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Review Article

Neuroprotection by Micronutrients and Cannabidiol (CBD) in Neurodegenerative Diseases

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ABSTRACT

The major objectives of this review are to elucidate the role of antioxidants and cannabidiol (CBD) in reducing oxidative stress, inflammation, and glutamate levels, which contribute to the pathogenesis of human neurological diseases. Antioxidants act by: (a) donation of electrons to molecules with unpaired electrons to neutralize them, (b) activation of ROS-resistant Nrf2 to enhance the levels of antioxidant enzymes, (c) restoration of deficiency of antioxidants to normal levels, (d) alterations in the expression of microRNAs, which guide their respective mRNAs to translate protective proteins, and (e) prevention of the release and toxicity of glutamate. CBD acts by: (a) activating endocannabinoid system, which consists of anandamide and archidonoylglycerol, cannabinoid receptors CB1R and CB2R, and their synthesizing and degrading enzymes, (b) acting as an agonist to non-cannabinoid receptors, such as dopamine, serotonin, and adenosine, (c) acting as an inhibitor of serotonin re-uptake, and (d) acting as an antagonist to glutamate receptors. Since antioxidants and CBD act primarily by different mechanisms, it is proposed that combination of the two may be more effective than either individually. No review on this topic has been published. Pre-clinical and clinical studies are suggested to test the efficacy of proposed combination in selected neurodegenerative diseases.

Introduction

Increased oxidative stress, chronic inflammation, and glutamate levels play a central role in the pathogenesis of Alzheimer's disease, Parkinson's disease, Huntington's disease, and post-traumatic stress disorder. Mammals have two highly evolved endogenous defense systems: antioxidant system and endocannabinoid system to protect against the above cellular defects. The evolution of antioxidant system started approximately 4 billion years ago when anaerobic organisms were forced to develop antioxidant system to protect against oxygen toxicity. The evolution of endocannabinoid system occurred much later, since it is found only in vertebrates [1]. Many antioxidant compounds were identified between 1912-1936; however, the discovery of endocannabinoid system was made in early 1990 [2-4]. An antioxidant system, which consists of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, and antioxidant compounds, such as dietary (vitamins A, vitamin E, and vitamin C) and endogenous antioxidants (glutathione and coenzyme Q10), can be activated by Nrf2 and dietary and endogenous antioxidant compounds whenever deficiency occurs. On the other hand, activation of endocannabinoid system, which consists of cannabinoid ligands anandamide and archidonoylglycerol (2-AG)), cannabinoid receptors CB1R and CB2R, and their synthesizing and degrading enzymes is achieved by cannabidiol (CBD), which is isolated from *Cannabis sativa* in 1940 [4-7]. The antioxidant and endocannabinoid systems are responsible for maintaining homeostasis in the body.

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Normally, activities of the antioxidant system and endocannabinoid system remain low. However, a short-term exposure to stressors, such as increased oxidative stress, pro-inflammatory agents can simultaneously enhance the antioxidant system and endocannabinoid system in order to protect against injurious effects of these stressors [8]. If the exposure to stressors is short-lived and mild, both the antioxidant system and endocannabinoid system may return to original levels after discontinuation of stressors. However, if the exposure to stressors is prolonged, they overwhelm protective effects of both the antioxidant system and the endocannabinoid system, leading to increased oxidative damage. Oxidative damage of cells, if not repaired, can lead to chronic inflammation. Both increased oxidative stress and chronic inflammation are involved in the onset and development of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and post-traumatic stress disorder (PTSD) [9-12]. Additionally, increased release of glutamate leading to excitotoxic events is involved in the pathogenesis of PD, HD, and PTSD.

The major functions of antioxidants in neuroprotection include: (a) donation of electrons to molecules with unpaired electrons to neutralize them; (b) activation of ROS-resistant Nrf2 to enhance the levels of cytoprotective enzymes including antioxidant enzymes; (c) restoration of reduced levels of dietary and endogenous antioxidant compounds to normal levels; (d) alterations in the expression of microRNAs, which allow translation of protective proteins from their respective mRNAs; and (d) Certain antioxidants (vitamin E and coenzyme Q10), and vitamin- B12 prevent the release and toxicity of glutamate [13-16]. By these mechanisms, antioxidants may provide neuronal protection against neurodegenerative diseases. These aspects have been previously discussed [9-11].

The major functions of CBD in neuroprotection include (a) activating the endocannabinoid system and non-endocannabinoid receptors; (b) enhancing the levels of cannabinoid ligand anandamide, which acts as an agonist to both CB1R and CB2R; (c) acting as an agonist of CB2R leading to a reduction in the levels of inflammation and pain; (d) acting as an agonist to transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors, adenosine receptor (A2A), and serotonin (5-HT1A) receptor and (e) acting as an antagonist to GPR55 and GPR18, and glutamate receptor (NMDA) [17-26].

The above studies suggest that antioxidants and CBD provide neuroprotection by different mechanisms. Therefore, the combination of antioxidants and CBD could be more effective than the individual agents in improving neuronal function in neurodegenerative diseases. No studies with antioxidants together with CBD on neurodegenerative diseases have been performed.

This review briefly describes: (a) function of the endocannabinoid system in the brain; (b) CBD-induced neuroprotection by activating and deactivating the endocannabinoid receptors and non-cannabinoid receptors, using primarily experimental models of Alzheimer's disease, Parkinson's disease, Huntington's disease, and post-traumatic stress disorder; and (c) presents scientific rationale in support of a hypothesis that combination of antioxidants with CBD may be more effective in enhancing neuronal protection in the neurodegenerative diseases than the individual agents.

Function of Endocannabinoid System

Natural and synthetic inhibitors of fatty acid amide hydrolase (FAAH), which degrades anandamide and monoacylglycerol (MAGL), which degrades 2-archidonoylglycerol (2-AG), and natural and synthetic agonists and antagonists of CB1R and CB2R are described in (Table 1). These agents have been used to investigate the mechanisms of action of endocannabinoid system in the brain. Endocannabinoids are called retrograde messenger because they travel in the opposite direction to other neurotransmitters, such as serotonin, dopamine, glutamate, and GABA (gamma amino butyric acid). Normally, these neurotransmitters are released from pre-synaptic neurons and travel to their respective post-synaptic neurons for further action. In contrast, when stress occurs, cannabinoid ligands anandamide and 2-AG are synthesized and released from post-synaptic neurons and travel backward to pre-synaptic neurons where CB1R and CB2R already present [27, 28]. Stimulation of these CB receptors by anandamide can inhibit release of inhibitory or excitatory neurotransmitters. Activation of CB1R inhibited GABA and glutamate release from pre-synaptic terminals, which may be one of the mechanisms of its neuroprotection [29, 30].

Table 1: Natural and synthetic inhibitors of FAAH and MAGL, and natural and synthetic agonists and antagonists of CB1R and CB2R.

Inhibitor of FAAH	URB597, CBD
Inhibitor of MAGL	JZL184
Agonist of CB1R and CB2R	WIN55, 212,2
Agonist of CB2R	CBD
Antagonist of CB1R	CBD, AM281, AM251
Antagonist of CB2R	AM360

FAAH: Fatty acid amide hydrolase, which degrades anandamide; MAGL: Monoacylglycerol, which degrades 2-archidonoylglycerol (2-AG); CB1R: Cannabinoid receptor CB1; CB2R: Cannabinoid receptor CB2; CBD: Cannabidiol.

Anandamide and 2-AG act as an agonist to CB1R and CB2R, and non-cannabinoid receptors. For example, anandamide activated the transient receptor potential cation channel subfamily V member 1 (TRPV1) that plays a significant role in synaptic transmission and pain regulation [31, 32]. Anandamide is involved in regulation of appetite and memory, whereas 2-AG is involved in regulation of emotion, protection from seizures, and cardiovascular health.

Anandamide activated GRP55 receptor, which increases intracellular calcium in the large dorsal root ganglion neurons where it is highly expressed [33-35]. Activation of CB1R reduced NO production, and increased expression of brain-derived neurotrpphic factor (BDNF) [36, 37]. Activation of CB1R also inhibited glutamate receptor (NMDA), which, in part, may be responsible for neuroprotection against excitotoxicity [25, 26].

CBD- Induced Activation of the Endocannabinoid Receptors and Non-Cannabinoid Receptors

Although a few synthetic compounds, which act as agonists or antagonists to cannabinoid and non-cannabinoid receptors are available (Table 1). CBD is the only naturally occurring phytocannabinoid, which is safe, legal, and increases the levels of anandamide by inhibiting its degradative enzyme fatty acid amide hydrolase (FAAH). Elevated anandamide then acts as an agonist to CB1R and CB2R [17, 18]. CBD also directly acts as an agonist of CB2R leading to a reduction in the levels of inflammation and pain [19]. CBD prevents the release of glutamate by activating anandamide, which stimulates CB1R that acts as an antagonist of glutamate receptor NMDR [25, 26]. CBD also acts as an agonist to non-cannabinoid receptors, such as dopamine receptors, serotonin receptors, adenosine receptors, and transient receptor potential vanilloid 1 (TRPV1) receptors [20-23]. Activation of TRPV1 receptors makes them resistant to further stimulation [38].

Thus, CBD-induced analgesic effect is mediated by activation of TRPV1 receptors. CBD-induced elevated anandamide activates the TRPV1 receptor, which regulates synaptic transmission and pain [39]. CBD treatment also stimulates serotonin (5-HT1A) receptor and inhibits serotonin re-uptake [22, 23]. On the other hand, CBD acts as an antagonist of GPR55 and GPR18 [24]. Thus CBD-induced reduction in inflammation may be mediated by decreasing the activities of GRP55 and GRP18 receptors. CBD under certain conditions also exhibits modest antioxidant and anti-inflammation activities [40-42].

Neuroprotection by Antioxidants and CBD in Selected Neurodegenerative Diseases

Antioxidants and CBD have been used individually primarily in animal models of Alzheimer's disease, Parkinson's disease, Huntington's disease, and Posttraumatic stress disorder. Although antioxidants have been used in most human neurodegenerative diseases, whereas, CBD has been used only in human Parkinson's disease and Huntington's disease. Although both antioxidants and CBD individually have produced beneficial effects on animal models, they have produced only transient minimal beneficial or no effects in human neurodegenerative diseases. The effects of antioxidants and CBD on neuropritectin the AD, PD, HD, and PTSD are separately described here.

Effects of Antioxidants and CBD on Alzheimer's Disease

I Alzheimer's Disease

Alzheimer's disease (AD) is a slow progressive neurodegenerative disease, which is characterized by gradual loss of cognitive function due to depletion of cortical neurons from the brain. In 2017, it was estimated that American develop AD every 66 second, and by 2050, someone would develop AD every 33 seconds [43]. This disturbing trend may continue until evidenced-based prevention and improved treatment strategies of AD are implemented. In order to develop such strategies, it is important to recognize early cellular or genetic defects, which initiate and promote the development and progression of AD. Extensive studies have identified several such deficits.

These include increased oxidative stress, chronic inflammation, mitochondrial dysfunction, generation of Aβ1-42 peptides from the cleavage of amyloid precursor protein (APP), proteasome inhibition, high cholesterol levels, heritable mutations in APP, presenilin-1 and presenilin-2 genes [44]. Investigations suggest that increased oxidative damage precedes other cellular deficits. Asymptomatic individuals carrying mutated AD gene exhibit increased levels of markers of oxidative damage and pro-inflammatory events [45, 46]. Therefore, attenuation of increased oxidative stress and sustained inflammation would be helpful in reducing the risk of development and progression of AD.

II Antioxidants in AD

The effects of individual antioxidants and their limitation on AD have been reviewed [44]. Administration of single antioxidants produced consistent benefits in prevention and improvements of some symptoms of AD in animal models; however, it produced inconsistent benefits varying from no effect to modest effect in early phase AD in humans. The failure to obtain consistent benefit in human AD could be due to the fact that a single antioxidant may not be sufficient to reduce oxidative stress and chronic inflammation at the same time.

In view of several limitations of using single antioxidants in populations at risk of developing AD, we have proposed that in order to simultaneously reduce oxidative stress and chronic inflammation, it is essential to elevate the levels of antioxidant enzymes through activation of Nrf2/ARE pathway, together with administration of dietary and endogenous antioxidant compounds. A comprehensive mixture of micronutrients containing dietary and endogenous antioxidants, curcumin, resveratrol, all B-vitamins, vitamin D3, and mineral selenium has been suggested [44]. Antioxidants present in this mixture also reduce the production and aggregation of beta-amyloids as well as their toxicity on neurons. These issues are discussed in a recent review [11, 44].

III CBD in AD

CBD prevented cognitive dysfunction in an animal model of AD by mechanisms, which, in part, are different from those produced by antioxidants (Table 2). Treatment with CBD prevented beta-amyloid - induced impairment of learning of a spatial navigation task. This beneficial effect of CBD was due to reduction in inflammatory events such as gliosis, activation of microglia, and induction of neurogenesis in mice as well as in transgenic rat model of AD [41, 42].

CBD treatment also reversed and prevented the development of cognitive dysfunction in rat model of AD. Treatment with CBD reduced the risk of AD by activating PPAR-gamma (peroxisome proliferator-activator receptor-gamma). CBD treatment also stimulated hippocampal neurogenesis by activating PPAR- gamma, which reduced inflammation in a rat model of AD. The role of PPAR-gamma in reducing beta-amyloid-induced gliosis and neuronal damage is supported by a report that treatment with an antagonist of PPAR-gamma prevented these effects of CBD on hippocampal neurons [47].

Treatment of primary culture of astrocytes with amyloid Aβ1-42 decreased viability and increased pro-inflammatory cytokines levels

leading to enhanced levels of inflammation; however, it also decreased PPAR-gamma and antioxidant enzyme Cu/Zn superoxide dismutase (SOD). These beta-amyloid-induced changes would increase the levels of oxidative damage and inflammation. Treatment of astrocytes with a synthetic cannabinoid WIN55, 212-2 prevented all the effects of amyloid Aβ1-42 [48]. It is likely that the endogenous cannabinoid anandamide, which is activated by CBD, would produce similar effects on astrocytes. CBD treatment of APP neurons (SHSY5Y) increased ubiquitination of APP leading to increased degradation of APP+, and decreased production of beta-amyloids, which resulted into increased survival of neurons.

Table 2: Differential actions of antioxidants and cannabidiol (CBD).

Action of Antioxidants	Action of CBD
Donate electron to molecules with unpaired electron	Antagonist to CB1R and agonist to CB2R
Activate ROS-resistant Nrf2	Elevates anandamide which acts as an agonist to CB1R and CB2R
Enhance the expression of microRNAs	Acts as an agonist to dopamine, serotonin, and adenosine receptors
Alter gene expression	Acts as an antagonist to glutamate Receptors
Reduce release and toxicity of glutamate	Activates PPAR-gamma
Reduce pro-inflammatory cytokines	Acts as an inhibitor of serotonin-re-uptake
	Increases expression of genes coding for anti-inflammatory cytokines
	Activates NGF receptor
	Week antioxidant and ant-inflammation activities

CB1R: Cannabinoid receptor CB1; Nrf2: Nuclear factor-erythroid-2-related factor-2; PPAR-gamma: Peroxisome proliferator-activator receptor-gamma; NGF: Nerve growth factor.

These effects of CBD are mediated via activation of PPAR-gamma in APP+ neurons [49]. CBD treatment prevented beta-amyloid-induced hyperphosphorylation of tau protein, and attenuated oxidative stress and mitochondrial respiration by activating PPAR gamma in neurons in culture (PC12 neuronal cell line). CBD also suppressed inflammatory signals through activation of PPAR-gamma [50].

Pre-treatment with CBD protected synaptic plasticity in an in vitro model of AD by such activation [51]. CBD treatment prevented the development of social recognition deficits as well as cognitive dysfunction in AD transgenic mice by reducing oxidative stress and inflammation [52]. Pre-treatment of mesenchymal stem cells in culture with CBD downregulated genes linked to AD, including genes coding for the kinases responsible for the phosphorylation of tau protein and for the enzyme's secretases, which cleaved APP to generate beta-amyloids. CBD also inhibited the expression of glycogen synthase kinase 3β (GSK3β), which plays an important role in the pathogenesis of AD by enhancing phosphoinositide-3-kinase/ Akt (PI3K/Akt) signaling [53]. CBD exhibits antioxidant and anti-inflammation activities *in vitro* [42]. No studies on the effect of CBD alone on Alzheimer's disease in humans have been performed.

Effects of Antioxidants and CBD on Parkinson's Disease (PD)

I Parkinson's Disease

Parkinson's disease is a slow progressive neurological disorder of the brain. This disease is characterized by the loss of dopamine neuron in the brain. The major symptoms include tremor, muscle rigidity, postural problem, gait disorders, speaking difficulties, cognitive dysfunction, and immobility. Parkinson Foundation estimates about 60,000 new cases each year in the United States. The risk of this disease increases after the age of 50 years.

Increased oxidative stress, chronic inflammation, and glutamate levels are involved in the initiation and progression of PD in animal and human models [10]. Therefore, attenuation of these cellular defects may help in reducing the risk of development and progression of PD.

II Antioxidants in PD

Most studies have utilized primarily single antioxidants in animal and human models of PD. Studies on animals revealed consistent benefits of single antioxidants; however, they have shown variable results ranging from no effect to modest effect on PD in humans [10]. A single antioxidant may not be sufficient to reduce oxidative stress, chronic inflammation, and glutamate at the same time in human PD. Problems associated with the use of a single antioxidant in human PD have been discussed in a recent review [10]. In order to avoid limitations of using single antioxidants, a comprehensive mixture of micronutrients proposed for Alzheimer's disease is also recommended for PD [10]. This micronutrient mixture may reduce increased oxidative stress, chronic inflammation and glutamate levels at the same time. Antioxidants present in this mixture also reduce aggregation of alpha-synuclein, which is neurotoxic to dopamine neurons. These issues are discussed in a recent review [10].

III CBD in Experimental Models of PD

Repeated treatment with reserpine induces motor impairment and cognitive deficits in rats; therefore, it has been considered as a model for PD. Administration of CBD attenuated reserpine-induced motor and cognitive dysfunction [54]. 1-Methyl-4-phenylpyridinium (MPP+) is used as a model compound to induce PD in animals and causes toxicity in dopamine neurons in culture. Treatment with MPP+ decreased the number of mouse mesencephalic cells in culture and length of neurite. These toxic effects of MPP+ were prevented by the treatment by CBD [55]. CBD treatment of neuronal cells in culture (PC12 cell line) before addition of MPP+ enhanced viability, differentiation, and the expression of axonal protein (GAP-43) as well as synaptic proteins. CBD did not enhance the expression of NGF, but it prevented its MPP+-induced decline in viability of neurons in culture. CBD also enhanced neurite formation, which was inhibited by NGF receptor (trkA) inhibitor (K252a), suggesting that neuroprotection effect of CBD against MPP+ is mediated via trkA and not by NGF [56].

Treatment with archidonoyl-2-chloroethylamide (ACEA), an agonist of CB1R, did not affect the damage cause by hydroxydopamine (OHDA)-induced unilateral lesions of nigrostriatal dopaminergic neurons; however, HU-308, an agonist of CB2R, partially promoted recovery of the lesion. Administration of CBD was effective in restoring dopamine levels in OHDA treated dopamine neurons when injected immediately after the lesion; but it was ineffective when injected one week later. This effect of CBD was likely mediated via its antioxidant activity since it increased the levels of only one antioxidant enzyme Cu/Zn-SOD. CBD-induced activation of CB2R contributes to the protection by reducing inflammation [40].

IV CBD in Human PD

A pilot study has found that CBD treatment improved quality of life measures in PD patients with no psychiatric comorbidities [57]. CBD treatment improves the non-motor symptoms, such as psychiatric disorders (psychosis, depression, and anxiety), rapid eye movement, sleep disturbance, and cognitive deficits [58].

Effects of Antioxidants and CBD on Huntington's Disease (HD)

I Huntington's Disease

Huntington's disease is a progressive, fatal, hereditary, and incurable neurodegenerative disease of the brain in which the striatum and cortex areas of the brain are gradually destroyed. The symptoms include involuntary jerky movements of the limbs, trunk, and face, psychiatric problems, muscle rigidity, and loss of control of voluntary muscle movements. The annual incidence of HD in the USA is about 1,550 new cases, and the prevalence of this disease in the USA, Europe, and Australia is 5-7 cases/100,000 individuals, whereas in the Asia, it is only 0.4 cases/100,000 [59]. It is estimated that the prevalence of HD enhances by 15-20% every decade [60].

Dysfunction of dopamine receptors is found in asymptomatic and symptomatic patients with HD as well as in animal model of HD [61, 62]. Genetic deletion of adenosine receptor (A2AR) in a transgenic HD mouse model aggravated motor performance and reduced survival [63]. Treatment with an A2AR agonist improved some of the electrophysiological symptoms of disease in mouse model of HD [64]. Several investigations have revealed that increased oxidative stress chronic inflammation, and glutamate level are involved in the initiation and progression of HD. In addition, functions of dopamine receptors, adenosine receptors, and glutamate receptors are impaired in HD [11]. Therefore, attenuation of these cellular defects may delay the onset as well as reduce the progression of the disease.

II Antioxidants in HD

The studies of antioxidants in the initiation and progression of HD has been discussed [11]. These studies primarily on animal models show that supplementation with individual antioxidants reduce the risk of developing and progression of HD-related symptoms. A single antioxidant may not be sufficient to reduce oxidative stress, chronic inflammation, and glutamate at the same time in human HD. Problems associated with the use of a single antioxidant in human HD have been discussed in a recent review. In order to avoid limitations of using single antioxidants, a comprehensive mixture of micronutrients proposed for Alzheimer's disease is also recommended for HD [11]. This micronutrient mixture may reduce increased oxidative stress, chronic inflammation and glutamate levels at the same time.

III CBD in Experimental Models of HD

Treatment with CBD reversed 3-nitropropionic acid (3-NP)- induced striatal lesion in rats, reduced gamma-aminobutyric acid (GABA) levels, and enhanced the levels of one antioxidant enzyme. These effects of CBD are not mediated via CBR2, Vanilloid TRPV1 receptor or adenosine receptor (A2A) [21]. Using huntingtin knockout mice, activation of CB1R protected neurons against glutamate-induced toxicity via PI3K/AKt signaling, which mediates its action by increasing the level of BDNF (brain-derived neurotrophic factor) [65]. Impairment of endocannabinoid system and dopaminergic neuronal function are one of the important markers of HD in Q175 mouse model of HD. Elevation of 2-AG, one of the cannabinoids, restored these changes [66]. Neurons (PC-12) expressing mutated huntingtin protein exhibit rapid cell death. However. Treatment of these cells with CBD markedly reduced the extent of cell death [67].

A transgenic mouse model of HD (R6/2 mice) is characterized by progressive degeneration of striatum in the brain, deterioration of rotarod (motor performance), and increased clasping behavior reflecting dystonia. Treatment with the sativex-like combination of THC and CBD at 1:1 ratio was ineffective in restoring motor performance, but decreased clasping behavior, and slowed down of striatal degeneration of these mice [68]. Malonate, an inhibitor of mitochondrial complex II, induced striatal degeneration by increasing microglia activation and apoptosis in rats. Treatment with Sativex reduced malonate-induced elevation of edema volume, microglia activation, iNOS (inducible nitric oxide synthase) induction, and increased survival of neurons. These effects of Sativex are mediated via CB1R and CB2R. This was confirmed by the observation that SR141716, an antagonist of CB1R and AM630, an inhibitor of CB2R, both blocked the effects of Sativex [69].

IV CBD in Human HD

Despite encouraging results observed in pre-clinical studies, the effects of CBD alone or in combination with THC (Sativex) have not produced any benefits in HD patients. In a double-blind, randomized, placebo-controlled trial on 15 neuroleptic-free patients with HD, administration of CBD at 700 mg/day for 6 weeks produced no effects on the symptoms compared to placebo group. CBD was found to be safe in this study [70]. In a pilot study on 25 HD patients, administration of Sativex for 12 weeks was safe, but did not improve symptoms [71].

Effect of Antioxidants and CBD on Posttraumatic Stress Disorder (PTSD)

I Posttraumatic Stress Disorder

Posttraumatic stress disorder is a complex mental disorder often resulting from exposure to sudden or repeated extreme traumatic events, such as war, terrorism, natural- or human-caused disaster, as well as

violent personal attack such as, rape, mugging, domestic violence, and accidents. PTSD affects approximately 7.7 million Americans over the age of 18. The symptoms of PTSD include unwanted re-experiencing of the trauma in memory, such as flashbacks, nightmares, triggered emotional responses; passive and active avoidance, such as emotional numbing, avoidance of discussions of traumatic events, and hyperarousal. In addition, patients with PTSD exhibit depression, cognitive dysfunction, substance abuse, and other psychiatric problems. These issues are described in detail in a recent review [12].

Analysis of studies suggests that increased oxidative stress, chronic inflammation, and glutamate levels are involved in the initiation and progression of PTSD in animal and human models [12]. Therefore, attenuation of these cellular defects may help in reducing the risk of development and progression of PTSD. Therefore, a comprehensive mixture of micronutrients, which may reduce these cellular defects at the same time, has been proposed to reduce these abnormalities [12].

II Antioxidants in PTSD

The studies of antioxidants in the initiation and progression of PTSD has been discussed in a recent review [12]. These studies primarily on animal models show that supplementation with antioxidants reduce the risk of developing and progression of PTSD-related symptoms. A single antioxidant may not be sufficient to reduce oxidative stress, chronic inflammation, and glutamate at the same time in human PTSD. Problems associated with the use of a single antioxidant in human HD have been discussed in a recent review [12]. In order to avoid limitations of using single antioxidants, a comprehensive mixture of micronutrients proposed for Alzheimer's disease is also recommended for PTSD. This micronutrient mixture may reduce increased oxidative stress, chronic inflammation and glutamate levels at the same time.

III CBD and PTSD

PTSD symptoms include anxiety and deficits in fear extinction. Chronic treatment with URB597, an inhibitor of the FAAH (fatty acid amide hydrolase), which increases the levels of anandamide, an endogenous agonist of CBRs, and WIN55, 212-2, a non-selective cannabinoid receptor agonist, decreased the above symptoms in rat model of PTSD. The therapeutic effects of URB597 and WIN55, 212-2 were dependent upon CB1R, because AM281, a selective antagonist of CB1R, blocked therapeutic effects of above agents [72]. CBD, which also inhibits FAAH, may also produce similar benefits in PTSD. In rat model of PTSD, hippocampal-dependent memory is impaired, whereas amygdala-dependent memory is enhanced.

Administration of CB1/2 receptor agonist WIN55-212,2 and elevation of anandamide prevented this opposite effect on memory in hippocampus and amygdala. These endocannabinoids reduced fear and facilitated fear extinction. These beneficial effects of endocannabinoids were blocked by CB1R antagonist, AM251 [73]. URB597, an inhibitor of FAAH, enhanced the levels of anandamide, which facilitates consolidation of memory through CB1R and CB2R. JZL184, an inhibitor of MAGL increased the levels of 2-AG, which facilitate consolidation of memory through CB2R [74]. Chronic exposure to stress also causes downregulation or loss of CB1R [8]. Thus, the endocannabinoid signaling represents an important regulatory system in the brain for neuroprotections against stresses.

IV Depression

Treatment of olfactory bulbectomy (OBX) mouse model of depression with CBD produces a fast-anti-depression effect by enhancing cortical 5HT/glutamate transmission via 5-HT1A receptor [75]. Administration of CBD induced fast and sustained anti-depression effect via activation of BDNF-TrkB signaling pathway in rats [76].

V Anxiety

One of the mechanisms of beneficial action of CBD on convulsion and anxiety is mediated by stimulating $GABA_A$ receptors [77]. Administration of CBD reduced anxiety in animal models and in humans with social anxiety disorder [78]. This effect was associated with serotonin receptor 5HT1A stimulation. In addition, CBD reduced psychoactivity of THC by acting as an antagonist of CB1R [79].

VI Fear

Although stress-induced contextual fear conditioning was similar in both wild-type and iNOS knockout mice, but fear extinction deficits in the medial prefrontal cortex were observed in iNOS knockout mice [80]. A decrease in the levels of NO and an increase in the levels of anandamide reduced fear expression and allowed fear extinction in wild-type mice. This result suggests that there is an inverse relationship between the levels of NO and anandamide in decreasing fear. Pharmacological elevation of anandamide blocked cortisol-induced increase in stress levels at both central and peripheral sites in rats [81]. In a rat model of fear, administration of CBD reduced fear and increased the rate of fear extinction. Both systemic and intra-dorsal hippocampus treatment with the AM251, antagonist of CB1R, or AM630, an antagonist of CB2R, prevented CBD-induced disruption of fear consolidation. Administration of the inhibitor of FAAH (URB597), which would increase the levels of anandamide, produced similar effect on fear consolidation mediated via dorsal hippocampus CB1R and CB2R [17, 82].

Scientific Rationale for Combining Micronutrients and CBD for Optimal Neuroprotection

The above studies with individual antioxidants and CBD primarily on experimental models of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Post-traumatic Stress disorder (PTSD) show that each of them provides neuroprotection largely by different mechanisms (Table 2). Despite impressive results on the beneficial effects of antioxidants and CBD on experimental models of neurodegenerative diseases, disappointing findings varying from minimal or no benefits in human have been reported.For example, CBD treatment of human PD has produced very limited benefits [57, 58]. In patients with HD, administration of CBD or Sativex did not improve the symptoms of HD [71]. No studies on the effects of CBD on AD or PTSD have been performed in humans. Because of limitations of using single antioxidants or CBD in humans, we propose that co-administration of a comprehensive mixture of micronutrients containing dietary and

endogenous antioxidants, curcumin, resveratrol, all B-vitamins, vitamin D3, and mineral selenium as suggested earlier for AD with CBD may be more effective than the individual agents in providing enhanced neuroprotection in neurodegenerative diseases [44]. Such micronutrients mixture with CBD together with standard therapy may also be helpful in increasing the effectiveness of treatment more than that produced by the individual agents. Pre-clinical and clinical studies should be performed to determine the efficacy of such a mixture of micronutrients with CBD in neurological diseases discussed above.

Conclusion

Studies suggest that increased oxidative stress, hightened inflammation, and glutamate levels are involved in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Post-traumatic stress disorder (PTSD). Mammals have two endogenous defense systems: the antioxidant system and the endocannabinoid system to protect against these stressors. In response to impaired endogenous defense systems, multiple antioxidants activate antioxidant system, whereas cannabidiol (CBD), one of the phytocannabinoids, activates endocannabinoid system. CBD acts as an agonist to cannabinoid receptor CB2R, and non-cannabinoid receptors, as well as an antagonist to CB1R and glutamate receptor (NMDR). By these mechanisms, CBD provides neuroprotection. On the other hand, antioxidants protect neurons by mechanisms that involve donation of electron to molecules with unpaired electron, activation of a nuclear transcriptional factor Nrf2, alterations in microRNAs expression, and increased production of anti-inflammatory cytokines.

Despite impressive findings on the beneficial effects of antioxidants and CBD on experimental models, similar experimental designs yielded disappointing results varying from minimal or no benefits in humans. Since using antioxidants and CBD individually failed to yield expected beneficial effects in humans, we propose that co-administration of a comprehensive mixture of micronutrients containing dietary and endogenous antioxidants with CBD may be more effective than the individual agents in providing enhanced neuroprotection in AD, PD, HD, and PTSD. The same micronutrients mixture with CBD when used in combination with standard therapy may also increase the effectiveness of treatment more than that produced by the individual agents. Pre-clinical and clinical investigations should be initiated to test the effectiveness of the proposed mixture of micronutrients with CBD in selected neurodegenerative diseases.

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None.

Conflicts of Interest

The author is Chief Scientific Officer of Engage Global, which sells nutritional products to the consumers.

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