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Chapter 2

Endocannabinoid Signaling in Neural Circuits of the Olfactory and Limbic System

Thomas Heinbockel, Ze-Jun Wang,
Edward A. Brown and Paul T. Austin

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63214

Abstract

The endocannabinoid system with cannabinoid receptors, specifically cannabinoid receptor type 1 (CB1R), and their endogenous activators, the endocannabinoids, has emerged as an important neuromodulator system. Our understanding of the endocannabinoid system has significantly advanced in limbic system areas such as the hippocampus and the amygdala. However, the study of this signaling system in the olfactory pathway is still in its infancy. Here, we review the role of endocannabinoids as signaling molecules in activity-dependent regulation of dynamically changing neural networks in the limbic and olfactory system and the relevance of the endocannabinoid system for synaptic plasticity. We highlight the prospects for cannabinoid-based therapies in the treatment of various brain disorders and the role of endocannabinoids as neuroprotective agents. An increased understanding of cannabinoid signaling has the potential to pave the way for developing cannabis-related substances as medications.

Keywords: amygdala, hippocampus, olfactory bulb, neuroprotection, retrograde signaling, neural plasticity

1. Introduction

Over the past decade, the endocannabinoid system with cannabinoid receptors, specifically cannabinoid receptor type 1 (CB1R), and their endogenous activators, the endocannabinoids, has been implicated as an important modulatory system in function and dysfunction of many brain areas. Endocannabinoids are small lipids that regulate normal behaviors, including pain reception [1] and feeding [2, 3]. Likewise, cannabinoids have therapeutic potential [4]. Endo-

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cannabinoids show a neuroprotective role against acute excitotoxicity [5] and facilitate functional recovery after brain injury [6]. They regulate human airway function and provide a means to treat respiratory pathologies [1]. Cannabinoids are widely used as recreational and psychoactive drugs and interact with other drugs of abuse, indicating the need to understand the endocannabinoid system and the neurobiological substrate of its mood-altering capacity [7, 8]. Furthermore, the endocannabinoid system is crucially involved in processes of learning and memory, for example, in the extinction of aversive memories [9]. Endocannabinoids influence synaptic transmission and different forms of short- and long-term plasticity [10–12]. They also influence growth and development such as synapse formation and neurogenesis. Other biological functions and human behaviors modulated by endocannabinoids include eating and anxiety [2, 3, 13].

A hallmark feature of endocannabinoids is their ability to serve as retrograde signaling molecules between activated postsynaptic principal neurons and presynaptic interneurons that express CB1R [10, 12, 14]. While the breadth of endocannabinoid function has become increasingly clear over the past years, we still have much to learn about their detailed signaling mechanisms.

Our understanding of the endocannabinoid system has significantly advanced in limbic system areas such as the hippocampus and the amygdala. However, the study of this signaling system in the olfactory pathway is still in its infancy. Recent work has started to shed light on the role of the endocannabinoid system in the olfactory pathway, specifically in the olfactory bulb as well as for its output to higher order olfactory centers and its centrifugal input [3, 15]. Here, we review the role of endocannabinoids as signaling molecules in activity-dependent regulation of dynamically changing neural networks in the limbic and olfactory system and the relevance of the endocannabinoid system for synaptic plasticity. We highlight the prospects for cannabinoid-based therapies in the treatment of various brain disorders such as epilepsy [16, 17]. An increased understanding of cannabinoid signaling may pave the way for developing cannabis-related substances as antiseizure medications.

2. Endocannabinoids as brain-derived signaling molecules

Endocannabinoids are fatty acid-derived endogenous ligands for $G_{i/o}$-protein-coupled CB1Rs [11]. Endocannabinoids are synthesized from membrane lipids [18]. They can diffuse through cellular membranes and are thus able to activate receptors in the same manner as exogenously applied cannabinoids such as the plant-derived compound Δ^9-tetrahydrocannabinol, THC, the bioactive ingredient of the drugs marijuana and hashish. Marijuana (cannabis) is a commonly abused illicit and recreational drug. The brain produces two endogenous cannabinoids, N-arachidonoylethanolamide (anandamide (AEA)) and 2-arachidonoylglycerol (2-AG). The two endocannabinoids bind to CB1R and have the same functional activity as marijuana. Based on the structural similarity between THC and endocannabinoids, THC is able to activate CB1R and, thereby, hijack this brain communication system. The evolutionary origin of this communication system rests with endogenously produced cannabinoids that bind and activate

CB1R. The discovery of AEA and 2-AG occurred in the 1990s ([19–21], for review see [22]). It took another decade before the function of these two cannabinoids in brain signaling was discovered. It is now well known that endocannabinoids serve as retrograde messengers. Endocannabinoids diminish excitatory and inhibitory transmission. Numerous studies have established their function as retrograde signals in various brain regions: the hippocampus [23–28], cerebellum [29–31], neocortex [32, 33], amygdala [34, 35], and olfactory bulb [15]. Furthermore, in the mediobasal hypothalamus, retrograde endocannabinoid signaling represents a key mechanism under physiological and pathological conditions whereby gonadotropin-releasing hormone (GnRH) neurons control their excitatory GABAergic inputs [36, 37]. Endocannabinoid signaling is terminated by reuptake into neurons and glia. AEA is hydrolyzed enzymatically inside the cell by fatty acid amide hydrolase (FAAH), whereas 2-AG is hydrolyzed by monoacylglycerol lipase (MAGL) [38].

Endocannabinoids serve as important signaling molecules throughout the body including the nervous system [10, 12, 39–44]. Endocannabinoids play important roles in bodily processes during both health and disease [45–48]. Their role in bodily functions has been shown for vertebrates and invertebrates [48]. Pharmacological and physiological experiments in brain slices have described novel aspects of classic brain signaling mechanisms and/or revealed unknown mechanisms of cellular communication involving the endocannabinoid system [41, 49–51]. Endocannabinoids are involved in several forms of cellular signaling [49]. The most distinguishing feature of endocannabinoids is their ability to act as retrograde messengers in neural circuits as first shown in the hippocampus [10, 26, 52].

3. Distribution of cannabinoid receptors in the CNS

Endocannabinoids, together with their G-protein-coupled cannabinoid receptors, form the endocannabinoid system. This system also includes an associated biochemical machinery with endocannabinoid precursors, synthetic and degradative enzymes for these lipidic neurotransmitters, and transporters [10, 12, 14, 40]. Cannabinoid receptors exist in all normal brains and serve many essential brain functions when activated by their natural ligands. Two types of cannabinoid receptors, CB1 (CB1R) and CB2 receptors with 44% amino acid sequence homology, have been described [53, 54]. They are not homogeneously expressed throughout the body; rather, CB1R is the most abundant G-protein-coupled receptor in the brain [55]. In contrast, CB2R is found mainly in immune cells and peripheral tissues [54]. More recent evidence suggests that CB2R is also present in the brainstem, cortex, and cerebellar neurons and microglia [56, 57]. CB1R has a high level of expression in the brain [58, 59], with a particularly strong presence at presynaptic axons terminals [60, 61]. THC, the bioactive ingredient of the drugs marijuana and hashish [62], and other cannabis-derived drugs are potent activators of CB1R. These drugs artificially activate CB1R and act as exogenous cannabinoids. CB1R is found in normal brains and carries out critical brain functions [55, 58, 59] principally through a $G_{i/o}$-protein-coupled mechanism with CB1R.

4. Mechanism of endocannabinoid action: retrograde signaling

Endocannabinoids mediate an unconventional type of neuronal communication, called DSI, **d**epolarization-induced **s**uppression of **i**nhibition (reviewed in [10, 22, 39]). In this communication system, a depolarized postsynaptic principal neuron releases endocannabinoids to regulate neurotransmitter release of presynaptic interneuron. Experimentally, a short rise in intracellular calcium concentration in a principal neuron, for example, a pyramidal cell of the hippocampus, results in a transient decline of incoming inhibitory signals in the form of the neurotransmitter GABA arriving from other neurons. During DSI, endocannabinoids travel from the postsynaptic neuron to the presynaptic GABA-releasing interneuron and turn off neurotransmitter release through activation of potassium channels and blockade of calcium channels. Classical chemical synapses are comprised of a presynaptic, neurotransmitter-releasing neuron and an activated postsynaptic neuron. For example, synaptic GABA release from an inhibitory hippocampal interneuron inhibits glutamatergic pyramidal cells. In contrast, in DSI, the inhibitory input onto an activated pyramidal cell is reduced. In DSI, endocannabinoids are retrograde signaling molecules. They communicate between postsynaptic pyramidal cells and presynaptic inhibitory interneurons resulting in a reduction of GABA release. Chemically, endocannabinoids are lipids. Therefore, their ability to diffuse in the watery extracellular environment of neurons is limited. Subsequently, DSI is a temporary phenomenon to allow individual neurons to pharmacologically break synaptic connections from their neighbors and, thereby, encode information [10]. DSI was mimicked by activating cannabinoid receptors whereas blockade of cannabinoid receptors prevented DSI [24, 26]. A corresponding phenomenon, DSE, **d**epolarization-induced **s**uppression of **e**xcitation, mediated by retrograde action of endocannabinoids, was identified at cerebellar excitatory synapses [28]. DSI and DSE are based on a presynaptic effect as shown by an increase in calcium in the postsynaptic cells and corresponding changes in paired pulse ratio of neurotransmitter release.

5. Endocannabinoids in the olfactory system

The main olfactory bulb offers an ideal platform for investigating how the endocannabinoid system modulates a functional neural network to achieve an integrated outcome. On the one side, the olfactory bulb directly receives sensory input from the nasal epithelium, and on the other side, it receives strong centrifugal cortical input that even outnumbers the cortical projections from the olfactory bulb. This structural organization makes the olfactory bulb preparation significantly different from the hippocampus, amygdala, neocortex, and cerebellum to address functional questions of CB1R modulation in the brain.

As detailed below, new evidence demonstrates that CB1R-mediated retrograde signaling exists among olfactory bulb glomerular neurons such that endocannabinoids released from glomerular neurons function as retrograde messengers to control the excitability of presynaptic neurons and to regulate their transmitter release [15]. Endocannabinoids have a distinct effect on sensory input, that is, they are involved in gain control through regulating presynaptic inhibition. Another new work emphasizes the relevance of cortical feedback to the olfactory bulb as a means to control odor detection and establishes the relationship of food intake and

http://dx.doi.org/10.5772/63214

olfactory processing [3]. The endocannabinoid system is a key player in these signaling pathways.

Odorants in the air that we breathe in activate olfactory receptor cells in the nasal epithelium. Each receptor cell sends an axon to the ipsilateral main olfactory bulb which serves as the first relay station in the central nervous system for processing olfactory sensory information. Cannabinoid receptors are expressed at high levels in the olfactory bulb, specifically in the input region, the glomerular layer [58, 63–65]. Furthermore, neurons in the glomerular layer are immunoreactive for enzymes that synthesize endocannabinoids [66–68]. Electrophysiological evidence has now established that the endocannabinoid system plays a functional role in regulating neuronal activity and signaling in olfactory bulb glomeruli [15].

Three types of neurons are housed in the glomerular layer of the main olfactory bulb, that is, these neurons have their cell bodies in the glomerular layer: periglomerular (PG), external tufted (eTC), and short-axon (SA) cells, reviewed in Ref. [49]. PG cells are neurochemically and functionally heterogeneous [69–71]. They are GABAergic, whereas SA cells express both GABA and dopamine and eTC cells are glutamatergic [71–73]. PG cells receive input from the olfactory nerve or dendrodendritic glutamatergic input from eTC or mitral cells, for example, as spontaneous bursts of excitatory postsynaptic currents (EPSCs) [70, 74, 75]. PG cells presynaptically inhibit olfactory receptor neurons through GABAergic transmission [76, 77]. eTC cells receive spontaneous bursts of inhibitory postsynaptic currents (sIPSCs) from PG cells at inhibitory GABAergic synapses as well as spontaneous glutamatergic EPSCs [77, 78]. Endocannabinoids are likely to be released by activated eTC cells in the glomerular layer.

Membrane properties of PG cells are potently regulated by cannabinoid drugs such as the CB1R antagonist AM251 and the potent CB1R agonist WIN 55,212-2 (WIN) [15, 49]. Cannabinoid receptors directly regulate PG cells since the effects of AM251 and WIN persist in the presence of ionotropic glutamate and $GABA_A$ receptor blockers (synaptic blockers: CNQX, APV, gabazine) [15], indicating that CB1R is expressed in PG cells. AM251 increases action potential firing of PG cells and triggers release of GABA. eTC cells are synaptic targets of PG cells such that CB1R-mediated effects on PG cells are affecting chemical synaptic transmission to eTC cells. CB1R is also expressed in eTC cells and may participate in modulating eTC cell activity.

Cannabinoid drugs such as AM251 or WIN have no effect on membrane properties such as firing frequency or membrane potential in eTC cells [15, 49]. In the presence of synaptic blockers, cannabinoid drugs have a modest effect on eTC cells such that AM251 slightly increases the firing rate of eTC cells without membrane depolarization. WIN slightly decreases firing of eTC cells in synaptic blockers without a clear change in membrane potential. The effects of AM251 and WIN in the presence of synaptic blockers, that is, during pharmacological isolation of eTC cells, indicate that CB1R mediates a direct effect on eTC cells. The direct excitatory effect of AM251 is relatively weak and contrasted by strong GABAergic input from PG cells onto eTC cells, namely, the enhanced GABA release from PG cells. The strong inhibitory effect mediated by AM251 acting on PG cells overshadows the direct AM251-evoked excitation of eTC cells.

Experimental evidence indicates direct and indirect effects of cannabinoid drugs on glomerular neurons [15]. In order to determine if endocannabinoids are involved in retrograde signaling in the glomerular neural circuitry, that is, if DSI is present, eTC cells are activated by a 5 s depolarizing voltage step from a holding potential of −60 mV to 0 mV. In eTC cells DSI is visible as a decrease in the amplitude and frequency of sIPSCs. A single depolarizing step evokes a suppression of sIPSC area by ~40% of control which then gradually recovers. Projection or output neurons in the main olfactory bulb can show regular action potential firing or burst firing. eTC cells exhibit a distinct intrinsic bursting pattern [73]. In order to mimic their spontaneous rhythmic bursting, a train of depolarizing steps can be applied to an eTC cell which allows determining a possible functional role of DSI in olfactory glomeruli. A train of depolarizing steps results in a transient 60% reduction in sIPSC area (20 steps, 0.75 Hz). DSI can be completely eliminated in the presence of AM251, indicating that DSI is mediated by CB1R. eTC cells burst at a range from 0.5 to 6.5 Hz with a mean frequency of 2.7 bursts/s [73]. Depolarizing voltage pulses at 2 Hz (20 steps, pulse duration: 250 ms) evoke DSI as a reduction of sIPSCs in eTC cells, similar to the results obtained with voltage steps at 0.75 Hz to 0 mV. In eTC cells, single depolarizing voltage steps as well as a train of voltage steps evoke suppression of inhibition (DSI). The evidence suggests that spontaneous rhythmic bursting of eTC cells triggers the release of endocannabinoids which function as retrograde messengers to reduce GABA release from PG cells [15, 49]. This, in turn, regulates the activity of PG cell synaptic targets such as eTC cells.

The results indicate that endocannabinoids regulate neuronal activity and signaling in olfactory bulb glomeruli and function in DSI through CB1R-mediated retrograde signaling among glomerular neurons [15, 49]. Endocannabinoids are synthesized and released from neuronal cell bodies as a result of cellular excitation [11]. Endocannabinoids in the olfactory bulb are likely to be synthesized and released from neurons that synapse with presynaptic cells, that is, PG cells, and receive feedback synaptic input from them. eTC cells could be a potential endocannabinoid source in the olfactory bulb which is supported by the fact that DSI is found in eTC cells. The extent of DSI in eTC cells is subject to the level of cellular activation, that is, voltage step duration and step number. DSI cannot be evoked with step durations of 1 s or less, while a step duration closer to 5 s evokes transient DSI. Likewise, increasing the number of number steps to more than three evokes strong DSI and inhibits sIPSCs. When eTC cells are activated and show rhythmic burst firing, endocannabinoids are released which in turn affects glomerular activity. Bursting is an intrinsic property of eTC cells [73, 78] and regulates the release of endocannabinoids from principal olfactory bulb neurons such as eTC cells. Bursting-induced endocannabinoid release may also occur also in other brain systems and represent a general phenomenon of endocannabinoid signaling.

Recently, the endocannabinoid system has been placed in a behavioral context by linking an internal metabolic state (hunger) to sensory perception and subsequent behavior, namely, food intake [3]. CB1 receptor-dependent control of excitatory drive from centrifugal feedback projections to the main olfactory bulb determines the efficiency of olfactory processes and food intake in fasted mice. This study focuses on neural processes deeper in the olfactory bulb, primarily involving those olfactory bulb neurons (GABAergic granule cells) that receive heavy

CNS feedback rather than direct sensory input from the nasal epithelium. Given this structural organization of the main olfactory bulb, the authors integrate three separate neural components: sensory (olfactory) input, central processing in the main olfactory bulb, and behavioral output in terms of feeding in the overall framework of the internal state of the animal (hunger). Cortical feedback to the main olfactory bulb is a means to control odor detection. The relationship of food intake and olfactory processing implicates the endocannabinoid system as a key player in this signaling pathway. Thereby, the endocannabinoid system helps to resolve the old question of how the smell of a cookie makes us want to eat it and which brain mechanism allows us to find food more rapidly and reliably when we are hungry. CB1 receptor-dependent control of olfactory processes has a determinant role in coupling the internal state of hunger with the execution of the behavior such as increased food intake. THC has an effect on both olfactory detection thresholds and habituation, while the latter effect had no correlation to food intake. The authors suggest that enhancement of olfactory detection is likely the main mechanism linking (endo)cannabinoid signaling in the main olfactory bulb to increased food intake. Possibly, by reducing overall granule cell-mediated inhibition of mitral cells, the key output neurons of the main olfactory bulb, mitral cells become more sensitive and that would lower the odor detection threshold. The authors suggest that activation of CB1R on terminals of feedback cortical centrifugal glutamatergic neurons in the main olfactory bulb directly reduces the excitatory drive onto granule cells, thereby regulating mitral cell activity to increase odor detection and food intake [3]. However, other cellular mechanisms might come into play as well. These mechanisms could work in the peripheral input region of the main olfactory bulb rather than in the deeper granule cell layer. Also, glutamatergic input to the main olfactory bulb is not the only centrifugal input. Rather, other areas of the brain also provide feedback cortical projections with cholinergic, dopaminergic, serotonergic, or noradrenergic input [69, 79] and might be subject to CB1R modulation.

6. Cannabinoid receptors and hippocampal neural plasticity

Our understanding of the endocannabinoid system has greatly benefited from studies of limbic system areas such as the hippocampus. Work in hippocampal slices first established the role of endocannabinoids as retrograde signaling molecules [26, 80]. One of the main functions of the hippocampus is to convert short-term memory into long-term memory [81]. A hippocampal formation exists in both hemispheres of the brain and is made up of the hippocampus, the dentate gyrus, and the parahippocampal gyrus. The hippocampus is composed of four regions called *cornu ammonis*, or CA1, CA2, CA3, and CA4. The parahippocampal gyrus contains the entorhinal cortex and the subiculum. The entorhinal cortex is connected to parts of the cerebral cortex; and the thalamus, the hypothalamus, and the brain stem send axons into the entorhinal cortex [82]. The organization of the hippocampal formation lends itself to the flow of information. Information flows along the perforant pathway in the hippocampus. Pyramidal cells, originating in the entorhinal cortex, extend axons into the granule cells of the dentate gyrus with secondary outputs into the CA1 and CA3 regions. They extend from the dentate gyrus into the CA3 region through granule cell axons (mossy fiber pathway). CA3 pyramidal cell

axons extend into the CA1 region and connect to fibers from the contralateral hippocampus. CA1 pyramidal cells project back into the entorhinal cortex and into the subiculum. The afferent fibers then extend from the subiculum and travel to the entorhinal cortex where other output fibers travel in pathways throughout the cerebrum, completing the pathway and flow of information [82].

Olfactory information is processed into long-term memory though the hippocampus. Sensory olfactory and synaptic information that is processed in the main olfactory bulb is sent to the piriform cortex and close to the orbital prefrontal cortex (PFC). The main olfactory bulb and these cortices project into the entorhinal cortex and the perirhinal area which relays the information through the perforant pathway to the hippocampus. Projections from the parahippocampal region extend to the piriform cortex, enabling a reciprocal and interconnected neural linkage [83].

Neural plasticity changes neuronal connectivity in the hippocampus. Through long-term potentiation and long-term depression (LTP), synaptic connections in the hippocampus are strengthened or weakened, respectively. Intracellular calcium release in postsynaptic neuron determines the level of neural plasticity. Receptors for CB1 are found throughout the hippocampus and are central to calcium-induced inhibition. The presence of the CB1R indicates that the hippocampus can be subject to depolarization-induced suppression of inhibition (DSI) which conversely affects the release of GABA from GABAergic neurons [10]. When endocannabinoids, 2-AG, and AEA are released by postsynaptic hippocampal neurons, GABAergic interneurons are inhibited, thus relieving principal neurons such as hippocampal pyramidal cells from inhibition [26]. This affects the information flow along the perforant pathway. The presence of more GABA increases the level of LTP and less GABA increases the amounts of long-term potentiation [26, 81] which affects memory production and learning. Unlike classical neurotransmitters, endocannabinoids can function as retrograde synaptic messengers. After release from postsynaptic neurons, they travel backward across synapses, activate CB1R on presynaptic axons, and suppress neurotransmitter release in order to modulate their inputs. The transient suppression of GABA-mediated transmission that follows depolarization of hippocampal pyramidal neurons is mediated by retrograde signaling through release of endogenous cannabinoids. Mechanistically, activation of CB1R inhibits presynaptic calcium channels through direct G-protein inhibition [27]. These synapses are unusual among brain synapses in that they use N- but not P/Q-type calcium channels for neurotransmitter release. A combination of patch-clamp electrophysiology in cultured hippocampal slices, calcium measurements, and flash photolysis of caged compounds, such as caged AEA, has allowed determining the temporal kinetics of the hippocampal endocannabinoid signaling cascade [15]. AEA and, by extension, other lipid signaling molecules do not simply serve long-term neuromodulatory functions but they are sufficiently fast to exert moment-to-moment control of synaptic transmission indicating that endocannabinoids are highly selective, rapid modulators of hippocampal inhibition.

http://dx.doi.org/10.5772/63214

7. Cannabinoid receptors as regulators of emotional memory

The amygdala is an almond-shaped nuclear structure located within the temporal lobe. It can be subdivided into three major nuclei: the basolateral nuclear complex, the central nucleus, and the medial nucleus. At the neuronal level, the emotional memory and emotional processes involve a brain network with limbic circuits including the amygdala, the medial PFC, and the anterior insula [84–87]. The amygdala is typically activated in response to emotional events, for example, dangerous situations by triggering and processing anger and fear [88]. Fear-conditioning experiments have delineated an amygdala-hippocampal-cortico-striatal circuit as a key brain circuit responsible for processing and storing fear-related memories and for coordinating fear-related behaviors [89, 90].

The basolateral amygdala is a critical component in the learning of conditioned fear responses [91], emotional processing, and encoding of associative memories with an affective component [92–95]. Animals with lesions to the basolateral amygdala complex produce serious deficits in learning new fear responses in a number of different conditioning tasks [96–99].

High levels of CB1R expression in the amygdala are observed in adult, fetal, and neonatal brains [58, 100–103] including GABAergic axonal terminals of the amygdala [104]. Endocannabinoids are known to retrogradely activate presynaptic CB1 receptors and modulate the release of several neurotransmitters (glutamate and GABA) [7, 15, 105]. Endocannabinoids regulate anxiety- and depressive-like behaviors mostly *via* stimulation of CB1R in emotion-related circuits of the PFC, amygdala, hippocampus, and cerebellum [7, 9, 87, 106–108]. Experiments with CB1R knockout mice revealed anxiogenic- and depressive-like phenotypes [109–111]. CB1 receptors play an important role in social interaction and aggressive behavior [107]. CB1 receptors in the amygdala and other brain areas such as the PFC have been shown to be critically involved in emotional learning and memory [112–117] and in fear learning, consolidation, retrieval, and extinction [118]. Using the fear-potentiated startle (FPS) paradigm, fear memory consolidation and retrieval, as well as extinction, were observed to be regulated differentially by amygdaloid and cortical CB1Rs [118]. Amygdala CB1Rs are involved in the development and maintenance of nicotine abstinence-related social anxiety-like behavior following a behaviorally sensitizing nicotine regimen. This suggests that changes in CB1R expression may contribute to perpetuation of nicotine relapse in vulnerable high responders, that is, in a rat model of novelty-seeking phenotype where animals respond with high locomotor reactivity to novelty [119].

It was found that CB1R expression is sensitive to stressful experiences, as animals submitted to a fear-conditioning paradigm presented CB1R upregulation in the PFC [90, 120]. Exposure to shock or stressful environments leads to an increase in endocannabinoids [121] and increased endocannabinoid release [9, 122] in the amygdala. Therefore, CB1R was considered as being a significant modulator for amygdala responses in social emotional negative situations [87].

The neuronal endocannabinoid system modulates synaptic transmission and plasticity *via* its two principal signaling lipids, AEA and 2-AG. It is commonly thought that both endocanna-

binoid-mediated short- and long-term plasticities are mediated through synaptic retrograde mechanisms with presynaptic CB1Rs [11, 68, 122–124]. However, polymodal activation of the endocannabinoid system has recently been found in the extended amygdala [125], that is, AEA and 2-AG are responsible for different forms of synaptic plasticity. Release of 2-AG triggered CB1R-mediated, retrograde, short-lasting inhibition of transmitter release, whereas mGluR5-dependent release of AEA activated postsynaptic TRPV1 receptors (transient receptor potential V1) and resulted in LTP [125]. The production of both endocannabinoids and different signaling pathways allows a single BNST (bed nucleus of the stria terminalis) neuron to take on two different forms of synaptic plasticity *via* the release of either 2-AG or AEA such that the endocannabinoid system acts as a polymodal signal integrator to diversify synaptic plasticity at the level of individual neurons [125].

It has been reported that in the amygdala FAAH, the enzyme that degrades AEA aggravates stress, whereas AEA protects and helps with recovery from stress [126]. Exposure to stress rapidly mobilizes FAAH to deplete the available pool of AEA and increases neuronal excitability in the basolateral amygdala, an anxiety-mediating region [126]. When FAAH is genetically deleted and pharmacologically inhibited, stress-induced reductions in AEA are prevented. Along the same line, long-term fear extinction is facilitated when FAAH is inhibited suggesting that the restoration of AEA levels in the basolateral amygdala by blocking FAAH with drugs might be clinically relevant to treat traumatic stress disorders.

The endocannabinoid system has become a major focus in the search for pharmacological interventions for fear extinction (for review see [91, 127, 128]). CB1R agonists and antagonists generate diverse cognitive effects and change extinction learning. CB1R is implicated in the sensory processing and learning. CB1R is expressed at high levels in the medial PFC, hippocampus, and basolateral amygdala. CB1R affects synaptic transmission and plasticity such as LTP in these brain areas.

Impairment of CB1R signaling affects the neuronal excitatory/inhibitory balance with effects on emotional function and anxiety- or depressive-like behaviors [129–132]. Drug use often starts during adolescence. During this time, the structure and function of the developing brain are particularly receptive to external stimuli such as cannabis. Adolescence is critical in the emergence of mental illness prior to its manifestation in adults but how does adolescent cannabis use affect brain development and function? Indeed, synaptic CB1R expression in adult mouse brain amygdala regions is downregulated by adolescent THC exposure, that is, it affects brain structure and function [133]. A recent study shows broad CB1R/b-arrestin2 co-expression in the medial PFC, amygdala, and hippocampus. This is paralleled by impairment of extracellular signal-regulated kinase signaling and elevation of vesicular glutamate transporter (VGluT1) at CB1R-expressing excitatory terminals in the medial PFC or vesicular GABA transporter (VGAT) at CB1R-expressing inhibitory terminals in the amygdala and hippocampus [132]. These alterations play a key role in the etiology of anxiety-like behaviors when occurring in the PFC, amygdala, and hippocampal circuits [129, 131].

Emotional dysfunction has been considered a hallmark of schizophrenia dating back to early days of research. Emotional disturbances in brain circuits, especially the amygdala, play a key part in symptoms of schizophrenia [134]. Adolescent cannabis use is an environmental risk to

exacerbate cognitive and emotional behavioral abnormalities in individuals with genetic vulnerabilities [133].

Deficiency of CB1R signaling is associated with anxiety and persistence of negative memories [135]. Endocannabinoid-CB1R signaling is reduced with pharmacologic antagonists or genetic deletion [136–138]. Blockade of endocannabinoid-CB1R signaling with CB1R antagonists results in increased anxiety-like behaviors [135, 139] and also results in delayed and ineffective extinction of fearful memories in an animal model [9]. Administration of CB1R antagonist to healthy humans increases anxiety [140]. Indeed, anxiety is a main adverse effect in humans treated with a CB1R antagonist for metabolic disorder and obesity [141]. Patients, particularly those with prior depressive symptoms, exhibit increased depressive symptoms, including suicidality after treatment with CB1R antagonists [142].

Endocannabinoids are strongly linked to stress, fear, and anxiety, which has led to a growing interest in developing novel medication for anxiety and other psychological disorders targeting the endocannabinoid system [126]. Robusting endocannabinoid-CB1R signaling is vital for appropriate stress responses and for the maintenance of emotional homeostasis, particularly in the face of chronic stress. Understanding the underlying mechanisms of endocannabinoids in controlling stress, fear, and anxiety has grown considerably in recent years, with some targets already having been advanced to preliminary clinical trials in patients [126].

8. Endocannabinoids as neuroprotective agents

Studies highlighting the effects of endocannabinoids point to their neuroprotective role in the brain. Endocannabinoid-like compounds such as arachidonoyl serine (AraS), which has a similar structure to the endocannabinoid 2-AG, have been found to reduce lesion size following the induction of traumatic brain injury in mice [143]. Brain diseases have been shown to cause alterations to endocannabinoid synthesis. In Alzheimer's disease, FAAH, the enzyme which terminates endocannabinoid signaling, is epigenetically regulated. Patients with late-onset Alzheimer's disease, LOAD patients, display an increase in FAAH, whereas other components of the endocannabinoid system remain unchanged [144]. Another example of alteration of FAAH resulting in an increase in endocannabinoid system activation has been shown through application of an FAAH inhibitor. Use of the FAAH inhibitor, PF3845, in a mouse model helped to relieve traumatic brain injury-induced impairments including impairments of fine motor movement, hippocampus-dependent working memory, and anxiety-like behaviors. An FAAH inhibitor can result in the promotion of neuronal survival, attenuation of inflammation, and improvement of functional recovery following traumatic brain injury [145]. Traumatic brain injury is the leading cause of death in young people in the USA. Therefore, studies on FAAH potentially have great benefit to society in terms of treating traumatic brain injury.

The endocannabinoid system has also been shown to be neuroprotective during neurological diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, and drug addiction. A role

of endocannabinoids has been shown in Alzheimer's disease when WIN 55,212-2, a CB1R agonist, was tested on the effect of the toxic peptide Aβ1–42 in cultured astrocytes. Peptide Aβ1–42 accumulates during Alzheimer's disease causing cellular damage. Treatment with WIN 55,212-2 resulted in an increase in cellular viability of astrocytes and a decrease in inflammation [146]. An area of current investigation is the role of endocannabinoids as neuroprotectants in motor degeneration diseases. In one study, endocannabinoids played a neuroprotective role in amyotrophic lateral sclerosis [147]. In addition to endogenous cannabinoids assisting in ameliorating the effects of disease such as traumatic brain injury and neuropathic pain, research has also shown that endocannabinoids help to reduce the effects of drugs of abuse on the brain, in particular amphetamine abuse. THC, an exogenous form of cannabinoid, has been shown to reduce the neurotoxicity of methamphetamine by reducing the methamphetamine-induced overexpression of neuronal nitric oxide synthase in the caudate putamen [148].

Endocannabinoids have been shown to play a neuroprotective role in the limbic system. CB1R in both the hippocampus and amygdala is sufficient for synaptic and behavioral functions. In a study using conditional CB1R knockout mice, genetic restoration of wild-type CB1R function, specifically in dorsal telencephalic glutamatergic neurons, fully restored hippocampus-dependent neuroprotection from chemically induced epileptic-like seizures [149]. Dopamine receptor (D3 receptor) null mice have been shown to exhibit changes in levels of endocannabinoid and TRPV1 (transient receptor potential cation channel subfamily V member 1, also known as the capsaicin receptor and the vanilloid receptor 1), but not in CB1R in the hippocampus, nucleus accumbens, amygdala, and striatum. This change is related to less anxious-like behavior when mice underwent the elevated maze plus test. Hence, the endocannabinoid and endovanilloid systems may interact with dopamine receptors in order to produce normal responses to excitotoxic or anxiogenic stimuli [150]. Following exposure to foot shocks and situational reminders which mimic post-traumatic brain disorder in mice, treating mice with WIN 55,212-2, leads to normalization of CB1R upregulation in the PFC and CA1 of the hippocampus. Consequently, cannabinoids aid in emotional processing by preventing the distraction of foot shock followed by situation reminders [90].

The endocannabinoid AEA has been shown to protect HT22 cells exposed to hydrogen peroxide. This occurs *via* inhibition of NADPH oxidase 2 (Nox2). Activation of neuronal Nox2 enhances oxidative damage of the brain, and inhibition of Nox2 can attenuate cerebral oxidative stress [151]. Using a mouse model of oxidative stress by exposing hippocampal HT22 cells (mouse hippocampal neuron cell line HT22) to hydrogen peroxide, researchers tested whether AEA can attenuate the effects of oxidative stress on the brain. Cells exposed to hydrogen peroxide and treated with AEA were shown to experience fewer symptoms of oxidative stress such as morphological changes, decreased lactate dehydrogenase (LDH) release, reduced metabolic activity, increased levels of intracellular reactive oxygen species (ROS) and oxidized glutathione (GSSG), reduced levels of superoxide dismutase (SOD) and neuronal glutathione (GSH), and increased expression of neuronal Nox2, a contributor to oxidative damage to the brain. AEA was shown to prevent the oxidative stress effects unless the CB1R antagonist AM251 is simultaneously administered [151].

Endocannabinoid action is needed for normal activation of focal adhesion kinase (FAK) and extracellular signal-regulated kinase (ERK ½, ERK1/ERK2 subtypes) induced synaptic integrity in the hippocampus. This has been determined by treating hippocampal cells with endocannabinoid antagonist AM281, resulting in FAK and ERK ½ activation being blocked. The blocking of FAK and ERK ½ results in a decrease in synaptic markers. These results support the notion that the endocannabinoid system is the key for the integrity and maintenance of synapses in the hippocampus [152]. Endocannabinoid signaling can be modulated not only through direct activation of CB1 receptors but also through inhibition of endocannabinoid transport and FAAH, two mechanisms of endocannabinoid inactivation. Dual modulation of endocannabinoid transport and the enzyme FAAH results in protection against excitotoxicity. When hippocampal slices are exposed to excitotoxic insult and then treated with endocannabinoid transport blocker AM404 and FAAH blocker AM374, neuroprotection occurs against cytoskeleton damage and a decrease of synaptic decline. Likewise, the blockers protect against behavioral impairment and memory impairment characteristic of excitotoxic insult [153]. In the hippocampus THC has been shown to protect neurons from excitotoxicity. Both WIN 55122, a full CB1R agonist, and THC, a partial CB1R agonist, elicit a neuroprotective effect on rat hippocampal cells when the cells are excitotoxically stimulated to mimic disease-generated excitotoxic neuronal death [154]. CB1R also plays a role in neural progenitor proliferation and neurogenesis induced by excitotoxicity. During excitotoxicity the brain will attempt to repair damage by stimulating neural progenitor cells. When CB1R is inhibited in the hippocampus, both basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), key factors in neural progenitor stimulation, are blocked [155]. Excitotoxicity results in an increase in CB1R-positive and bFGF-positive cells, which proceeds neural progenitor cell proliferation. These results point to the importance of the endocannabinoid system in cellular regeneration from excitotoxic cellular damage in the hippocampus [155]. The endocannabinoid N-arachidonoyldopamine (NADA) has been shown to exert a neuroprotective effect in response to excitotoxic neuronal damage [156]. The neuronal damage occurs *via* CB1R. Excitotoxic lesioning of hippocampal slices by applying N-methyl-D-aspartate (NMDA), and subsequent treatment with NADA, determines whether endocannabinoids can be neuroprotective. NADA treatment protects dentate gyrus cells in organotypic hippocampal slice cultures. At the same time, the number of phagocytic microglia, which are attracted to sites of brain injury, decreases slightly [156].

Additionally, endocannabinoids have been shown to be neuroprotective in other disorders and anatomical systems such as obesity, endocannabinoid deficiency syndrome, and anti-inflammation. The endocannabinoid system has a direct relation with obesity because rimonabant (SR141716, trade names Acomplia, Zimulti), an anorectic anti-obesity drug, is an inverse agonist for CB1R. Rimonabant is a selective CB1 receptor blocker that was originally approved for use but has been withdrawn from the market because of potentially negative side effects. Since rimonabant has been shown to be an anti-obesity drug by inactivating the endocannabinoid system, it can be argued that the endocannabinoid system when activated can assist with weight gain, an issue faced by people experiencing weight-compromising diseases including cancer and people facing food absorption diseases including Crohn's disease [157]. The endocannabinoid system can potentially be used in clinical interventions. A

growing area of research documents the "endocannabinoid deficiency syndrome" which is linked to migraine, fibromyalgia, irritable bowel syndrome, and psychological disorders [158]. Activation of nuclear receptor protein peroxisome proliferator-activated receptor-gamma has been shown to play a key role in the neuroprotective anti-inflammatory role of 2-AG in the brain [159].

Endocannabinoids and their receptors are expressed through the central nervous system and immune system suggesting a critical functional role for endocannabinoids in the operation of these systems. Activation of the endocannabinoid system is directly related to bodily recovery from a disease state such that endocannabinoids play a neuroprotective role in the nervous and immune system. This neuroprotective effect can be seen specifically in response to neurological disorders and injury such as Alzheimer's disease and traumatic brain injury. Likewise, endocannabinoids show neuroprotective effects following spinal cord injury. These data suggest that the endocannabinoid system as a neuroprotective agent has the potential for new therapeutic interventions during diseases of the nervous system and immune system.

Acknowledgements

This work was supported in part by grants from NIH (MD007597) and NSF (IOS-1355034) to TH. PTA was supported through The Advanced Research Training Corps: A Novel Initiative for URM Students, NIH-NIGMS [GM101997].

Author details

Thomas Heinbockel*, Ze-Jun Wang, Edward A. Brown and Paul T. Austin

*Address all correspondence to: theinbockel@howard.edu

Department of Anatomy, Howard University College of Medicine, Washington, DC, USA

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