Review



# Endocannabinoids Modulate Olfactory System Development and Function

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*Review*

# Endocannabinoids Modulate Olfactory System Development and Function

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**Abstract**

The endocannabinoid system is expressed in brain centers involved in a wide variety of functions which makes it an ideal target for disease therapy and prevention. Unlike major excitatory and inhibitory neurotransmitters such as glutamate and GABA, endogenously produced cannabinoids have been shown to play a complimentary role as neuromodulators by acting as gain regulators of neural signals. The endocannabinoid system consists of cannabinoid receptors, CB1R and CB2R, and endogenously generated lipid-based neurotransmitters, 2-AG (2-arachidonoylglycerol) and anandamide, the endocannabinoids. In the central nervous system, these signaling molecules are released from postsynaptic cells in an on-demand manner. This retrograde transmission from post- to presynaptic neurons and the binding of endocannabinoids onto the presynaptic CB1 receptors modulates the magnitude of release of glutamate and GABA, either enhanced or inhibited, depending on the brain area under study. Research has focused on the role of the endocannabinoid system in the limbic system such as the hippocampus and amygdala. Research is increasing regarding the role that endocannabinoids play in other brain centers such as the olfactory system with particular emphasis on the role of the endocannabinoid system in neural networks of the main olfactory bulb. This review aims to bring together research within the overlap of the olfactory system and the endocannabinoid system. By better understanding the unique neuromodulator and neurodevelopmental role of endocannabinoids in the brain, insight into understanding how to mitigate disease states that result from aberrant release of glutamate and GABA such as stroke, epilepsy, and schizophrenia is expected to be gained.

**Keywords:** cannabinoid; endocannabinoid system; olfactory system; olfaction; CB1R; CB2R; retrograde signaling

## 1. Introduction

Brain diseases such as epilepsy, stroke, pain and mental brain disorders such as schizophrenia continue to have a major impact on brain health. In the 1990s, endocannabinoids, the endogenous correlate of the neurochemical compound found in the plant *Cannabis sativa*, were isolated and found to play a neurochemical role throughout the brain and body [1,2]. At this point in history, the public debates whether the drug marijuana (cannabis) should be made legal. Currently, cannabis is considered as a Schedule I drug (https://www.dea.gov/drug-information/drug-scheduling). The Controlled Substances Act (CSA) consists of five Schedules (I-V). Scheduling determines how a drug is classified under the statute. Schedule I drugs are handled in a very restrictive manner and are the most controlled substances. The handling and controls are more relaxed as one moves down the schedules. If cannabis would move from Schedule I to III by the Drug Enforcement Agency (DEA), it would greatly relax the control and restrictions on the drug. Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Marijuana (cannabis), as a Schedule I drug, is considered to have a high potential for abuse and no currently accepted medical use in treatment in the United States. Since Schedule I is the most restrictive category, cannabis is placed in the same category as substances like heroin and lysergic

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acid diethylamide (LSD). The idea that cannabis could be a Schedule III drug is related to the public debate about its classification and potential for medical use. Parts of the public are advocating for cannabis legalization and decriminalization, which could lead to changes in its classification. While cannabis is federally illegal, many states in the United States have legalized or decriminalized it for recreational or medical use. For some people, cannabis shows medicinal benefit while for others it serves recreational purposes. Research has pointed to potential health benefits, especially brain health benefits of the endocannabinoid system and cannabis sativa. In the United States, 24 states, two territories, and the District of Columbia have legalized recreational cannabis while medical cannabis is legal in 40 out of 50 states [3].

## 2. Endocannabinoids

THC, tetrahydrocannabinol, the exogenous cannabinoid isolated from the plant *Cannabis sativa* [2,4,5], was found in the late 1990s to have endogenous correlates in the form of two compounds that have come to be known as endocannabinoids because they are produced endogenously by the human body. The two different endocannabinoids are N-arachidonylethanolamide, (anandamide, AEA), and 2-arachidonoylglycerol (2-AG). Two endocannabinoid receptors have been described, cannabinoid 1 receptor, CB1R [6], which is found primarily in the brain, and cannabinoid 2 receptor, CB2R, found primarily in the immune system. Unlike neurotransmitters manufactured in the cell soma and transported down to the axon terminal and stored there until synaptic release is triggered, endocannabinoids are formed upon demand from the membrane lipid bilayer [7]. A second unique quality of endocannabinoids is that rather than being released from a presynaptic cell onto a postsynaptic cell, endocannabinoids are released from the postsynaptic cell and then bind onto receptors on the presynaptic cell. This function of the cellular signaling system, called retrograde signaling, is to allow the modification of signal input onto the postsynaptic cell by the presynaptic cell [7–10]. Examples of this type of retrograde signaling have been found in several brain regions and termed Depolarization-induced Suppression of Inhibition (DSI). Postsynaptic endocannabinoid release results in inhibition of a presynaptic inhibitory cell. DSI was identified in the hippocampus, cerebellum, and amygdala [7]. A second signaling system is termed Depolarization-induced Suppression of Excitation (DSE), in which postsynaptic endocannabinoid release results in inhibition of an excitatory cell as found in the cerebellum [11,12].

Key functions of the endocannabinoid system have been observed in brain regions that include the hippocampus, amygdala, and cerebellum. Until recently, an open question in cannabinoid research was the relevance of the endocannabinoid system for olfactory processing. This review aims to provide answers to this question: What unique interactions can be found between the cannabinoid and the olfactory system (13-18)? Through a greater understanding of the role of the endocannabinoid system new brain treatments and therapies (19-20) as well as more responsible usage of the exogenous form, *Cannabis sativa* might be achievable.

Endocannabinoids are synthesized by neurons and are degraded by both neurons as well as astrocytes [21]. Exogenous cannabinoids and endocannabinoids bind to the same cannabinoid receptors. From the discovery of endocannabinoids in the 1990's to the present, advances in our understanding of the endocannabinoid system have been made by identifying endocannabinoid physiology. NAE, or N-acylethanolamine, is a class of fatty acid amides that includes endocannabinoids like anandamide (AEA) and 2-AG. NAEs are a group of lipids characterized by a fatty acid linked to ethanolamine. N-acylphosphatidylethanolamine (NAPE) and NAE are lipid molecules involved in various biological processes, including endocannabinoid signaling and potential roles in metabolic regulation and neurodegeneration. NAPE is a phospholipid, while NAE is derived from NAPE and acts as a signaling molecule.

Anandamide, for example, is an endocannabinoid that binds to cannabinoid receptors (CB1 and CB2) similarly to how THC (tetrahydrocannabinol) from cannabis does. Anandamide, along with other NAE's are formed in a two-step process: first, N-acylation of phosphatidylethanolamine generates NAPE via $Ca^{2+}$ dependent N-acetyltransferase and, second, a phosphodiesterase of the

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phospholipase D type (NAPE-PLD) causes the release of NAE from NAPE [22]. DAGL-alpha, the enzyme which synthesizes endocannabinoids, is located in dendritic spines of hippocampal cells and Purkinje cells of the cerebellum [6]. DAGL-alpha (Diacylglycerol lipase-alpha) plays a crucial role in the biosynthesis of 2-AG. Specifically, it hydrolyzes diacylglycerol to produce 2-AG. DAGL-alpha is primarily found in the central nervous system and is involved in various processes, including synaptic plasticity, neurogenesis, and the regulation of axonal growth. The activation of phospholipases results in the generation of endocannabinoids which can cause changes to synaptic activity in a retrograde fashion for tens of seconds, causing short and long-term changes to synaptic transmission [6,12]. Chloride gradients play a key role in whether endocannabinoid-induced synaptic depression results in reduction or enhancement of neural synaptic activity [23]. Other reviews on endocannabinoids have provided detailed information on cannabinoid receptors, the biochemistry of endocannabinoids, endocannabinoid short-term depression and long-term depression, subcellular distribution of endocannabinoids, and physiological roles of endocannbainoids and that information will not be repeated here [6]. A greater understanding of the role that the endocannabinoid system plays in key brain regions such as the olfactory system provides new routes for the treatment for brain disorders including substance addiction [13].

The endocannabinoid hydrolyzing enzyme fatty acid amide hydrolase (FAAH) is a serine hydrolase enzyme that plays a crucial role in the breakdown of endocannabinoids and other fatty acid amides. It catalyzes the hydrolysis of anandamide into arachidonic acid and ethanolamine, effectively inverting its activity. FAAH is also involved in the degradation of other lipid mediators like oleamide and N-acyltaurines. In the hippocampus FAAH has been shown to be present in the somata and dendrite of cells postsynaptic to cells which have CB1R. This helps to clarify the retrograde signaling mechanism of the endocannabinoid course of action [24]. An inhibitor of FAAH has been shown to increase endogenous endocannabinoids such as anandamide. When 5 types of FAAH were studied to determine their effect on a learning and memory task, non-matching to procedure task in rats, one of four FAAH inhibitors, AM3506, resulted in a decrease in accuracy, whereas the other four, URB597, URB694, PF-04457845, and ARN14633, had no effect, pointing to the need for further study of how FAAH inhibitors act and the role a more activated endocannabinoid system on learning and memory tasks [25]. The endocannabinoid system modulates immune system cells including mesenchymal such as fibroblasts which are related to cartilage erosion that occurs during rheumatoid arthritis. The presence of endocannabinoids including anandamide were shown to reduce inflammatory cytokines in human synovial fluid tissue as well as for reducing rheumatoid arthritis-related arthritis in mice [26]. Glucagon-producing alpha cells of the pancreas are activated by endocannabinoid 2-AG which results in the recruitment of insulin-producing beta cells via CB1R activation in mouse fetuses and human pancreatic islet tissue, highlighting that endocannabinoids are involved in pancreatic islet cell proliferation and glucose utilization [27].

## 3. Structural and Functional Organization of the Olfactory Bulb

Olfactory sensory neurons project their axon to the ipsilateral olfactory bulb where the axon terminals can form synapses with several cell types in olfactory glomeruli such as mitral cells, external tufted cells (ET), periglomerular cells and short-axon cells (SA cells) which are long-range connecting cells. Certain SA cells are dopaminergic (DA) and GABAergic. One group of dopaminergic, GABAergic SA cell projects to five to twelve glomeruli, hence they are called "oligoglomerular." Of these, one third receives direct input from the olfactory receptor nerve, ON → SA, whereas the other two thirds receive indirect input from the olfactory receptor nerve, ON → ET → SA. A second set of dopaminergic, GABAergic SA cells send their projections to tens to hundreds of glomeruli in an extensive network, hence these are called "polyglomerular" [28]. Dendrodendritic microcircuits within olfactory bulb glomeruli, specifically those of periglomerular cells, upon releasing GABA, are involved in the inhibition of principal tufted cells, retrograde inhibition of sensory input and lateral signaling onto neighboring principal cells [29]. There are at least two

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functionally distinct GABAergic circuits in the olfactory bulb that contribute to olfactory coding which include both a phasic and tonic pulse [30].

External tufted cells have extensive dendrites which project to one or sometimes two glomeruli. External tufted cells have low threshold calcium dependent firing as well as sodium channel generated firing in response to olfactory nerve stimulation. ET cells exhibit intrinsically generated rhythmic bursts of action potential firing (~1-8 action potentials/sec). ET firing becomes entrained when the olfactory nerve is stimulated [31]. ET cells that innervate the same glomerulus exhibit synchronized firing. This is achieved by coordinated synchronized synaptic transmission and gap junction coupling [32]. Even though ET cells are spontaneously active, their activity is controlled by both excitatory and inhibitory inputs to ET cells [33]. Like mitral cells, ET cells receive monosynaptic input from the olfactory nerve terminals. ET spontaneous burst firing persists even when synaptic transmission is blocked and is controlled by $Na^+$, $Ca^{2+}$, and $K^+$ currents culminating in a burst of action potentials [34]. At least two functionally distinct GABAergic circuits exist in the olfactory bulb, contribute to olfactory coding and include both a phasic and tonic pulse [30].

## 4. The Endocannabinoid System, Olfaction, and Behavior

The endocannabinoid system is expressed throughout the brain with key functions and structures being memory, reward and addiction, motor coordination, pain perception, feeding and appetite, coping with stress, schizophrenia and epilepsy. Due to the broad distribution of the endocannabinoid system throughout the brain, both the therapeutic as well as possible adverse effects and addictive potential of pharmaceutical-based endocannabinoid treatments should be studied [35]. Cannabinoid receptors are highly expressed in the main olfactory bulb and have a direct effect on olfactory bulb synaptic circuitry [16–18].

The appetite-enhancing effect of *Cannabis sativa* has been known from ancient times. Recent studies have confirmed the involvement of the endocannabinoid system in maintaining energy balance through involvement of 1) the limbic system (the hedonic evaluation of foods), 2) hypothalamus and hindbrain (integration systems), 3) intestinal tissue, and 4) adipose tissue reinforcing the interaction between the endocannabinoid system and energy balance. Furthermore, the endocannabinoid system plays a role in oral motor control of suckling in newborns due to the presence of endocannabinoids in maternal milk and activation of the CB1R [36]. The internal state of an organism is an important modulator of perception and behavior. The link between hunger, olfaction and feeding behavior is one of the clearest examples of these connections [14,37]. The endocannabinoid system has been shown to link these three behaviors: 1) hunger (need) with 2) olfaction (sense) and 3) food intake (behavior) [14]. The endocannabinoid system has been shown to be important for the behavior of olfactory foraging and novel exploration tasks, which are both compromised upon dysfunction of the endocannabinoid system [38]. Quantitative autoradiography revealed that the binding of a CB1 receptor ligand was elevated following three weeks of HF (High fat feeding) in areas including the medial/ventral anterior olfactory nucleus, agranular insular cortex, and the hypothalamus compared to LF (low fat) controls [39]. Endocannabinoid activity is beneficial when access to food is scarce or unpredictable. However, when food is plentiful, the endocannabinoid system favors obesity and metabolic disease [40]. The endocannabinoid system, i.e., 2-AG levels, increase in sustentacular cells, the support cells in the olfactory epithelium, when animals are hungry, which points to an involvement of the endocannabinoid system in boosting sensory inputs of food when an animal is in a state of hunger [41]. Agonists of CB1R are thought to increase appetite while inverse agonists decrease appetite. Some aromatic compounds stimulate CB1R and are thought to be a route through which food intake can be controlled more effectively [42].

The endocannabinoid system is involved in supporting the emotional and motivational factors that food stimuli elicit which contributes to psychological factors, hunger, and cravings leading to eating and overeating beyond simply eating to sustain energy needs [43]. Hunger leads to increased sensory perceptions leading to the behavior of food intake. The body's energy needs activate the brain which signals the main olfactory bulb to become activated which results in an increase in odor

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sensitivity via activation of CB1R receptor in the main olfactory bulb [14]. Endocannabinoids are synthesized in olfactory receptor neurons and sustentacular cells of the olfactory epithelium. 2-AG production in sustentacular cells has been shown to depend on the animal's hunger state. The effect of 2-AG on the olfactory receptor neurons is to determine the odor receptor threshold via the CB1R receptor [41]. Data indicates that the endocannabinoid system, and particularly CB1 receptor signaling, appears to be highly significant for the mediation of hedonic aspects of reward processing [44,45]. Advanced cancer patients treated with THC reported better chemosensory perception and that food tasted better, as well as experiencing an increased caloric intake and a better quality of sleep [46]. Eating provides a strong stimulus for food consumption resulting in psychological drive. Obese subjects were found to have a lower olfactory capacity compared to non-obese ones. Furthermore, elevated fasting plasma 2-AG levels correlate with lower olfactory capacity [47]. The link between obesity and body mass was shown such that human subjects with a higher body mass index have a lower olfactory threshold discrimination identification (TDI) and higher levels of fasting plasma 2-AG levels [47].

Endocannabinoid levels have been shown to be altered in the olfactory bulb during mating in rats [48]. Studying the relationship between the olfactory bulb and endocannabinoids has shown to be a potential target for understanding and treating psychological disorders. Drugs that enhance 2-AG signaling, such as 2-AG degradation inhibitors, might be useful in human brain disorders modeled by bilateral olfactory bulbectomy such as depression and schizophrenia [49]. Social interaction impairment (SII) behavior in rats was studied with intra piriform injection of the dopamine receptor family D1R/D5R agonist SKF38393, the D2R/D3R/D4R agonist quinpirole, or both. This was done with or without pretreatment with dopamine receptor antagonists, D1R or D5R antisense oligonucleotides, the cannabinoid CB1 receptor antagonist AM281, or the endocannabinoid transporter inhibitor VDM11. The results indicate that social interaction impairment induced by coactivation of PirC D1R and D2R requires the endocannabinoid system [50]. In another study in rats, THC and the fatty acid amide hydrolysis inhibitor URB-597 were examined in auditory and olfactory go/no-go discrimination tasks. The authors found impairment of cognitive flexibility, specifically reversal learning, by cannabinoids. They observed noteworthy sensitivity of auditory discrimination performance to THC and enhanced endocannabinoid signaling produced by URB-597 [51].

During a study of hedonic eating in healthy volunteers in which volunteers ate beyond satiation, it was found that levels of the endocannabinoid 2-AG along with ghrelin were increased, while interestingly there was a decrease in levels of the endocannabinoid anandamide as well as anandamide-related mediators oleoylethanolamide and palmitoylethanolamide when both pleasurable and non-pleasurable isoenergetic foods were eaten, showing the involvement of the endocannabinoid system in hedonic eating, i.e., eating for pleasure behavior [45]. Because endocannabinoids are an important stress buffer and are important for emotion and cognition function, the endocannabinoid system is being studied for the relationship between malfunction of the endocannabinoid system and psychiatric disorders such as attentional deficits disorder, anorexia nervosa, bulimia nervosa, and post-traumatic stress disorder, specifically through the understanding of polymorphisms of CB1R and FAAH [52].

## 5. The Endocannabinoid System, Olfaction, and Neurodevelopment

The endocannabinoid system plays a role in neurodevelopment of the olfactory system, including the olfactory bulb. Following birth, neural stem cells in the subventricular zone (SVZ) continue to generate neuroblasts that travel through the rostral migratory stream and ultimately differentiate into interneurons within the olfactory bulb. This migration is essential for ensuring that newly produced neurons are incorporated correctly into established neural circuits. Throughout development and into early postnatal life, neural stem cells located in the SVZ give rise to neuroblasts that travel along the rostral migratory stream before reaching the olfactory bulb. Many molecules are known to influence this migratory journey. Recent studies have focussed on their specific roles in guiding cells through the intact rostral migratory stream. Zhou et al conducted an analysis of how

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endocannabinoid signaling, brain-derived neurotrophic factor (BDNF), and fibroblast growth factor receptor (FGFR) affect neuroblast motility and directional control [53]. The authors examined whether their actions differ across distinct regions of the rostral migratory stream. They found that blocking cannabinoid receptors markedly reduced cell motility and disrupted directional movement. Similar deficits occurred when synthesis of endocannabinoids was inhibited with diacylglycerol lipase (DAGL) blockers, indicating that endocannabinoid signaling is essential for guided migration at both the entry and exit points of the rostral migratory stream. Inhibition of BDNF signaling produced comparable impairment in movement and orientation throughout the entire pathway. In contrast, manipulating FGFR activity diminished motility and altered guidance only at the proximal portion of the rostral migratory stream. In vivo FGFR blockade also led to a graded shortening of the leading processes of migrating neuroblasts along the rostral migratory stream. These findings demonstrate that all three signaling systems contribute to neuroblast navigation in the intact rostral migratory stream, with FGFR signaling displaying a distinctive region-specific requirement [53].

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The endocannabinoid system increases newborn neurons in the olfactory bulb of young adult animals, while also stimulating newborn neurons in older animals [54]. More specifically, ependymal and proliferating cells in the adult mouse subventricular zone, the site of neurogenesis, express enzymes that synthesize cannabinoid receptor ligands such as DAGLs. When these enzymes and CB2 receptors are antagonized, proliferation of cultured neural stem cells and progenitor cells in young animals is inhibited. In contrast, proliferation is enhanced when CB2 receptor agonists are applied in vivo, especially in younger animals [54]. The enzyme fatty acid amide hydrolase (FAAH) breaks down cannabinoids such as anandamide. When FAAH is inhibited and breakdown of cannabinoids is prevented, proliferation is increased, and more neuroblasts migrate from the subventricular zone to the olfactory bulb [54]. Application of a CB2 receptor antagonist results in opposite effects with fewer newborn neurons reaching the olfactory bulb, whereas CB2 receptor agonists increase the number of newborn neurons in older animals. These observations are relevant in terms of naturally occurring reduced adult neurogenesis during aging processes [54]. Other results from the same lab confirmed the role of the endocannabinoid system in neurodevelopment [55]. Neural stem cells in the adult brain divide within the subventricular zone and give rise to neuroblasts that normally migrate along the rostral migratory stream to supply the olfactory bulb with newly generated neurons. Because these immature cells can also move toward sites of brain damage, identifying the signals that guide their movement is relevant for potential repair mechanisms. This study [55] focused on the involvement of the endocannabinoid system in the migratory phase of neuroblasts. Neuroblasts in the mouse rostral migratory stream express cannabinoid receptors as well as the enzymes DAGL-$\alpha$, which produces the endocannabinoid 2-AG, and monoacylglycerol lipase, which degrades it. Using a wound-healing assay in a neural stem cell line and explant preparations from the rostral migratory stream, the authors observed that blocking either DAGL activity or CB1/CB2 receptors markedly reduces neuroblast motility. Conversely, stimulating cannabinoid receptors or limiting 2-AG breakdown enhances their migration. Time-lapse imaging of primary neuroblasts shows that the eCB system dynamically regulates nucleokinesis and shapes the length and branching patterns of migratory processes. Comparable effects occur in vivo, where GFP-labeled neuroblasts in brain slices from mice treated with CB1 or CB2 antagonists display altered morphology. Together, these results identify a previously unrecognized function of endocannabinoid signaling in directing neuroblast migration in the adult brain, underscoring its broader significance in the regulation of adult neurogenesis [55].

The endocannabinoid system is also important for the development of olfactory placodes during embryonic and larval stages of *Xenopus laevis* and for olfactory sensory neuron and basal cell development [56,57]. CB1R has been found within the olfactory epithelium of canine embryos [58]. The olfactory epithelium continues to produce new neurons throughout life and the mechanisms that govern this ongoing neurogenesis remain under continued study. Hutch and Hegg investigated how

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cannabinoid signaling influences cell production in the mouse olfactory epithelium [59]. Using both C57BL/6 mice and strains lacking cannabinoid receptors CB1 and CB2, the authors evaluated proliferation and lineage outcomes after administering cannabinoids either directly (WIN 55,212-2 or 2-arachidonylglycerol ether) or indirectly by blocking enzymes responsible for endocannabinoid degradation. In neonatal and adult animals, cannabinoid exposure led to an increase in proliferating cells, whereas this effect was absent in adult mice deficient in both cannabinoid receptors. Furthermore, pretreatment of adult mice with the CB1 antagonist AM251 reduced the proliferative response to cannabinoids. Although cannabinoids stimulated cell division, the number of newly formed neurons or non-neuronal cells was unchanged 16 days later. Cannabinoid treatment instead produced a transient rise in apoptosis at 72 hours, with levels returning to baseline by day 16. Their observations suggest that cannabinoids enhance proliferation without promoting the formation of mature neuronal or non-neuronal cell populations, and that cannabinoid receptor signaling may influence the equilibrium between progenitor cell survival and division within the adult olfactory epithelium [59,60]. A similar pattern occurs in neural stem cells exposed to eicosapentaenoic acid, which elevates 2-AG concentrations and triggers CB1/CB2 receptor activity along with p38 MAPK (Mitogen Activated Protein Kinases) signaling. The p38 MAPK pathway is a signaling cascade that responds to stress, such as UV light, oxidative stress, and inflammatory cytokines, and regulates cellular processes like inflammation, apoptosis, and cell cycle progression. Consistent with this, progenitor cells derived from CB1 knockout mice exhibit reduced self-renewal and proliferative capacity (reviewed in [60,61]).

The migration of neuroblasts from the SVZ to the olfactory bulb is essential for ensuring that newly produced neurons are incorporated correctly into established neural circuits. Numerous extracellular cues that influence neuroblast movement have been identified, while the intracellular pathways that govern this process remain less clear. Work by Sonego et al. [62] demonstrates that the actin-bundling protein fascin is strongly upregulated in migrating neuroblasts derived from the mouse SVZ. Mice lacking fascin-1 show marked abnormalities in the organization of the rostral migratory stream and exhibit reduced olfactory bulb size. Bromodeoxyuridine incorporation studies, to quantify newly born cells in the brain, indicate that fascin deficiency diminishes neuroblast migration without noticeably altering cell proliferation. Loss of fascin also disrupts the polarized morphology characteristic of migrating rat neuroblasts. Their findings identify fascin as a key determinant of neuroblast movement and suggest that a finely tuned cycle of phosphorylation and dephosphorylation, shaped by external cues, is required to maintain neuroblast polarity and support effective neurogenesis [62].

While some progress has been made, the mechanisms that govern neurogenesis after brain development are still being clarified [63]. This process includes the division of neural stem and progenitor populations, their migration to appropriate regions, and their eventual differentiation and incorporation into existing neural circuits. A range of internal signaling pathways and external factors, such as neurotrophins, neurotransmitters, cytokines, and hormones, shape how these cells proliferate and mature. Endocannabinoids and their synthetic analogues have emerged as important regulators of these neural events. Growing evidence shows that activation of CB1 and CB2 receptors influences multiple stages of neonatal and adult neurogenesis. Over the past decade, extensive research has begun mapping the cellular and molecular pathways through which cannabinoids impact neural development. The endocannabinoid system affects the differentiation and maturation of neural progenitor cells through both intrinsic and extrinsic signaling mechanisms targeted by cannabinoids. The cannabinoid system is thereby a key contributor to neurogenesis and offers new insights into neurogenic processes that persist in the mature mammalian brain [60–63].

## 6. The Endocannabinoid System and Olfactory Bulb Physiology

The link between hormone distribution and olfactory perception is providing insight into how to combat metabolic diseases that are a result of a lack of homeostasis. DAGL-alpha, the main biosynthesizing enzyme of endocannabinoids, exists in the olfactory bulb as well as other forebrain

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structures [54,64]. Immunochemistry of the rat brain shows that large principal cells, such as mitral cells in the olfactory bulb show some of the strongest expression of FAAH, the enzyme that catalyzes endocannabinoids present in the rat brain [65,66]. The presence of N-acyltransferase, an enzyme involved in the biosynthesis of N-arachidonoyl phosphatidylethanolamines (NArPEs or N-arachidonoyl PE) which is a precursor for anandamide, is present in the rat olfactory bulb [67]. NArPEs are a group of glycerophospholipids that serve as the biological precursors to anandamide. Acute stress is able to increase endocannabinoid system activity in the olfactory bulb, resulting in inhibiting GABA release in the olfactory bulb [68]. An N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) that catalyzes formation of NAEs was shown to be highly present in the axons of the vomeronasal nerve which projects to the accessory olfactory bulb suggesting that NAEs, such as the endocannabinoid anandamide, act as an anterograde synaptic signaling molecule [24].

Cannabis extract reduces epileptiform type bursting in the rat olfactory cortex [69,70]. Cannabis extract and Delta9-THC act via CB1 receptors and inhibit muscarinic agonist-induced epileptiform bursting in rat olfactory cortical brain slices. The natural compounds, sesamol and curcumin, both similar to amitriptyline, a medication used in the treatment of depression and anxiety, increase both neurotrophins and endocannabinoid concentration in the brain [71].

## 7. Endocannabinoid Receptor and Vanilloid Receptor

The vanilloid receptor (TRPV1 or VR1) is a molecular integrator of various painful stimuli, including capsaicin, acid, and high temperature, and can be activated by the CB1R agonist anandamide. TRPV1 has been found to be present in the olfactory bulb [72]. The vanilloid receptor, which upon binding to its ligand capsaicin, is used to relieve neuropathic pain, uremic pruritus, and bladder overactivity, but has also been shown to bind to sensory neurons since vanilloid receptors are found in the olfactory bulb [73,74]. All major cell types involved in cerebrovascular control pathway - endothelium, smooth muscle, neurons, pericytes, microglia - have been shown to produce endocannabinoid-related proteins, including CB1 and CB2 receptors as well as transient vanilloid type 2 receptors. The endocannabinoids have been shown to play a role in the cerebrovascular system, specifically causing vasodilation via the relaxation of smooth muscle, and the release of vasodilation mediators from endothelium. Also, the endocannabinoid system has been shown, during brain pathologies such as subarachnoid hemorrhage, trauma and ischemic brain injury, to activate CB2 receptors resulting in greater blood perfusion. However, during stress conditions (restrained conscious animals experiencing hypoxia or hypercapnia) the result was a decrease in cerebral blood flow [75].

Compounds which bind to the vanilloid receptor TRPV-1, a relative of the cannabinoid receptor, such as capsaicin, have been studied for the protective role that TRPV-1 activation plays in oxidative stress on keratinocytes and human blastoma cells in vivo, as well as protective role it plays in cytotoxicity and analgesia [76]. FAAH/TRPV1 and FAAH/COX-2 inhibitors interact with both endocannabinoid and endovanillanoid systems. Both systems are regulated by lipid mediators, i.e., prostaglandins produced by COX enzyme, pointing to the interconnectedness of both systems [77]. Anandamide has been shown to inhibit squamous cell proliferation. PUFA, poly-unsaturated based enthanolamines like the endocannabinoid anandamide, D-docosahexaenoyl enthanolamides (DHEA), and N-arachidonoyl-L-alanine (NALA) have both been shown to inhibit head and neck squamous cell carcinoma line proliferation (HNSCC). However, their action was thought to work in an endocannabinoid system dependent fashion. When both endocannabinoid receptors, CB1R and VR1, were inhibited, this inhibition of cellular growth did not persist [78]. The endocannabinoid receptor TRPV1 has been reviewed as a potential anti-nausea and anti-vomiting treatment target because it has been implicated in the pathways of nausea and vomiting along with other diverse transmitter systems including acetylcholine, dopamine, endorphins, glutamate, histamine, 5-hydroxytryptamine, and substance P [79]. Based on the experience of altered senses in people with advanced cancer and the impact on their quality of life including impaired ability to perceive and

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appreciate sensations, it has been suggested that additional research should be carried out to identify how senses are perceived in order to determine how to overcome the chemosensory altered experiences of cancer patients. Alterations can include persistent bad tastes, phantom smells, hypersensitivity to odors and food flavors. For the purpose of overcoming these chemosensory alterations, more studies of sensory science should be done. The presence of cannabinoid receptors in the olfactory bulb could prove to be helpful in bridging our understanding of the endocannabinoid involvement in chemosensory processing [46].

## 8. Conclusions

The endocannabinoid system is expressed in many brain centers and has been shown to functionally regulate various bodily functions which makes it an ideal target for disease therapy and prevention. In the olfactory system, endocannabinoids modulate functions at all levels of the system such as periphery and central olfactory stations as well as during different developmental stages. Endocannabinoids are released from postsynaptic cells in an on-demand manner. This retrograde signaling from post- to presynaptic neurons and the binding of endocannabinoids onto the presynaptic CB1 receptors modulates the presynaptic release of glutamate and GABA, either enhanced or inhibited, depending on the brain area under study. Research is increasing regarding the role that endocannabinoids play in the olfactory system with particular emphasis on the role of the endocannabinoid system in neural networks of the main olfactory bulb. This review brings together research of the olfactory system and the endocannabinoid system. By better understanding the role of endocannabinoids in the brain, new forms of treatment and clinical insights might help to mitigate disease states that result from aberrant release of glutamate and GABA such as stroke, epilepsy, and schizophrenia.

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