differentiation of human NSCs.

In a study performed in a mouse model of Parkinson's disease, Shi *et al.* found that AM1241 dose-dependently increased survival of neurons damaged by the neurotoxin 1-methyl-4-phenylpyridinium, along with normalizing the levels of dopamine and serotonin and stimulating neurogenesis in the *substantia nigra* [25••]. These CB_2-dependent effects appeared to involve activation of PI3K/Akt/MEK pathway, and to be mediated via enhanced expression of Parkin/PINK1, two proteins that function in mitochondrial quality control [25••].

Moreover, long-term administration of a selective CB_2 agonist, MDA7, in a mouse model of Alzheimer's disease was found to enhance neurogenesis in the hippocampus along with (*i*) promoting Aβ plaque clearance, (*ii*) suppressing microglial activation, (*iii*) strengthening hippocampal synaptic plasticity, and (*iv*) ameliorating cognitive decline [26].

Using a model of focal brain ischemia, Bravo-Ferrer *et al.* found that, after cortical stroke, activation of CB_2 by

Figure 2



Impact of targeting CB_1, CB_2, FAAH and MAGL on adult neurogenesis. See text for details.

JWH133, another selective CB_2 agonist, promoted neuroblast migration to (and differentiation at) the infarct site [27]; these effects were reverted by the CB_2 antagonist SR144528. In agreement with the pro-homeostatic role of CB_2, absence of this receptor in knockout mice was associated with robust reduction of stroke-induced neurogenesis in peri-infarct cortex [27].

The key role of CB_2 in modulating adult neurogenesis has been further confirmed in a model of ethanol-induced neurotoxicity, where CB_2 receptor activation by JWH133 was found to counteract the anti-neurogenic effect of alcohol-exposure in SGZ and SVZ of the adult brain of rats [20].

Overall, these results strengthen the notion that CB_2 signaling may primarily participate in the control of adult neurogenesis under pathological conditions, by eliciting mechanisms able to protect newborn neurons from excitotoxic, oxidative and inflammatory damages, as it has been widely observed in several models of brain injury [13,14].

eCB metabolic enzymes-dependent effects

A pharmacological strategy to circumvent the CB_1-mediated psychotropic and CB_2-mediated immunosuppressive effects associated with cannabinoid receptor agonism is to use inhibitors of eCB-degrading enzymes, namely FAAH and MAGL, which allow to increase the levels of AEA and 2-AG, respectively, only in the sites where these eCBs are produced and released. In the last five years, the use of URB597 and JZL184, two specific inhibitors of FAAH and MAGL respectively, led to results that are somewhat conflicting with earlier data, again stressing the complexity of basal eCB tone in regulating neural proliferation, differentiation and survival in the adult brain.

It has been proposed that the inhibition of FAAH may be a promising strategy to promote neurogenesis as a consequence of enhanced AEA signaling [28,29]. However, recent reports have disclosed a puzzling scenario where no effect, or even anti-neurogenic effects, can be demonstrated by inhibiting FAAH *in vivo*. Indeed, Rivera *et al.* showed that chronic administration of URB597 specifically reduced neurogenesis in the SGZ of adult rat brain [30], without reverting the anti-neurogenic effects of alcohol intake in a rat model of ethanol-induced neurotoxicity [20]. Interestingly, they also reported that acute administration of URB597 induced an increase of the neural proliferation in the SVZ of the lateral ventricles in adult rats [30]. These authors commented that this apparent discrepancy could be explained by (*i*) URB597-induced downexpression of the hippocampal CB_1 receptors, and (*ii*) putative participation of non-eCB signaling as a consequence of the activation of additional AEA targets, such as transient receptor potential vanilloid type-1 ion channels, and the nuclear peroxisome proliferator-activated receptor α. Finally, when co-administered with JZL184, URB597 efficaciously increased neurogenesis in olfactory epithelium of adult mice, suggesting a synergic activity of AEA and 2-AG in the control of neuronal proliferation in this tissue [19]. Interestingly, the same study reported that in the presence of both FAAH and MAGL inhibitors the number of adult-born neural cells reached its maximum value at two days, but it was not maintained afterwards. Indeed, these newly proliferated cells underwent apoptosis before 14 days after treatment, indicating that in olfactory epithelium the eCB system regulates the proliferative state of NSCs, but not their differentiation into mature neurons [19]. An opposite result was observed *in vitro* on human NSCs, where inhibition of FAAH by URB597 led to their differentiation [21•].

As a proof-of-principle that MAGL inhibition may represent a potential strategy for the development of pro-neurogenic treatments [10], it has been found that chronic inhibition of this enzyme by JZL184 prevented neurogenesis impairment in SGZ, restored long-term potentiation in the hippocampus, and attenuated depressive-like behaviors on mice that were subjected to the chronic unpredictable stress model of depression [31•]. Zhang *et al.* speculated that JZL184 produced these neurogenic and antidepressant-like effects by reversing a defective 2-AG signaling that, in turn, could lead to CB_1-mediated-activation of mTOR-dependent signal transduction in the hippocampus [31•,32].

Conclusions

In summary, adult neurogenesis is emerging as an important player in brain homeostasis that could be involved in brain plasticity and repair in adulthood. Finding more about the regulatory mechanisms that dictate NSC biology, and that can promote the process of generating new functional neurons in the adult brain, may lead to strategies for preventive and/or therapeutic approaches against cognitive decline, as well as against age-related brain disorders.

Herein, we have discussed recent studies on the pathophysiological relevance of eCB signaling both in health and in the context of different neuropathological conditions accompanied by impaired neurogenesis, including stroke, epilepsy, alcohol intoxication, Alzheimer's disease and Parkinson's disease. A considerable body of evidence now supports the intriguing possibility that the eCB system is involved in the regulation of proliferation, survival and migration of NSCs and their progeny in the adult brain (Figure 2).

However, the ubiquitous expression of this pro-homeostatic system, along with the complexity of its signaling activity and pharmacology, makes it difficult to fully characterize how its various components may contribute to control genesis and functional integration of adult-born neurons within the post-developmental brain. We believe that future

research on the precise role played by distinct components of the eCB system in NSC biology will contribute to improve our mechanistic understanding of adult neurogenesis, and could provide the basis for new therapeutic applications of eCB-based drugs.

Conflict of interest statement

Nothing declared.

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