Endocannabinoid system and cannabinoids in neurogenesis – new opportunities for neurological treatment? Reports from experimental studies

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▌Abstract

Neurogenesis is one of the most important phenomenona affecting human life. This process consists of proliferation, migration and differentiation of neuroblasts and synaptic integrations of newborn neurons. Proliferation of new cells continues into old age, also in humans, although the most extensive process of cell formation occurs during the prenatal period. It is possible to distinguish two regions in the brain responsible for neurogenesis: the dentate gyrus (DG) of the hippocampus and the sub-ventricular zone (SVZ). Hippocampal neurogenesis is very sensitive to various physiological and pathological stimuli. The functional integration of the newly-born dentate granule cells into hippocampal circuitry, and their ability to mediate long-term potentiation in DG, has led to the hypothesis that neurogenesis in the adult brain may play a key role in learning and memory function, as well as cognitive dysfunction in some diseases. Brain disorders, such as neurodegenerative diseases or traumatic brain injuries, significantly affect migration, proliferation and differentiation of neural cells. In searching for the best neurological drugs protecting neuronal cells, stimulating neurogenesis, while also developing no side-effects, endocannabinoids proved to be a strong group of substances having many beneficial properties. Therefore, the latest data is reviewed of the various experimental studies concerning the analysis of the most commonly studied cannabinoids and their impact on neurogenesis.

▌Key words

INTRODUCTION

Effective brain development depends on the coordination of proper proliferation, migration and differentiation of new-born neuronal cells. Among the variety of mechanisms involved in the regulation of neural development, there can be distinguished G-protein-coupled receptors, involved in signal transduction [1], neurotransmitters like gamma-aminobutyric acid (GABA) and glutamic acid (Glu) actively involved in instructing neural progenitor (NP) cell proliferation [2]. Additionally, the endocannabinoid system (eCB) is expressed since early stages of neural tissue formation [3]. The involvement of the eCB system in the regulation of neural plasticity is mainly based on its neuromodulatory function as an endocannabinoid receptor 1 (CB1) showing a wide regulatory role in most types of synapses [4]. Many pharmacological studies have evidenced that endocannabinoids (eCBs) and drugs targeting the eCB system (synthetic agonists and antagonists, plant derived) can affect neuronal development and specification [5]. This review presents an overview of the newest scientific reports on the effects of eCB system, as well as endogenous and exogenous cannabinoids, on the process of neurogenesis from various animal studies.

Endocannabinoid system and endocannabinoids. eCB is a complex of metabolic enzymes, endocannabinoids, and receptors detecting their presence and initiating a cascade of chemical responses. Cannabinoid signaling was shown to be involved in neurogenic processes (neuronal proliferation, specification, and maturation) and in the maintenance and survival of differentiated neural cells [4, 5].

eCB is composed of two 7-transmembrane-domain and G protein-coupled receptors (GPCRs) for THC CB1 receptor and CB2 receptor and their 2 endocannabinoid signaling molecules, anandamide (AEA) and 2-arachidonoylglycerol (2-AG, Fig. 1) [6, 7].

Both humans and animals produce the AEA and 2-AG compounds, which help to regulate many biological functions. AEA and 2-arachidonoylglycerol are known to regulate human cardiovascular functions and homeostasis [8]. AEA has been shown to control the cell choice between growth and death, and 2-AG was shown to be a direct substrate of the cyclooxygenase COX and *lipoxygenase* LOX pathway [9]. Moreover 2-AG and AEA are endocannabinoids that have been implicated in many physiologic disorders, including obesity, metabolic syndromes, hepatic diseases, pain, neurologic disorders, and inflammation [10].

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Figure 1. Chemical structures of the endocannabinoids AEA and 2-AG

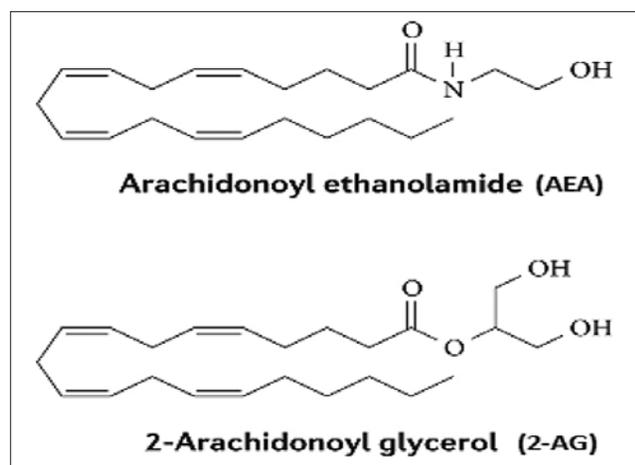**Figure 2.** Chemical structures of the exogenous cannabinoids

The endogenous cannabinoid ligands (anandamide, *N*-arachidonoyl ethanolamide and 2-arachidonoylglycerol) are substances synthesized from lipid precursors in the neuronal membrane. AEA and 2-AG are synthesized 'on demand', not stored in the cell, and are degraded quickly [11]. Synthesis of both of the endocannabinoids is mainly dependent on intracellular Ca2+ concentrations. The primary pathway through which AEA is synthesized involves the Ca2+-dependent cleavage of its membrane precursor N-arachidonyl phosphatidylethanolamine by phospholipase D [12], whereas diacylglycerol lipase-α (DGLα) and diacylglycerol lipase-β (DGLβ) are mainly responsible for the synthesis of 2-AG [13]. The main metabolizing enzymes of anandamide and 2-arachidonoylglycerol are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which act upon AEA and 2-AG respectively [14 15]. Both AEA and 2-AG bind to the CB1 and CB2 receptors; however, AEA has a higher affinity to the CB1 receptor, whereas 2-AG favours the CB2 receptor [16]. Manipulations of endocannabinoid degradative enzymes, CB_1 and CB_2 receptors, and their endogenous ligands have been shown to play an important role in modulating cellular and molecular changes in traumatic brain injury (TBI) including: cell death, excitotoxicity, neuroinflammation or cerebrovascular breakdown [17].

CB1 and CB2 receptors have also been associated with postnatal oligodendrogenesis. Increase in the number of glial precursors in the subventricular zone of postnatal rats is caused by activation of CB1 receptor, whereas activation of the CB2 receptor increases polysialylated neural cell adhesion molecule expression, which is necessary for the migration of oligodendrocyte precursors [15 18]. CB receptor activation is associated primarily with regulation of ion channels through inhibition of Ca^{2+} channels and activation of K^+ channels [19, 20]. These receptors inhibit adenylate cyclase and the formation of cyclic AMP [21]. In addition, cannabinoids activate different protein kinase cascades (e.g., the mitogen-activated protein kinases MAPK and the phosphatidylinositol 3-kinase/Akt). The endocannabinoid system plays an important role in controlling neural cell fate. On the one hand, it can exert a pro-survival action of different neural cell types [22], but if transformed cells are found they are directed to apoptosis by cannabinoid treatment and therefore the system exerts an antitumoral action against different types of cancer [23].
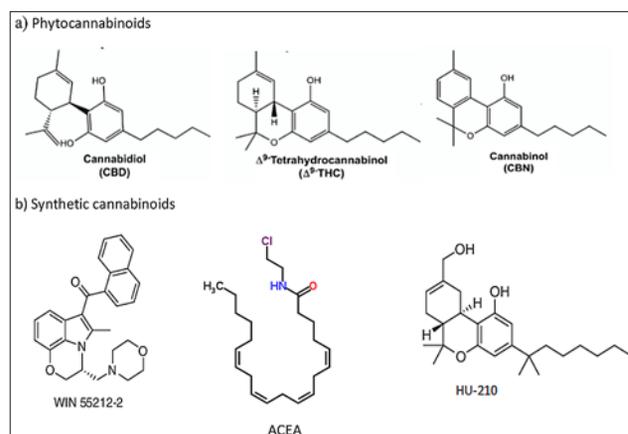
Exogenous cannabinoids. The term 'cannabinoids' designates a family of compounds with activity upon cannabinoid receptors and encompasses all substances structurally related to cannabis. Exogenous cannabinoids were first extracted from the plant *Cannabis sativa*. and they belong to the group of phytocannabinoids.

Into a class of *Cannabis* plant-derived cannabinoids fall: cannabinol, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC, Fig. 2a). Most of the psychoactive effects of cannabis are mediated by Δ9-THC [24]. The second group of exogenous cannabinoids is manufactured by chemically-synthetic cannabinoids, such as HU-210, WIN55,212–2 mesylate or arachidonyl-2'-chloroethylamide ACEA (Fig. 2b).

All types of cannabinoids are known to act through two cannabinoid receptors, CB_1 and CB_2 [6, 21]. As mentioned above, the major cannabinoid receptor in the central nervous system is cannabinoid receptor 1 (CB1), first described and cloned in the early 1990s [25]. CB1 receptors are highly expressed in regions of the brain which are responsible for movement, memory processing and pain modulation [26]. A second cannabinoid receptor, the CB_2 receptor, was also cloned in the 1990s [27]. CB_2 receptors are found mainly in cells and tissues of the immune system, but are also present in the brain [28].

Marijuana, through its ability to regulate the endocannabinoid system, has anticonvulsant, antipsychotic, antidepressant and anxiolytic properties [29, 30]. The authors of the presented review distinguish several important mechanisms of action of cannabinoids, one of which is the ability to promote neuronal plasticity [31]. Additionally, by inhibiting calcium and potassium channels activation, cannabinoids are able to alter brain activity [32]. They are also involved in the control of glutamate-induced excitotoxicity [33]. Another important mechanism of action of cannabinoids has been its regulatory role of adult hippocampal neurogenesis.

Neurogenesis. Neurogenesis is the process of creating new neurons in the brain from precursors. For many years, the belief was prevalent that neurogenesis occurs only during the embryonic and perinatal stages in mammals [34]. In 1965, Altman's pioneering studies provided evidence for the formation of new neurons in adult rats [35]. These studies used a technique that labeled dividing cells with [3H] thymidine, which incorporates into the replicating DNA [36]. This initiated intensive studies on adult neurogenesis.

78

Journal of Pre-Clinical and Clinical Research, 2017, Vol 11, No 1

Aleksandra Drab, Mirosław Zagaja, Agnieszka Haratym-Maj, Jarogniew Jacek Łuszczki, Marta Andres-Mach. Endocannabinoid system and cannabinoids in neurogenesis…

Adult neurogenesis occurs continuously in the subventricular zone (SVZ) of the rostral lateral ventricles, as well as the subgranular zone of the dentate gyrus (DG) of the hippocampus. This usually includes four key stages. In the first stage, the quiescent neural stem cells (nsCs) start to proliferate to generate the transit amplifying cells (TACs). The TACs then undergo fate specification and give rise to the neuroblasts. Depending on where newly-generated cells originate, they migrate to different places. Neuroblasts from the SVZ get into the main olfactory bulb (MOB), andcells from the subgranular zone migrate within the DG. Most of these cells differentiate into neurons and integrate into the existing olfactory circuitry (cells derived from SVZ) and DG circuitry (cells from subgranular zone). Adult-generated DG neurons may play a role in spatial learning, long-term spatial memory retention, trace conditioning, and contextual fear conditioning. Neurons in the olfactory bulb likely play a role in short-term olfactory memory, olfactory fear-conditioning, and long-term associative olfactory memory [37, 38]. There is also evidence suggesting that adult neurogenesis occurs in other neurogenic regions of the brain and, in particular, in the neocortex [39, 40, 41], piriform cortex [40], and striatum [42].

Neurogenesis and cannabinoids. Adult neurogenesis has been shown to be a good example of brain plasticity modulated by the endocannabinoid system. In recent years, several studies have provided evidence that the endocannabinoid system is being expressed on neural stem cells. It was shown that the downstream activation of CB_1 and CB_2 cannabinoid receptors, as well as the enzymes responsible for the synthesis of the endocannabinoid 2-AG, diacylglycerol lipase α (DAGLα) and DAGLβ, and degradation, monoacylglycerol lipase (MAGL), can modulate neurogenesis by a number of neuroimmune molecules (cytokines) in glial cells, neurons and NSCs [43]. Plant–derived extracts of cannabinoids, such as Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), were studied in female C57Bl/6 and Nestin-GFP-reporter mice in order to assess their effects on the proliferation and maturation of neuronal progenitor cells, together with spatial learning performance [44]. Obtained results indicate that THC and CBD differed in their effects on spatial learning and adult neurogenesis. CBD did not impair learning but increased adult neurogenesis, whereas THC reduced learning capability without affecting adult neurogenesis. Moreover, CBD exerts therapeutically promising effects on human mental health, such as inhibition of psychosis, anxiety and depression. The anxiolytic effect of cannabidiol on chronically-stressed mice depends on hippocampal neurogenesis and is an outcome of the proneurogenic action of CBD which, in turn. facilitates endocannabinoid-mediated signaling [45]. Abboussi et al. [46] investigated the behavioural neurogenic effects of chronic exposure to the endocannabinoid agonist WIN55,212–2 during adolescence, by evaluating emotional and cognitive performances, and the consequences on neurogenesis along the dorso-ventral axis of the hippocampus in adult rats. Obtained results suggest that long-term exposure to WIN55,212–2 may affect more potently spatial learning and memory in adolescents, compared to adult rats, via a negative action on hippocampal plasticity. In subsequent studies, Compagnucci et al. [47] investigated the role of endocannabinoids as modulators of neuronal functions, including neurogenesis. Obtained results showed that the Type-1 (CB_1) cannabinoid receptor

Table 1. *In vivo* effects of cannabinoids on NCPs proliferation and neurogenesis – review of literature of the past few years

Cannabinoid	Animal model	Results	Reference
WIN55,212–2	F-344 rats	Increase	[50]
– CBD – THC	C57Bl/6 and Nestin-GFP-reporter mice	-decreased neurogenesis – no changes in neurogenesis	[40]
HU-308	CB_2 receptor knock-out mice	Increased NCPs proliferation	[47]
-CBD -THC	C57Bl/6 mice	– Increased neurogenesis -Decreased neurogenesis	[41]
WIN55,212–2	Wistar rats	Reduced neurogenesis	[42]
AM1241	GFAP/Gp120 Tg mice	Enhanced neurogenesis	[44]
THC	Sprague-Dawley rats	No changes in neurogenesis	[48]
ACEA	C57Bl/6 mice	Increased neurogenesis	[51]
WIN55,212–2	C57BL/6 mice	Increased NCPs proliferation	[49]

favoured differentiation of neural progenitors into neurons and enhanced their maturation in a culture. This effect was accompanied by reduced activity of the extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) pathway, and by changes in gene expression that support neuronal differentiation and morphological maturation. In other studies concerning the cannabinoid CB_2 receptor agonist AM1241, it was found that AM1241 enhances neurogenesis in GFAP/Gp120 transgenic mice displaying deficits in neurogenesis [48]. Jin et al. [49] showed that CB_1 receptor regulates adult neurogenesis *in vivo*, as measured by the increased level of BrdU cells positive cells located in neuroproliferative zones of the brain and that express neuronal lineage marker proteins. Moreover, neurogenesis is impaired in mice lacking CB1R, implying that endogenous signaling through this receptor promotes basal levels of neurogenesis *in vivo*. The CB_2 receptor agonist rescued impaired neurogenesis caused by HIV-1/Gp120 insult. Thus, CB_2 receptor agonists may act as neuroprotective agents, restoring impaired neurogenesis in patients with HAD. While GFAP/Gp120 Tg mice exhibited impaired neurogenesis and a decrease in cells with proliferating cell nuclear antigen (PCNA), administration of AM1241 to GFAP/Gp120 Tg mice resulted in enhanced *in vivo* neurogenesis in the hippocampus. An endogenous metabolite of docosahexaenoic acid and its derivatives (N-docosahexaenoylethanolamine and N-docosahexaenoylethanolamide) were shown to stimulate neurite growth, synaptogenesis, glutamatergic synaptic activity and neuronal differentiation of neural cells in hippocampal neurons [50, 51]. Results of subsequent studies also confirmed the influence of the endocannabinoid system on neural progenitor cells (NCPs) regulation. CB2 cannabinoid receptors were found to promote neural progenitor cell proliferation via the mammalian target of rapamycin complex 1 mTORC1 signaling *in vitro* in hippocampal HiB5 progenitor cell line, NP-derived neurosphere cultures, organotypic embryonic cortical cultures, but also *in vivo* on hippocampal adult neurogenesis experiments, providing a mechanism of action and a rationale for the use of nonpsychotomimetic CB(2) receptor-selective ligands as a novel strategy for the control of NP cell proliferation and neurogenesis [52]. Results obtained by Steel et al. [53] using a spatial training protocol indicated that THC-treatment had no effect on reduced hippocampal proliferation, and increased survival

Aleksandra Drab, Mirosław Zagaja, Agnieszka Haratym-Maj, Jarogniew Jacek Łuszczki, Marta Andres-Mach. Endocannabinoid system and cannabinoids in neurogenesis…

of new-born hippocampal cells by training. Hutch and Hegg [54] indicated that cannabinoids WIN 55,212–2 or 2-arachidonylglycerol induce proliferation, but do not induce neurogenesis nor non-neuronal cell generation in the mouse olfactory epithelium. On the other hand, it was reported that neurogenesis in aged rats can be significantly increased by a low, continuous, non-psychoactive dose of a cannabinoid receptor agonist, WIN-55,212–2 [55]. In the current study, the last investigations by the authors using ACEA, showed stimulation of neurogenesis in mice treated with valproic acid (VPA), whereas long term administration of VPA itself slightly decreased the amount of newly-born neurons in the mouse dentate subgranular zone, when compared to the control group [56]. Similar results were obtained in a mouse pilocarpine model of epilepsy [57]. The differences in the amount of newborn cells in the dentate gyrus between control healthy and ACEA+VPA treated mice are displayed in Fig. 3.

CONCLUSIONS

Every day, new information is being discovered from the world of science on the uniqueness and the potential of the human brain. This uniqueness is even greater when dealing with brain disorders. The endocannabinoid system is emerging as a key regulator of many neuronal systems relevant to neurodegenerative disorders. Scientists are constantly looking for drugs which have strong neuroprotective properties and no side-effects. Thus, the problem concerning the effect of cannabinoids as potential neuroprotective substances in the process of neurogenesis in various degenerative disorders is very interesting, and certainly requires more advanced and intensive research.

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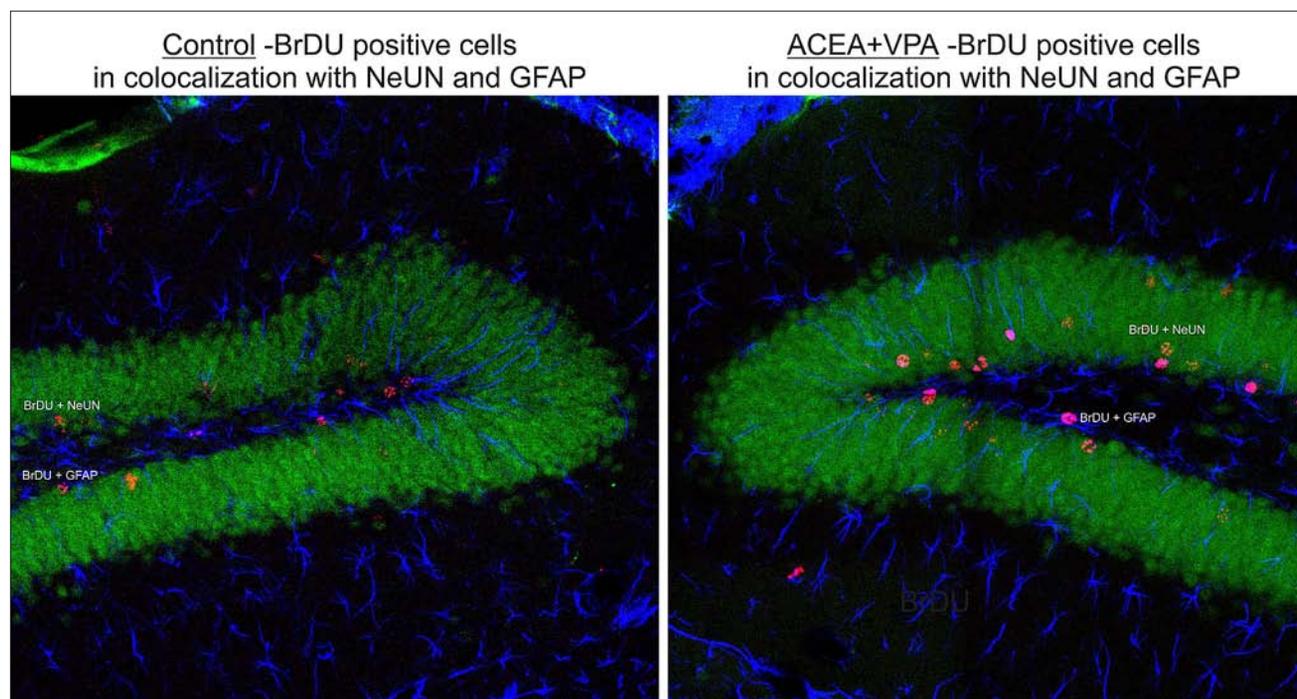
Figure 3. BrDU positive cells in colocalization with NeuN and GFAP in control healthy and VPA+ACEA treated mice
The number of BrdU positive cells displaying astrocyte-specific (GFAP), neuron-specific (NeuN), bromodeoxyuridine (BrdU)- specific markers was determined using confocal microscopy to score the colocalization of BrdU and phenotypic indicators.

80

Journal of Pre-Clinical and Clinical Research, 2017, Vol 11, No 1

Aleksandra Drab, Mirosław Zagaja, Agnieszka Haratym-Maj, Jarogniew Jacek Łuszczki, Marta Andres-Mach. Endocannabinoid system and cannabinoids in neurogenesis…

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