Review

(Endo)cannabinoids and cognitive functions in animals: healthy and pathological brain

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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). Over the past three decades, a lot of data have been accumulated on the involvement of eCBs in the mechanisms of memory and other cognitive functions. These functions are impaired in neurodegenerative diseases such as Alzheimer's disease (AD) and temporal lobe epilepsy (TLE). The main pathological feature of neurons in AD and TLE is increased excitability; therefore, an activation of the endocannabinoid system, which controls cellular excitation, may be a promising approach in their therapy. The available information about the effect of (endo)cannabinoids on cognitive functions is contradictory, which may depend on the drugs used, their dose, and the experimental conditions. 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. This review, focusing on the recent researches, is devoted to the analysis of the effects of endocannabinoid system activation on cognitive functions in norm and in the brain with neurodegeneration that occurs in AD and TLE diseases. Possible reasons for inconsistencies in the available data 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 and TLE models.

Keywords: cannabinoids; endocannabinoid system; endocannabinoidom; cognitive functions; learning; memory; neurotransmitters; CB receptors; inhibitors of endocannabinoid catabolism; Alzheimer's disease; temporal lobe epilepsy; protection

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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
- CBR – cannabinoid receptors
- CB1R - type 1 cannabinoid receptors
- CB2R - type 2 cannabinoid receptors
- CBD - cannabidiol (CBR partial agonist)

 doi:10.20944/preprints202304.0224.v1

- 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
- GPR55, GPR18 - G-protein coupled receptors
- LTD - long-term synaptic depression
- LTP - long-term synaptic potentiation
- MAGL - monoacylglycerol lipase, 2-AG degradation enzyme
- mTOR - mammalian target of rapamycin
- NAPE-PLD – anandamide synthesizing enzyme
- PEA - palmitoylethanolamide (endogenous analogue of AEA)
- PET - positron emission tomography
- PPAR - receptors activated by peroxisome proliferators, a group of cell nucleus receptors that function as a transcription factor
- THC - Δ9-tetrahydrocannabinol (partial agonist at both CB1 and CB2 receptors)
- TLE - temporal lobe epilepsy
- TRPV - vanilloid receptors, nonspecific cation channels
- TRPV1, TRPV2, PPARα, PPARγ, GPR55, GPR18 - receptors included in the endocannabinoidom
- WIN-2 - synthetic agonist of CB1/CB2 receptors WIN 55,212-2

1. Introduction

The endocannabinoid system (ECS) plays an important role in cognition, mainly by being involved in synaptic responsiveness and plasticity [1]. The cortex is a key structure in the performance of cognitive functions, and it is this area that is especially rich in cannabinoid type 1 receptors (CB1R). Significant concentrations of 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 CB1R 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-lasting manner and triggering the long-term depression of inhibition (iLTD) [7]. Disinhibition can increase the excitation in the neural network and thereby contribute to 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 (CBR), eCBs, and enzymes that regulate their synthesis and degradation, form the ECS [18,19].

CB1Rs in the mammalian brain are the most abundant G protein-coupled receptors in neurons [20]. In regard to CB2R, it was initially assumed that they are predominantly distributed in immune tissues and cells [21]; later, it was shown that CB2Rs are present in brain stem neurons [22] and glial cells (astrocytes and microglia) [23]. Usually, the level of CB2R expression in the CNS is much lower than in the cells of the immune system, but in neurodegenerative diseases and strokes, the amount of CB2R in the brain sharply

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increases [24,25]. CB1Rs expressed on astrocytes [26] play a crucial role in glial-neuronal interactions, affecting synaptic transmission [27,28]. Thus, the ECS is regarded as a ubiquitous regulator of synaptic transmission in the brain, which mediates numerous forms of plasticity [29]. In addition, eCBs control the neuronal energy metabolism, in particular, due to the localization of CB1R on mitochondria [30].

eCBs can also affect TRPV1 and TRPV2 receptors, nonspecific cation channels (see review [31]. Importantly, AEA at high micromolar concentrations can also affect L-type Ca^{2+} channels, causing effects not directly related to CB1R in vivo (see [32,33]).

eCBs are involved in the regulation of homeostasis of cell, tissue, organ and whole organism, brain development, neurotransmission and synaptic plasticity, and neuronal energy metabolism, as well as the release of cytokines from microglia and, therefore, take part in neurological disorders. By participating in the plastic processes that underlie the cognitive activity, eCBs regulate both short-term plasticity (depolarization-induced suppression of excitation (DSE) and inhibition (DSI) [6], and long-term plastic processes, LTP and LTD [29]. Besides, CB1Rs are intimately involved in regulating excitatory glutamatergic inputs and energy balance at the brain level [34].

eCBs are synthesized and released from postsynaptic cells "on demand", in response to various signals (Marsicano et al. 2003) and, acting on CBR located at the terminals of axons of the same or nearby cells [18], reduce the release of various mediators (5,6,35]. eCBs should be distinguished from exogenous cannabinoids, which include phytocannabinoids (THC and CBD) and synthetic cannabinoids or CBR agonists (eg JWH-133 and WIN55,212-2). Research data in recent decades have shown that the effects of exocannabinoids are mediated by their action on the ECS.

In recent years, the ECS has been considered more broadly as an endocannabinoidom, 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, including peroxisome proliferator-activated receptor (PPARα), Orphan GPCR 119 (GPR119), Orphan GPCR 55 (GPR55), and TRPV1 [33]. These receptors may play an opposite role compared to CBR [36-38]. Another enzyme, MAGL (hydrolyzing 2AG) has substrates including monoacylglycerols other than 2-AG [39], which also act on receptors other than CB1 and CB2, including TRPV1 and GPR119 [38,40]. Cannabinoids have been found to activate the PI3K/Akt/mTOR signaling pathway in immune and non-immune cells [41-45].

The literature on the effects of cannabinoid drugs on the cognitive function is highly controversial. This review has attempted to summarize the main available information on the role of the ECS in cognitive brain functions in a normal animal and in the models of neurodegenerative desorders that occur in Alzheimer's disease (AD) and temporal lobe epilepsy (TLE). An attempt to find out the reasons for the existing contradictions was also undertaken.

2. 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 [46]. Of all the cannabinoids found in cannabis, Δ9-tetrahydrocannabinol (THC) is the most extensively studied; it has strong affinity for CB1 and CB2 receptors (47,48] and, as a result, can directly affect the brain [49-51]. The effects of cannabidiol (CBD) on cognitive functions have also been intensively studied now.

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

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

The data obtained in studies on rodents indicate that the ECS modulates specific aspects of learning and memory. Thus, Pério and co-authors showed that SR141716

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(rimonabant, a selective CB1R antagonist) dose-dependently improved the performance of the social recognition task in rats and also attenuated the deficit exhibited in aged mice and rats performing the same task [52]. Consistent with these data, an improvement in memory performance for object recognition in CB1R knockout mice (-/-) compared with CB1 (+/+) wild-type mice was found [53]. Also, 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 than in the control [54]. The beneficial effect of rimonabant on memory was confirmed in the work by Wolff and Leander [55]; rimonabant also reversed THC- or anandamide-induced memory deficits [56] and attenuated sleep deprivation-induced memory impairment in rats [57]. 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 [58]. Another selective CB1R antagonist, AM251, may attenuate short- and/or long-term memory deficits in the inhibitory avoidance test [59]. On the other hand, WIN 55,212–2 (WIN), a potent CB receptor agonist, impaired recognition memory in rodents [60,61] or showed no effects on methamphetamine-induced impairment of object recognition and sociability [58].

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 [62-64]. Thus, when studying the effect of cannabinoid drugs on the learning of rats, which had to memorize a different sequence of three items, SR141716A, a CB1R antagonist, as well as the CB1R agonists anandamide and CBD, did not affect the speed and accuracy of the performance of this task. In contrast, THC and the long-acting endogenous ligand analogue R-methanandamide caused a dose-dependent increase in the error rate and a slower response. SR141716A (1 mg/kg) removed the effects of THC and R-methanandamide. 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 [62]. 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 [51].

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 [65]. In the studies by Lichtman and colleagues, when CP55,940 was injected into the hippocampus, this drug dose-dependently reduced the accuracy of task performance, although did not increase the time of its execution; therefore, the authors suggested that the effects of THC, WIN-2, and CP55,940 on working memory were mediated through the CBR in the hippocampus [66,67]. 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, with a fixed position of the platform hidden in the water and with a visible platform, 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 [68].

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 [69].

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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 [70]. Besides, in a study using functional imaging (PET), this long-term introduction of WIN-2 affected brain metabolism and functional connection between the hippocampus and the prefrontal cortex, between the thalamus and the prefrontal cortex, and between the hippocampus and the perirhinal cortex, i.e., between the structures involved in memory processes. The injection of AM 251, an antagonist of CB1R, removed the disturbances in the NORT task in mice [71].

Interestingly, the effects of cannabinoids on cognitive performance in animals change with age, with stronger negative effects being observed in the pubertal phase compared to the adult [72-74]. In view of this, Verrico and colleagues carried out a research of the effect of THC on working spatial memory and object recognition memory in adolescent monkeys. Monkeys were injected intravenously with THC, and the chronic effect of the drug on the efficiency of working memory was studied depending on the time of testing (delay time) after the last injection. In control animals, a clear increase in the accuracy of performing the task for spatial working memory was found with a greater delay (71 h), while in THC animals with this delay, a dose-dependent decrease in performance accuracy was observed. However, regarding the object recognition tasks, which do not have an emotional component, no THC effects have been identified in adolescent monkeys [75]. In adolescent mice, the chronic administration of THC led to immediate and long-term impairments in the performance of object recognition and working memory tasks; there was also an increase in anxiety of animals. Likewise, chronic administration of WIN-2 to rats of late adolescence led to a memory deficit in the object recognition test; on the contrary, the administration of THC to adult mice caused only an immediate but not long-term deterioration in object recognition and working memory [76]. Thus, these data support the notion that adolescence is a vulnerable period and that long-term exposure to THC during this period can adversely affect the cognitive function and behavior. Interestingly, the co-administration of THC with CBD prevented both cognitive and behavioral disturbances caused by THC in adolescent mice [73].

It was also demonstrated that exposure to THC in adolescent rats (35-45 days) can cause deficits in short-term memory in adult animals tested in the Y-maze [74]. Interestingly, in this study, exposure of juvenile rats to THC induced a malfunction of the kynurenine pathway in the adult brain, specifically increasing the level of kynurenic acid in the medial prefrontal cortex.

In contrast to the results of studies of spatial and nonspatial memory on animals in the pubertal phase, no significant effect of chronic administration of THC was found on adult rodents [77]. Moreover, it was recently found that in adult rats in an object recognition test, acute and chronic administration of THC (at a dose of 1.5 mg/kg, i.p., but not 0.75 and 3.0 mg/kg) improved cognitive performance; at the same time, an increase in the expression of dablcortin (a protein associated with microtubules) and the brain growth factor BDNF, as well as neurogenesis in the hippocampus were observed [78]. This work on adult animals convincingly showed a parallel increase in cognitive functions and markers of plastic processes in the brain under the influence of THC in a specific dose.

Thus, 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.

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. Thus, it was determined in a recent study by Abd El-Rahman and Fayed whether the D-galactose-induced impairment of cognitive behavior in ovariectomized female rats can be restored via CB2R activation [79]. 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 [80]. The authors demonstrated that a low dose of THC reversed the age-

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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 CB1R 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 [67,76,81,82], 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 [83]. Analysis of the results allowed the authors to conclude that the effects of WIN-2 on memory consolidation were mediated predominantly by CB1R activation, with the involvement of CB2R.

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 [84-86]. 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 [87]. 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 [84,85]. 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 [88] 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. By the authors' oppinion, minor cognitive impairments caused by the administration of WIN-2 may be associated with a possible increase (above normal) in the concentration of 2-AG in PFC. For genes associated with AEA metabolism, no correlation was found between molecular and behavioral data [88].

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 [82] 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. In these experiments, the activity of place cells forming the internal "spatial map" was not disturbed; thus, no "remapping" was observed, but the binding of the activity of the place cells to the phase of theta wave was 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 [82]. Thus, according to the authors, cannabinoids do not

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change the representation of space but disrupt the coordination and synchronization of the activity of hippocampal cell ensembles, which encode information and thereby disrupt spatial memory.

Interestingly, the aforementioned study by Marsicano and colleagues [28] demonstrated a new mechanism for astroglial control of synaptic plasticity and memory through the D-serine-dependent modulation of NMDA receptors. The authors found the memory impairment in mutant mice lacking CB1 receptors on astroglial cells (GFAP-CB1-KO), when they had to recognize new objects in the L-maze; a decrease in LTP in the hippocampal CA3-CA1 synapses *in vivo* and *in vitro* was also observed. The activation of CBR by the administration of the WIN-2 agonist increased the intracellular astroglial Ca^{2+} level and the extracellular level of the co-agonist of synaptic NMDA receptors, D-serine, in hippocampal slices. Accordingly, in *in vivo* experiments, GFAP-CB1-KO mice exhibited a lower occupancy of the D-serine binding site. The administration of 5 μM WIN-2 selectively increased the level of D-serine; at the same time, LTP impairment and memory disturbance were completely prevented in GFAP-CB1-KO mice [28]. Thus, the activation of astroglial CB1R controls the activity of NMDA receptors and hippocampal LTP by regulating the synaptic level of D-serine, a signaling amino acid.

As regards the role of CB2 receptor activation in modulating cognitive functions, interesting results were obtained by Manzanares and co-authors [89]. This work clearly showed that memory (as assessed by the hippocampal-dependent passive avoidance test) of CB2R knockout mice was impaired compared to wild-type animals. The selective CB2R agonist JWH133 was shown to improve memory consolidation, while the CBR antagonist AM630 worsened memory responses. Later, Kruk-Slomka and Biala [90] 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 Alarcon and colleagues [88]. 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 [91]. Thus, it can be assumed that CB2R ligands are of particular importance in the formation of long-term hippocampus-dependent memory. 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 et al. [92], where an original learning model, the so-called *mediated learning*, was used [93]. 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 [94,95]. 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 [93,96]. Busquets-Garcia et al. [92] used this model of incidental learning and found that this learning was impaired in CB1R knockout mice (CB1R-KO). 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

 doi:10.20944/preprints202304.0224.v1

different from the conditioned one (with indirect learning) or the same content (with direct learning). The authors have convincingly shown that in CB1R-KO mice the mediated learning was impaired, while direct learning was preserved. This demonstrates that CB1Ps 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. 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 CB1R 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 [92]. 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 [97]. 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. Genetic removal of mitochondrial CB1 receptors in hippocampal neurons prevented cannabinoid-induced impairment in mitochondrial motility, synaptic transmission, and memory formation, which was accompanied by the normalization of mitochondrial respiration and ATP production. 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 [97].

2.2. 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. The inhibition of the two main endocannabinoid hydrolase enzymes, FAAH and MAGL, enhances the level of the endocannabinoids accessible for interaction with their receptors. Most importantly, this manipulation augments no relevant side effects (for details, see reviews [33, 98]).

In the work by Yasar and colleagues [99], 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 CB1R); therefore, the blockade of the FAAH enzyme by URB597, which leads to an increase in the level of AEA, 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 [99]. These results demonstrated novel mechanisms for enhancing learning through PPARα activation: either directly through the injection of a PPARα agonist, or indirectly through the administration of an FAAH inhibitor.

Busquets-Garcia et al. 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) [100]. 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. The authors showed that an increase in the 2-AG level did not affect memory consolidation and mTOR

 doi:10.20944/preprints202304.0224.v1

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) [100]. Besides, the pharmacologically elevated AEA level (above normal concentrations) impairs LTP in hippocampal slices, as well as learning, and memory in behaving mice (spontaneous alternation and spatial recognition memory in the Y maze); 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 [56].

Thus, a diversity in the effects of increased content of the two eCBs was found: 2-AG did not change the memory, and AEA caused its deficiency.

However, Campolongo and co-authors [83] convincingly showed that the consolidation of *aversive* hippocampus-dependent memory is facilitated by increasing the level of AEA by the administration of URB597 through the activation of CB1 and CB2 receptors. A year later, these authors found that memory consolidation in the avoidance task was also facilitated by an increase in the concentration of 2-AG caused by the systemic administration of JZL184 immediately after training. In this case, the memory consolidation was facilitated by the activation of CB2 receptors and the prevention of the mTOR signaling activation in the hippocampus through the CB2R-dependent mechanism [101]. Thus, these two works [83,101] 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 should be also emphasized that conflicting results regarding the effect of URB597-mediated increase in the AEA level on memory consolidation were obtained: no effect [99], deterioration [100], and improvement [83]. Some studies also revealed different effects of the JZL184-mediated increase in the 2-AG content on memory consolidation: no change [100] or facilitation [101]. 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. Thus, it was reported that the facilitation of learning in the task of passive avoidance under the influence of URB597 was mediated mainly by another biologically active lipid, oleoylethanolamide (OEA), which affects PPARα, but not CBR [99]. OEA was shown to play an important role in the regulation of the activity of the basolateral amygdala [102]; besides, the level of AEA in this area was modulated by emotional stimuli [103].

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 CB1R 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.

3. The endocannabinoid system as a target for influence in the models of Alzheimer's disease and temporal lobe epilepsy

3.1. Investigation of the role of the ECS in experimental models of Alzheimer's disease

Alzheimer's disease (AD) is the commonest form of neurodegenerative disease and is characterized by irreversible decline in cognitive functions. The precise etiology of AD remains unclear. There is a tendency to regard Aβ as a trigger for disease progression [104]. At the morphological level, the most characteristic changes in AD are the damage

 doi:10.20944/preprints202304.0224.v1

to/death of neurons, especially in the hippocampus and neocortex, and the rearrangement of neural networks [105,106].

Unfortunately, all the drugs influencing the production, clearance, and aggregation of Aβ which have been tested are clinically ineffective [107]. 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 [80]. 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 [108]. In addition, the administration of AM404 (an inhibitor of endocannabinoid transport) prevents the Aβ-induced degeneration of hippocampal neurons [109]. This suggests that the ECS activation may prevent the development of AD.

Indeed, treatment with cannabinoids, especially CBD, is known to have great potential. As shown by Hampson and Deadwyler [64], CBD exhibits antioxidant and neuroprotective properties that are more potent than those of ascorbate or tocopherol (which also act on NMDA receptors), but without associated toxicity. Subsequently, it was found that CBD inhibited the formation of beta-amyloid plaques, prevented the production of free oxygen and lipid peroxidation in Aβ-stimulated neuronal PC12 cells, and also limited neuronal apoptosis by decreasing caspase 3 and counteracting the increase in intracellular Ca^{2+}. In addition, CBD promoted neurogenesis after treatment with Aβ [110]. Studies using an in vivo model of AD demonstrated that CBD had an anti-inflammatory action due to a reduction in inducible NO synthase (iNOS) and release of interleukin IL-1β and inhibited hyperphosphorylation of tau protein in PC12 cells [111]. The injection of an eCB transport inhibitor (VDM-11) to rodents to increase the eCB content in the brain decreased the toxicity of Aβ given into the neocortex [112]. Besides, THC competitively inhibited acetylcholinesterase, promoting an increase in the acetylcholine level, and prevented an increase in the level and aggregation of Aβ [113].

In rodent models of AD, cannabinoids reduce Aβ accumulation and improve memory [114,115]. Administration of low doses of THC in rats was associated with enhanced neurogenesis in the brain, especially in the hippocampus, and an improvement of cognitive functions; the ultralow doses of THC protected the mice brain from neuroinflammation-induced cognitive damage [116]. Besides, as shown by Naguib and colleagues, 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 [117].

Studies using a model of AD 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 [26]. 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 [118-121].

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 [122]. 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 [115]. 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 [26,111,123].

Recently, a translational model of early-onset familial AD was used to investigate if CBD improves the cognitive function. On 5xFAD transgenic mice (expressing human APP and PSEN1 transgenes with a total of five AD-linked mutations) it was demonstrated that

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CBD treatment ameliorated the symptoms of AD and retarded cognitive decline [124]. 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 3**). Further, immunofluorescence staining demonstrated a reduction in the level of amyloid-β in brain tissues of CBD treated 5xFAD mice.

Interestingly, the inhibition of FAAH by OL-135 accelerated acquisition and extinction rates in a spatial memory task [125]. 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 FAAH and MAGL or dual inhibition of FAAH/MAGL followed by an increase in anandamide and 2-AG promotes a reduction in Aβ-protein deposition in a rodent model of AD. The majority of studies involved URB597, although several classes of reversible and irreversible covalent FAAH inhibitors have been developed, such as URB597, JNJ-40355003, and JNJ-42165279. URB597 promoted an increase in the endocannabinoid anandamide by inhibiting FAAH activity [126,127]. Furthermore, URB597 efficiently suppressed Aβ42-induced glutamate toxicity in primary hippocampal neurons and stimulated the mitochondrial membrane potential [128]. URB597 treatment is associated with the reduction in the level of interleukin (IL)-1β, and restoration of long-term potentiation in aged rats [129]. Hai and colleagues [130] 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 [131]). In the study by Hai and colleagues, spatial learning and memory were assessed using the Morris water maze. The expression of the protein associated with microtubules-2 (MAP-2), synaptophysin, CB1R, brain neurotrophic factor BDNF, and PI3K/AKT was determined by Western blotting. The introduction of WIN-2 and URB597 improved the abilities for learning and memorizing; these effects were reversed by the coadministration of LY294002, a PI3K/AKT inhibitor. Moreover, WIN-2 and URB597 compensated for the decrease in MAP-2 and synaptophysin expression caused by cerebral hypoperfusion and stimulated the expression of BDNF and CB1R [130]. 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 CB2R was shown to counteract the Aβ-induced neurotoxicity [26,112,115,132], mainly via modulating activated microglia. The oral administration of JWH133, a selective CB2R agonist, for four months prevented memory impairment in mice with a model of AD, with normalization of cerebral glucose metabolism measured by PET; furthermore, it counteracted microglial activation [114]. 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 [133]. It was also observed that CBD and THC promoted memory retention and decreased astrogliosis and inflammation in APP/PS1 mice [123].

Recent reviews have demonstrated the potential of cannabinoid drugs in AD therapy and indicated also their limitations [134,135]. More research is needed to avoid the negative consequences of using ECS activation in AD treatment.

3.2. Investigation of the role of the ECS in experimental models of temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is one of the most widespread forms of focal epilepsy, which is characterized by recurrent spontaneous seizures, hippocampal sclerosis, and cognitive deficits [136-138]. The epileptic focus in TLE is localized in medial temporal structures, most often in the hippocampus or amygdala, or in both structures [136,139]. The mechanisms of TLE are not fully understood; in about 70% of cases, the cause of seizures remains unknown. Although many antiepileptic drugs are used in clinical practice, they essentially act on the symptoms rather than the molecular mechanisms of the disease

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and often lead to severe side effects [140]. In this regard, investigations of possible use of cannabinoid drugs for the treatment of epilepsy are of great interest.

In the sclerotic hippocampus in humans with epilepsy and in epileptic mice, an increase in the density of CB1 immunoreactive GABAergic fibers in the molecular layer of the dentate gyrus was detected. This indicates the sprouting of the CB1-expressing axons of inhibitory cells in the hippocampus or an increase in the level of CB1R on them. The enhanced perisomatic inhibitory signaling may increase the synchronization of principal cells and contribute to the generation of epileptic seizures and interictal spikes [141]. On the other hand, it was found that the generation of seizure activity in the hippocampus significantly increases the eCB level [142-145]. In particular, it was shown that the introduction of excitotoxin kainic acid increases the level of AEA in the hippocampus, which is regarded as a neuroprotective response to the toxic effect of the convulsant, leading to a significant decrease in the intensity of seizure activity [142]. Thus, when this pathological activity occurs, the enhancement of eCB signaling can stop seizures; therefore, it is considered as a synaptic "circuit breaker" [146].

The role of the ECS in the control of the excitability of neural networks points to the prospect of using cannabinoids in the treatment of epilepsy [147,148].

In experiments with mice, various components of cannabis were investigated as anticonvulsants, and CBD was recognized as an excellent candidate for drug development due to the absence of adverse psychoactive effects. A special study showed that THC in 100% of cases provided a reduction in the intensity of seizures, while phenobarbital and diphenylhydantoin did not [143]. Facts were obtained that demonstrated the neuroprotective influence of cannabinoid drugs and their anticonvulsant effect in the development of acute seizure activity (143,147, 149-154].

Besides, protective effects of cannabinoid drugs against the development of chronic disorders in models of TLE were also demonstrated [138,155,156]. Moreover, it was shown in a kainic acid model of TLE in mice that the subchronic systemic administration of PEA, an endogenous analogue of AEA, significantly reduces the seizure intensity, has a neuroprotective effect, and also induces eCB modulation in blood plasma and the hippocampus [157].

The blockers of eCB inactivation (AM404 and URB597) significantly weakened status epilepticus, reducing its behavioral manifestations and the duration of seizures [153]. In addition, the use of these modulators led to a weakening of brain pathological manifestations in the chronic kainic acid model of TLE: a decrease or complete elimination of disturbances of electrical activity, damage to and/or death of cells, and the reorganization of hippocampal neural networks [153,158,159]. As mentioned above, the enhancement of eCB signaling can stop the onset of seizures. It was shown that this property is exhibited by CBRs on glutamatergic neurons of the forebrain [142,160,161]. In particular, mice lacking CB1 receptors on glutamatergic forebrain neurons were found to be more susceptible to seizures and neurotoxic effects of kainic acid in the hippocampus [142].

Interestingly, the effect of many FAAH inhibitors on the development of seizure activity was biphasic [162]. Apparently, this is the reason for the discrepancy in the data obtained in different works using drugs that inhibit FAAH activity [163,164].

The central protective mechanism in the development of seizure pathology is a rapid CB1 receptor-dependent hyperpolarization of the membrane, mainly by an increase in potassium and a decrease in calcium conductance [163]. In addition, the activation of immediate early genes (c-fos, c-jun, zif268) and kinases regulated by external signals (ERKs), as well as of neurotrophic factors, plays a significant role in the protective function of CB1R [142,144,166,167].

The development of TLE is known to cause cognitive impairment [136, 137, 168, 169]. Unfortunately, there is little data on the effect of ECS activation on cognitive deficits in temporal lobe epilepsy.

In the study by Sarne and colleagues [170] it was determined whether an extremely low dose of THC could protect mice from severe cognitive impairments induced by the epileptogenic drug pentylenetetrazole (PTZ). THC (0.002 mg/kg, a dose that is three to

 doi:10.20944/preprints202304.0224.v1

four orders of magnitude lower than the doses that induce the conventional effects of THC) was administered to mice 1–7 days before, or 1-3 days after the injection of PTZ. The consequences of this treatment were studied 3–7 weeks later by behavioral tests that evaluated different aspects of memory and learning. The authors found that a single administration of THC either before or after PTZ abolished the PTZ-induced long-lasting cognitive deficits. The results suggest that a pre- or post-conditioning treatment with extremely low doses of THC, several days before or after brain injury, may provide safe and effective long-term neuroprotection [170].

Suleimanova et al. [138] showed that the administration of WIN-2 normalized emotional behavior of animals in an elevated maze, disturbed after status epilepticus and subsequent spontaneous seizures, and reduced the death of neurons in the hippocampus. However, no improvement in open field behavior and spatial memory impaired by seizure activity was found. Another study showed that URB597, an inhibitor of FAAH (an enzyme that breaks down AEA), restored LTP at the synapses of the perforant path to granular cells of the dentate gurus, which was reduced by seizures [171]. These data suggest that increasing the eCB level rather than general CB1R activation may be a potential strategy for the development of a new class of drugs for the treatment of both seizures and concomitant cognitive impairment associated with epilepsy. Interestingly, it was shown that chronic administration of phytocannabinoid CBD reduced the behavioral comorbidities of epilepsy in the hole-board task of spatial memory in rats [172] .

Thus, there is an interrelation between changes in the functioning of the ECS and the development of TLE. It was shown that disorders occurring in the epileptic brain lead to the activation of the ECS, which indicates its adaptive role. Clinical data point out that the use of cannabinoid drugs is a promising approach to the treatment of TLE. Unfortunately, too little datawere accumulated on the ability of eCBs to modulate cognitive functions in seizure pathology; encouraging results in this aspect were obtained in the studies where impaired plastic properties of hippocampal neurons could be recovered by increasing the eCB level in the brain.

4. CONCLUSIONS

The review, which includes the results from cognitive neuroscience, showed the presence of contradictions in the data obtained by different authors. The lack of consensus in this aspect is explained by many factors, ranging from the use of unequal doses of drugs to differences in the individual characteristics of animals. To understand this problem, it is necessary, first of all, to take into account that the main function of endogenous cannabinoids (eCBs) is the maintenance of cellular homeostasis; they are released on demand of the brain in certain sites and in limited time intervals. Therefore, their action may differ from that of exogenous cannabinoids, which non-selectively affect CB receptors and can alter the functioning of the ECS. In addition, many other mediators chemically related to eCBs have other targets in the brain. In this regard, it must be emphasized that cannabinoids and eCBs can affect both CBRs and other receptors (e.g., PPARα), which can lead to different changes in cognition. All these issues have 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 cognitive processes can be opposite, depending on the mechanisms involved in cognitive function (in particular, direct or mediated learning; with or without the participation of emotional components). Thus, these effects should not be considered solely in terms of impairing or improving cognitive functions, but be associated with their mechanisms of action.

Analysis of experimental data obtained in the models of AD and TLE in animals, in most cases indicate a positive role of eCBs in the functioning of the brain, in particular, in its cognitive functions. The main pathological feature of neurons in the AD and TLE brain is hyperexcitability; therefore, activating the ECS, which controls cellular excitation, is a promising approach to the threatment of these diseases.

The therapeutic potential of (endo)cannabinoids is clearly manifested in the development of the neuropathologies, such as AD and TLE; 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 ECS in the cognitive brain functions.

Conflicts of Interest statement: Nothing declared.

Acknowledgments. This work was supported by the Russian Science Foundation, projects No. 20-65-46035. The author is grateful to L.V. Shubina and S.V. Sidorova for help and discussion of the material presented in this review article.

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