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Review Article

Simultaneous Elevation of Antioxidant and Endocannabinoid Defense System May Prevent Dementia and Improve Cognitive Function in Humans

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Abstract

The incidence of dementia with or without Alzheimer's disease (AD) is increasing despite extensive mechanistic studies and holistic approaches. There are no effective strategies for prevention or treatment with drugs. Analysis of cellular and molecular investigations suggest that increased oxidative stress is the earliest damage that initiates subsequent cellular defects such as chronic inflammation, mitochondrial dysfunction, increased production of Aβ1-42 by cleavage of amyloid precursor protein (APP), hyperphosphorylation of tau protein, proteasome inhibition, and shortening of telomere, which are involved in increasing the risk of dementia. Humans have developed antioxidant defense system (ADS) and endocannabinoid defense system (ECDS) to protect against external and internal stressors. Increased oxidative stress and chronic inflammation damage both defense systems. Therefore, simultaneous elevation of these two defense systems may reduce the risk of dementia, improve cognitive function, and the effectiveness of drug therapy. Treatment with individual antioxidant compound or elevation of endocannabinoids alone has failed to achieve the above goals. This review has proposed that a comprehensive mixture of micronutrients together with a stimulator of ECDS may simultaneously enhance the levels of ADS and ECDS, which can lead to decreased the risk of dementia, enhanced cognitive function, and improved the efficacy of drug therapy in humans. Such an approach would simultaneously reduce the levels of oxidative damage and markers of chronic inflammation. Pre-clinical and clinical studies should be initiated to test the effectiveness of proposed hypothesis.

Keywords: Dementia; Cognition; Antioxidants; Endocannabinoids; Oxidative stress; Inflammation.

Introduction

The incidence of dementia with or without Alzheimer's disease (AD) is increasing in the USA despite suggested preventive strategies, which include modifications in diet and lifestyle. Approximately 85% of dementia is associated with AD, the remaining is attributed to other forms of dementia including mutations in AD genes. In 2013, the prevalence of AD was 5 million; however, this number has increased to 6.2 million in

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2021. The annual cost of AD treatment increased from $203.00 billion in 2013 to $355.00 in 2021. If no effective preventive strategies are developed and implemented, the number of AD cases and treatment cost would continue to increase. It is estimated that the number of AD cases among 65 years or older individuals would double (13 million) in 2050, and the cost may increase to 1.1 trillion (in 2021 dollars) [1]. Current drug treatment remains unsatisfactory, because the efficacy of drugs for modest improvement in cognitive function lasts for a short period of time.

Therefore, it is imperative that a non-toxic agent that can be combined with current drugs and holistic suggestions for reducing the risk of AD dementia is developed and implemented. During last decades, several cellular and molecular defects that can be used as targets to develop new drugs that can be used in the treatment of AD have been determined. They include increased oxidative stress [2-5], chronic inflammation [6-8] mitochondrial dysfunction [9-11] excessive production of Aβ1-42 (also called beta-amyloids) by cleavage of amyloid precursor protein (APP) [12,13] cholesterol-induced generation of beta-amyloids [14], hyperphosphorylation of tau protein [15,16], proteasome inhibition [17], and mutation in APP, presnelin-1 and presenilim-2 [18-21].

In an effort to identify the earliest biochemical defect that causes other cellular and genetic defects leading to AD, a review has carefully analysed these defects and proposed a hypothesis that increased oxidative stress is the earliest cellular abnormality that initiate and participate in the progression of AD by affecting subsequent damages [22,23]. The strongest support for this hypothesis comes from patients with familial AD who have elevated levels of markers of oxidative stress and inflammation long before the appearance of symptoms of dementia [24,25]. If oxidative damage is not healed, chronic inflammation that releases additional free radicals, proinflammatory cytokines, complementary proteins, and adhesion molecules that are toxic to brain cells," occurs. Thus, increased oxidative stress and chronic inflammation plays a central role in in the initiation and progression of dementia.

Therefore, simultaneous attenuation of these two cellular defects may reduce the risk of developing dementia, and in combination with drugs may further improve cognitive function. Humans have antioxidant defense system (ADS) and endocannabinoid defense system (ECDS) to protect against increased oxidative and inflammatory damages. These two defense systems maintain homeostasis of redox signals. Any shortcomings of the ADS, the ECDS or both can result in redox imbalance leading to excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). This review briefly describes the constituents of ADS and ECDS, and unique function of each that in part differs from each other.

This review presents evidence to show that increased oxidative stress and chronic inflammation can impair both ADS and ECDS that increase the risk and progression of dementia. It proposes that simultaneous elevation of both defence systems may be essential for reducing the risk of dementia and improving the efficacy of drug therapy in enhancing cognitive function. To achieve

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this goal, use of a comprehensive mixture of micronutrients, which elevates ADS together with a stimulator of ECDS for preventing dementia and improving cognitive function is suggested.

Constituents of ADS in the Cells

The ADS includes enzymatic antioxidants such as glutathione peroxidase, superoxide dismutase (SOD), and catalase together with non-enzymatic antioxidants that include vitamin A, vitamin C, vitamin E, glutathione, alpha-lipoic acid, and coenzyme Q10.

Constituents of ECDS in the Cells

The ECDS consists of cannabinoid ligands anandamide and 2-archidonoylglycerol (2-AG), cannabinoid receptors CB1R and CB2R, and their synthesizing and degrading enzymes. Cannabinoid ligands anandamide and 2-AG are synthesized when needed and metabolized when activating signal is turn off [26,27].

Anandamide is degraded by the enzyme FAAH (fatty acid amide hydroxylase) [28], whereas 2-AG is degraded by MAGL (monoacylglycerol) [28]. Dietary flavonoids such as kaemferol found in apples, tomatoes, grapes, onion, broccoli increase anandamide levels by inhibiting FAAH activity [20]. Diacylglycerol lipase-alpha (DAGL-alpha) is responsible for the synthesis of anandamide and 2-AG [30].

ADS and ECDS Reduce Oxidative Stress and Inflammation by Different Mechanisms

The mechanisms of antioxidants include donation of an electron to a molecule with an unpaired electron, activation of ROS-resistant Nrf2, alterations in the expression of microRNAs that regulates the production of protective proteins, changes in gene expression, reduction in the release and toxicity of glutamate and pro-inflammatory cytokines [31-34].

Endocannabinoid ligands anandamide and 2-archidonoylglycerol (2-AG), which stimulate G-protein-coupled receptors CB1R and CB2R [35-37], attenuated oxidative stress-induced neurotoxicity in PC12 neuronal cells in culture by stimulating CB1R [38,39]. In addition, stimulation of CB2R also reduced lipopolysaccharide (LPS)-induced generation of free radicals in mouse microglia cells in culture (BV2 cell line) [40] as well as in the brain [41], kidney [42], heart [43], and liver [44]. Thus, elevation of both ADS and ECDS reduce oxidative damage by different mechanism.

Unique Function of ECDS not Shared by ADS

The endocannabinoids are called retrograde messenger because they travel in the opposite direction to other eurotransmitters, such as serotonin, dopamine, glutamate, and GABA (gamma-amino butyric acid). Normally, these neurotransmitters are released from presynaptic 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 are already present [45,46]. Stimulation of these CB receptors by anandamide can inhibit the release of

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inhibitory or excitatory neurotransmitters. Activation of CB1R inhibited GABA and glutamate release from pre-synaptic terminals, which may be one of mechanisms of neuroprotection [47,48].

Anandamide and 2-AG also simulate non-cannabinoid receptors such as the transient receptor potential cation channel subfamily V member 1 (TRPV1) that plays a significant role in synaptic transmission and pain regulation [49,50].

Increased Oxidative Stress and Chronic Inflammation Initiate and Promote Dementia by Impairing ADS

Based on published data [51,52], it is proposed that increased oxidative stress may be the earliest cellular abnormality. If oxidative damage is not healed, chronic inflammation occurs. Other subsequent cellular injuries such as mitochondrial defects, shortening of telomere, and damage to DNA, RNA, proteins, and lipids may all be secondary to oxidative stress [33,53,54].

Oxidative stress also increases the production of beta-amyloids [55,56] that causes degeneration of cholinergic neurons by generating free radicals leading to dementia associated with Alzheimer's disease [57-59]. Thus, increased oxidative stress and chronic inflammation play a dominant role in accelerating the risk of dementia. Increased oxidative stress and chronic inflammation decrease enzymatic antioxidants, such as catalase, superoxide dismutase (SOD) and glutathione peroxidase as well as non-enzymatic antioxidant compound, such as vitamin A, vitamin C, vitamin E, and glutathione [60,61]. Deficiency in antioxidant enzymes and antioxidant compounds can lead to cognitive dysfunction [33,62-65]. Impaired ADS increased the risk of dementia.

Increased Oxidative Stress and Chronic Inflammation Promote Dementia by Impairing Endocannabinoid Defense system (ECDS)

Increased oxidative also impairs the ECDS causing damage to neurological function mediated by its receptors [66,67]. The hippocampal region of the brain is considered the most sensitive to neurodegeneration. In mice, the levels of 2-AG decreased due to activation of its inhibitor enzyme MAGL, and a decreased the synthetic enzyme diacylglycerol lipase-alpha (DAGL-alpha) [68]. Neuroinflammation participates in the initiation and progression of neurodegenerative diseases including dementia. Cannabinoids suppresses neuro-inflammation activities in the brain.

This is supported by the fact that mice lacking CB1R showed an early onset of cognitive dysfunction [69]. Genetic deletion of CB1R causes decreased in production of BDNF (brain-derived neurotrophic factor) and neurogenesis [69,70]. Furthermore, old mice lacking CB1R (-/-) or having Cnr1 (gene coding for CB1R) deleted produced decreased amounts of anandamide, increased neuronal loss and pro-inflammatory activities, and impaired learning and memory ability compared to wild-type mice [25,69-71].

These changes in CB1R deleted mice were particularly marked in the hippocampus. Mice lacking CB2R (-/-) showed reduced responsiveness to pro-inflammatory stimuli

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as well as reduced microgliosis. The studies discussed above suggest that increased oxidative stress and chronic inflammation accelerate the risk of cognitive dysfunction by impairing the ADS and ECDS. Therefore, it is proposed that simultaneous elevation of these two defense systems may reduce the risk of dementia and improve cognitive function.

Effects of Elevation of ADS on Dementia

Since increased oxidative stress and chronic inflammation are the primary events which initiate and promote neurodegeneration leading to dementia, it was rational to investigate the effects of antioxidants on the prevention and treatment of dementia in animal models and humans. Most individual antioxidants failed to improve the cognitive function in AD.

Treatment with alpha-lipoic acid reduced the rate of progression of cognitive dysfunction in patients with mild AD [72]. Treatment with melatonin was ineffective in improving the cognitive function in AD [73]. Vitamin E treatment was not useful in prevention or treatment of dementia in AD [74]. However, treatment with vitamin E slowed the rate of deterioration of cognitive function in patients with moderate impairment of memory [75].

Supplementation with vitamin E or vitamin C did not delay the incidence of AD or dementia [76]. Vitamin E or vitamin C alone or in combination did not reduce the risk of AD or dementia [77]. These data suggest that one or two antioxidants have no significant effect on prevention of dementia in AD. Such an approach may also have no effect on improving cognitive function in well-established AD, but may have a minimal effect in improving cognitive function in early phase AD.

Effects of Elevation of ECDS on Dementia

Genetic deletion of CB1R caused age-related decline in learning ability and cognitive function in mice. In older mice genetic deletion of CB1R impaired the learning ability that was associated with the loss of cholinergic neurons in the hippocampus [69]. The endocannabinoid ligand anandamide acts as an agonist of CB1R. Experimental data suggested that the use of CB1R agonists may be useful in the treatment of human dementia [78].

Agonist of CB1R protected against toxicity produced by beta-amyloid protein -induced activation of microglia in rat cortical culture [79]. Chronic treatment with an agonist of CB1R before the appearance of the symptoms and during the symptoms, attenuated cognitive dysfunction as well as decreased activity of microglia and beta-amyloid level in the cortex of transgenic mice (APP2576 and APP/PS1) [80]. An agonist of CB1R induced autophagy that removes damaged cellular materials in cancer cells [81,82] as well as non-cancerous cells [83]. In older individuals, cannabinoid ligands such as anandamide may improve age-related cognitive dysfunction [84].

An agonist of CB1R win-55212-2 reduced spatial memory defect, reduced the number of activated glia cells [85], and caused neurogenesis [86]. Inhibitors of FAAH also enhanced neurogenesis in older individuals [87]. A review has discussed the role of CB2R

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activation in AD pathology and suggested that CB2R could be one of the targets for developing therapeutic drugs [88]. A CB2R agonist devoid of psychoactive effects decreased brain pathology associated with AD as well as inflammatory changes that contribute to AD development and progression.

Activation of CB2R also improved cognitive function in animal models of AD. An agonist of CB2R removed beta-amyloids by human macrophages as observed in autopsied brain samples of AD [89], and by microglia in cell culture [90]. Genetic deletion of CB2R enhanced the accumulation of beta-amyloid levels and the number of amyloid plaques in adult mouse brains [88,91]. Chronic treatment with the specific agonist of CB2R decreased the hyper-phosphorylation of tau protein in APP/PS1 transgenic mice [41].

Failure of Individual Antioxidants and Cannabinoids to Improve Cognitive Function in Humans

- Failure of Individual antioxidants: Contradictory observations between animal models and human AD were also reported when single antioxidants such as vitamin E was used in human AD [74,92]. The potential reasons for the failure of single antioxidant in improving cognitive function in human AD has been discussed [22]. In brief, some of them are listed here.
    a) The brains of patients with AD are likely to have an excessively pro-oxidant environment. A single antioxidant administered in a highly oxidative environment would be oxidized and then would act as a pro-oxidant rather than as an antioxidant.
    b) Different antioxidants are distributed in different amounts in various organs, and in the sub-cellular compartments of the same cell. Administration of a single antioxidant is unlikely to accumulate in adequate amounts in all organs and in all subcellular compartments to provide protection against oxidative stress.
    c) Alpha-tocopherol is a more efficient in removing free radicals at a reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective at a higher oxygen pressure. Therefore, administration of one antioxidant may be insufficient to provide protection against oxidative damage.
    d) The elevation of both levels of antioxidant enzymes and of antioxidant compounds is likely to provide optimal protection. Administration of a single antioxidant cannot achieve this goal.
    e) Administration of a single antioxidant which is always predominantly water soluble or lipophilic, cannot protect both the aqueous and lipid compartments of the cell

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against oxidative and inflammatory damage.

Similarly, it is possible that the endocannabinoid receptors CB1R and CB2R do not exhibit anti-oxidation and anti-inflammatory activities in human AD in sufficient amounts to reduce cognitive dysfunction. The issue of whether a combined stimulation of ADS and ECDS can be useful in mitigation of dementia in AD remain unresolved.

- Failure of cannabinoid receptors alone: Despite impressive results with agonists of cannabinoid receptors CB1R and CB2R in animal models of AD, the relevance of these observations has not been confirmed in human AD.

Proposed Combination of ADS and ECDS

The failure of individual antioxidants or cannabinoid receptors to yield expected benefits in human AD dementia led us to propose that in order to simultaneously reduce oxidative stress and chronic inflammation, the levels of ADS and ECDS should be elevated at the same time. Such a combination may be useful in prevention of dementia in humans.

An Elevation of Antioxidant Defense System (ADS)

- **Oral supplementation with antioxidant compounds:** Oral supplementation with a mixture of antioxidant compounds can enhance their tissue levels. However, increasing the levels of enzymatic antioxidants requires an activation of the nuclear transcriptional factor Nrf2. A brief description of steps needed to activate Nrf2 is presented here.

An Elevation of Antioxidant enzymes

- **Processes of Activation of Nrf2:** The processes of activation of Nrf2 have been described [22]. Briefly, under normal physiological conditions, reactive oxygen species (ROS) is required to activate Nrf2. Activated Nrf2 dissociates itself from Keap1- CuI-Rbx1 complex in the cytoplasm and migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of cytoprotective enzymes including antioxidant enzymes.

During the prolonged oxidative stress commonly observed in human AD, activation of Nrf2 becomes resistant to ROS. This is evidenced by the fact that increased oxidative stress continues to occur in AD despite the presence of Nrf2.

However, some antioxidants can activate this ROS-resistant Nrf2. Activation of Nrf2 and antioxidant compounds can decrease both oxidative stress and chronic inflammation.

An Elevation of Endocannabinoid Defense System (ECDS)

Although several synthetic and natural agonists and antagonist of CB1R and Cb2R are available, a few examples are provided here (Table 1). In addition, inhibitors of

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enzyme FAAH which increases the levels of anandamide and an inhibitor of MAGL which enhances the level of 2-AG are also available (Table 1). Among them cannabidiol (CBD) is a naturally occurring agent without psychoactive feature which is safe and legal. CBD enhances the levels of anandamide by inhibiting FAAH activity. Anandamide activates both CB1R and CB2R [93,94]. CBD also acts directly as an agonist of CB2R causing reduction in inflammatory changes and pain. Therefore, CBD has been selected for elevating the levels of cannabinoid receptors. Synthetic agonist of CB1R and CB2R could be toxic to humans. Treatment with CBD attenuates fear memories by blocking their generalization and reconsolidation in animal models. This was further demonstrated in which injection of CBD immediately or 1h after fear conditioning mitigates memory consolidation in the dorsal hippocampus of rats. This effect of CBD was associated with decreased expression of Arc protein and mediated via CB1R, CB2R, and elevated anandamide and PPAR-gamma receptors [95]. Despite some controversies, most studies suggest that CBD could be considered for the treatment of anxiety, depression, and psychotic disorders [96].

Inhibitors of FAAH	URB597 Synthetic), CBD (natural)
Inhibitor of MAGL	JZL184 (synthetic)
Agonist of CB1R	Win55, 212,2 (synthetic)
Agonist of CB2R	CBD (natural) Win55 (synthetic)
Antagonists of CB1R	AM281, AM251 (synthetic)
Antagonist of CB2R	AM360

Table 1. Natural and synthetic inhibitors of FAAH and MAGL, and agonist and antagonists of CB1R and CB2R.

FAAH: Fatty acid amide hydrolase, which degrades cannabinoid anandamide; MAGL: Monoacylglycerol, which degrades cannabinoid 2-archidonoylglycerol (2-AG); CB1R: Cannabinoid receptor 1; CB2R: cannabinoid receptor-2; CBD: Cannabidiol.

Proposed Combination of Elevated ADS and ECDS for Reducing Dementia and Improving Cognitive Function

Elevated ADS

For Elevating ADS, a comprehensive mixture of micronutrients containing vitamin A, mixed carotenoids, vitamin C, alpha-tocopheryl acetate, alpha-tocopheryl succinate, vitamin D3, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, quercetin, green tea extract, all B vitamins, and minerals selenomethionine, and zinc for reducing the risk of dementia and improving cognitive function is proposed. This micronutrient mixture may increase the levels of antioxidant enzymes by activating the ROS-resistant Nrf2 and enhancing the levels of dietary and endogenous antioxidant compounds at the same time.

Elevated ECDS

For elevating ECDS, Dietary flavonoids such as kaempferol found in apples, tomatoes, grapes, onion, broccoli , which enhances anandamide levels by inhibiting FAAH activity is used [29]. In addition, cannabidiol (CBD), a naturally occurring non-toxic and non-psychoactive agent stimulates

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cannabinoid receptors and non-cannabinoid receptors is utilized.

Proposed Combination ADS and ECDS

For most individuals, a combination of micronutrient mixture and dietary flavonoids, which may reduce dementia, is proposed, whereas for individuals, who have pain, anxiety, depression, and increased risk of dementia with or without Alzheimer's disease, a combination of micronutrient mixture with CBD is suggested.

Combination of elevated ADS and ECDS may be more effective than the individual agent in reducing the risk of developing dementia, improving cognitive function, and increasing the efficacy of drug therapy. The efficacy of proposed mixture of micronutrients with a stimulator of ECDS in reducing the risk of dementia or improving cognitive function in humans has never been tested.

An oral administration of a multivitamin preparation reduced the risk of cancer in men by about 10% [97], and attenuated the progression of HIV disease, and prolonged the time period of initiating the anti-viral therapy [98]. Since these two clinical studies utilizing a commercial preparation of multivitamin have produced beneficial effects in certain human diseases, it is likely that proposed micronutrient in combination with a stimulator of ECDS would reduce the risk of dementia and improve cognitive function.

Pre-clinical and clinical studies are needed to test the efficacy of the proposed micronutrient mixture together with a stimulator of ECDS in attenuating the risk of dementia and improving cognitive function.

Conclusions

The number of ageing population with dementia is increasing. There are no effective strategies that can help in reducing the risk of dementia in humans. Recommendations of modifications in diet and lifestyle have had no impact in reducing the risk of cognitive dysfunction. This could have been due to the fact that human behaviors are difficult to change. Increased oxidative and inflammatory products increase the risk of dementia by impairing both ADS and ECDS. Therefore, it was logical to investigate the effects of antioxidant supplement or stimulation of endocannabinoid receptors (CB_1R and CB_2R) in reducing the risk of cognitive dysfyunction and improving the cognitive function in animal models. The results were impressive in animal models. However, such approaches did not produce similar results in humans. Therefore, a comprehensive mixture of micronutrients containing dietary and endogenous antioxidant compounds, certain flavonoids, all B-vitamins, and minerals selenomethionine, and zinc, which may increase the levels of cytoprotective enzymes including antioxidant enzymes and antioxidant compounds by activating the ROS-resistant Nrf2 for humans, is proposed. Such a micronutrient mixture in combination with a dietary flavonoid or a cannabidiol (CBD) may reduce the risk of dementia, and improve cognitive function as well as the efficacy of drug therapy by simultaneously reducing oxidative stress and chronic inflammation. Pre-clinical and clinical investigations should be initiated to test the efficacy proposed suggestion in reducing the risk of dementia and improving the cognitive function.

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