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(Endo)cannabinoids and Cognitive Functions in Animals: Healthy and Pathological Brain

Kitchigina VF*
Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Pushchino, Moscow region, 142290 Russia

Abstract

Cognitive functions are based on neuronal plasticity, which is provided by various mechanisms involving numerous bioactive molecules, the most important of which are endocannabinoids (eCBs). Alzheimer's disease (AD) is known to impair cognitive function. The main pathological feature of neurons in AD is increased excitability; therefore, an activation of the endocannabinoid system, which controls cellular excitation, may be a promising approach in their therapy. Neurobiological evidence regarding the effects of eCBs on cognition is inconsistent. There is an extensive literature indicating a protective effect of cannabinoids in the treatment of neurodegenerative diseases in humans and in animal models of cognitive deficits. Possible approaches to the therapy of cognitive disorders in this disease are discussed.

Highlights

– Information on (endo)cannabinoid influences on cognitive functions in animals is highly controversial.
– Endocannabinoids and exogenous cannabinoids may oppositely modulate cognitive function.
– Different doses of cannabinoid drugs can have diverse effects on cognition.
– Effects of cannabinoids can be opposite depending on the mechanisms involved in cognitive functions
– Promising results have been obtained in studies using cannabinoid drugs in AD.

Keywords: Cannabinoids; Endocannabinoid system; Endocannabinoidom; Cognitive functions; Learning, memory; Neurotransmitters; CB receptors; Inhibitors of endocannabinoid catabolism; Alzheimer's disease; Protection

Abbreviations:

2-AG: 2-arachidonylglycerol (endogenous ligand of CBR); Aβ: β-amyloid peptides; AEA: N-arachidonylethanolamide, anandamide (endogenous ligand of CBR); AD: Alzheimer's disease; CBRs: Cannabinoid Receptors; CB1Rs: type 1 cannabinoid receptors; CB2Rs: type 2 cannabinoid receptors; CBD: Cannabidiol (CBR partial agonist); eCBs: endocannabinoids; ECS: Endocannabinoid System; DAGL-α, DAGL-β: diacylglycerol lipases, enzymes for the synthesis of 2-AG; FAAH: fatty acid amide hydrolase, AEA degradation enzyme; fMRI: functional Magnetic Resonance Imaging; LTD: Long-term synaptic Depression; LTP: Long-term Synaptic Potentiation; MAGL: Monoacylglycerol Lipase, 2-AG degradation enzyme; mTOR: Mammalian Target of Rapamycin; PEA: Palmitoylethanolamide (endogenous analogue of AEA); PET: Positron Emission Tomography; THC: Δ9-tetrahydrocannabinol (partial agonist at both CB1 and CB2 receptors); WIN-2: synthetic agonist of CB1/CB2 receptors WIN 55,212-2

Introduction

The endocannabinoid system (ECS) plays an important role in cognition, mainly by being involved in synaptic responsiveness and plasticity [1]. Significant concentrations of cannabinoid type 1 receptors (CB1Rs) in the human brain have been found in the hippocampus and neocortex (in particular, in somatosensory, prefrontal, entorhinal, and perirhinal areas); they are also abundant in some subcortical structures (dorsal striatum, amygdala, cerebellum, and substantia nigra) [2,3]. A similar distribution of CB1Rs has been described in animals [4]. In the hippocampus, where CB1Rs are mainly expressed at the terminals of GABAergic neurons [5], endocannabinoids (eCBs) exert a disinhibitory effect, by reducing GABA release in a short- [6] or long-term mode [7] and thus promote associative learning [8]. By reducing the inhibition, eCBs facilitate the occurrence of long-term potentiation (LTP) in the hippocampus [7,9]; the increase in LTP induction may contribute to the formation of temporal associative memories [10].

Scientific interest in cannabinoids arose in the 1960s, when the main psychoactive component of hemp (Cannabis sativa), Δ9-tetrahydrocannabinol (THC), was chemically characterized [11]. Somewhat earlier, another component of cannabis, cannabidiol (CBD), was identified [12], which does not have a pronounced psychoactive effect. In the early 1990s, two types of cannabinoid receptors were cloned, CB1 and CB2 [13,14]). Subsequently, ligands of these receptors, endogenous cannabinoids (eCBs), derivatives of arachidonic

acid, N-arachidonylethanolamide (AEA or anandamide) and 2-arachidonylglycerol (2-AG), as well as enzyme systems for their synthesis, transport and degradation were identified [15-17].

Cannabinoid receptors (CBRs), eCBs, and enzymes that regulate their synthesis and degradation, form the endocannabinoid system (ECS) [18-20].

eCBs are involved in the regulation of homeostasis of cell, tissue, organs and whole organism, brain development, neurotransmission and synaptic plasticity [6], in particular, LTP and LTD [21]. Besides, CB1Rs are intimately involved in regulating excitatory glutamatergic inputs and energy balance at the brain level [22].

eCBs are synthesized and released from postsynaptic cells “on demand”, in response to various signals [23] and, acting on CBRs located at the terminals of axons of the same or nearby cells [18], reduce the release of various mediators [5,6,24]. eCBs should be distinguished from exogenous cannabinoids, which include the phytocannabinoids (THC and CBD) and synthetic cannabinoids or CBR agonists.

In recent years, the ECS has been considered more broadly as endocannabinoidome, which includes some mediators biochemically associated with eCBs, their receptors and metabolic systems. Thus, the FAAH enzyme (hydrolyzing AEA) also activates other endogenous substrates that act on other receptors. Another enzyme, MAGL (hydrolyzing 2AG) has substrates including monoacylglycerols other than 2-AG [25], which also act on receptors other than CB1 and CB2 receptors [26,27]. Detailed information on the mediators, enzymes, and signaling pathways involved in the endocannabinoidom has been presented previously [25-33].

The literature on the effects of cannabinoid drugs on the cognitive functions is highly controversial. In my previous publication, the composition and properties of the ECS were discussed in detail; the effect of exogenous cannabinoids on cognitive functions has also been described, mainly in humans [34]. In the present review, which includes research from recent years, I have focused on the role of the ECS in animal cognition. Based on the presented data, possible approaches to the treatment of cognitive disorders in Alzheimer's disease (AD) are discussed.

Effect of cannabinoid drugs on cognitive functions of the healthy brain

Cannabis (or hemp, or marijuana) contains about 70 cannabinoids; in addition, it includes terpenoids, flavonoids and alkaloids [35]. Of all the cannabinoids found in cannabis, THC is the most extensively studied; it has strong affinity for CB1 and CB2 receptors [36,37] and, as a result, can directly affect the brain [38-40]. The effects of cannabidiol (CBD) on cognitive function have also been intensively studied now.

Animal experiments provide good opportunities for brain research. However, the data are often ambiguous.

Alterations in cognitive functions upon direct action on CB receptors and after the deletion of CB receptors

The findings of the last two decades show that the ECS modulates certain aspects of learning and memory. Thus, the results of the study by Lichtman in which rats were trained to perform a task in a radial eight-ray maze showed a better task performance after the administration of SR141716 (rimonabant, a selective CB1R antagonist) than in the control [41]. Consistent with these data, an improvement in memory performance for object recognition in CB1R knockout mice compared with wild-type mice was found [42]. The beneficial effect of rimonabant on memory was confirmed in the work by Wolff and Leander [43]. Rimonabant also reversed THC- or anandamide-induced memory deficits [44] and attenuated sleep deprivation-induced memory impairment in rats [45]. Recently, Ghazvini and colleagues also revealed a positive effect of rimonabant: this CB1R antagonist improved the methamphetamine-induced impairment of object recognition and social behavior [46]. Another selective CB1R antagonist, AM251, may attenuate short- and/or long-term memory deficits in the inhibitory avoidance test [47]. On the other hand, WIN 55,212–2 (WIN-2), a potent CB receptor agonist, impaired recognition memory in rodents [48,49] or showed no effects on methamphetamine-induced impairment of object recognition and sociability [46].

However, the effects of improving memory during CB1R blockade were not observed when animals performed the tasks where the participation of working memory was necessary [50-52]. Thus, the CB1R antagonist SR141716A in a dose effective for blocking the action of THC and R-methanandamide, by itself, did not affect the performance of the task in the working memory test [50]. When training rats in the test for spatial memory in the Morris water maze, the effects of improving memory with CB1R blocking were also not observed [40].

In contrast, systemic administration of THC, WIN-2, and CP55,940 (CBR agonists) impaired working memory in rats; interestingly, unlike the listed drugs, anandamide (CB1R agonist) and CBD had no visible effect on working memory [53]. It has been suggested that the effects of the aforementioned CBR agonists on working memory are mediated through CBRs in the hippocampus [54,55]. In another early work, the effect of the synthetic CB1/CB2 receptor agonist HU-210 on learning and memory consolidation was studied; two variants of the Morris maze, were used. The administration of HU-210 60 min before training at doses of 50 and 100 μg/kg/daily for four days disrupted learning only in a more complex task (with a hidden platform). In contrast, at a dose of 25 μg/kg, HU-210 facilitated training in any platform position. Thus, different doses of this CBR agonist oppositely affected the learning in a complex task in the Morris maze. Importantly, as noted by the authors, the CBR agonist HU-210 at doses of 50 and 100 μg/kg caused tigmotaxis, which is observed on increased arousal; therefore, the effect of HU-210 in this case may be mediated not by direct action on CB receptors but by other mechanisms [56].

Learning the task in the Morris water maze is dependent on the hippocampus; this task is used to investigate spatial navigation and memory. It is interesting that a single injection of an extremely low dose of THC (0.001 mg/kg) significantly affected the performance of the task by mice in the complex Morris water maze test 3 weeks later. THC-injected mice showed both longer escape latencies and lower

scores in the execution of this test compared to their matched controls, indicating the induction of cognitive deficits [57].

The long-term administration of the CBR agonist WIN-2 led to a deterioration in the performance of the task of recognizing a new object (NORT) in mice [58]. Besides, in a study using functional imaging (PET), long-term introduction of WIN-2 affected brain metabolism and functional connection between the hippocampus, perirhinal cortex, and thalamus i.e., between the structures involved in memory processes. The injection of AM 251, an antagonist of CB1Rs, removed the disturbances in the NORT task in mice [59].

Interestingly, the effects of cannabinoids on cognition in animals changed with age, with stronger negative effects observed in the pubertal phase compared to adults (60-66]. Besides, in tests for object recognition and spatial memory, the authors obtained opposite results regarding the effects of CBR agonists on cognitive performance depending on the age of the animals and the dose of the administered drugs [61,62,65,66].

The cognitive function can also be enhanced by activating CB2 receptors; for example, this activation restored the impaired behavior of rats in hippocampus-dependent tests [67]. The authors examined rats using the novel object recognition and the Morris water maze tests and found the return to normal behavior in both cases by injection of the CB2R agonist AM1241.

Interestingly, aging animals showed improved cognitive performance under the influence of THC. Thus, Bilkei-Gorzo and colleagues [68] demonstrated that a low dose of THC reversed the age-related cognitive decline in mice aged 12 and 18 months when performing a hippocampus-dependent spatial memory task in the Morris water maze. This effect was accompanied by an increase in the expression of synaptic marker proteins and in the density of spines in the hippocampus. The restoration of transcriptional gene patterns in this structure was also observed. Besides, the expression profiles of these genes in 12-month-old mice treated with THC were very similar to those without THC in mice at the age of 2 months. The transcriptional effects of THC were critically dependent on CB1Rs on glutamatergic neurons, since their inhibition blocked the positive effects of THC. The authors suggested the optimistic conclusion that the restoration of CB1 signaling in the elderly may be an effective strategy for treating age-related cognitive impairment.

It is noteworthy that although some early works have provided evidence of selective deficits in the hippocampus-dependent memory under the influence of cannabinoid drugs [55,60,69,70], in a recent study, it was found that a low dose of the CBR agonist WIN-2 (1 mg/kg) and URB597 (a potent selective inhibitor of FAAH, 0.2 mg/kg) improved avoidance memory consolidation [71].

In addition to the hippocampus, the medial prefrontal cortex (mPFC) was found to be a critical site for CB1R-dependent modulation of acquired fear responses [72-74]. However, in the experiments of these authors on rats, not a context, but a certain signal (smell or sound) was used as a conditioned stimulus, and the reaction was considered as hippocampus-independent. Exposure to odor, previously associated with an electrocutaneous irritation, increased the burst activity in a subpopulation of neurons in the mPFC [72]. When a CB1R antagonist was injected into mPFC, the acquisition of a conditioned freezing reaction was blocked, which was associated with impaired neuronal bursting activity in this area of the neocortex and a decrease in LTP in the synapses of afferent fibers from the basolateral amygdala to PFC [72,73,75]. These data indicate that CB1R signaling at amygdala-mPFC synapses is involved in the coding of the fear response to olfactory conditioning.

The results of a recent work by Pires and colleagues [76] confirm the facts obtained in early experiments. Using the Morris maze and chronic (up to 22-29 days) administration of WIN-2 (2 mg/kg, i.p.) in different groups of mice, they studied its effect on different phases of memory, learning (with the injection of the drug before the test for working memory) and consolidation (after this test), with parallel assessment of gene expression in the hippocampus and the prefrontal cortex. Insignificant cognitive impairments were found only in short-term working memory, which interfered with learning; however, long-term memory (consolidation) was not disturbed. Besides, an increase in the expression of DAGL-α, an enzyme for the synthesis of 2-AG, and a decrease in the level of MAGL, its degradation enzyme, were found in PFC in animals that received WIN-2 before training; at the same time, mice injected after training to assess memory consolidation, showed opposite changes. For genes associated with AEA metabolism, no correlation was found between molecular and behavioral data [76].

In a number of studies on the effect of activation of the ECS on learning and memory, the neural activity in the hippocampus and, in parallel, the temporary coordination of this activity by the field theta rhythm were analyzed. In particular, Robbe and Buzsáki [70] showed that the synthetic CB1R agonist CP55940 caused cognitive deficit in rats performing a spatial task of delayed alternation in a modified T-maze and decreased the power of theta, gamma, and ripple oscillations in the hippocampus. The binding of the activity of the place cells to the phase of theta wave was also significantly deteriorated. The temporal coordination of cell ensembles was also impaired in short time intervals (<100 ms). The authors believe that cannabinoids can impair memory primarily by disturbing the temporal dynamics of hippocampal neurons, regulated by theta rhythm [70] and thereby disrupt spatial memory.

Interestingly, the study by Marsicano and colleagues [77] demonstrated a new mechanism for astroglial control of synaptic plasticity and memory through the D-serine-dependent modulation of NMDA receptors. The authors showed that activation of astroglial CB1Rs controls the hippocampal LTP by regulating the synaptic level of D-serine, a signaling amino acid [77].

As regards the role of CB2 receptor activation in modulating cognitive functions, interesting results were obtained by Manzanares and co-authors [78]. This work clearly showed that the selective CB2R agonist JWH133 was shown to improved memory consolidation, while the CBR antagonist AM630 worsened memory responses. Later, Kruk-Slomka and Biala [79] showed that JWH133 at a low dose (0.5 mg/kg) had no effect on learning but enhanced the consolidation of long-term memory in the passive avoidance

test. At the same time, JWH133 at higher doses (1 and 2 mg/kg) improved both the acquisition and consolidation of long-term memory. Subsequently, similar results were obtained by Pires and colleagues [76]. At the same time, it was found in another work on CB2 receptor knockout mice that hippocampal-dependent long-term contextual fear memory was impaired, while hippocampus-independent cued fear memory was normal. In contrast to CB2 receptor knockout, acute blockade of CB2 receptors by AM603 in C57BL/6J mice did not affect memory [80]. It should also be noted that the specific effects of CB2R ligands on cognitive processes seem to be quite complex and still cannot be exactly assessed.

An important role of the ECS in cognitive functioning was revealed in the work by Busquets-Garcia and colleagues [81], where an original learning model, the mediated learning, was used [82]. A typical initial behavioral procedure in this model is sensory preconditioning, where pairs of two minor stimuli (smells, light, tones, gustatory stimuli) are accompanied by the classical conditioning of one of them with an aversive or appetitive unconditioned reinforce. As a result of these associations, subjects avoid or prefer a stimulus that has never been clearly combined with a conditioned stimulus [83,84]. Sensory preconditioning involves three different, sequential processes. First, an incidental association is formed between low-significant stimuli during the preconditioning phase; second, direct association of one of initial signals with the reinforce stimulus enhances its salience during the conditioning phase; third, the presentation to the subject of any of the initial signals (directly associated with the conditioned stimulus or never associated with it) reveals the retrieval of direct or mediated memory, respectively. It should be noted that the behavior of animals in natural life is more often associated precisely with mediated learning based on previous experience; the same applies to human behavior [82,85]. Busquets-Garcia and colleagues [81] used this model of incidental learning and found that this learning was impaired in CB1R knockout mice (CB1R-KO) (Figure 1). In this investigation, wild-type and CB1R knockout mice were preconditioned with pairs of stimuli: smell–taste (banana (+) and almonds (-) as smells; sucrose (+) and maltodextrin (-) as taste), followed by conditioning one of two stimuli, pleasant or unpleasant; then a test stimulus was presented that was different from the conditioned one (with indirect learning) or the same content (with direct learning) (Figure 1A). The authors have convincingly shown that in CB1R-KO mice the mediated learning was impaired (Figures 1B, 1C), while direct learning was preserved (Figures 1D, 1E). This demonstrates that CB1Rs are essential for this type of wildlife training. At the same time, control mice showed no significant difference in the two learning models, classical and mediated. Interestingly, CB1R knockout mice (CB1R-KO) exhibited impaired mediated learning regardless of the sensory modality of the test stimulus (Figures 1B, 1C).

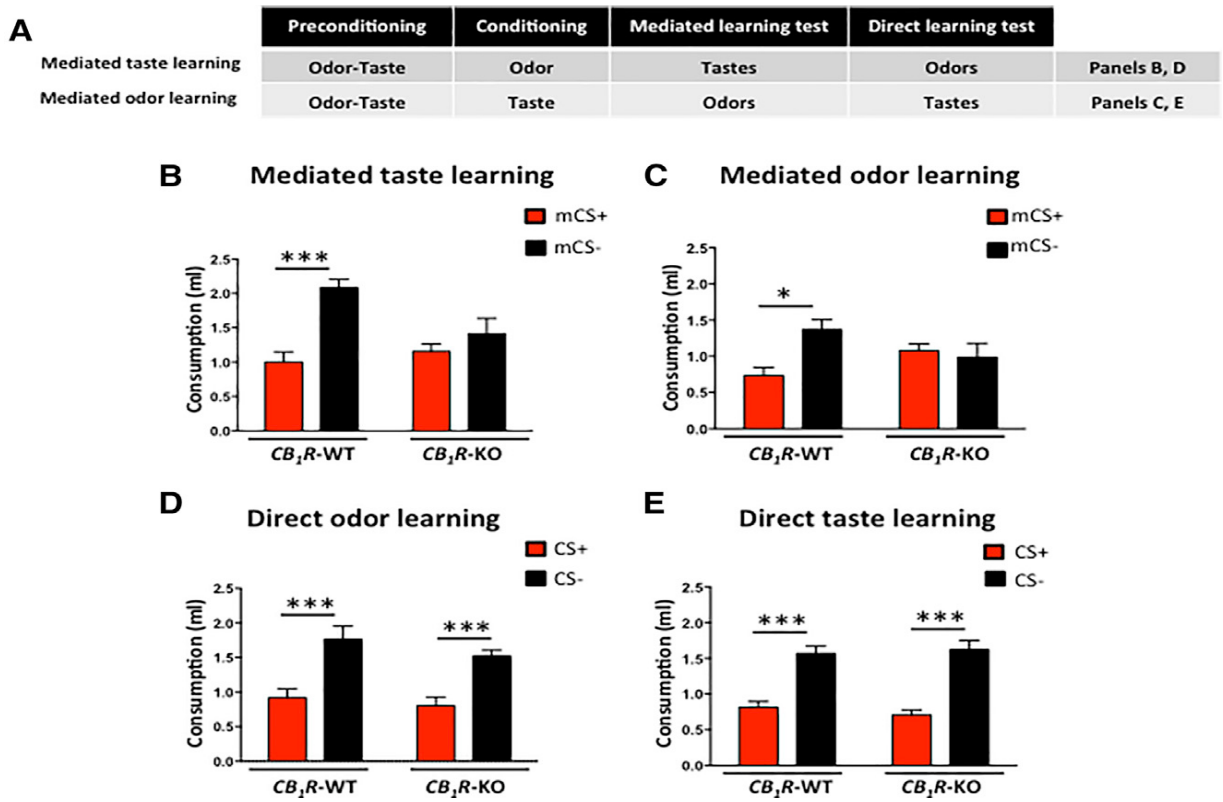

Figure 1: CB1R Are necessary for odor – taste-mediated learning. (A) Schematic table of the odor-taste sensory preconditioning protocol. (B and C) Liquid consumption under conditions of mediated taste (B) or odor (C) aversion in CB1R-KO mice and wild-type littermates (CB1R-WT). (D and E) Liquid consumption under conditions of direct odor (D) or taste (E) aversion in CB1R-KO mice and CB1R-WT. *p < 0.05; ***p < 0.001 (mCS+ versus mCS_ or CS+ versus CS-). Detailed explanations in the text.

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This study also provided evidence that the activity of cholecystokinin-containing CB1R expressing GABAergic hippocampal neurons plays a crucial role in mediated learning. The authors ultimately concluded that fine regulation of hippocampal GABAergic interneurons via CB1Rs can explain how humans and animals integrate and associate a variety of randomly occurring low-salience signals so that, as a result, they develop a seemingly unreasonable attraction or aversion to specific objects, places, or people [82,85]. Thus, the use of nonstandard strategies in the study of the ECS can reveal its specific role in cognitive behavior.

Interesting results were also obtained by the research group of Bénard & Marsicano who showed the dependence of cognitive deficits caused by CBR agonists on mitochondrial CB1 receptors [86]. In their study of hippocampus-dependent memory, it was demonstrated that the synthetic cannabinoids WIN-2 and HU210, administered intrahippocampally, cause acute memory impairment in mice during the recognition of new objects in an L-maze. Thus, the data of these authors evidenced that bioenergetic processes occurring in mitochondria of hippocampal cells operate as subcellular regulators of cognitive functions mediated by CB1 receptors [86].

Changes in cognitive functions upon modulation of metabolism of eCBs

Modulating the levels of the eCBs (i.e., anandamide and 2-AG by the pharmacological blockade of their catabolism) is a promising approach to the treatment of AD. Most importantly, this manipulation augments no relevant side effects (for details, see reviews [36,87].

In the work by Yasar and colleagues [88], the effects of URB597 (a FAAH inhibitor) and WY14643 (an agonist of PPARα) on the learning of rats in the hippocampus-dependent passive avoidance task were investigated. The drugs were injected before or immediately after the training session (to assess the effect on memory acquisition and consolidation, respectively) or before a test conducted 24 h after the training session to determine their effect on memory retrieval. URB597 and WY14643 induced significant improvement in learning. This facilitation was blocked by MK886, a PPARα antagonist. It is known that PPARα is a target of the eCB AEA (except for CB1Rs); therefore, the blockade of the FAAH enzyme by URB597, had the same effect as the administration of the PPARα agonist. On the other hand, no effects on consolidation or memory retrieval were observed after the administration of WY14643 [88].

Busquets-Garcia and colleagues studied the role of the endocannabinoids AEA and 2-AG, as well as rapamycin, in modulating the specific types of memory (contextual hippocampus-dependent memory and memory on object recognition in the V-maze) [89]. In these experiments, two inhibitors of eCB catabolism, which increase the levels of AEA and 2-AG, as well as THC and rapamycin were injected to the mice of different groups. An increase in the 2-AG level did not affect memory consolidation and mTOR signaling in the hippocampus; at the same time, the modulation of AEA and the administration of THC induced the disturbance of these processes, which was removed by rimonabant (i.e., through CB1R) [89]. However, any significant effect on CB1R protein levels was not revealed. As the authors beleaved, the elevated AEA level inhibits CaMKIV and CREB phosphorylation via the activation of CB1Rs [44].

Thus, a diversity in the effects of increased brain level of the two eCBs was found: 2-AG did not change the memory [89], and AEA caused its deficiency [44]. However, the later two works [71,90] showed the role of both CB1 and CB2 receptors in the consolidation of memory in the model of memorizing negative experiences that require the activation of inhibitory mechanisms. It is important to note that these studies did not always control the modulation of the levels of other biologically active lipids; differences in their concentration may be the reason for the observed inconsistencies in the results.

Summing up the effects of eCBs on cognitive functions in animals, one can conclude that the use of the most adequate experimental approaches, for example, mediated learning or the application of olfactory signals that are of the greatest importance for rodents, allowed one to demonstrate the positive influence of ECS activation on both learning and plastic processes in the hippocampus. These approaches break the popular opinion about predominantly negative influence of eCBs on cognition. In addition, taking into account the presence of CB1Rs on astroglial cells, experiments revealed their significant role in memory and the development of LTP in the hippocampus. Using a test based on the involvement of the hippocampus in the control of behavior, it was convincingly shown that the consolidation of hippocampus-dependent memory is facilitated by an increase in the level of AEA, through the competitive activation of CB1 and CB2 receptors, and in the level of 2AG, mainly via the activation of CB2 receptors.

Endocannabinoid system as a brain target in models of Alzheimer's disease

Alzheimer's disease (AD) is a debilitating neurodegenerative disease characterized by declining cognition and behavioral impairment. The precise etiology of AD remains unclear. There is a tendency to regard Aβ as a trigger for disease progression [91]. At the morphological level, the most characteristic changes in AD are the damage to/death of neurons, especially in the hippocampus and neocortex, and the rearrangement of neural networks [92,93].

Unfortunately, all the drugs influencing the production, clearance, and aggregation of Aβ which have been tested are clinically ineffective [94]. Although the pathophysiological role of the ECS in AD is still elusive, the lack of CB1 receptors has been associated with a faster decline in the cognitive function and loss of neurons in the hippocampus in wild-type mice [69]. On the other hand, the administration of β-amyloid (Aβ1-42) increased the level of endogenous 2-AG and PEA, while exogenous PEA weakened the Aβ-induced expression of proinflammatory molecules [95]. In addition, the administration of AM404 (an inhibitor of endocannabinoid transport) prevents the Aβ-induced

degeneration of hippocampal neurons [96]. This suggests that the ECS activation may prevent the development of AD.

Indeed, cannabinoid treatments, especially CBD, have great potential [52, 97-100]. Thus, in rodent models of AD, cannabinoids reduce Aβ accumulation and improve memory [101,102]. Administration of low doses of THC in rats was associated with an improvement of cognitive functions; the ultralow doses of THC protected the mice brain from neuroinflammation-induced cognitive damage [103]. Besides, a CB2 agonist (MDA7) promotes Aβ clearance, decreases the IL-1β level, and improves memory in rats with cognitive impairment induced by bilateral microinjections of Aβ into the hippocampus [104].

Studies using an AD-relevant rodent model induced by the administration of Aβ25-35 showed that the injection of WIN-2 into rats prevented the Aβ-induced activation of microglia, cognitive impairment in a spatial learning task, and neuronal death [105]. Later, it has been shown that the neuroprotective effect of CB1R activation is provided by different mechanisms: the inhibition of the release of glutamate, calcium, cytokines, tumor necrosis factor alpha and inducible NO synthase, the blockage of the voltage-dependent calcium channel, and Aβ clearance [106-109].

In 2019, in a rat model of sporadic form of AD (generated by streptozotocin injection), a cognitive impairment was revealed, which was reversed by the administration of ACEA, a CB1R agonist, which was found to increase the level of the anti-apoptotic protein Bcl-2 [110]. Besides, the oral administration for four months of JWH133, a selective CB2R agonist, prevented memory impairment in AD mice, while normalizing the cerebral glucose metabolism as measured by PET; it also counteracted the activation of microglia [102]. In addition, CB1R agonists were reported to decrease Aβ toxicity, restoring the electrophysiological properties of pyramidal neurons in hippocampal field CA1, decreasing tau hyperphosphorylation and the inflammatory response, and reversing the behavioral changes in rodents [96,105,111].

Recently, on 5xFAD transgenic mice (expressing human APP and PSEN1 transgenes with a total of five AD-linked mutations) it was demonstrated that CBD treatment ameliorated the symptoms of AD and retarded cognitive decline [112]. In this study, the authors used the New Object Recognition behavior testing method and showed that CBD improved cognitive function compared to untreated animals (Figure 2). Further, immunofluorescence staining demonstrated a reduction in the level of amyloid-β in brain tissues of CBD treated 5xFAD mice.

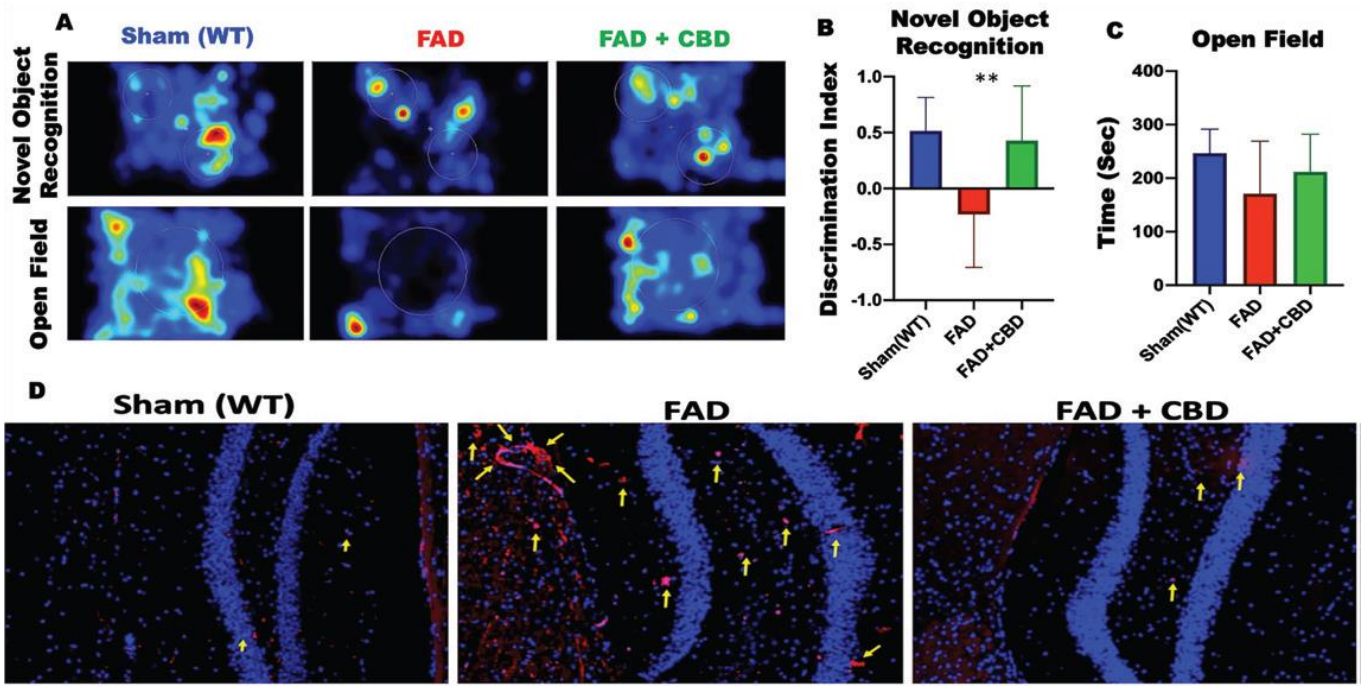

Figure 2: CBD treatment improved cognitive function and ameliorated the pathophysiology of Alzheimer's disease (AD). A-C) The Novel Object Recognition method (A upper panel and B) of behavior testing showed that CBD improved cognitive function, as compared to untreated animals (∗p ≤ 0.04). Open Field testing method (A Lower panel and C) suggested that CBD treatment could ameliorate the cognitive function in 5×FAD mice. D) Immunofluorescence staining demonstrated the reduction of beta-amyloid expression in the brain tissues of 5×FAD mice treated with CBD, indicating the protective effects and potential reduction in the pathophysiology of AD. Panels are representing 6–10 animals per each experimental group showing deposition of amyloid-_ (yellow arrows) in the hippocampus area of WT mice brain, and 5×FAD mice brain treated/untreated with CBD. Localization of amyloid-β (red) on the nucleus is visualized by imposing red staining over blue, creating pink images. The blue color is representing DNA staining with DAPI (4', 6-diamidino-2-phenylindole) to identify the nuclear presence and cell viability. Images are all shown in 100× magnification.

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Interestingly, MAGL inhibition was associated with several anti-AD effects: reduction in neuroinflammation, improvement of synaptic plasticity, spatial learning, and memory in AD animals [1]. Later it was shown that the selective pharmacological inhibition of MAGL and FAAH or dual inhibition of FAAH/MAGL followed by an increase in anandamide and 2-AG [113-115] promotes a reduction in Aβ-protein deposition in a rodent model of AD [see 34,36]. Furthermore, URB597 efficiently suppressed Aβ42-induced glutamate toxicity in primary hippocampal neurons and stimulated the mitochondrial membrane potential [116]. URB597 treatment is associated with the reduction in the level of interleukin (IL)-1β, and restoration of long-term potentiation in aged rats [117]. Hai and colleagues [118] using the Morris water maze investigated the protective effects of the FAAH inhibitor URB597 and the CBR agonist WIN-2 on cognitive impairment in rats caused by chronic cerebral hypoperfusion, which is considered one of the causes of AD and other neurodegenerations (see [119]). The expression of the protein associated with microtubules-2 (MAP-2), synaptophysin, CB1R, and brain neurotrophic factor BDNF was determined by Western blotting. The introduction of WIN-2 and URB597 improved the abilities for learning and memorizing [118]. Thus, these data suggest that WIN-2 and URB597 prevent cognitive impairment via the PI3K/AKT pathway.

Since CB1 receptors are primarily related to the unwanted psychotropic effects of marijuana-derived cannabinoids, the CB2 receptor becomes really attractive as a druggable target. The activation of CB2Rs was shown to counteract the Aβ-induced neurotoxicity [99,102,105,120], mainly via modulating activated microglia. Experiments on an APP/PS1 model of AD in mice showed that CBD reduced cognitive impairments, preventing the development of a deficit in social recognition [121]. It was also observed that CBD and THC promoted memory retention and decreased astrogliosis and inflammation in APP/PS1 mice [111].

Recent reviews have demonstrated the potential of cannabinoid drugs in AD therapy and indicated also their limitations [122,123]. More research is needed to avoid the negative consequences of using ECS activation in AD treatment.

Conclusions

An analysis of neurobiological data showed that the opinions of different authors on the role of the ECS in cognitive functions do not coincide. To understand this problem, it is necessary, first of all, to take into account that the action of eCBs may differ from that of exogenous cannabinoids, which non-selectively affect CB receptors and can alter the functioning of the ECS. This issue has complicated the determination of the specific role of (endo)cannabinoids in cognitive processes. It is also important to stress that the effects of certain cannabinoid drugs on mental processes can be opposite, depending on the mechanisms involved in cognitive functions.

Analysis of experimental data obtained in the animal models of AD, in most cases indicate a positive role of eCBs in the functioning of the brain, in particular, in its cognitive functions. It is known that the ECS controls cellular homeostasis, which disturbed in brain with this pathology, and, therefore, its activation is a promising approach to the treatment of this disease.

The therapeutic potential of (endo)cannabinoids is clearly manifested in the development of AD; this makes it possible to estimate how the activation of the ECS affects cognitive functions in these diseases. At the same time, the inconsistency of available data in this aspect indicates a great need for further investigations using modern approaches to fully understand the role of the eCBs in the cognitive functions.

Conflict of interest statement

Nothing declared.

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***Corresponding author:** Valentina F. Kitchigina, Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Pushchino, Moscow region, 142290 Russia; Email: vkitchigina@gmail.com

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