REVIEW ARTICLE

Neuroprotection Following Concussion: The Potential Role for Cannabidiol

Jyotpal Singh, John Patrick Neary

ABSTRACT: Cannabidiol (CBD) has been generating increasing interest in medicine due to its therapeutic properties and an apparent lack of negative side effects. Research has suggested that high dosages of CBD can be taken acutely and chronically with little to no risk. This review focuses on the neuroprotective effects of a CBD, with an emphasis on its implications for recovering from a mild traumatic brain injury (TBI) or concussion. CBD has been shown to influence the endocannabinoid system, both by affecting cannabinoid receptors and other receptors involved in the endocannabinoid system such as vanilloid receptor 1, adenosine receptors, and 5-hydroxytryptamine via cannabinoid receptor-independent mechanisms. Concussions can result in many physiological consequences, potentially resulting in post-concussion syndrome. While impairments in cerebrovascular and cardiovascular physiology following concussion have been shown, there is unfortunately still no single treatment available to enhance recovery. CBD has been shown to influence the blood brain barrier, brain-derived neurotrophic factors, cognitive capacity, the cerebrovasculature, cardiovascular physiology, and neurogenesis, all of which have been shown to be altered by concussion. CBD can therefore potentially provide treatment to enhance neuroprotection by reducing inflammation, regulating cerebral blood flow, enhancing neurogenesis, and protecting the brain against reactive oxygen species. Double-blind randomized controlled trials are still required to validate the use of CBD as medication following mild TBIs, such as concussion.

RÉSUMÉ : Rôle neuroprotecteur potentiel du cannabidiol à la suite d'une commotion cérébrale. Le cannabidiol suscite un intérêt croissant pour la médecine en raison de ses propriétés thérapeutiques et d'une absence apparente d'effets secondaires négatifs. De plus, des travaux de recherche suggèrent que des doses élevées de cannabidiol peuvent être administrées de façon constante avec peu ou aucun risque. Cette étude entend mettre l'accent sur les effets neuroprotecteurs de ce cannabinoïde présent dans le cannabis et insister plus particulièrement sur ses effets lorsqu'on se remet d'un traumatisme cranio-cérébral (TCC) léger ou d'une commotion cérébrale. On le sait, il a été démontré que le cannabidiol peut influencer le système endocannabinoïde, entre autres les récepteurs cannabinoïdes et d'autres récepteurs tels que les récepteurs vanilloïdes de type 1, les récepteurs de l'adénosine et la sérotonine (5-HT), par l'entremise de mécanismes indépendants. Quant aux commotions cérébrales, elles peuvent entraîner de nombreuses conséquences physiologiques pouvant potentiellement produire un syndrome post-commotionnel. Bien qu'on sache qu'une série de déficiences physiologiques de nature cérébrovasculaire et cardiovasculaire peuvent apparaître à la suite d'une commotion cérébrale, il n'existe malheureusement pas de traitement unique pour améliorer la récupération des patients. Ceci étant dit, la preuve a été faire que le cannabidiol peut agir sur la barrière hémato-encéphalique, sur les facteurs neurotrophiques dérivés du cerveau, sur la capacité cognitive d'un individu, sur sa « *cérébrovasculature* », sa physiologie cardiovasculaire et sa neurogénèse, des aspects dont on sait qu'ils sont tous altérés par une commotion cérébrale. En conséquence, il se pourrait que le cannabidiol puisse potentiellement constituer un traitement permettant d'améliorer la neuroprotection des patients en réduisant l'inflammation, en régulant le débit sanguin cérébral, en renforçant la neurogénèse et en protégeant le cerveau contre des dérivés réactifs de l'oxygène. Des essais cliniques randomisés à double insu demeurent toutefois nécessaires afin de confirmer l'utilisation du cannabidiol à titre de médicament à la suite d'un TCC, par exemple une commotion cérébrale.

Keywords: Cannabidiol, Endocannabinoid, Neuroprotection, Concussion, Cerebrovasculature

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Introduction

With over 10 million traumatic brain injuries (TBIs) resulting in death or hospitalization occurring annually,[1,2] there is a need for an effective treatment strategy to recover from these injuries. TBIs can cause difficulty in performing day-to-day activities and even return to normal physiological functioning does not assure that symptoms will clear.[3] The majority of head injuries, such as concussions, are considered mild traumatic brain injuries (mTBIs) and rarely receive full medical treatment.[4] Alongside TBIs, there has been an enormous increase in research done in the area of endogenous cannabinoids (endocannabinoids) and the *Cannabis sativa* and *Cannabis indica* plants.[5] Research into phytocannabinoids (plant based), endocannabinoids, and the synthetic development of cannabinoids has hinted at TBI as a potential therapeutic target.[1,6]

Cannabidiol (CBD) is a major nonintoxicating compound found in *C. sativa* and *C. indica*, along with hemp and other plants,[7,8] and is thought to possess therapeutic potential due to its major neurological and anti-inflammatory properties.[9,10] It is thought that when CBD is administered alongside other

From the Faculty of Kinesiology & Health Studies, University of Regina, Regina, Saskatchewan, Canada

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Corresponding to: J. Patrick Neary, 3737 Wascana Parkway, Faculty of Kinesiology & Health Studies, University of Regina, Regina, Saskatchewan S4S 0A2, Canada. Email: Patrick.neary@uregina.ca

phytocannabinoids, such as tetrahydrocannabinol (THC or Δ9-THC), there is an entourage effect that elevates the therapeutic properties of both CBD and THC.[11-13] Human research in this realm in relation to concussion is very limited, presumably due to ethical issues surrounding administration of intoxicating and often illegal compounds such as THC, even if CBD does have the potential to counteract THC psychosis.[14,15] Numerous animal studies have supported the idea that CBD and THC administered simultaneously can lead to changes in behavioral effects[16] and altered THC metabolism.[17] It is also important to note that human studies observing pharmacokinetic and pharmacodynamic effects of CBD are also very limited,[18-20] although it has been suggested that the maximum measured plasma concentration of CBD increases in a dose-dependent manner, occurring between 0 and 4 h, depending on administration route.[19]

This review will focus on the neuroprotective effects of cannabinoids, specifically the phytocannabinoid CBD following TBI. Considering the prevalence of the entourage effect, it is also important to discuss what the research suggests regarding the combined effects of endocannabinoids and phytocannabinoids, specifically related to concussion. While an animal model has suggested a role for CBD to regulate glutamate and gamma-aminobutyric acid (GABA)[21] responses following mTBI, the fundamental mechanisms underlying these effects are still not clear, especially when considering human studies.

The Endocannabinoid System

After the identification and synthesis of THC,[22] the scientific world expanded much of their knowledge of the cannabis plant constituents. This increase in interest of the exogenous cannabinoids also led to a greater understanding of the endocannabinoid system, which is known to help regulate pain processing and perception,[23] maintain immune system homeostasis,[24] and influence cardiovascular functioning.[25] The endocannabinoid system consists of at least 2 receptors coupled through G-protein inhibition: cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2).[26-30] Other receptors sensitive to cannabinoids include vanilloid receptor 1 (TRPV1),[31,32] adenosine receptors,[33,34] 5-hydroxytryptamine ($5\text{-}HT_{1A}$),[35,36] and G-protein coupled receptors.[37]

The CB_1 receptors are most abundant within the central nervous system, located primarily on the axon and synaptic terminals on the neurons,[38] while the CB_2 receptors are much more concentrated within the peripheral nervous system, such as the immune system.[38,39] Interestingly, CB_2 receptors are also present at the brain microglia.[40-42] CB_2 receptors are therefore present at the central nervous system as well, suggesting that the CB_2 receptor is not only a peripheral receptor, as implied by earlier studies.[26,43,44] Specifically, CB_2 mRNA expression was found on B Cells in the immune system,[44] spleen macrophages,[26] and the thymus.[43] With CB_1 receptors densely concentrated in the central nervous system,[45] this led to the belief that the CB_1 and CB_2 receptors can be considered as tissue-selective antigens,[44] although the presence of CB_2 at the microglia does put this statement into question. Microglia activation can result in a release of proinflammatory cytokines and reactive oxygen intermediates[46] and the presence of the CB_2 receptor at the microglia suggests a neuroprotective purpose. For example, CB_2 receptor stimulation in CB_1 receptor knockout mice produced antinociceptive effects in response to inflammatory pain.[47] Discussed in more detail in the following section, activation of the CB_1 receptor is thought to be responsible for the common psychosis symptoms associated with THC,[30] while activation of the CB_2 receptor can attenuate inflammation and accelerate regeneration in many disease states,[41] including liver regeneration in an animal model of acute hepatitis[48] and attenuation of inflammation and tissue injury in an animal model of spinal cord injury.[41,49] Therefore, the CB_1 and CB_2 receptors are present in neural and peripheral tissue, suggesting involvement in many physiological processes.

The entourage effect suggests a synergistic effect when different phytocannabinoids are administered together. For assistance across the blood brain barrier, adenosine triphosphate-binding cassette transporters have been shown to aid in THC efflux,[50] and with CBD's ability to inhibit these transporters,[51] it is possible that THC may exert its therapeutic influence at the brain for longer periods.[52] This evidence suggests that the location of CB_2 receptors on the microglia can be due to a protective mechanism as THC has been shown to increase CB_2 receptor protein expression, thereby attenuating inflammatory responses, an effect which was abolished when CB_2 receptor antagonists were introduced.[53] Furthermore, sustaining high level of THC at the brain can increase its influence on the brain's dopamine system.[54] Considering that TBIs can impair the nigrostriatal and mesocorticolimbic (mesolimbic and mesocortical) pathways,[55] THC's ability to potentially increase dopamine firing rates on dopaminergic neurons can aid to alleviate dopamine synthesis, reuptake, and metabolism following TBI.[55]

Concussion Implication and Endocannabinoid Neurophysiology

Introduction to Concussion

Concussion or mTBI-related injuries have been a growing issue, both in adults and youths.[56-59] While return to baseline after 3 weeks is common in individuals aged 5–14 years,[58] post-concussion syndrome (concussion-like symptoms lasting over 3 months following mTBI) has been shown to persist for over 6 months in 40% of mTBI patients.[60] Post-concussion syndrome can have negative effects on the individual's day-to-day activities, as shown through its negative associations with health-related quality of life, assessed by the 36-item Short-Form Health Survey and Perceived Quality of Life Scale.[60] Persistence of one symptom was much more common than multiple symptoms (with headache, fatigue, forgetfulness, and poor concentration among the most common),[61,62] and being female was a significant predictor of symptoms lasting 12 months post injury.[62]

Concussion can initiate a neurometabolic cascade,[63] which can lead to an energy crisis, thereby impairing cerebral blood flow,[64] increasing intracellular calcium (Ca^{2+}) levels,[63,65] and disrupting autonomic functioning,[66,67] among other physiological consequences (Figure 1).[63,66,68-76] mTBIs generally occur due to rotational or twisting forces (accelerations or decelerations)[77,78] of the brain within the skull, thereby resulting in a disruption in homeostasis. In comparison, the endocannabinoid system is thought to have neuroprotective properties,[79,80] which could therefore ameliorate these disturbances in physiological homeostasis. This may partly be due to the fact that the endocannabinoids are retrograde messengers with the ability to cause depolarization-induced suppression of inhibition.[81] Once neurotransmitters are released from the presynaptic neuron, they bind to the postsynaptic receptors to

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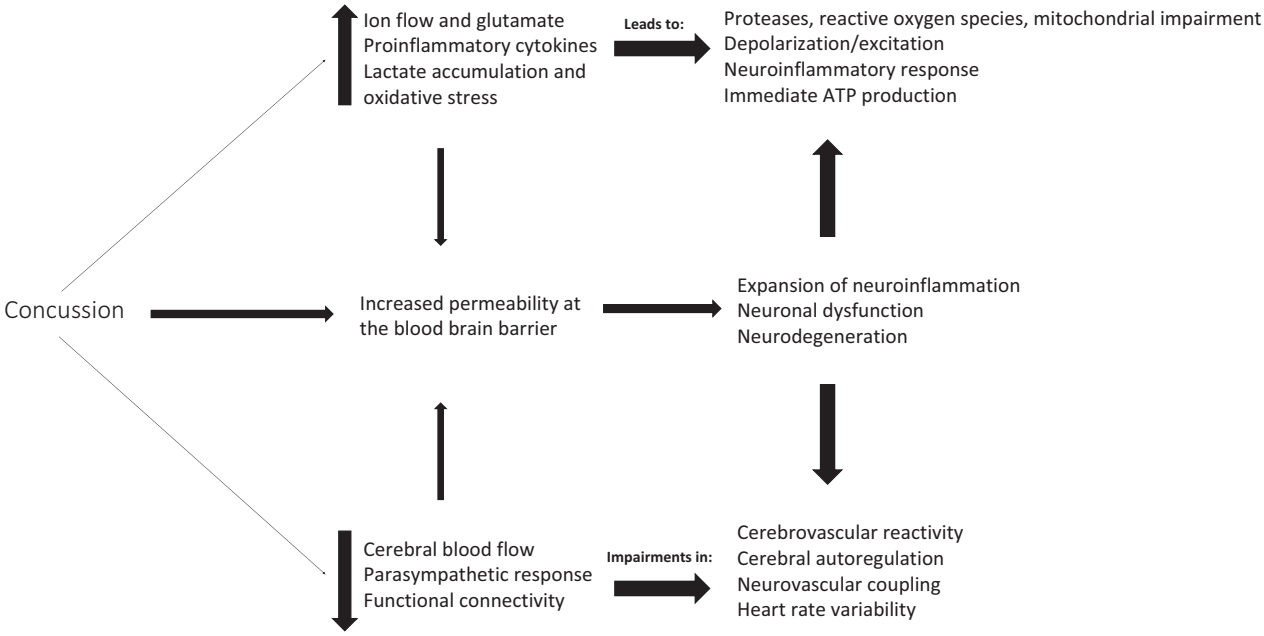

Figure 1: *Overview of physiological consequences following concussion.*

induce either excitatory or inhibitory postsynaptic potentials. This binding to the postsynaptic receptors allows for entry of Ca^{2+} into the cell, leading to the activation of phospholipase (PL) and diacylglycerol lipase (DAGL).[82] Activation of PL and DAGL in combination with arachidonic acid leads to biosynthesis of N-arachidonylethanolamine (also called anandamide; AEA) and 2-arachidonoyl glycerol (2-AG).[83-85] These endocannabinoids are thought to be produced *in vivo* where increased intracellular Ca^{2+} concentration is the major trigger for synthesis.[86] The endocannabinoid ligands, such as AEA and 2-AG,[29] are released from cells in a stimulus-dependent manner by cleavage of membrane lipid precursors.[87-89] These endocannabinoids travel back to the presynaptic neuron and bind to the CB_1 receptors which causes a decrease in presynaptic neurotransmitter release across the synaptic cleft. This is done by inhibition of adenylate cyclase (leading to a decrease in sodium (Na^+) inflow) and calcium channels, along with activation of the potassium (K^+) channels,[81] thus potentially leading to hyperpolarization as depolarization-induced suppression of inhibition decreases the frequency of miniature inhibitory postsynaptic currents. Taken together, these changes in ionic balance can increase the percentage of synaptic failures.[81]

The endocannabinoid ligands are synthesized by the body from arachidonic acid of membrane phospholipids[90] in response to pain, inflammation, anxiety, emotional and physical stressors, and pathological conditions. Completion of the endocannabinoid signaling is thought to require cellular reuptake through a carrier-mediated transport process followed by enzymatic degradation by enzyme fatty acid amide hydrolase primarily for AEA[91] and monoacylglycerol lipase for 2-AG.[90] The Ca^{2+}-dependent synthesis and release of endocannabinoids for its retrograde mechanism could have a significant role in protecting the body by limiting overstimulation, such as protection against the energy crisis which occurs during the neurometabolic cascade following a mTBI.[63]

Cannabidiol Implications for Neuroprotection following Concussion

CBD is a phytocannabinoid found in the *C. sativa* and hemp plant that is well known for its therapeutic potential but is devoid of psychosis.[92,93] Phytocannabinoids, including CBD, are also known to act on other receptors aside from the CB_1 and CB_2 receptors in the body (Table 1). CBD can inhibit fatty acid amide hydrolase, thereby inhibiting the enzymatic hydrolysis and uptake of AEA[101] from the synapse. This implies that CBD can therefore indirectly influence the effects on AEA in the endocannabinoid system, possibly allowing for sustained neuroprotective effects of AEA,[102,103] such as influencing CB_2 receptors to alleviate lipopolysaccharide-induced neuroinflammation.[104]

TRPV1 is a ligand-gated ion channel and acts on afferent neurons where it is expressed both presynaptically, and postsynaptically. This receptor is involved in the sensation of pain and thermal hyperalgesia.[105] CBD can function as a weak TRPV-1 agonist, which may explain its therapeutic ability in neuropathic pain,[94,101] as 10 $mg \cdot kg^{-1}$ of CBD administered to rats with acute inflammation showed an antihyperalgesic response.[94] Research by Benyó et al[106] highlights that the activation of TRPV1 is known to control vascular responses, thus hinting at the idea of CBD having different actions within the cerebral vasculature. Furthermore, Benyó et al suggest that phytocannabinoids and endocannabinoids have the ability to directly influence cerebrovascular resistance and blood perfusion of the brain[106] and that all cerebrovascular control pathways contain cells capable of being modulated by the different forms of cannabinoids. Considering that concussions can impair cerebrovascular reactivity,[73,107,108] it is possible that CBD's influence on TRPV1 can protect against these changes.

Another group of receptors upon which CBD is known to act are adenosine receptors, such as A2a receptors. These receptors can downregulate the release of other neurotransmitters such as dopamine and glutamate, and CBD is thought to increase brain

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Table 1: Non CB_1 and CB_2 receptors stimulated by CBD and their relevance to concussion pathophysiology

Receptor	Implications for concussion	Dose and model	Model of injury	Reference
TRPV1	Antihyperalgesic effect in response to inflammation	Male Wistar rats with acute inflammation; CBD 10 $mg \cdot kg^{-1}$	Intraplantar injection of 0.1 ml carrageenan (1%) in saline	Costa et al.[94]
5-HT_{1A}	Decrease in excitotoxicity, inflammation, and oxidative stress	1–2-day-old male piglets; CBD 1 $mg \cdot kg^{-1}$	Interrupted carotid blood flow and reduced inspired oxygen fraction to 10% to induce 30-min long cerebral hypoxic ischemia	Pazos et al.[95]
	Increase in cerebral blood flow	Male mice; CBD 0.1 to 10 $mg \cdot kg^{-1}$	Occlusion to the middle cerebral artery	Mishima et al.[96]
PPARγ	Suppress the increase in the blood brain barrier permeability (also an effect of 5-HT_{1A})	Human brain microvascular endothelial cells and human astrocytes; CBD 100 nM, 1 μM, and 10 μM	–	Hind et al.[97]
	Promotion of hippocampal neurogenesis and reduction in inflammatory biomarkers	Adult male Sprague-Dawley rats; CBD 10 $mg \cdot kg^{-1}$	Intrahippocampal injection of fibrillar Aβ (1–42) peptide	Esposito et al.[98]
A2a	Downregulate inflammatory biomarkers and attenuate microglia activation	Female mice; CBD 5 $mg \cdot kg^{-1}$	Intracerebral inoculation in the right hemisphere with plaque-forming units	Mecha et al.[99]
	Reduce inflammatory biomarkers and glutamate in hypoxic–ischemia	Forebrain of 7-to-10-day-old C57BL6 mice; CBD 0.1 to 1000 μM	Forebrain slices from 7-to-10-day-old subjected to oxygen–glucose deprivation	Castillo et al.[100]

TRPV1 = vanilloid receptor 1; A2a = adenosine receptor; 5-HT_{1A} = 5-hydroxytryptamine; PPARγ = peroxisome proliferator-activated receptor gamma; CBD = cannabidiol.

adenosine levels by reducing adenosine reuptake.[9] Furthermore, CBD-mediated activation of A2a receptors may also allow for increased anti-inflammatory effects, further increasing CBD's potential for enhancing neuroprotection.[100] Indeed, CBD was shown to downregulate inflammatory biomarkers and attenuate microglia activation in a viral mouse model of multiple sclerosis by interacting with A2a receptors.[99] Finally, it was suggested that CBD can blunt the THC-induced cognitive and memory impairments in an A2a receptor-dependent manner,[109] as shown by A2a receptor knockout mice performance in a two-object recognition test.[109]

CBD is also known to act directly upon the 5-HT_{1A} receptor, which is found in the brain in large concentrations, with large densities at the prefrontal cortex, hippocampus, and amygdala.[110,111] CBD has been shown to exhibit a high potency for this receptor and serves as an agonist, to further stimulate the receptor's properties of decreasing anxiety, pain, and headaches. 5-HT_{1A} is a G-protein-coupled serotonin receptor, which further suggests the potential of CBD to provide therapeutic benefits,[35] similar to those of serotonin itself. For example, it was found that CBD can enhance both serotonergic and glutamate cortical signaling in a mouse model, possibly allowing for rapid-acting antidepressant-like effects.[112] Furthermore, human cell culture, rat, and pig research has also shown CBD to be neuroprotective by inhibiting the reuptake of 5HT,[35,95] resulting in decreased excitotoxicity, inflammation, and oxidative stress.[95]

Peroxisome proliferator-activated receptor (PPAR) gamma (γ) is also thought to be influenced by phytocannabinoids to produce therapeutic effects.[113] PPARs are nuclear receptor proteins that function as transcription factors and are essential in the body's ability to regulate energy homeostasis and metabolic function.[114] As such, their involvement becomes increasingly important in stabilizing cell homeostasis. For example, it was shown that CBD suppresses the increased permeability of the blood brain barrier associated with oxygen–glucose deprivation by PPARγ and 5-HT_{1A} activation.[97,113] This was done using human brain microvascular endothelial cells and human astrocytes,[97] providing a valuable *in vitro* point of view rather than an animal model. In relation to other neurodegenerative disorders, cell culture research has shown that CBD reduces β-amyloid expression[113,115] and can possibly induce apoptosis in some forms of cancer cells, such as lung tumor cells,[113,116] via PPAR activation. PPARγ is thought to inhibit the expression of inflammatory cytokines,[114,117] suggesting possible CBD and PPARγ synergy to further regulate inflammation. This was further shown by CBD's inhibition of necrosis factor kappa b, nitric oxide, tumor necrosis factor alpha, and interleukin 1 beta, along with promoting hippocampal neurogenesis in a rat model. It is important to note that CBD's neuroprotective effects were completely abolished after introduction of a PPARγ antagonist (GW9662).[98]

Finally, a receptor initially known as the endothelial cannabinoid receptor, now thought to be G-protein-coupled receptor 18,[118,119] also serves as a receptor at which abnormal CBD (ABN-CBD), a synthetic CBD product, was shown to react.[118-120] This receptor is believed to be in existence as administration of CBD to mice lacking the cannabinoid receptors still resulted in hypotension and endothelium-dependent mesenteric vasodilation, yet administration of a CB_1 antagonist was shown to block the CBD effect.[106] It is therefore possible that CBD can help to regulate cerebral blood flow due to its influence on vasomotor control, meaning that the endothelial cannabinoid receptor and G-protein-coupled receptors stimulated by CBD can mediate neuroprotective effects and regulate cell migration.

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Concussion can result in a cascade of pro- and anti-inflammatory cytokines,[121] ionic imbalance,[63] increased lactate accumulation due to increased glycolysis and oxidative stress,[122,123] and impaired cerebral blood flow.[73] Through its influences on the cerebrovasculature, its anti-inflammatory properties, and its neuroprotective properties, CBD can theoretically help to reduce impairments following concussion. Furthermore, to control for the calcium sequestration and ionic inflow,[69] it has been suggested that CBD can regulate Ca^{2+} homeostasis against mitochondrial dysfunction and toxins, and Ca^{2+} dysregulation, as shown in tissue cultures of rat pups.[124]

Due to its neuroprotective capabilities and its lack of intoxicating side effects, CBD shows promising potential in helping individuals with TBIs. Mice induced with bilateral common carotid artery occlusion were administered 10 $mg{\cdot}kg^{-1}$ CBD which attenuated hippocampal neurodegeneration and white matter injury, increased hippocampal brain-derived neurotrophic factor protein levels, stimulated neurogenesis, and promoted dendritic restructuring.[125] Furthermore, CBD administration to mice both before and after occlusion of the middle cerebral artery showed that CBD suppressed the impairment in cerebral blood flow by the failure of cerebral microcirculation after reperfusion, providing further evidence of CBD's neuroprotective properties.[126] Adding to this evidence of neuroprotective potential, CBD administration to piglets exposed to acute hypoxia-ischemia increased the brain activity post-ischemia back to normal as shown by brain electrical activity, cerebral tissue oxygenation, and neurobehavioral responses, such as motor performance.[127]

Blood Brain Barrier

Concussions can alter cerebrovascular actions by disrupting the blood brain barrier integrity.[128] Cannabinoids, specifically 2-AG and dexanabinol, a synthetic cannabinoid also known as HU-211, have been shown to decrease proinflammatory cytokines such as tumor necrosis factor-alpha[129] and necrosis factor kappa b.[130] Cytokines have been shown to overexpress following concussion,[121] which can lead to a heightened sensitivity for disease, such as multiple sclerosis or Alzheimer's, at the blood brain barrier.[131] Furthermore, head injuries tend to enhance the activity of water-soluble antioxidants in the brain.[132]This occurs along with an increase in 2-AG,[133] which can further increase the levels of the water-soluble antioxidants,[134] suggesting a regulator ability for the endocannabinoid in neuroprotection with the blood brain barrier,[133] especially as synthetic 2-AG administration in a mouse model resulted in reduced brain edema, infarct volume, and hippocampal cell death.[133] The blood brain barrier controls the amount of material transported into the brain, and in combination with the CB_1 and CB_2 receptors, it can limit and protect the brain against the influx of neurotoxins, immune cells, and macromolecules,[135] thus allowing maintenance of an optimal extracellular environment in the brain.[106] This allows for prevention of apoptosis, glia cell activation, and scar tissue formation, among other symptoms caused by these substances. While CB_1 and CB_2 receptors are involved in the blood brain barrier, 2-AG is effective as a full CB receptor agonist,[136,137] which may help explain its anti-inflammatory properties[39,100] due to its influence on the CB_2 receptor. CBD's lipophilic properties allow it to easily pass the blood brain barrier.[9] While research pertaining to CBD's influence at the blood brain barrier in humans is limited, it has been shown that CBD can preserve the barrier's integrity (permeability), possibly by protecting against the loss of tight junction proteins by acting on PPARγ and 5-HT1A receptors.[97,138]

Adding to CBD's neuroprotective properties, oxidative stress is greatly modulated by CBD as well.[139-142] Following a TBI, there is an increase in free radical production, such as reactive oxygen species.[143,144] Under oxidative stress, the protective effect of CBD is thought to be mediated by a decrease in reactive oxygen species production.[140] This can be due to the electrophilic aromatic molecular region and hydroxyl groups of CBD, potentially allowing it to act as an antioxidant itself.[145-147] Post TBI, N-methyl-d-aspartate (NMDA) receptor binding by glutamate allows for intracellular accumulation of Ca^{2+}, causing cellular damage via proteases, reactive oxygen species, and mitochondrial impairment.[69,70] NMDA-induced retinal neurotoxicity in rats was also shown to be treated by intravenous injection of CBD to the eye at 2 $mg{\cdot}kg^{-1}$, which further shows the antioxidative properties of CBD, as it reduced both oxidative and nitrative stress.[148]

Brain-Derived Neurotrophic Factors

Brain-derived neurotrophic factors (BDNF) is a protein that promotes the survival of nerve cells. It is known to increase the frequency of miniature excitatory postsynaptic currents, possibly strengthening excitatory, glutamatergic synapses and weakening inhibitory, GABAergic synapses.[149,150] In cases involving encephalopathy, the administration of 5 $mg{\cdot}kg^{-1}$ CBD was shown to help restore BDNF levels in mice through the activation of the $5\text{-}HT_{1A}$ receptor.[151] Furthermore, withdrawal from amphetamines can diminish BDNF levels due to oxidative stress.[152] This decrease in BDNF has been shown to be blocked by the administration of 60 $mg{\cdot}kg^{-1}$ dosages of CBD in a rat model,[153,154] suggesting that CBD may have a great potential for aiding in addiction recovery and attenuate reductions in BDNF levels. Finally, 30 $mg{\cdot}kg^{-1}$ dosages of CBD have been shown to upregulate BDNF following cerebral malaria in a rodent model through the nitric synthase pathway.[155] This ability of CBD to increase BDNF expression can suggest an important role in neuroprotection, leading to decreased neuronal damage.[153] BDNF is also thought to enhance neurogenesis,[149] further suggesting CBD's restorative potential. At the prefrontal cortex and hippocampus, CBD was shown to elevate BDNF levels, resulting in sustained antidepressant-like effects in mice.[156] Considering that BDNF levels can be impaired following TBI in humans[157,158] and there is a correlation between BDNF serum levels and cognitive impairments,[159] it is possible that CBD administration post-concussion can further aid in the recovery process.

Cognitive Capacity

Cognitive capacity is the total amount of information the brain can retain at any moment. Functional magnetic resonance imaging (fMRI) is a neuroimaging method used to measure brain activity by observing correlations relative to blood flow, thus allowing measurements of neural mechanisms of cognitive capacities.[160] Using this fMRI technique, for example, it was found that THC and CBD have distinct effects on regional brain activation,[161] sometimes even completely opposite effects[161,162] when 10 mg THC, 600 mg CBD, or placebo capsules were

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administered to 14 healthy human volunteers. This study found that found that THC decreased the activation of bilateral temporal cortices during auditory processing and was associated with increases in anxiety, intoxication, and positive psychotic symptoms. It also influenced visual processing. In contrast, CBD administration did not have any reductive effects on areas such as visual processing and showed no significant symptomatic effects such as psychotic symptoms and increases in anxiety,[161,162] suggesting that CBD alone can provide therapeutic benefits without the intoxication of THC.

Interestingly, THC and CBD have also shown opposite effects on cognition-related brain activation. It has been suggested that the harmful effect of cannabis might be driven by high THC/low CBD compositions,[163] as shown by poor performances on verbal memory task,[164] reduced emotional processing accuracy,[165] and poorer verbal memory performance.[166] Combination of CBD and THC allows a reduction in the psychotic effects of THC, and thus CBD is able to partially prevent the detrimental effects of THC on working memory.[163,166] Finally, higher THC concentrations found in hair strands were shown to negatively impact memory and psychological well-being, whereas lower psychosis-like symptoms were found in individuals with higher CBD concentrations in their hair,[167] further showing CBD's nonintoxicating therapeutic influence.

Cerebrovasculature

CBD administration following TBI possesses strong potential to significantly reduce inflammation via the reduction in microglia activation and proinflammatory cytokines.[90,134,153] As discussed earlier, during brain trauma, the endocannabinoid system is activated by the rise in intracellular Ca^{2+}. Activation of the endocannabinoid system suggests that it is part of the compensatory repair mechanism for the brain.[168] Since cerebral blood flow is tightly regulated by myogenic, endothelial, metabolic, and neural mechanisms, all major cell types involved in cerebrovascular control pathways are capable of synthesizing endocannabinoids.[106] Finally, CBD administration has been shown to increase cerebral blood flow following middle cerebral artery occlusion by action on 5-HT_{1A} receptors.[96,169] As such, it is logical to hypothesize that the endocannabinoid system modulates the regulation of cerebral circulation[170] under both physiological and pathophysiological conditions.[106]

Regulation of blood flow following a TBI can be beneficial in assuring adequate nutrient supply to areas of altered metabolic activity. This compensatory phenomenon in healthy individuals is internally regulated through a mechanism known as neurovascular coupling. While no direct studies have shown CBD's influence on this mechanism, the role of the endocannabinoid system in cerebral circulation[106] and the presence of TRPV1 at the sensory vagal afferent neurons and the tunica of blood vessels[25] give CBD the cardioprotective potential. Concussion may lead to changes in the neurovascular coupling response,[67,76,171] and CBD has been shown to regulate cerebral blood flow[172] and influence pial vessel responses by regulating vascular effects in combination with protecting the blood brain barrier.[173] Keeping in mind that the cannabinoid receptors and TRPV1 are located at the cerebrovasculature,[106] CBD's ability to sustain high AEA levels by inhibiting fatty acid amide hydrolase[174] suggests an indirect effect on CB receptors. Further stimulation of CB_2 receptors by AEA can allow for regulation of nitric oxide, thereby potentially suppressing neuroinflammatory reactions,[104] which suggests great potential in combination with the CB_1 receptor stimulation to promote neuroprotection, as the neuroprotective effects of AEA are also mediated by the CB_1 receptor.[102]

Finally, functional connectivity impairments have also been shown following concussion. Specifically, patients with persistent post-concussion symptoms have reduced connectivity and reduced coherence during memory tasks,[175] and reduced connectivity in the default mode network during resting states has also been shown in subacute patients and patients assessed less than 3 weeks post injury.[176,177] Human research has shown that THC intake resulted in decreases in the default mode network activation (a large scale of interacting brain regions known to have activity highly correlated with each other, especially during task disengagement[178]), whereas a combination of THC and CBD attenuated the disruption in this network seen when THC is taken alone.[179] Patients with autism spectrum disorder were administered 600 mg of CBD and they also showed changes in functional connectivity as assessed by the fractional amplitude of low-frequency fluctuations.[180] While the direct underlying mechanism by which CBD regulates functional connectivity requires more research, there is a clear therapeutic effect on functional connectivity following CBD intake.

Dopaminergic Impairments following Concussion

TBIs can result in impaired dopamine signaling at the brain. Specifically, the long axonal projections in the dopaminergic nigrostriatal and mesocorticolimbic pathways can be disrupted due to mechanical damage, which induces oxidative stress, axonal damage, and postsynaptic neuron impairments.[55,181] Following these acute changes, sustained dopamine impairments due to TBI results in BDNF reduction, increase in inflammatory processes, and metabolic dysregulation.[55] In combination with epigenetic effects and mitochondrial dysregulation,[55,182] TBIs can therefore result in impairments in dopamine synthesis and metabolism.[55] Rodent studies have shown that THC can result in increased dopamine neuron firing rates, while human studies have shown mixed responses.[54] CBD has been shown to be a partial agonist at dopamine receptors in rat striatal tissue, potentially explaining some of its antipsychotic effects.[183] Furthermore, in a rat model of Parkinson's disease, CBD was shown to attenuate loss of dopaminergic neurons and microglia activation.[184,185] CBD and THC both seem to aid in neuroprotection of dopaminergic pathways following mTBI and TBI.

Cardiovascular Physiology in Relation to Concussion

CBD has also been shown to exert its protective influences over the cardiovascular system. For example, diabetes is known to cause dysfunction and cardiac autonomic abnormalities[186] by mechanisms such as hyperglycemia-induced overproduction of reactive oxygen species and impaired antioxidant enzyme activities. Administration of ABN-CBD has been shown to attenuate these effects in rats and even promote vagal responses (such as decreased heart rate and mean arterial pressure), supported by a high frequency increase in the electrocardiogram (ECG) R-R index spectral analysis.[187] It is important to note that heart rate variability impairments have been noted following concussion,[74,188,189] although the specific physiological mechanism(s) is still unknown.

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As concussion can occur due to any transient neurologic dysfunction resulting from a biomechanical force,[63] an injury leading to autonomic dysfunction may further lead to changes in heart rate variability. Furthermore, decreased global heart rate variability is also thought to be related to arrhythmic mortality.[190-192] CBD's ability to reduce arrhythmic events (ventricular tachycardia and total length of arrhythmias)[193] suggests further potential to treat cardiovascular complications arising from concussion. It has been shown that there are some changes in heart rate variability when getting the participant to exercise,[66,188] but the data are still unclear as to what the changes imply. Regardless, it is clear is that dysfunction occurs following concussion, and considering the effect of ABN-CBD to influence endothelial cannabinoid receptors, it follows that phytocannabinoids can potentially help regulate the cardiovascular system following dysfunction.

Neurogenesis

Following mTBI, neuronal cell death is usually a result of increased intracellular Ca^{2+} concentration, as this increases glutamate release across the synapse, activation of NMDA receptors, and thereby increasing Ca^{2+} concentration. This can further lead to increased enzymatic activity, specifically enzymes which can induce apoptosis. The ability of phytocannabinoids and endocannabinoids to inhibit N- and P/Q-type calcium channels[194] and the ability of CBD to induce a hyperpolarizing shift in the steady state inactivation potentials of the T-type calcium channels[195] imply that there is potential for CBD to aid in neurogenesis and protection against neurodegenerative processes.

Endocannabinoids are known to be produced by neural progenitor cells which can stimulate proliferation at the hippocampal and subventricular zones via CB_1 receptors, as documented by neurosphere generation.[196] CBD has been suggested to have a restorative effect on regions of the hippocampus which may be damaged due to prolonged cannabis use.[197] Furthermore, mice with knocked-out fatty acid amide hydrolase enzyme express a higher concentration of 2-AG, which has been shown to induce astrogliogenesis.[198] The mechanism behind CBD's ability to regulate neurogenesis seems to involve the mitogen-activated protein kinase (MAPK) pathway, activation of which allows neural progenitor cell proliferation, whereas the CB_1 receptor -mediated inhibition of the proliferation is due to the attenuation of sustained MAPK activity.[196,199] These results suggest that CBD and the endocannabinoids themselves can be key compounds in neurogenesis.

Gaps and Limitations in the Literature

While there is strong preclinical and basic science evidence to show that CBD has the potential to be a candidate for concussion treatment, it is important to note that no double-blind, randomized controlled trials have been completed to show CBD as an efficacious medication following these mTBIs. As our review suggests, there is substantial evidence shown through rodent models which does imply that there are benefits for administration of CBD for concussion recovery. Following this note, there is a clinical trial currently in the recruitment phase (Identifier number: NCT03826368) utilizing CBD as a dietary supplement to aid in recovery from brain injury in humans. Pharmacological treatment for concussion and post-concussion syndrome has been a persistent issue because of the complex nature of the injury,[63] underreporting of the injury,[200] and the absence of common physiological impairments or symptomology.[3] The exact pathophysiology of concussion is still being researched, and as such there may be effects of CBD upon concussion which can potentially go unnoticed. Regardless, the presented research does provide a strong framework for future studies on the therapeutic evaluation of CBD on concussion.

Conclusion

This review presents research to suggest the potentially beneficial effects of CBD in treatment following mTBI such as concussion. CBD appears to regulate ionic balance, act as an anti-neuroinflammatory, attenuate dopaminergic pathway damage, and suppress the impairments of cerebral blood flow, heart rate variability, and the blood brain barrier. The general consensus for treatment following concussion is continuing to evolve,[201] as the exact pathophysiology is not yet understood. Because there are many physiological consequences that arise due to head trauma, a single remedy to treat all impairments seems like a monumental task without assuming a polyprescription approach, which may result in a large amount of unwanted side effects. Although direct human research and double-blind randomized controlled trials are still lacking, there is much preclinical evidence and theoretical framework available to support the idea of using CBD following concussion due to its neuroprotective properties.

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Statement of Authorship

JS and JPN conceived and revised this paper.

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