The Changing Brain: The Interactive Role of Brain-Derived Neurotrophic Factor, Cannabinoids, and the Endocannabinoid System in Neurogenic and Neuroplastic Processes of the Brain

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Abstract

The brain remains the most complex organ within the mammalian body with an immense capacity for plasticity and change throughout an individual's life history. This review examines brain-derived neurotrophic factor (BDNF) and endocannabinoid (eCB) signalling cross-talk within a variety of neurodevelopmental, genic, and plastic processes that occur in the brain. The action of eCB and BDNF cross-talk in embryonic and adult neurogenesis is a bidirectional dynamic process of high complexity that facilitates neural proliferation, differentiation, spatial development, synaptic development, and programmed cell death events. The coupled action of BDNF eCB signalling serves as a functional regulator of neuroplasticity, modulating synaptic signalling strength within both inhibitory and excitatory neurons. This also regulates long-term potentiation and long-term depression processes, which play important roles in the neurobiology of learning and memory. Understanding BDNF and eCB signalling has the potential to offer new insights into brain function and develop novel therapeutic treatment for psychiatric disorders, neurodegenerative disorders, and brain injury recovery.

Keywords: brain-derived neurotrophic factor, endocannabinoids, neuroplasticity, embryonic neurogenesis, adult neurogenesis, cannabinoids

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Until the late 20th century, it was thought that the brain remained morphologically static in adulthood (Doidge, 2007). However, advances in research technology have shown that the brain has an immense capacity for plasticity and change throughout an individual's lifespan. Specifically, within processes of neurogenesis, the generation and proliferation of new neurons from precursor cells, and neuroplasticity, changes in strength and morphology of synaptic connections. Understanding the mechanisms and modulators of these dynamic systems can offer immense insight into an array of neuropsychological and biological phenomena. Two neuromodulatory systems that play an important role in a number of neurodevelopmental, genic, and plastic processes are brain-derived neurotrophic factor (BDNF) signalling and the endocannabinoid system, which encompasses both endogenous and exogenous cannabinoid signalling. These systems will remain the focus of this review.

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a member of the neurotrophin family of molecules and is present in nearly all regions of the mammalian brain (Kowianski et al., 2018). Its function is region-specific, and it is known to play important roles in neural development, regulation of neuro-, glio-, and synaptogenesis, neuroprotection, and synaptic interactions involved in learning and cognition (Kowianksi et al., 2018). BDNF protein is synthesized in the endoplasmic reticulum in a precursor form, pre-pro-BDNF, whereupon it is translocated to the Golgi apparatus for the formation of pro-BDNF (Foltran & Diaz 2016; Lu, 2003). The pro-BDNF is further cleaved, eventually reaching the mature isoform, m-BDNF (Foltran & Diaz 2016; Mizui, Ishikawa, Kumanogoh, & Kojima, 2016). It is in this mature form, m-BDNF, that the bulk of research has focused on; however, it should be noted that the action of pro-BDNF and m-BDNF binding elicit opposing functions within neuronal systems (Guo, Nagappan, & Lu, 2018). BDNF binds with high affinity to tropomyosin receptor kinase B (TrkB), which leads to the activation of downstream mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), and phospholipase C-γ (PLCγ) pathways (Guo et al., 2018). The downstream physiological effect of BDNF/Trk B activation depends on pathway activation and can include: modulation and enhancement of synaptic plasticity, enhanced dendritic growth and branching, upregulation of diacylglycerol (DAG) synthesis, and increased growth of neuronal fibers (Figure 1) (Kowianski et al., 2018). BDNF also binds to pan-neurotrophin receptor $p75^{NTR}$ with lower affinity (Guo et al., 2018). Additionally, BDNF appears to act in both anterograde and retrograde fashion (Sasi Vignoli, Canossa, & Blum, 2017). The action of BDNF signalling is varied, which leads us to wonder how such differential effects can result from a single molecule, often on the same cell type. One explanation is that differential effects depend on whether activation is transient or sustained. Sustained TrkB activation promotes neuronal dendritic arborization and increased generation of dendritic spines, whereas transient activation facilitates dendritic growth and changes in spine morphology (Guo et al., 2018).

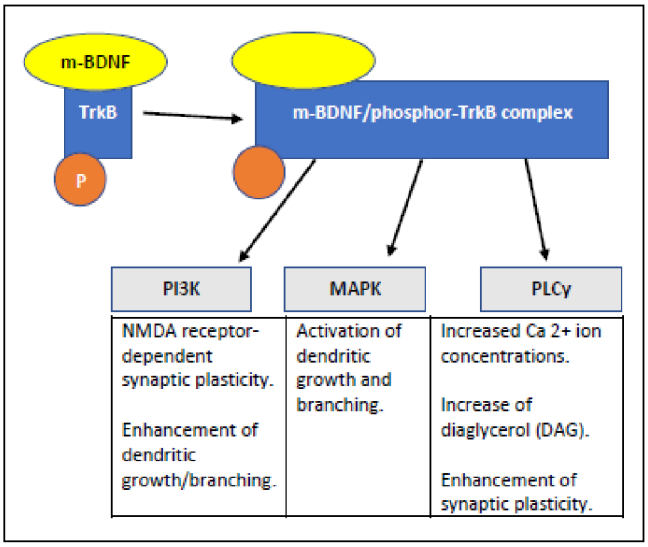


Figure 1: A representation of BDNF/TrkB signalling pathways and the downstream cascade effects.

The Endocannabinoid System

The prevalence and importance of the endocannabinoid (eCB) system in neurophysiology was inadvertently discovered through attempts to elucidate the physiological and pharmacological action of *delta*9-tetrahydrocannabinol (THC), the main active compound of marihuana (Mechoulam & Parker, 2013). It is now known that the mammalian body produces numerous endogenous cannabinoids, the two most abundant being 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide; or AEA), both of which bind to G-protein coupled CB1 and CB2 cannabinoid receptors prevalent throughout the central nervous system (CNS) and numerous peripheral organs (Mechoulam & Parker, 2013; Prenderville, Kelly, & Downer, 2015). The localization of cannabinoid receptors throughout the brain encompasses various midbrain, hindbrain, and forebrain areas, suggesting its involvement in a vast range of neurocognitive and physiological processes (Glass, Dragunow, & Faull, 1997). Endocannabinoids primarily act as fast retrograde messengers, travelling from the postsynaptic cell to activate presynaptic cannabinoid receptors, which leads to the inhibition of neurotransmitter release from presynaptic vesicles (Basavarajappa, 2007; Gerdeman, 2008;

Mechoulam & Parker, 2013). Unlike other neurotransmitters, eCBs are not stored in vesicles but are activity-dependent and synthesized when needed (Basavarajappa, 2007; Mechoulam & Parker, 2013). Given the widespread nature of eCB receptors and the unique nature of eCB activity, their candidacy as functional modulators for an array of neural processes becomes apparent. CB1 and CB2 receptor activation plays a modulatory role in adult neurogenesis in the hippocampus and lateral ventricles, whereby endocannabinoid signalling is intricately associated with neuronal differentiation, survival, maturation, and migration (Prenderville et al., 2015). The eCB system is also involved in neuroplastic processes in the prefrontal cortex (PFC), serving as a mediator of synaptic transmission (Worley, Hill, & Christianson, 2018).

TrkB and CB1 receptors are colocalized throughout the neocortex, and BDNF/eCB cross-talk has been investigated in the hippocampus, neocortex, and cerebellum (Lemtiri-Chlieh & Levine, 2010; Ferreira et al., 2018; Maison et al., 2009). Given the localized abundance and common involvement of BDNF and eCBs in neural functioning, understanding the nature and existence of cross-talk between these two systems seems a relevant and fruitful endeavour. In this review, the current literature on the mechanisms of interaction between BDNF and the eCB system will be presented and discussed. The focus will mainly remain on neurogenesis and neuroplasticity as they represent important processes underlying a number of homeostatic and novel functions within brain development, memory, learning, cognition, and neuroprotection as well as within the etiology of various psychiatric disorders.

BDNF and eCB Signalling, Biosynthesis, and Receptor Expression Regulation

In order to understand their role in wider neurophysiological processes, it is first important to understand how BDNF and eCBs interact at a neurobiological level, specifically in cell signalling, neurotransmitter synthesis, and other synaptic processes.

The BDNF/TrkB PLCγ signal cascade is initiated through the phosphorylation of a tyrosine at the carboxy-terminal end of TrkB (Sasi et al., 2017). The PLCγ cascade leads to the upregulation of DAG, a precursor molecule of 2-AG (Kowianski et al., 2018). Functionally, this is accomplished through PLCγ-mediated hydrolysis of membrane phospholipids which produces DAG, which is in turn subsequently converted to 2-AG by diacylglycerol lipase activity (Basavarajappa, 2007). BDNF/TrkB binding also leads to an influx of Ca^{2+} ion concentration via CAM kinase and protein kinase C activation and PLCγ initiation, where the increase of intracellular Ca^{2+} ion concentration subsequently stimulates the biosynthesis of AEA and 2-AG (Basavarajappa, 2007; Kowianski et al., 2018; Sasi et al., 2017). Intracellular Ca^{2+}, as regulated by activity-dependent processes, also plays a role in controlling the expression and secretion of BDNF (Sasi et al., 2017). The outcome of BDNF upregulation of eCBs has been observed experimentally within the mammalian forebrain *in vitro*. In pyramidal cells in layers two/three of the somatosensory cortex, BDNF/TrkB signalling induces postsynaptic eCB release via downstream PLCγ signalling (Yeh, Selvam, & Levine, 2017; Lemtiri-Chlieh & Levine, 2010). Similarly, BDNF/TrkB signalling induces postsynaptic 2-AG release within hippocampal cells (Selvam, Yeh, & Levine, 2019). Both of the aforementioned processes were observed at inhibitory synapses.

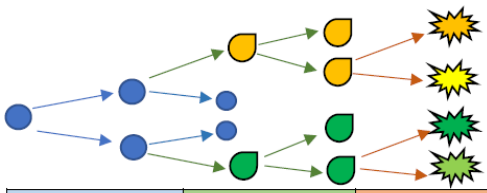
In addition to biosynthesis, the action of BDNF/TrkB binding also affects neuronal sensitivity to endocannabinoid signalling. *In vitro*, the application of exogenous BDNF to a culture of cerebellar granule neurons increases the expression of CB1 receptor transcripts and downregulates monoacylglycerol lipase (MAGL) expression, a protein that functions in the degradation of 2-AG (Maison et al., 2009). This rapid BDNF upregulation of CB1 and simultaneous downregulation of MAGL occurs within a matter of hours and heightens neuronal eCB sensitivity. Similarly, eCB action affects TrkB receptor levels in the PFC. The administration of AEA increases phosphorylated TrkB levels in cultured cortical cells at both pre- and postsynaptic sites (Diniz et al., 2019). This is accomplished through AEA/CB1 binding, as the upregulation of TrkB is dependent on AEA/TRPV1 binding activity, indicating a dual mechanism interaction.

BDNF and eCB activity both play a regulatory role in each other's function, whereby the receptor binding action of one has downstream consequences for the other molecule. This cyclical and modulatory relationship remains a common theme throughout the various neurophysiological processes in which they share roles.

The Role of BDNF and the eCB system in Embryonic and Developmental Neurogenesis

The neural development of the CNS primarily occurs in the neural tube, of which the anterior portion forms the fore-, mid-, and hindbrain (Price, Jarman, Mason, & Kind, 2017). Neurogenesis is the process by which functional neurons are produced and can be generally broken up into the following 6 stages: embryonic stem cell proliferation, neural progenitor proliferation, neural precursor differentiation and maturation, migration, and integration (Figure 2) (Price et al., 2017).

The action of BDNF and eCB signalling can be seen at the outset of neurogenesis. Within embryonic stem cells, eCB production is increased via intracellular Ca^{2+}, and BDNF



Stem Cell Proliferation	Neural Progenitor Cell Proliferation	Neural Precursor Cell Differentiation and Maturation	Migration	Integration
Greater CB2 abundance within stem cells. Increased eCB production and increased BDNF activity promotes embryonic stem cell differentiation into neural progenitor cells. CB1 activation plays a role in the proliferation, expansion, and survival of the NSC pool.	Greater CB2 abundance within progenitor cells. CB1 receptor expression and activation controls proliferation of pyramidal cell progenitors.	Greater CB1 abundance during neuronal lineage specification.	CB1 expression and activation controls migration of immature pyramidal cells within the embryonic cortex. CB1 activation governs migration of interneurons during corticogenesis.	CB1 activation: • involved in cortical layer organization; • regulates axonal growth and shape of dendritic arborization; • governs integration of interneurons during corticogenesis.

Figure 2: This table depicts the general stages of developmental neurogenesis at the cellular level. The relevant processes and neuromodulators are presented at each stage. Note the differentiation between CB1 and CB2 receptors

activity promotes embryonic stem cell differentiation into neural progenitor cells (NPCs) (de Oliveira et al., 2019; Descamps et al., 2018). Likewise, CB1 receptor activation appears to play an important role in neural stem cell (NSC) proliferation and the expansion and survival of the NSC pool (Aguado et al., 2006; de Oliveira et al., 2019; Keimpema et al., 2013a). Throughout neurodevelopment, the role of CB1 and CB2 receptor activation varies and eCB signalling plays various roles. The receptor abundance of CB2 is greater in stem and progenitor cells, whereas CB1 is predominant during neuronal lineage specification (de Oliveira et al., 2019). As the stages of neurogenesis progress, spatial regulation, along with temporal regulation, begins to guide the development of progenitor subtypes. CB1 receptor activation is involved in the organization of cortical layers and mice lacking CB1 expression experienced abnormal cortical layer V development resulting in disorganization and severe motor deficits (de Oliveira et al., 2019; Diaz-Alonso et al., 2015). Likewise, eCB signalling controls the proliferation of pyramidal cell progenitors and the migration of immature pyramidal cells within the embryonic cortex through CB1 receptor expression and activation (de Oliveira et al., 2019; Mulder et al., 2008). eCB signalling thus acts as a key modulator maintaining a necessary balance between progenitor and precursor cells during neural proliferation and spatial development.

Axonal growth and guidance are necessary for the production of new neural networks and the integration of recently mature cells into already existing neural networks. CB1 activation by endogenous and exogenous cannabinoids regulates axonal growth and the shape of dendritic arborization (Berghuis et al., 2005; de Oliveira et al., 2019; Roland et al., 2014). Additionally, the ablation of CB1 receptors in the embryonic cortex can inhibit neurite outgrowth (Keimpema et al., 2013b). Moreover, excessive 2-AG signalling is associated with abnormal axonal growth (Alpar et al., 2014). CB1 receptor activation also governs migration and integration of interneurons during corticogenesis, which is done through TrkB dependent signalling pathways that regulate neuronal-subtype migration and specification (Berghuis et al., 2005). BDNF/TrkB signalling also enhances dendritic growth and branching and regulates the synaptic connectivity between neural cells (Kowianski et al., 2018).

Adult Neurogenic Processes by Region	**BDNF Dependent Neuronal Differentiation**	**BDNF Dependent NSC and NPC Proliferation**	**WIN55, 212-2 Facilitated Neuronal Differentiation**	**WIN55, 212-2 Facilitated Cell Proliferation**
Hippocampal Dentate Gyrus (DG)	CB2 activation	CB2 activation	CB1 and CB2 co-activation	CB1 and CB2 co-activation
Subventricular Zone (SVZ) of the Lateral Ventricles	CB1 and CB2 co-activation	CB2 activation	CB1 and CB2 co-activation	CB1 activation

Table 1: The above table organises the differing roles of CB1 and CB2 receptor activation during adult neurogenic processes in the hippocampus and lateral ventricles. BDNF dependent processes are distinguished from cannabinoid agonist (WIN55, 212-2) facilitated processes.

During the development of a neural system, NPCs are commonly overproduced, leading to an excess of metabolically costly cells that need to be stripped away as they are no longer required (Price et al., 2017). Cells such as pioneer neurons must also be disposed of since they were once useful at a previous developmental stage but are no longer functionally necessary. Thus, apoptosis plays an important role in the latter stages of neurogenesis. BDNF signalling regulates the survival and programmed death of neural precursor cells, whereby TrkB binding signals a survival cascade (via P13K/Akt pathway), and the differential binding of $p75^{NTR}$ signals either a survival or cell death cascade (Altar et al., 1997; Caleo et al., 2000; Coulson et al., 2004; Kowianski et al., 2018).

In addition to mammalian animal models, studies of fish animal models have found BDNF mRNA expression widely abundant throughout the brains of 7-day old zebrafish larvae (Cacialli et al., 2016). The application of exogenous cannabinoids, namely THC and cannabidiol (CBD), to developing zebrafish interrupted regular neurogenesis during key developmental stages accompanied by affected production of BDNF (Carty et al., 2019). Taken together, this suggests a universal role for BDNF and eCB signalling in the development of neural networks throughout the animal kingdom that was established early on in our phylogenetic history.

The Role of BDNF and the eCB system in Adult Neurogenesis

Adult neurogenesis appears to be mainly restricted to the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) (Urban & Guillemot, 2014). Adult neurogenesis is similar to that of embryonic neurogenesis and can be loosely broken down into four stages: NSC and NPC proliferation, migration, neuronal differentiation, and integration within existing functional synaptic networks (Prenderville et al., 2015).

CB1 receptor expression appears to be necessary for effective adult neurogenesis (Jin et al., 2004). In the hippocampus, the use of CB1 and CB2 agonists stimulates proliferation of neural precursor cells via PI3K/Akt pathways (Prenderville et al., 2015). Similar agonists have also been shown to promote neuronal differentiation in hippocampal cell lines (Penderville et al., 2015). 2-AG and AEA also play functional roles, whereby increased concentrations are associated with increases in cell proliferation in the SVZ and DG, respectively (Aguado et al., 2005; Goncalves et al., 2008). Similar to embryonic neurogenesis, eCB signalling plays a regulatory role in neural lineage specification (Harkany, Keipmema, Barabas, & Mulder, 2008). CB1 receptors within hippocampal NSCs are functionally necessary for controlling and regulating the proliferation of the stem cell pool and neuronal differentiation, specifically during dendritic maturation (Zimmerman et al., 2018). Much like embryonic neurogenesis, selective programmed cell death and survival is functionally important to adult neurogenesis. CB1 receptor activation promotes striatal neuron survival by inducing a downstream cascade via the PI3K/Akt pathway (Blazquez et al., 2015). Exogenous application of THC has also been shown to enhance hippocampal markers of neurogenesis, including the upregulation of BDNF expression (Suliman, Taib, Moklas, & Basir, 2018).

Within the DG and SVZ differential CB1 and CB2 receptor activation has differing modulation of neurogenic processes (Table 1). Rodrigues et al. (2017) found the cannabinoid receptor agonist WIN55, 212-2 promoted cell proliferation in the DG, which required CB1 and CB2 co-activation. Additionally, they found that WIN55, 212-2 facilitated neuronal differentiation in the SVZ and DG also required CB1 and CB2 co-activation. Likewise, BDNF and eCB cross-talk mediation of various neurogenic processes depends on the differential activation of CB1 and CB2

receptors (Ferreira et al., 2018). BDNF promotes SVZ and DG NSC and NPC proliferation, an effect that requires CB2 receptor availability. Whereas the CB1 activation-increase in SVZ and DG cell proliferation is dependent upon BDNF availability and action. Facilitation of neuronal differentiation in both the SVZ and DG by CB1 and CB2 activation is dependent upon endogenous BDNF availability. However, BDNF-promoted neuronal differentiation in the SVZ requires CB1 and CB2 co-activation, whereas only CB2 activation is required in the DG. Thus, Ferreira et al. (2018) effectively show that eCB/BDNF mediation of SVZ and DG neurogenesis requires bidirectional signal interactions.

CREB activity is one proposed link in the cross-talk between BDNF and eCBs, whereby CB1 activation is known to induce MAPK-CREB phosphorylation, which in turn facilitates BDNF gene expression (Mallipeddi, Janero, Zvonok, & Makriyannis, 2017; Zhang et al., 2016). This finding was supported by Lujan, Castro-Zavala, Alegre-Zurano, and Valverde (2018) who found that CBD-induced neurogenesis was associated with significant increases in MAPK-CREB phosphorylation and enhanced BDNF expression.

Neuroplasticity and Learning

Neuroplasticity describes the way in which neural networks change and incorporate new information, whereby morphological changes at the synapse, receptor density, and neurotransmitter abundance are functional aspects of this process. BDNF signalling has recently come to be understood as a key regulator and facilitator of neuroplasticity, specifically in regard to synaptic plasticity (Kowianski et al., 2018). eCB signalling also plays a role in regulating signal transmission via retrograde activity (Dow-Edwards & Silva, 2017). Both will be discussed below in their role in synaptic plasticity and neurobiological learning processes.

Synaptic plasticity

The action of BDNF/TrkB binding initiates various signal cascades as a result of TrkB phosphorylation with downstream effects on neuroplasticity (Kowianski et al., 2018). Activation of the PI3K/Akt pathway modulates NMDAR-dependent synaptic plasticity and enhances dendritic growth and branching (Gonzalez, Moya-Alvarado, Gonzalez-Billaut, & Bronfman, 2016; Jaworski et al., 2005; Kumar, Zhang, Swank, Kunz, & Wu, 2005; Park & Poo, 2013). BDNF activation of the MAPK signalling pathway is involved in the activation of dendritic growth and branching in hippocampal neurons (Kwon, Fernandez, Zegarek, Lo, & Firestein, 2011; Segal, 2003). Finally, activation of the PLCγ pathway enhances overall synaptic plasticity (Kowianski et al., 2018). eCB signalling appears to interact with BDNF functions via downstream regulation of synaptic signalling. The application of exogenous CBD has shown to increase BDNF levels in the hippocampus and medial PFC (mPFC) of a mouse brain, enhancing both acute and long-term markers of synaptic plasticity (Sales et al., 2019). Acute effects were attributed to BDNF/TrkB/mTOR signalling and increased dendritic spine density on the synapse in the mPFC, whereas long-term effects may be associated with general improved synaptic functioning via the same pathway. Dendrite spine density represents an important marker of synaptic plasticity and is highly correlated with various forms of learning and memory (Halbach & Halbach, 2018). Thus, given that BDNF appears to be a key facilitator of spine density and synaptic morphology, developing a better understanding of how eCB signalling interacts within this context could provide useful insights into the effects of exogenous cannabinoid administration.

Synaptic signalling

The strength of synaptic signalling represents an important function in neuroplasticity. Specifically, the processes of long-term potentiation (LTP) and long-term depression (LTD) play important roles in the neurobiology of learning and memory. As abundant retrograde messengers throughout the CNS, eCBs are important regulators of glutamatergic and GABAergic synaptic transmission (Dow-Edwards & Silva, 2017). Furthermore, the coupled action of BDNF and eCB signalling serves as a functional regulator of synaptic signalling strength within both inhibitory (GABAergic) and excitatory (glutamatergic) neurons, although the role of eCBs in LTP is less well understood (Bennett, Arnold, Hatton, & Lagopoulos, 2017).

LTP is an activity-induced long-lasting increase in excitatory synaptic signalling resulting from high-frequency stimulation. It is associated with an increase in dendritic spine density and is thought to represent a cellular correlate of learning and memory (Halbach & Halbach, 2018). BDNF is a regulator of stable late-phase LTP at excitatory glutamatergic synapses (Panja & Bramham, 2014). One line of research proposes this process occurs through BDNF-induced rescue of protein synthesis necessary for LTP (Lu, Christian, & Lu, 2008; Panja & Bramham, 2014). Alternatively, BDNF/TrkB binding may contribute through dendritic protein synthesis, and upregulation of dendritic spine density formation (Panja & Bramham, 2014). Through the modification of glutamatergic postsynaptic morphology and receptor density, BDNF action increases cell sensitivity to neurotransmitter release (Kowianski et al., 2018). Additionally, 2-AG and AEA activation of the CB1 receptor's downstream MAPK, ERK, and CREB pathways may possibly enhance BDNF maintenance of LTP through increased BDNF expression (Bennett et al., 2017)

LTD is a long-lasting reduction in synaptic signalling strength from prolonged low-frequency stimulation. LTD is associated with a decrease in dendritic spine formation and

plays an integral role in the processing and retention of information (Halbach & Halbach, 2018). eCB dependent LTD has been shown to require endogenous BDNF/TrkB signalling, as evidenced through the use of Trk receptor inhibitors and agonists (Zhao, Yeh, & Levine, 2015). At inhibitory GABAergic neurons in the somatosensory cortex, BDNF signalling induces eCB retrograde suppression of GABA release (Yeh et al., 2017). Likewise, in hippocampal GABAergic neurons, BDNF/TrkB signalling induces 2-AG retrograde suppression of GABA release (Selvam et al., 2019).

The Role of BDNF and eCBs in Neuropsychological Disorders, Neurodegenerative Diseases, and Brain Injury Recovery

A range of psychiatric and neurological disorders are more recently being understood to involve BDNF and eCB signalling within their various pathophysiologies. This section will briefly discuss a few in which the actions of both processes are known to occur and are somewhat better understood.

Schizophrenia

Schizophrenia is a neuropsychological disorder that includes positive (present, e.g., hallucinations) and negative (absent, e.g., flat affect) symptoms. A BDNF Val66Met polymorphism is involved in the genetic etiology of schizophrenia development, leading to decreased activity-dependent BDNF secretion and reduced overall neuroplasticity (Decoster et al., 2011). Indeed, it has been found that in females the combination of early cannabis-use, and BDNF Val66Met-carriers, was associated with earlier age at illness onset (Decoster et al., 2011). CNR1 and CNR2 genes encode CB1 and CB2 receptors, respectively, and polymorphisms of these alleles are also associated with the genetic etiology of schizophrenia, as they have been identified in patients and were shown to influence symptomology of patients who consumed cannabis (Fakhoury, 2017). Given the functional role of eCB signalling, recent hypotheses of the neurophysiological correlates have led to a focus on abnormal glutamatergic signalling and abnormal neurogenesis during development (Fakhoury, 2017; de Oliveira et al., 2019). Animal models of schizophrenia have also found that THC exposure led to decreased hippocampal BDNF secretion and related cognitive deficits (Fakhoury, 2017). However, exogenous BDNF administration ameliorates these effects in genetically susceptible mice (Segal-Gavish et al., 2017). Taken together, these observations suggest a role for eCB and BDNF action in the development of schizophrenia, whereby interruption of normal functioning via exogenous THC exposure during critical periods of development may lead to an increased risk of schizophrenia for genetically susceptible individuals.

Major Depressive Disorder (MDD)

In more recent years, the Neuroplasticity Hypothesis of Depression has gained increasing attention, and it is based on three lines of evidence: first, depression is frequently characterized by decreased neuroplasticity in the hippocampus and PFC; second, depression is frequently accompanied by decreased concentrations of BDNF; third, antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), elevate neurotrophic factor and BDNF concentrations and improve neuroplasticity in the hippocampus and PFC (Liu, Liu, Wang, Zhang, & Li 2017). Blockade of the degradation of 2-AG, and subsequent increased CB1 activation, has been shown to enhance hippocampal neurogenesis and restore LTP in the DG, a process associated with neuroplasticity (de Oliveira et al., 2019). CBD administration can exert acute and sustained anxiolytic-like and antidepressant-like effects, associated with increased dendritic spine density in the mPFC, and elevated BDNF levels in the mPFC and hippocampus (Sales et al., 2019). These neuroplastic changes were attributed to the activation of the BDNF/TrkB signalling pathway. Indeed, it appears as though eCB and BDNF signalling aids in the modulation of stress, a prominent risk factor of MDD, via neuroplastic and neurogenic processes in the mPFC and hippocampus (Liu et al., 2017; Scarante et al., 2017; Sales et al., 2019; Worley et al., 2018). The relative infancy of this area of research opens the possibility for new avenues in the development of novel neuropharmacological treatment regimens for depression.

Brain Ischemia Recovery

Ischemia, or stroke, begins with a breakdown in the neural membrane of the cell, which leads to massive glutamate release and oxidative stress, eventually resulting in cell death. When blood and oxygen re-enter the infarcted area, membrane degradation, mitochondrial damage, neuroinflammation and apoptosis may occur. Neurogenesis acts as a protective mechanism in the counteraction of these processes, and eCB signalling appears to be involved, indicated by the associated increased expression of CB1 receptors in the ischemic area (Sun et al., 2013). CB2 activation plays a faciliatory role in this neurogenic response, as the genetic inhibition of CB2 expression interrupted stroke-induced neurogenesis (Bravo-Ferrer et al., 2017). In an animal stroke model, administration of WIN55,212-2 agonist significantly attenuated brain swelling and hippocampal neuron loss, promoted progenitor cell proliferation, and the activation of CB1 prevented neural cell death (Sun et al., 2013). Likewise, WIN55,212-2 enhanced

cell proliferation and neuroblast generation in the SVZ and striatum of newborn rats exposed to hypoxic ischemia (Fernandez-Lopez et al., 2010). CBD administration has also been found to play a positive role in neuroprotection post-ischemia, whereby CBD attenuated hippocampal neurodegeneration, increased hippocampal BDNF, promoted dendritic restructuring, and stimulated overall neurogenesis. (Mori et al., 2017). CB1 receptor activation also promotes striatal neuron survival via BDNF activation (Blazquez et al., 2015). Taken together, this highlights the role of BDNF and eCB signalling within protective neurogenic responses post-stroke.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disorder that results in motor and cognitive dysfunction. Inflammatory cells are known to infiltrate a variety of brain regions resulting in the modulation of regular neuronal function, synaptic signal formation, and brain plasticity (Ksiazek-Winiarek, Szpakowski, & Glabinski, 2015). In addition to repair mechanisms like remyelination, an important factor within disease progression lies in neuronal plasticity, whereby structural and functional reorganization occurs throughout the life history in MS patients. BDNF and CB1 receptor activity have been implicated as potential therapeutic targets in the functional recovery of acute phase MS (Ksiazek-Winiarek et al., 2015). CB1 is suggested to act as a regulator of glutamate transmission, acting as a buffer for excitotoxicity effects and helping to maintain LTP-like neuronal plasticity. Additionally, BDNF secretion appears to be reduced in lymphocytes, and targeting this reduction could enhance and prolong various neuroprotective effects. Within a mouse model of MS, PI3k/Akt pathways are shown to become downregulated; however, CBD treatment is able to restore this through increased phosphorylation of the PI3K/Akt pathway (Giacoppo, Pollastro, Grassi, Bramanti, & Mazzon, 2017). This effect was accompanied by an increase in BDNF-levels, an action involved in the activation of the PI3K/Akt pathway. CBD treatment was also found to promote neuronal survival and reduce pro-inflammatory cytokines.

Conclusion

BDNF and eCBs are present in nearly all regions of the mammalian brain. BDNF, acting as both retrograde and anterograde messenger, and eCBs, as retrograde messengers, are important functional neuromodulators for an array of neural processes. Their functionalities are region-specific, playing important roles in neural development, regulation of neuro-, glio-, and synaptogenesis, neuroprotection, and synaptic interactions involved in learning and cognition. BDNF and eCB activity both play a regulatory role in the functionality of each other, whereby the binding action of one has downstream consequences for the other. BDNF/TrkB binding leads to upregulation of eCB synthesis and eCB receptor expression. Contrastingly, the dual binding action of AEA leads to the upregulation of TrkB expression. This highlights the cyclical and modulatory relationship common throughout the various neurophysiological processes they share roles in.

The action of eCB and BDNF cross-talk in embryonic and adult neurogenesis is a bidirectional dynamic process of high complexity. Within neurogenic processes, eCB signalling acts as a key modulator maintaining a necessary balance between progenitor and precursor cells during neural proliferation and spatial development. BDNF and eCB signalling also play functionally important roles in synaptic development, and programmed cell death events. One possible mediator of this relationship may exist in CREB phosphorylation, and further research in this area is recommended.

In neuroplastic processes, eCB signalling appears to influence BDNF function via downstream regulation of synaptic signalling. Long-term potentiation and long-term depression play important roles in the neurobiology of learning and memory. As abundant retrograde messengers throughout the CNS, eCBs are important regulators of glutamatergic and GABAergic synaptic transmission, and the coupled action of BDNF eCB signalling serves as a functional regulator of synaptic signalling strength within both inhibitory (GABAergic) and excitatory (glutamatergic) neurons. Developing a better understanding of how eCB signalling interacts with BDNF in synaptic morphological changes could provide useful insights into the effects of exogenous cannabinoid administration.

Finally, the mechanisms of interaction between BDNF and the eCB system within neurogenesis and neuroplasticity are highly relevant to healthcare and clinical settings. As key components that underlie a number of homeostatic functions within brain development, memory, learning, cognition, and neuroprotection, there exists the potential for the development of novel therapeutic treatments that could improve the symptomology of a variety of neurophysiological conditions. Further research using in vivo animal models could also help elucidate the neurobiological effects of adolescent cannabis use and help to better understand the role of cannabis as a risk factor during neural development and in the progression of mental illness.

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