Review

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Considering the Effects of Cannabinoids and Exercise on the Brain: A Narrative Review

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Abstract

Recently, there has been a rising interest in the use of cannabis and its derivates as therapeutic tools to support brain health. Cannabis-based substances interact with the endogenous cannabinoid (i.e., endocannabinoid) system, comprised of an intricate network of cellular receptors, signaling proteins, and essential enzymes. The endocannabinoid system is involved in widespread physiological functions, including inflammation, vascular response, and neuronal transmission that influences brain function, positioning it as a prime target for brain health interventions. In other work, the benefits of exercise for brain health have been prominently noted. Such benefits are similarly attributed to influences on the immune, vascular, and nervous systems that promote overall brain health. Despite large bodies of work on both cannabinoid and exercise influences on brain function, there appears to be an understudied overlap in their physiological effects. Indirect and direct interactions between these two therapeutic avenues have potential to introduce additive, synergistic, or opposing effects that may need to be considered in applied work. In this narrative review, we describe the mechanisms and actors involved in the aforementioned physiological systems, with consideration of common and contrasting influences of cannabinoids and exercise on the brain.

Keywords: endocannabinoid; cannabidiol; tetrahydrocannabinol; cannabis; inflammation; vascular; neuroplasticity

1. Introduction

There is increasing public interest in therapeutic applications of cannabis and its derivates, due in part to its decriminalization in multiple Western countries (Farrelly et al., 2023). Alongside this interest, there is a growing body of research dedicated to enhancing knowledge of the endogenous cannabinoid (i.e., endocannabinoid) system and the use of cannabis-based or related substances as medications and nutritional supplements (Cerino et al., 2021). Although the endocannabinoid system has widespread involvement in human physiology, its potential to support brain function has drawn particular attention (Ameri, 1999; Chye et al., 2021). Notable impacts of the endocannabinoid system on brain physiology occur via influence on inflammatory processes (Pandey et al., 2009), vascular responses (O'Sullivan, 2015), and neuronal transmission (Kreitzer, 2005). These effects may have implications for development of strategies to address an array of brain health challenges, ranging from psychiatric to neurological (Zanettini et al., 2011; Fine & Rosenfeld, 2013). Yet, many gaps in knowledge remain surrounding the efficacy and long-term effects of therapeutic applications that target the endocannabinoid system, as well as potential interactions with other interventions (e.g., medications, dietary supplements, behavioural strategies).

In other work investigating therapeutic strategies to enhance brain health, research demonstrating the benefits of exercise on brain function is increasingly recognized (Cotman et al., 2007; Crozier et al., 2018; Vecchio et al., 2018; Young, 1979). The physiological effects of exercise are perhaps more wide-ranging than any other intervention. As such, many of the effects of exercise on

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the brain appear to overlap with those tied to the endocannabinoid system. For example, both habitual and acute exercise are tied to alteration of inflammatory processes (Metsios et al., 2020), vascular responses (Green & Smith, 2018), and neuroplasticity (Won et al., 2021), all of which are partly regulated by the endocannabinoid system (Dietrich & McDaniel, 2004; Matei et al., 2023). Moreover, some beneficial effects of exercise on the brain may occur through direct activation of the endocannabinoid system (Matei et al., 2023; Sparling et al., 2003). Nevertheless, there has been limited work to date that provides a clear overview of the seemingly vast interactions between the endocannabinoid system and exercise effects on the brain.

In this narrative review, we aim to improve understanding of the mechanistic overlap of endocannabinoid system activation and exercise effects on brain function. To this end, brain function is broadly defined as the overall operations of the brain, spanning cognitive and non-cognitive activities, and physiological processes. Following a brief description of the endocannabinoid system, focal points of the review will consider synergistic effects of cannabinoids and exercise on inflammation, vascular function, and neuroplasticity.

2. Overview of the Endocannabinoid System

The endocannabinoid system is a vast cell-signaling system that includes endocannabinoids, their receptors, and the enzymes responsible for their synthesis, activation, and degradation (Lu & Mackie, 2016). The endocannabinoid system plays a major role in many physiological functions but its widespread regulatory activities suggest a primary role in maintaining homeostasis across the body and brain (Li et al., 2020).The term cannabinoid refers to a group of chemical substances that bind cannabinoid receptors, and may be divided into 3 groups: endogenous cannabinoids, phytocannabinoids, and synthetic cannabinoids (Kaba & Ray, 2024). Endogenous cannabinoids, or endocannabinoids, are activity-dependent signaling molecules which are produced de novo and have regulatory roles in multiple organs, mainly the central nervous system (CNS) (Heifets & Castillo, 2009) and the immune system as both a neuromodulator and an immunomodulator (Chiurchiù, 2016). Phytocannabinoids are naturally occurring molecules that are found in the cannabis or hemp plant (Cannabis Sativa), with Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most common examples. Synthetic cannabinoids (e.g. Epidiolex, Dronabinol, Nabilone) refer to a class of laboratory-manufactured substances that chemically resemble cannabinoids and are produced for medical or illicit drug use purposes (Alves et al., 2020; National Institute on Drug, 2016). Phytocannabinoids and synthetic cannabinoids may interact with receptors of the endocannabinoid system, of which the family of G-protein-coupled receptors (i.e., metabotropic) are the most well-studied (de Almeida & Devi, 2020) and known as cannabinoid receptors 1 and 2 (CB1 and CB2). Of note, synthetic cannabinoids generally interact more strongly with endocannabinoid receptors than phytocannabinoids, which can lead to discrepancies in their downstream effects (Kelly & Nappe, 2025; Teixeira, 2025).

CB1 is primarily found in the CNS within presynaptic neurons of the cerebral cortex, basal ganglia, dorsal root ganglia, and spinal dorsal horn (Li et al., 2020), but is also present in other parts of the body, including the peripheral nervous system, the gastrointestinal tract, and reproductive organs (Matsuda et al., 1990). In contrast to CB1, CB2 is primarily distributed throughout peripheral tissues, such as immune and endothelial cells, as well as in cardiovascular and gastrointestinal organs (Zádor et al., 2021). While CB2 can be found on glial cells and astrocytes, it is generally less prevalent in the CNS than CB1 (Forteza et al., 2021; Ward & Tuma, 2014). Outside of CB1 and CB2, another family of endocannabinoid receptors are the transient receptor potential cation channel subfamily. The most studied receptor of this type is the transient receptor potential vanilloid receptor type 1 (TRPV1). TRPV1 is abundant in the cardiovascular and peripheral nervous systems as well as cerebrovascular spaces (Marrone et al., 2017).

The endocannabinoids that interact with these receptors are cellular messengers that are mainly derived from cellular membrane phospholipids. Contrary to many neurotransmitters and neuropeptides, endocannabinoids are not stored in pre-formed synaptic vesicles. Instead, elevation

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of intracellular calcium triggers 'on-demand' synthesis of the endocannabinoids (Pandey et al., 2009; El Manira & Kyriakatos, 2010). Several endocannabinoids have been identified, of which two are known to have major impacts in the CNS and the immune system. These endocannabinoids include N-arachidonoyl ethanolamine (AEA), commonly known as anandamide, and 2-arachidonoylglycerol (2-AG). Both AEA and 2-AG act as retrograde messengers (Castillo et al., 2012; Thompson et al., 2024). AEA initiates a relatively slow retrograde signal and is a low-affinity selective ligand for CB1 (Ohno-Shosaku & Kano, 2014; Ward & Tuma, 2014). 2-AG is the most abundant endocannabinoid in the brain and provides a rapid and temporary retrograde signal. It has shown a similar affinity towards both CB1 and CB2. When their signaling activities are complete, endocannabinoids are inactivated and degraded through catabolic enzymes of the endocannabinoid system (El Manira & Kyriakatos, 2010).

3. Targeting the Endocannabinoid System to Alter Brain Function

The prevalence of endocannabinoids and their receptors throughout the CNS and immune system, and the potential for exogenous activation of the endocannabinoid system via phytocannabinoids, has led to conjecture regarding potential therapeutic applications for brain function. The two most abundant and well-studied phytocannabinoids, THC and CBD, both interact with endocannabinoid receptors (CB1 and CB2), and both have shown psychoactive properties. However, only THC is considered an intoxicating compound (Singh et al., 2025). THC's psychoactive effects manifest through its binding with CB1 (Ketcherside et al., 2017), with these effects largely balanced by the negative allosteric modulation of CBD on CB1 activation (Thompson et al., 2024). Both THC and CBD act as agonists to CB2 (Malfitano et al., 2014) and demonstrate affinity towards the TRPV1 endocannabinoid receptors of the cardiovascular and peripheral nervous systems (Alfulaij et al., 2018). Notably, evidence suggests that physical exercise can also provide a stimulus to activate the endocannabinoid system without administration of exogenous substances (Matei et al., 2023). Indeed, brain function is influenced by inflammation, vascular response, and neuroplasticity, all of which are influenced by exercise and regulated in part via the endocannabinoid system. Inflammation in the CNS can suppress neurogenesis (Ekdahl et al., 2003; Kohman & Rhodes, 2013), disrupt growth factor signaling (Venters et al., 2001; Cotman et al., 2007; Tong et al., 2008), and promote neurodegeneration (Chitnis & Weiner, 2017), among other deleterious effects. Likewise, vascular function is critical to ensure delivery of oxygen and nutrients and clearing of waste or pathogenic molecules within the CNS (Iadecola et al., 2023). Finally, neuroplasticity refers to the capacity of the CNS to undergo adaptive structural and functional change, a process that is critical for preserving and supporting brain function (Lovinger, 2008). In the following sections, we will consider the influences of the endocannabinoid system on each of these processes, exploring effects of exogenous activation via phytocannabinoids and endogenous activation via exercise, and consequences for brain function.

4. Regulating Inflammation

Inflammation is a function of the body that brings about actors of the immune system from circulation to areas where they are required to eliminate hostile agents, such as pathogens or damaged cells, and thus restore homeostasis (Antonelli & Kushner, 2017). Considering brain function, neuroinflammation is a hallmark of many neurological conditions and may accumulate via immune activity in the CNS, autoimmune reactions, or systemic inflammation from the rest of the body. Endocannabinoid signaling is highly involved in immunoregulation related to inflammation, including neuroinflammation. From involvement in cell functions like apoptosis and proliferation, to influences on cytokine production and release, endocannabinoid signaling is generally associated with downregulation of pro-inflammatory, and upregulation of anti-inflammatory, responses. Nevertheless, the type of cell and the activated receptor ultimately determines the type of inflammatory response that is promoted.

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CB2 receptors are more prominent in the immune system than CB1 receptors, and are expressed on multiple cells including B-cells (white blood cells), neutrophils, and natural killer cells (Walter & Stella, 2004; Pandey et al., 2009). CB2's activation typically promotes immune suppression via an increase in anti-inflammatory factors, decrease in pro-inflammatory factors, and an increase in cytokines production and regulation (Rieder et al., 2010; Turcotte et al., 2016). In contrast, CB1 activation bolsters pro-inflammatory activity (Matei et al., 2023) or anti-inflammatory activation depending on the context. For example, in neuronal injury animal models that are relevant to concussion in humans, CB1 agonism reduces glutamate-mediated excitotoxicity and has anti-inflammatory effects (Shohami et al., 2011).

AEA and 2-AG have also been studied for their specific roles in inflammation. AEA inhibits pro-inflammatory responses by blocking lymphocyte T cells' migration, and suppressing monocytes and microglia cells from production and release of pro-inflammatory cytokines, such as interleukin-2 (IL-2), interleukin-6 (IL-6), and interferon gamma (IFNγ) (Chiurchiù et al., 2016). AEA has also been shown to have a dose dependent effect on macrophage cells, where higher concentrations block macrophage cell migrations (Pestonjamasp & Burstein, 1998). In animal models, 2-AG was shown to counteract the inflammatory effects of (interleukin-1) IL-1, IL-6 and TNF-α through its influence in the mitogen-activated protein kinase (MAPK) pathway (Kobayashi et al., 2001; Leonard & Aricioglu, 2023), blocking lymphocyte B and T cells' proliferation (Rahaman & Ganguly, 2021), formation of antibodies (Sido et al., 2016), and mobilization of the natural killer cells (Rahaman & Ganguly, 2021). Together, the modulatory actions of AEA and 2-AG reduce inflammatory effects of cytokines and immune system activity (Ruhl et al., 2021) that may otherwise disrupt brain function.

Several studies have indicated that the intake of phytocannabinoids, such as CBD and THC, leads to a reduction of pro-inflammatory activities via the endocannabinoid system. For example, CBD and its analogues induced significant decreases in IL-1, IL-6, and tumor necrosis factor-α (TNF-α) concentration in animal models (Burstein, 2015). In studies of inflammation among humans with neurological disorders (e.g., Parkinson's and Huntington's disease), activation of CB2 receptors and glial cells via CBD and THC intake reduced production of inflammatory factors (Fernández-Ruiz et al., 2011). On the other hand, research on rodent models indicated that chronic intake of THC during adolescence could induce an increase in pro-inflammatory factors like TNF-α and a decrease in anti-inflammatory factors like interleukin-10 (IL-10) in the CNS, potentially due to long-term upregulation of CB2 receptors on glial cells and a downregulation of CB1 receptors on other cells (Zamberletti et al., 2015).

Inflammation is also largely influenced by exercise. Direct effects of exercise on inflammatory activity include activation of macrophages and neutrophils that repair and build muscle and the secretion of cytokines from muscle (i.e., myokines) that support hypertrophy and myogenesis (Sellami et al., 2021). The myokines also activate secondary messengers and cascades, including actors in the MAPK pathways, that boost immunity (Metsios et al., 2020). Generally, the myokines released with exercise are anti-inflammatory, such as IL-10, and inhibit production of pro-inflammatory cytokines (e.g., TNF-α) (Petersen & Pedersen, 2005; Sellami et al., 2021). Further, the myokines secreted with exercise elicit increases in growth factors, such as insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic factor (BDNF), which counter inflammation and provide neuroprotective effects.

A growing body of work indicates that the endocannabinoid system is likely an important contributor to, or mediator of, the effects of exercise on inflammatory activity, including neuroinflammation. For example, single bout of treadmill running (Raichlen et al., 2013) or cycling (Sparling et al., 2003) increased AEA concentration increased in systemic blood. With its lipophilic profile, AEA has potential to pass through the blood brain barrier and induce central effects (Dietrich & McDaniel, 2004). Notably, exercise effects on AEA are optimized at moderate intensities and attenuated at low and high intensities (Raichlen et al., 2013). In other work, 12 weeks of resistance training amplified the expression and activity of CB1 and CB2 in skeletal muscle in older adults (Dalle & Koppo, 2021), and as such, their potential influences on the inflammatory pathways described

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above (Matei et al., 2023). Exercise also modulates the expression of CB receptors in immune system cells, such as natural killer cells and lymphocytes (Valencia-Sánchez et al., 2019). These findings demonstrate extensive interplay between exercise, the endocannabinoid system, and inflammation in potentially supporting brain function.

While inflammation is generally a protective physiological function, there are instances in which it becomes excessive and may contribute to, rather than counteract, pathology (Lyman et al., 2014). Unlike most other cells, neurons have minimal capacity for repair after damage (Ransohoff, 2016) and disproportionate inflammatory responses can be of substantial detriment (Russo & McGavern, 2016). Excessive inflammation also has the potential to disrupt the blood brain barrier and permit peripheral inflammatory factors to migrate into the CNS (de Vries et al., 1996; Laflamme et al., 1999) where they could disrupt neuronal transmission (Cunningham et al., 1996), regulatory growth factor signaling (Labandeira-Garcia et al., 2017), mitochondrial function (Akbar et al., 2016), and ultimately contribute to degeneration of neurons (Carson et al., 2006). As such, the robust and generally anti-inflammatory effects of both phytocannabinoid intake and engagement in habitual exercise are notable, especially when considered in combination. For instance, both phytocannabinoids (Burstein, 2015) and habitual exercise (Petersen & Pedersen, 2005) may suppress production of pro-inflammatory cytokines (e.g., TNF-α) and exercise may enhance anti-inflammatory cytokines (e.g., IL-10) (Petersen & Pedersen, 2005), providing an additive effect to mitigate systemic and central inflammation. Likewise, increases in AEA and 2-AG with exercise (Sparling et al., 2003; Raichlen et al., 2013) may attenuate immune cell migration and proliferation (Ruhl et al., 2021), while exercise-induced increases in CB1 and CB2 expression (Dalle & Koppo, 2021) could provide greater opportunity for endocannabinoid system activation via phytocannabinoid intake. These plausibly synergistic effects could provide major contributions to regulation of cytokines and other inflammatory immune system activity that influence brain function.

5. Regulating Vascular Function

The vascular system uses the heart and blood vessels to transport oxygen-rich blood and nutrients throughout the body and brain. It removes low-oxygen blood and waste products, in addition to circulating immune cells to protect the body from disease and infection. Vascular function influences brain function largely through regulation of cerebral blood flow. Human vascular function is regulated by various physiological pathways, including key actors of the endocannabinoid system. Documented endocannabinoid system effects on the vascular system range from alteration of blood pressure (O'Sullivan, 2015), to influences on heart rate variability (Alfulaij et al., 2018), to moderation of cerebral blood flow under conditions of hypercapnia and hypoxia (Benyó et al., 2016). Notably, it has been suggested that endocannabinoid effects on vascular function may be most critical under pathologic conditions when its homeostatic and potentially cardioprotective effects become increasingly active (Hiley, 2009).

Within the vascular system, CB receptors are primarily expressed in the endothelium and myocardium, where they have varied effects (Puhl, 2020). Generally, activation of CB1 receptors on the myocardium decrease myocardial contraction and those on endothelial cells promote vasodilation and reduce blood pressure (Hillard, 2000; Alfulaij et al., 2018). Likewise, CB2 activation in the vascular system is thought to suppress release of the pro-inflammatory TNF-α in response to cardiovascular pathology (Fulmer & Thewke, 2018). While these CB receptor effects may indirectly support brain function, such as by mitigating systemic inflammation, CB receptors may also impact the brain more directly through involvement in cerebrovascular regulation (Benyó et al., 2016). Cerebral blood flow depends on cerebral arterioles and capillaries, which are controlled by smooth muscle cells and pericytes (Paulson et al., 1990). Endothelial cells, neurons, and glial cells release peptides and hormones that influence blood vessel diameter. Each of these cell types expresses CB receptors and releases endocannabinoids (i.e., AEA and 2-AG) that may modulate cerebral circulation (Benyó et al., 2016). For example, CB1 activation generally suppresses smooth muscle contractility and promotes vasodilation by the endothelium to increase cerebral blood flow, but under stress (e.g.,

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hypoxia), activation of CB1 receptors on neurons induce a decrease in cerebral blood flow (Benyó et al., 2016). Other work demonstrates that CB2 receptor activation in coronary endothelial cells may attenuate pro-inflammatory response and increase blood perfusion in sub-acute cerebrovascular pathology, such as subarachnoid hemorrhage and traumatic brain injury (Fujii, Sherchan, Krafft, et al., 2014; Fujii, Sherchan, Soejima, et al., 2014). Related research demonstrates a role for AEA in modulating systemic arterial pressure, heart rate, and cerebral blood flow (Pacher et al., 2005; Stein et al., 1998). The study of AEA in animal models of vascular function determined that its activation of TRPV1 induces bradycardia, hypotension, and vasodilation (Montecucco & Marzo, 2012), with other studies showing a vasorelaxation effect that is specific to the renal and mesenteric arteries (Stanley et al., 2016). Thus, as with other aspects of endocannabinoid system function, the type of receptor activated and the condition of activation determines specific vascular effects that regulate cerebral blood flow and contribute to maintenance of a healthy extracellular neural environment. The endocannabinoid system's flexibility, responsiveness, and compensatory actions in variable conditions are critical to health.

Studies of cannabinoid intake provide additional evidence for influences on vascular function and cerebral blood flow. For example, use of cannabis (Mathew et al., 1992) and acute administration of THC (Mathew et al., 1999; Ogunbiyi et al., 2020) increased cerebral blood flow in the majority of studies in humans and animal models (Wagner et al., 2001). Some discrepancies in findings (Bloom et al., 1997; Mathew & Wilson, 1992) have been explained by the diverse actions of the endocannabinoid system, such that a vasodilatory effect of cannabinoids on cerebral vessels may increase cerebral blood flow while a cannabinoid-mediated suppression of synaptic activity may decrease cerebral blood flow demands (Benyó et al., 2016). Studies in human and animal models have specified that the intake of phytocannabinoids derived from CBD have almost no effect on resting heart rate and blood pressure but reduce stress-induced rises in heart rate and blood pressure (Sultan et al., 2017), and promote vasorelaxation (Stanley et al., 2013). On the other hand, a case series suggested that administration of CBD and a combination of CBD and THC increased blood pressure variability and supported recovery in people experiencing post-concussion syndrome (Singh et al., 2022). Additionally, while acute THC-predominant cannabis uses causes hypertension, tachycardia, and an increased risk of cardiovascular events (e.g., stroke, myocardical infarction) (Matei et al., 2023; Cheung et al., 2024), chronic cannabis use is not associated with hypertension and cardiovascular disease (Haleem et al., 2021; Corroon et al., 2023). However there are contrasting effects in regular cannabis users indicating that a downregulation of CB2 receptors can occur with chronic THC consumption (Hirvonen et al., 2012; Piscura et al., 2023).

Exercise is recognized as a major component of treatment strategies and preventive measures against vascular risk factors and disorders (Tian & Meng, 2019). For example, long term regular aerobic exercise improves the structure and the morphology of the cardiac muscles and increases myocardium wall thickness (Arbab-Zadeh et al., 2014). Likewise, regular resistance and endurance exercise increases blood flow reserve under stress (Bloor, 2005; Joris et al., 2018) and lowers blood pressure in both healthy (Cornelissen & Smart, 2013; Lopes et al., 2021) and hypertensive populations (Fagard & Cornelissen, 2007; Alpsoy, 2020). Exercise induces specific changes to the arteries and veins, increasing blood vessel diameter, preventing production and buildup of plaques, and boosting angiogenesis (Green & Smith, 2018). As acute exercise increases heart rate and cardiac output, cerebral blood flow is increased, primarily based on the accumulation of arterial blood gases (i.e., CO2, O2), to support delivery of oxygen and nutrients and meet the metabolic demand of the brain. With habitual exercise, changes in cerebral blood flow become increasingly refined and responsive (Murrell et al., 2013) through improved brain vascularization and blood vessel adaptation (Ainslie et al., 2008; Steventon et al., 2018). Exercise-induced changes to vasculature and cerebral blood flow are linked to production of proteins, such as vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), by smooth muscle and endothelial cells (Bloor, 2005; Viboolvorakul & Patumraj, 2014). Likewise, increases in catecholamines with exercise are also thought to support heart function, enhance endothelial repair mechanisms, and promote angiogenesis (Bolduc et al., 2013).

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Together, these vascular adaptations to exercise enhance cerebrovascular endothelial processes to support brain function.

In many ways, the documented effects of the endocannabinoid system and exercise on vasculature are overlapping and complementary in their resultant influences on brain function. Improvements in cardiac output, blood flow reserve, and the structure and morphology of vasculature with habitual exercise (Bloor, 2005; Cornelissen & Smart, 2013; Arbab-Zadeh et al., 2014) could potentially mitigate acute negative effects of cannabis use on hypertension, heart rate, and risk of myocardial infarction (Matei et al., 2023; Cheung et al., 2024). In some cases, exercise effects on vascular function are likely mediated, in part, by the endocannabinoid system. For example, exercise-induced increases in systemic levels of cannabinoids (Sparling et al., 2003; Raichlen et al., 2013) and CB receptor sensitivity (De Chiara et al., 2010) may promote binding to CB receptors in the vascular system, such as on endothelial and smooth muscle cells, to promote vasodilation and related benefits for blood pressure, heart rate, and cerebral blood flow. Likewise, evidence of the importance of the endocannabinoid system in moderating cerebral blood flow under hypoxic and hypercapnic conditions (Benyó et al., 2016) suggests that it also contributes to the control of cerebral blood flow during exercise. The intersection of cannabinoid and exercise influences on cerebral blood flow represents their most direct link to brain function. Recently, a review by From & Crosby (2025) highlighted the bidirectional relationship between endocannabinoids and nitric oxide in modulating cerebrovascular dynamics. Endocannabinoids influence nitric oxide synthesis and downstream signaling pathways, which regulate vascular tone and cerebral blood flow. Conversely, nitric oxide modulates endocannabinoid levels and their associated signaling cascades, creating a reciprocal interplay (From & Crosby, 2025). Cerebral blood flow is critical to ensure optimal delivery of oxygen and nutrients to the brain and relates closely to mechanisms of intracranial pressure maintenance (de-Lima-Oliveira et al., 2018). These mechanistic effects are corroborated by evidence that both exercise pre-conditioning (Taylor et al., 2015) and CB2 activation (Fujii, Sherchan, Krafft, et al., 2014; Fujii, Sherchan, Soejima, et al., 2014) may support recovery from brain injury, and suggest a potentially powerful, additive impact of cannabinoid intake and exercise participation. Jointly, the general vasodilatory effects of cannabinoids (Alfulaij et al., 2018), endogenous activation of the endocannabinoid system through exercise (Matei et al., 2023), and angiogenic influences of habitual exercise (Green & Smith, 2018) has great potential to create a vascular system that effectively supports brain function.

6. Promoting Neuroplasticity

Neuroplasticity refers to the capacity of the CNS to change and reorganize its connections in response to experience. Changes may include alterations in synaptic efficacy, dendritic branching, and formation of new neurons. Neuroplasticity is critical for brain function, with direct involvement in memory formation and learning, compensation for age-related changes in cognition, and recovery from neurological injury or illness (Fuchs & Flügge, 2014). The endocannabinoid system is highly integrated within the CNS, exhibiting effects on brain function through mechanisms such as depolarization-induced suppression of inhibition (DSI) and excitation (DSE). Generally, the primary role of the endocannabinoid system within the CNS is to maintain homeostasis by modulating neuronal activity and synaptic transmission accordingly (Chen, 2015). Yet, behavioural influences of the endocannabinoid system include effects on memory (Lunardi et al., 2020), pain regulation (Woodhams et al., 2015), mood (Ashton & Moore, 2011), and appetite (Kurtov et al., 2024).

While all CB receptors can be found in the CNS, CB1 is most abundant in neurons and is distributed throughout cortical, subcortical, and spinal regions (Li et al., 2020). In contrast, while CB2 is most commonly found in the periphery on circulating immune cells, it is also found in the CNS glial cells and astrocytes (Forteza et al., 2021; Ward & Tuma, 2014), and TRPV1 on sensory neurons involved in nociception (T. Xiao et al., 2022). DSI and DSE are forms of short-term brain plasticity that depend specifically on CB1 receptor activation (Wilson & Nicoll, 2001; Diana & Marty, 2004; Mackie, 2006, p. 20; Dudok et al., 2024). In DSI, endogenous cannabinoids are released from the post-synaptic

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neuron after it is depolarized. The cannabinoids bind to CB1 receptors on nearby pre-synaptic neurons, acting as retrograde messengers to reduce presynaptic release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Kreitzer & Regehr, 2001; Ohno-Shosaku et al., 2001; Wilson & Nicoll, 2001). Various studies provide corroborating evidence of cannabinoid-mediated DSI, such as by demonstrating that activation of CB1 through microinjection of AEA inhibited sympathetic nervous system activity (Seagard et al., 2004), and that administration of 2-AG in the rat hippocampus decreased release of GABA (Lee et al., 2015). DSE follows a similar mechanism but suppresses the release of the excitatory neurotransmitter glutamate (Kreitzer & Regehr, 2001). While strong evidence generated from experiments with CB1 knockout mice demonstrates that CB1 is critical to DSI, the postulated endocannabinoid influences on DSE are less established (Diana & Marty, 2004). Although DSI and DSE were first reported in cerebellar and hippocampal circuits, they have since come to be recognized as relatively universal throughout the brain.

Despite the short-term nature of DSI and DSE effects on neuronal excitability, they may influence mechanisms of long-term neuroplasticity to contribute to more lasting neural change. For example, strengthening of synaptic efficacy by long-term potentiation (LTP) is facilitated during periods of DSI (Carlson et al., 2002). Likewise, endocannabinoids are thought to contribute to induction of long-term depression (LTD) through DSE (Diana & Marty, 2004). While DSI and DSE require only a single depolarization to become active and last for only seconds, their influences on LTP and LTD (which depend on repeated depolarizations and persist in the long-term) demonstrate their potential to exert more extensive impacts on neuroplasticity. In other work, it was discovered that the N-methyl-D-aspartate receptor (NMDAr), a critical receptor for LTP in glutamatergic neurons, can combine with CB2 receptors to form a heteromer complex with alternate functionality. In this complex, CB2 receptor activation reduces the signaling output of NMDA receptors, potentially in a manner that combats excitotoxicity, a form of maladaptive neuroplasticity (Rivas-Santisteban et al., 2021). Related research demonstrates the neuromodulatory effects of cannabinoids further, with evidence that cannabinoid binding suppresses the release and actions of several neurotransmitters other than GABA and glutamate, including glycine (Jennings et al., 2001), acetylcholine (Gifford & Ashby, 1996), dopamine (Cadogan et al., 1997), norepinephrine (Ishac et al., 1996), and serotonin (Nakazi et al., 2000). Yet, the conditions of activation must again be considered, as animal studies of drug addiction also suggest that CB1 binding can increase dopamine release in the nucleus accumbens (Cheer et al., 2007).

Consumption of cannabis and its derivates is widely known to influence neuroplasticity. As noted previously, THC is the primary psychoactive component, with strong affinity to CB1 receptors that are spread across the brain and mainly reduce synaptic transmission (Felder et al., 1995; Chowdhury et al., 2024). Nevertheless, CBD can also be neuromodulatory, such as through the negative allosteric modulation of the CB1 receptors interactions with CB2 receptors, and its effects in reducing activity of the fatty acid amide hydrolase (FAAH) enzyme, which leads to an increase in available naturally secreted anandamide. Most work in this topic area suggests that regular THC dominant cannabis use disrupts positive, adaptive neuroplasticity. For example, the non-specific activation of CB1 receptors by THC may disrupt the physiological, activity-dependent effects of endocannabinoids and globally suppress release of neurotransmitters that typically promote functional connectivity throughout the brain (Testai et al., 2022). On the other hand, human neuroimaging studies suggest that CBD intake may increase both GABA and glutamate concentrations in the basal ganglia and prefrontal cortex (Pretzsch et al., 2019). Additionally, studies in mouse models show that CBD intake increases levels of BDNF (Sales et al., 2019), an important protein involved in neuroprotection and neuroplasticity. Molecular analysis revealed, however, that BDNF increases are dose and location specific, where a single CBD dose upregulated BDNF in the medial prefrontal cortex, while repeated dosing increased BDNF in the striatum but slightly decreased it in the medial prefrontal cortex (Mottarlini et al., 2022). Given the broad distribution and varied influences of endocannabinoid receptors within the CNS, intake of synthetic or phytocannabinoids has potential to exert a range of effects on neuroplasticity, which depend on factors such as the cannabinoid, dosage, and use as well as individual characteristics, such as age and sex (Chowdhury et al., 2024).

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A large body of research has also demonstrated a direct impact of exercise on brain function (Umegaki et al., 2021; Silva et al., 2024). Investigation of gene expression in animal models indicate that nearly 40% of genes upregulated by exercise play a role in mechanisms of neuroplasticity (Tong et al., 2001; Liang et al., 2021). These increases in gene expression enhance production and availability of numerous neurotrophic growth factors (i.e., BDNF) (Szuhany et al., 2015) that promote synaptic strengthening, dendritic branching, and neurogenesis (Cotman et al., 2007; Liang et al., 2021). Such exercise effects amass to positively alter many characteristics of brain function, such as increased functional connectivity between brain regions (Moore et al., 2022), increased integrity of white matter (Zhang et al., 2024), and increased brain volume (Aghjayan et al., 2021; Wilckens et al., 2021; Hendrikse et al., 2022). Additional research demonstrates that long-term potentiation-like plasticity induced by non-invasive brain stimulation in humans is enhanced in those with high levels of physical activity (Cirillo et al., 2009). The impacts of habitual exercise are underpinned, in part, by the cumulative effects induced by single bouts of exercise. Acute, exercise provides a robust physiological stimulus that alters brain function. For example, lactate, a byproduct of muscle contraction during exercise, may both induce expression of neurotrophic growth factors and be used as fuel within the brain (Hayek et al., 2019; Müller et al., 2020). Related studies using transcranial magnetic stimulation indicate that exercise decreases GABAergic and increases glutamatergic activity acutely in the human brain (Smith et al., 2014; A. M. Singh & and Staines, 2015). Further studies using non-invasive brain stimulation indicate that various forms of long-term potentiation-like neuroplasticity are increased immediately following exercise in humans (Mellow et al., 2020). Frequent exposure to these acute, exercise-induced increases in neurotrophic growth factors, decreases in inhibitory activity, and increases in plasticity may then be postulated to evolve into the longer lasting changes in structure and function observed with ongoing engagement in regular exercising.

There is increasing interest in the potential interactions of the endocannabinoid system with exercise effects on neuroplasticity. Endocannabinoids that are produced peripherally in response to exercise can cross the blood-brain barrier and exert direct effects on brain function (Maccarrone et al., 2006), such as those associated with the concept of the “runner’s high” (Tantimonaco et al., 2014). Likewise, observation of positively correlated increases in peripheral AEA and BDNF immediately and 15 minutes following exercise in male cyclists (Heyman et al., 2012) suggest that activation of the endocannabinoid system might influence expression of neurotrophic growth factors and related effects on neuroplasticity. Considering DSI (Wilson & Nicoll, 2001), suppression of GABAergic inhibition by cannabinoids could play a part in reports of cortical ‘disinhibition’ (Smith et al., 2014; A. M. Singh & and Staines, 2015) and increased LTP-like plasticity after exercise (Mang et al., 2014, 2016) or with high levels of physical activity fitness (Cirillo et al., 2009). On the other hand, evidence for DSE (Diana & Marty, 2004) and results demonstrating that THC-dominant cannabis use disrupts long-term potentiation-like plasticity (Testai et al., 2022) may suggest some alternate effects whereby cannabinoid intake and exercise effects run counter to each other. Further, exercise literature generally demonstrates increases in production and activity of neurotransmitters (Liang et al., 2021), while cannabinoid binding is more closely associated with a suppression of neurotransmitter release (Testai et al., 2022). Nevertheless, these down-regulating effects of cannabinoids are mostly tied to CB1 activation by THC (Testai et al., 2022) whereas CBD intake largely augments neurotransmitter release (Pretzsch et al., 2019), such as serotonin (5HT) by way of agonism at 5HT1A receptor. As such, the complexity of the endocannabinoid system introduces challenges in interpreting how exercise and cannabinoid intake may ultimately interact to influence neuroplasticity. Certainly, exercise supports a neural environment that is conducive to adaptive neuroplasticity (Liang et al., 2021), including those processes mediated by the endocannabinoid system and triggered by exercise. Speculating on interactions of cannabinoid intake and exercise on neuroplasticity, it appears that the effects of exercise and CBD may be somewhat aligned and additive, whereas potentially negative effects linked to regular THC intake may be attenuated through neurophysiological benefits achieved through habitual exercise.

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7. Conclusion

The endocannabinoid system is a vast and complex biological regulatory system. Its effects are dependent on many factors, including the tissues, receptors, and (phyto)cannabinoids involved, as well as the conditions of activation and inter-individual physiology. The endocannabinoid system is activated primarily via binding of cannabinoids with CB1, CB2, and TRPV1 receptors. While all endocannabinoid receptors are distributed across the body and brain, CB1 receptors are most prevalent in the CNS, and CB2 and TRPV1 most commonly found in the immune and vascular systems, respectively. Endocannabinoid receptors exert a major influence on brain function, both indirectly, through alteration of inflammation and vascular function, and directly, through influences on neuroplasticity. Generally, the homeostatic effects of the endocannabinoid system reduce inflammation and promote measured regulation of cerebral blood flow towards maintaining and supporting a healthy neural environment under both normal and aberrant (e.g., pathologic) circumstances. In the CNS, the activity-dependent, regulatory effects of the endocannabinoid system may balance adaptive (e.g., strengthening of synapses to support memory) and maladaptive (e.g., excitotoxicity after neurological injury) processes of neuroplasticity.

With 'on-demand' synthesis of endocannabinoids such as AEA and 2-AG, the endocannabinoid system is continuously active and contributing to various physiological functions. Yet, intake of phytocannabinoids, THC and CBD, provide an exogenous means to further activate the system and potentially accentuate its effects. While THC is most well-known for its psychoactive effects, increasing evidence indicates that CBD can also impact brain function. Studies of THC provide somewhat contradictory results when considering its potential influences on brain function. For example, administration of THC can reduce inflammation (Fernández-Ruiz et al., 2011), but if consumed regularly during adolescence, may increase inflammation (Zamberletti et al., 2015). THC intake can also acutely cause hypertension, tachycardia, and increase risk of cardiovascular events (Matei et al., 2023; Cheung et al., 2024), whereas chronic use prevents hypertension and cardiovascular disease (Thomas et al., 2014). Likewise, administration of THC may suppress release of neurotransmitters linked to promotion of functional connectivity (Testai et al., 2022). In contrast, most work exploring CBD intake and brain function suggest anti-inflammatory ((Fernández-Ruiz et al., 2011), vasodilatory (Stanley et al., 2013), and neurotrophic effects (Sales et al., 2019).

Exercise is a powerful intervention to alter brain function through activation of numerous physiological pathways, with the endocannabinoid system recognized as a major contributor to the exercise induced adaptations. Systemic levels of endocannabinoids AEA and 2-AG are increased peripherally with an acute bout of exercise and have the capacity to pass through the blood brain barrier (Raichlen et al., 2013; Sparling et al., 2003). Moreover, regular participation in resistance training is associated with increased activation of CB receptors (Dalle & Koppo, 2021). These exercise-induced increases in endocannabinoid production and binding partly underpin the wide-reaching health benefits of exercise for reducing systemic inflammation and improving vascular function that indirectly support brain function. Involvement of the endocannabinoid system in exercise effects on brain function are perhaps most emphatically demonstrated in research examining the "runner's high" ((Tantimonaco et al., 2014); however, other work suggesting endocannabinoid involvement in exercise effects on inhibitory and excitatory neural activity is also significant (Smith et al., 2014; A. M. Singh & and Staines, 2015).

Both cannabinoid intake and exercise provide means to increase activation of the endocannabinoid system and potentially realize benefits for brain function. Given the homeostatic effects and finely tuned nature of endocannabinoid system signaling, there is some potential that intake of exogenous cannabinoids (i.e., THC) might be disruptive to these processes, such as by suppressing neurotransmitter release (Liang et al., 2021). Nevertheless, any potentially detrimental effects of THC appear to be largely countered by CBD and may be further mitigated by activation of the endocannabinoid system by exercise (Matei et al., 2023). Although speculative, it is plausible that habitual exercise could be particularly beneficial in providing an endogenous stimulus that provides guidance for effective physiological use of cannabinoids administered exogenously. Future research

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considering interactions between cannabinoid use and exercise will be critical as separate work exploring the potential benefits of each of these tools for brain function continues to garner scientific, clinical, and public interest.

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