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Review Article

Attenuation of Beta-Amyloids and Other Risk Factors by a Micronutrient Mixture, Probiotics, Collagen Peptides, Omega 3, and CBD in Alzheimer's Disease

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Abstract

During last decades several endogenous risk factors which participate in the development and progression of Alzheimer's Disease (AD) have been identified. They include increased oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, autophagic dysfunction, progressive loss of acetylcholine, oxidation of omega-3 fatty acids, increased production of beta-amyloids, hyperphosphorylation of tau protein, loss of collagen, and intestinal dysbiosis. Among these risk factors, beta-amyloids have drawn significant attention from neuroscientists and neurologists. Using beta-amyloids as a target, antibodies have been developed for the treatment of AD. These anti-amyloids antibodies have serious side effects and produce only a short-term benefit in patients with early phase AD. Another risk factor involves gradual decline in the levels of acetylcholine. To address this, drugs which increase the levels of acetylcholine in the cholinergic neurons by inhibiting acetylcholinesterase were developed. The effectiveness of these drugs depends upon the viability of neurons. Since they do not address the cause of neuronal death, the beneficial effects of these drugs last only for a few months. Neither anti-beta-amyloids antibodies nor acetylcholinesterase inhibitors have any role in prevention of AD. This review proposes a prevention plan for AD which addresses all endogenous risk factors including beta-amyloids at the same time. It also suggests that combining drugs with prevention plan together with CBD (cannabidiol) may prolong the effectiveness of drugs, improve behavior abnormalities associated with AD, and possibly reduce the potential toxicity of drugs.

INTRODUCTION

Alzheimer's disease (AD) is a progressive irreversible neurological disease and is characterized by memory loss, reduced ability of thinking and reasoning, difficulty in performing daily tasks, and neuropsychiatric disorders. Alzheimer's disease has been grouped into two forms sporadic AD and familial AD. This disease undergoes three phases during progression (a) Minimal Cognitive Impairment (MCI), (b) early stage of AD, and (c) full-blown AD. During last decades, several endogenous risk factors that participate in the development and progression of AD have been identified. They include increased oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, autophagic dysfunction, overproduction of beta-amyloids, hyperphosphorylation of tau protein, oxidation of omega-3-fatty acids, intestinal dysbiosis, loss of collagen, and reduce glucose metabolism.

The discovery of an association of cholinergic neurons with AD provided an opportunity to develop drugs that can increase the levels of acetylcholine which stores memory and learning ability. The discovery of beta-amyloids provided an opportunity to develop antibodies against beta-amyloid peptide which can protect cholinergic neurons from its toxicity. Most other endogenous risk factors have not drawn significant attention for prevention or improved treatment of AD. Despite valuable dietary recommendations for the prevention of AD, the incidence of this disease continues to increase in the USA and world-wide.

This review discusses the importance of internal risk factors other than beta-amyloid and hyperphosphorylation of tau protein for prevention and improved treatment of AD. It also suggests that addressing all risk factors at the same may be more effective than addressing one risk factor at a time in prevention and improved treatment of AD.

BRIEF HISTORY OF BETA-AMYLOIDS CAUSING AD

In 1984, Glenner and Wong showed that amyloidogenic protein accumulates in the brain of AD patients and proposed that this protein could be a causative agent for this neurodegenerative disease [1]. The amyloid fibril protein isolated from cerebrovascular amyloid deposits was found in 92% cases of AD and 100 % cases of Down's syndrome over the age 40 years. The involvement of beta-amyloids in AD was further confirmed

by several investigators [2-7]. Cleavage of Amyloid Precursor Protein (APP) by beta-secretase and gamma-secretase produces beta-amyloid peptides (Aβ1-42) (Figure 1).

DEVELOPMENT OF NEW DRUGS TARGETING BETA-AMYLOIDS

The development of antibodies against beta-amyloids provided further support for the hypothesis that beta-amyloids play a key role in the development of AD. The FDA approved anti-amyloid antibody includes lecanemab, aducanumab, and donanemab [8]. In patient with early phase AD, treatment with donanemab for 76 weeks improved cognitive function and ability to perform daily function of living compared to placebo group. In early phase AD, treatment with lecanemab for 18 months, reduced the levels of beta-amyloids, but it decreased only modestly the rate of cognitive decline. Toxicity of this treatment includes cerebral edema or effusion (mostly asymptomatic) [9-11]. In addition, these anti-amyloid antibodies do not influence the rate of production of new beta-amyloids; therefore, under the best condition, their effectiveness in improving AD symptoms may not last for a long period. Another approach which could be useful in treatment of AD is to reduce the production of beta-amyloids. Beta-amyloids induce death of cholinergic neurons by generating free radicals [12,13]. Therefore, identification of agent which can neutralizes free radicals produced by beta-amyloids would be useful in the treatment of AD. This approach if successful would further strengthen the beta-amyloid hypothesis.

Hyperphosphorylation of microtubule-associated protein tau

In 2008, it was proposed that hyperphosphorylation of microtubule-associated protein tau is involved in the development and progression of in AD [14]. Aggregated hyperphosphorylated tau protein form Neurofibrillary Tangles (NFTs) within the neuron [15] which is one of the two pathological hallmarks of AD. It causes degeneration of AD neurofibrillary [15]. Dephosphorylation of tau protein inhibited neurofibrillary degeneration [16]. Beta-amyloid can enhance the hyperphosphorylation of tau by activating several kinases. In vitro studies suggest that beta-amyloid and hyperphosphorylation have direct and indirect cytotoxic effects that leads to synaptic loss and dysfunction in neurotransmitter release [17]. No drugs that can prevent phosphorylation or dephosphorylate hyperphosphorylated tau protein are available for the treatment of AD.

Discovery of cholinergic neurons: In 1976, when the cholinergic hypothesis was proposed by Davies and Maloney [18]. Using autopsied samples of 20 regions of AD and control brains, they demonstrated that the activity of choline acetyltransferase the key enzymes involved in the synthesis of acetylcholine, was markedly decreased in the amygdala, hippocampus, and cortex, and the concentration of acetylcholine was reduced at synapses [19-21]. This suggested that the damage to cholinergic neurons may be involved in development and progression of AD. Acetylcholinesterase degrades the levels of acetylcholine in the cholinergic neurons. Thus, identification of cholinergic neurons provided a new opportunity to identify agents that can protect them. In addition, cholinergic neurons became the target to develop novel drugs for the treatment of AD.

DISCOVERY OF DRUGS BASED ON CHOLINERGIC NEURONS FOR THE TREATMENT OF AD

The current treatments of AD utilize acetylcholinesterase inhibitors such as Donepezil (Aricept), Galantamine, and Rivastigmine (Exelon) [22] or Xanomeline, a stimulator of muscarinic receptor [23] to increase the levels of acetylcholine in the cholinergic neurons. The effectiveness of these drugs in improving cognitive functions lasts only for a few months because of continued death of the cholinergic neurons. These drugs do not affect the levels of oxidative stress and chronic neuroinflammation which are the main cause of neuronal death. Therefore, reducing oxidative stress and neuroinflammation may prolong the effectiveness of drug therapy in patients with AD for a longer period.

DRUGS USED TO TREAT BEHAVIOR ABNORMALITIES IN PATIENTS WITH AD

The patients with advanced AD also exhibit several behavior abnormalities which include anxiety, depression, apathy, aggression, agitation, sleep disturbances, and psychosis (hallucinations, and delusion) [24,25]. Currently used drugs for treatment of anxiety and depression include fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvux), citalopram (Celexa), escitapram (Cipralex), and sertraline (Zoloft). These drugs have adverse side-effects after a long-term consumption. Therefore, non-toxic agents that can improve these behavioral symptoms should be identified.

CELLULAR RISK FACTORS OTHER THAN BETA-AMYLOIDS AND HYPERPHOSPHORYLATION OF TAU PROTEIN WHICH PARTICIPATE IN THE DEVELOPMENT AND PROGRESSION OF AD

In addition to over production of beta-amyloids [2-7] and hyperphosphorylation of tau protein [14,15,26], there are other cellular risk factors which participate in the development and progression of AD. They include increased oxidative stress [27], chronic neuroinflammation [28,29], mitochondrial dysfunction [30], autophagy defects [31,33], oxidation of omega-3 fatty acids [34], intestinal dysbiosis [35], loss of collagen [36-38], and reduced glucose metabolism [39].

INCREASED OXIDATIVE STRESS INITIATES SOME SUBSEQUENT ADVERSE CELLULAR EVENTS

We have suggested that increased oxidative stress represents the earliest cellular defect which initiates subsequent cellular damages that participates in the development and progression of AD [40]. If oxidative damage of the cell is not fully repaired, chronic neuroinflammation, which releases additional free radicals, pro-inflammatory cytokines, complement proteins, and

adhesion molecules, all of which are toxic to neurons, occurs. Thus, increased oxidative stress and chronic neuroinflammation are closely linked and they participate in the initiation and progression of AD [41,42].

Mitochondrial dysfunction is associated with the development of AD. The brain utilizes approximately 25% of respired oxygen and 2% unused oxygen leaks out of mitochondria and produces additional free radicals. Thus, mitochondria are exposed to high levels of free radicals, and at the same time they are very vulnerable to the free radical damage. Thus, increased oxidative stress in the brain impairs mitochondrial function [43,44]. The increased oxidative stress impairs autophagy system [45] and oxidizes omega 3 fatty acids make them ineffective in maintaining function of the brain [34].

The enhanced oxidative stress increases the activity of gamma-secretase, which enhances the cleavage of APP into beta-amyloids [46-48], which cause the death of cholinergic neurons by generating free radicals [12,13]. Enhanced oxidative stress also induces hyperphosphorylation of tau protein which plays an important role in the progression of AD and may contribute to the death of cholinergic neurons [26,49]. Therefore, decreasing oxidative stress may prevent the production of beta-amyloid and the hyperphosphorylation of tau protein.

The patients with MCI (Minimal Cognitive Impairment), early phase AD, and advanced AD exhibit increased oxidative stress which also occurs in individuals carrying mutated APP, preselinin-1, or preselinin-2) long before the symptoms of AD appear [50,51]. Thus, increased oxidative stress increases the risk of early appearance of symptoms in familial AD. This suggests that reducing the levels of oxidative stress may delay the appearance of the symptoms of familial AD.

INTERNAL RISK FACTORS THAT ARE NOT RELATED TO INCREASED OXIDATIVE STRESS

The cellular risk factors for the development of AD that are not related to oxidative stress include loss of collagen which impairs structural integrity of the brain contributing to cognitive dysfunction [36-38], intestinal dysbiosis (changes in the composition of probiotics favoring increased number of harmful bacteria) which promotes the onset of AD by increasing the production and deposition of beta-amyloids, inducing mitochondrial dysfunction, and enhanced production of pro-inflammatory cytokines [35,52], and abnormal behaviors which include anxiety, depression, agitation, and psychosis [24,25].

From the endogenous risk factors presented above, it appears that addressing them one at a time may not be adequate for the prevention or improved treatment of AD. We have suggested that addressing all risk factors at the same time may be best for an effective prevention and improved treatment of AD [40].

PROPOSED PREVENTION PLAN FOR AD

(a) Changes in diet, lifestyle, and reduction in exposure to environmental toxins

(b) Supplementation with a proposed micronutrient mixture which would simultaneously reduce oxidative stress, chronic neuroinflammation, improve mitochondrial function, autophagy function, prevent oxidation of omega-3 fatty acids and insulin receptor, reduce production and action of beta-amyloids and hyperphosphorylation of tau protein.

(c) Supplementation with probiotics with prebiotics would reverse the intestinal dysbiosis.

(d) Supplementation with omega-3 fatty acids would improve brain function including memory and would directly restore glucose metabolism by activating the insulin receptor-linked signaling protein AKT which would cause translocation of Glucose Transporter-4 (GLUT-4) from the cytoplasm to the cell surface membrane which then allows the entry of glucose inside the neurons for generating energy.

(e) Supplementation with collagen peptides would restore collagen level, and thereby, improve structural integrity of the brain and cognitive function.

CHANGES IN DIET, LIFESTYLE, AND REDUCTION IN EXPOSURE TO ENVIRONMENTAL TOXINS

The importance of diet in the development of age-related dementia has been studied for decades. Among various diets, consumption of Mediterranean diet, which includes primarily plant-based food and fishes is recommended, because it appears to be associated with a reduced risk of developing dementia [53,54].

Changes in lifestyle is equally important for reducing the loss of age-related decline in cognitive function. They include performing regular physical and mental exercise, increasing social interaction, brain stimulation, stopping tobacco smoking and consuming excess alcohol, and reducing stress by vacationing, meditation, or sports.

Avoiding exposure to environmental toxins include reduction in the levels of exposure to EMF (Electromagnetic Field) radiation from cell phone, laptops, and Wi-Fi, aluminum, heavy metals such as mercury and lead, and to polluted water and air. Similar recommendations have been suggested by the Federal and private organizations.

Despite valuable dietary, lifestyle, and environmental recommendations for reducing the risk of cognitive dysfunction, the risk of AD is increasing. One of the reasons could be that human behaviors with respect to diet and lifestyle are difficult to change. Exposure to environmental toxins is often beyond our control. Nevertheless, it is essential to keep trying to educate public about the value of recommended changes in diet, lifestyle, and exposure to environmental pollution for their health. Other reasons for the failure could be that diet and lifestyle changes alone may not be sufficient to attenuate all internal risk factors that participate in the development and progression of AD.

Therefore, a comprehensive approach that can address all major internal risk factors at the same time is proposed.

PROPOSED SUPPLEMENTATION WITH A MICRONUTRIENT MIXTURE

We have suggested that simultaneous reduction of oxidative stress and chronic neuroinflammation is essential for reducing the risk of developing of AD and improving the current treatment of AD [41, 42]. Let us examine, how to achieve this goal. Antioxidants are known to reduce oxidative stress and chronic inflammation; therefore, supplementation with antioxidants could be useful. Supplementation with a single antioxidant such as alpha- lipoic acid [55-57], acetyl-L-carnitine [58], vitamin A [59], vitamin E [60], coenzyme Q10 [61], and resveratrol [62] reduced oxidative stress and chronic inflammation in animal model of AD and improved cognitive function in these animals. In contrast to animal studies, a few human studies using a single antioxidant such as vitamin E [57,63] and curcumin [64] failed to improve cognitive function in patients with AD; a transient limited benefit in improving cognitive function was obtained with vitamin E in an early stage of AD [65,66]. Some of the potential reasons for the failure of a single antioxidant to produce consistent benefits in patients with AD are described here.

a) Increased levels of oxidative stress and chronic inflammation are associated with patients with AD. Supplemented single antioxidant in the above environment would be oxidized and then acts as a pro-oxidant rather than as an antioxidant. Therefore, a single antioxidant is not expected to reduce oxidative stress and chronic inflammation at the same time.

(b) Different antioxidants are distributed in different amounts in various organs as well as in the sub-cellular compartments of the same cell. Administration of a single antioxidant at an arbitrarily selected dose cannot accumulate in all organs and in all parts of the cell in sufficient amounts to reduce oxidative stress and chronic inflammation.

(c) The levels of oxygen vary from one organ to another. The efficacy of antioxidant varies depending upon the levels of oxygen. For example, vitamin E is more effective scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure of the cells [67]. Therefore, administration of one antioxidant may not retard oxidative stress and chronic inflammation.

(d) Simultaneous elevation of both antioxidant enzymes and dietary and endogenous antioxidant compounds are needed to achieve maximal reduction in oxidative stress and chronic inflammation, because they act by different mechanisms. Antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes destroy H202 and the superoxide radical by catalysis, converting them to harmless molecules such as water and oxygen. Administration of a single antioxidant cannot achieve this goal.

(e) Since most antioxidants are either lipophilic or hydrophilic, administration of a single antioxidant cannot protect both the aqueous and lipid compartments of the cell against oxidative damage.

(f) Different antioxidants activate Nrf2 in the cells by altering the expression of different microRNAs [68]. For example, some antioxidants can activate Nrf2 by upregulating miR-200a that inhibits its target protein Keap1, whereas others activate Nrf2 by downregulating miR-21 that binds with 3'-UTR Nrf2 mRNA [69]. Thus, different antioxidants activate Nrf2 (Nuclear Factor-Erythroid-2- Related Factor 2) by different mechanisms. Administration of a single antioxidant cannot act on all the relevant microRNAs.

REQUIREMENTS FOR SIMULTANEOUS REDUCTION IN OXIDATIVE STRESS AND CHRONIC NEUROINFLAMMATION

In order to reduce oxidative stress and chronic neuroinflammation at the same time, simultaneous elevation of antioxidant enzymes, and dietary and endogenous antioxidant compounds is essential [41]. The levels of antioxidant compounds can be enhanced by supplementation; however, enhancing the levels of antioxidant enzymes requires an activation of a nuclear transcriptional factor Nrf2 [42,70]. Therefore, a brief description of the activation processes of Nrf2 is described here.

Activation of Nrf2

During transient acute oxidative stress, ROS (Reactive Oxygen Species) activates Nrf2 which dissociates itself from Keap1-CuI-Rbx1 complex in the cytoplasm and then migrates to the nucleus where it heterodimerizes with a small Maf protein and then binds with the Antioxidant Response Element (ARE) leading to increased expression of target genes coding for several cytoprotective enzymes including antioxidant enzymes [71,72]. The level of Nrf2 is reduced in AD [73]. Chronic oxidative stress which is present in AD may have decreased the transcription of Nrf2. ROS is available during chronic oxidative stress in the brain, but they do not activate Nrf2 [73-75], indicating the existence of ROS-resistant Nrf2. The question arises how to activate ROS-resistant Nrf2.

CERTAIN ANTIOXIDANTS ACTIVATE ROS-RESISTANT NRF2

Antioxidants which activate ROS-resistant Nrf2 include vitamin E and genistein [76], alpha-lipoic acid [77], curcumin [78], resveratrol [79,80] omega-3-fatty acids [81,82] glutathione [83], N-acetylcysteine (NAC) [84], and coenzyme Q10 [85]. The mechanisms of antioxidant-induced activation of ROS-resistant Nrf2 have not been investigated.

Binding of Nrf2 with the ARE in the nucleus

Activation of Nrf2 alone is not sufficient to increase the levels of antioxidant enzymes. Activated Nrf2 must bind with the ARE in the nucleus to enhance the expression of target genes coding for the antioxidant enzymes.

The binding ability of Nrf2 with ARE was impaired in aged rats; however, supplementation with alpha-lipoic acid restored this binding defect [77].

Activated Nrf2 and antioxidant compounds reduce oxidative stress and chronic inflammation

Activation of Nrf2 decreased the levels of oxidative stress and chronic inflammation [86,87]. Many antioxidant compounds also attenuate oxidative stress and chronic inflammation [80,88-92].

Supplementation with the proposed micronutrient mixture may reduce the risk of developing AD by simultaneously reducing the oxidative stress and chronic neuroinflammation

To simultaneously reduce oxidative stress and chronic inflammation, it is essential to increase the levels of antioxidant enzymes and antioxidant compounds at the same time. A mixture of micronutrients which can reduce these cellular defects at the same time in patients with AD was suggested [41,42]. This mixture includes vitamin A (retinyl palmitate), vitamin E (both d- alpha-tocopherol acetate and d-alpha-tocopheryl succinate), natural mixed carotenoids, vitamin C (calcium ascorbate), vitamin D3, all B-vitamins, coenzyme Q10, alpha-lipoic acid, N-acetylcysteine (NAC), resveratrol, curcumin, quercetin, green tea extract, and minerals selenium and zinc. This micronutrient mixture has no iron, copper, or manganese. Although these trace minerals in tiny amounts are essential for the growth and survival, slight excess of free iron and copper can increase the risk of chronic diseases, because these trace minerals when combined with vitamin C produce extensive amounts of free radicals and they in the presence of antioxidants are rapidly absorbed. This micronutrient mixture also has no heavy metals such as vanadium, zirconium, and molybdenum, because increased levels of these heavy metals are neurotoxic. There are no methods of elimination of either trace minerals or heavy metals from the body; therefore, taking them with a micronutrient mixture could be harmful after a prolonged consumption.

Supplementation with the Proposed micronutrient mixture may improve autophagy, mitochondrial, and omega 3 functions in AD

Antioxidants improve autophagy function [93], and thereby, enhance the ability of autophagy to remove damaged proteins and cell debris from the neurons. This mixture may also improve mitochondrial function and omega 3 function by protecting them from oxidative damage in AD.

Supplementation with the proposed micronutrient mixture may protect cholinergic neurons from oxidative stress, beta-amyloids, and phosphorylated Tau protein

Increased oxidative can enhance the death of cholinergic neurons; therefore, micronutrient mixture may protect these neurons from oxidative damage. Other cellular defects which are characteristics of AD include increased production of beta-amyloids [46], which causes death of cholinergic neurons by generating free radicals [12,13], and hyperphosphorylation of tau protein [26], which participates in the progression of AD. Antioxidants reduce production and toxicity of beta-amyloids, and hyperphosphorylation of tau protein [94-96]. Therefore, it is likely that the proposed micronutrient mixture may also reduce the production of beta-amyloids by inhibiting the activity of gamma-secretase which cleaves APP to generate beta-amyloids. It may also reduce the phosphorylation of tau protein. Proposed micronutrient mixture cannot reverse intestinal dysbiosis, restore loss of collagen, or improve glucose metabolism in insulin resistance AD cases.

SUPPLEMENTATION WITH PROBIOTICS WITH PREBIOTICS MAY REVERSE INTESTINAL DYSBIOSIS IN AD

Intestinal dysbiosis occurs in AD [52,97,98]. Supplementation with Probiotics with prebiotics may reverse intestinal dysbiosis by changing composition of bacteria in favor of beneficial bacteria which produces short- chain fatty acids such as butyric acid during fermentation of prebiotics, reduces the markers of pro-inflammatory cytokines, improves immune function, as well as cognitive function in animal models of AD, Mild Cognitive Impairment (MCI) and patients with AD [97,98].

SUPPLEMENTATION WITH OMEGA 3 IMPROVES GLUCOSE METABOLISM IN INSULIN RESISTANCE PATIENTS WITH AD

In the brain of AD patients, reduced utilization of glucose causes decreased production of energy [39]. Reduced metabolism of glucose can lead increased beta-amyloids deposits and hyperphosphorylation of tau protein. Normally, insulin receptor-mediated activation of AKT, also called protein kinase B, causes translocation of Glucose Transporter-4 (GLUT-4) from the cytoplasm to the cell surface membrane which then allows the entry of glucose inside the neurons for generating energy. The development of insulin resistance in the brain increases the risk of developing AD [99] because of reduced uptake of glucose. It has been reported that diabetes type II increases the risk of AD by 50% [100, 101]. In AD patients with insulin resistance, omega-3 directly activates insulin receptor-linked AKT to improve glucose uptake [102].

SUPPLEMENTATION WITH COLLAGEN PEPTIDES MAY IMPROVE STRUCTURAL INTEGRITY AND COGNITIVE FUNCTION BY RESTORING LOSS OF COLLAGEN

Collagen represents approximately 30% of total body's protein [103]. One of the most important functions of collagen

in the brain is to maintain its structural integrity and the levels of collagen type VI which acts as a neuroprotective agent [104,105]. Loss of collagen gradually occurs in the brain because of increased collagenase activity leading to impairment of structural integrity and loss of memory. Importance of collagen in maintaining structure was demonstrated by a clinical study in which daily supplementation with 5 g of collagen hydrolysates for a period of 4 weeks improved structural integrity of the brain and cognitive function in AD [104]. Collagen hydrolysates help recovery from the brain injury by promoting angiogenesis [106] and protected the brain from inflammatory damage [107]. Neuroprotective effect of collagen type VI was shown by the observation in which reduction of collagen type VI increased the toxicity of beta amyloids. Treatment with soluble collagen type VI prevented binding of beta-amyloid oligomers with the neurons, and thereby, prevented neurons from dying [105]. To maintain increased levels of collagen in the brain for a long time, collagen peptides formulation must contain inhibitors of collagenase.

PROPOSED PLAN FOR IMPROVED TREATMENT OF AD BY COMBINING DRUGS WITH THE PREVENTIVE PLAN

Suggested prevention plan in combination with drugs may prolong their effectiveness in improving cognitive function and learning ability by protecting cholinergic neuron from oxidative and inflammatory damages. The efficacy of acetylcholinesterase inhibitors drugs in improving memory depends upon the viability of cholinergic neurons which are dying from oxidative stress and chronic neuroinflammation. Treatment with suggested prevention plan would protect cholinergic neurons from oxidative and inflammatory damages, and thereby, prolong the efficacy of these drugs. Anti-beta-amyloids antibodies protect cholinergic neuron from the toxic effect of beta-amyloids, but they cannot prevent increased production of beta-amyloids. Treatment with suggested prevention plan would reduce the production of beta-amyloids by inhibiting the activity of gamma-secretase. None of acetylcholinesterase inhibitors drugs or anti-amyloids antibodies can reverse intestinal dysbiosis, increase collagen levels or improve glucose uptake in insulin resistance cases of AD. Proposed prevention plan would reverse intestinal dysbiosis, improve structural integrity of the brain and cognitive function, and increase the levels of collagen type VI which acts as neuroprotective agent, and improve glucose uptake in insulin resistance patients with AD. Proposed prevention plan does not address abnormal behaviors associated with advanced AD. Reducing the symptoms of abnormal behaviors would improve the quality of life during treatment. Treatment with CBD would improve behavior abnormalities associated with advanced AD.

SUPPLEMENTATION WITH CBD (CANNABIDIOL) MAY REDUCE ABNORMAL BEHAVIORS ASSOCIATED WITH ADVANCED AD

The patients with advanced AD exhibit several behavior abnormalities which include anxiety, depression, apathy, aggression, agitation, sleep disturbances, and psychosis (hallucinations, and delusion) [24,25]. Treatment with CBD reduced agitation and anxiety [108]. CBD acts as a partial agonist of dopamine receptor D2 and produced anti-psychotic effect like that produced by prescription a drug aripiprazole [109]. In a mouse model of depression, administration of CBD caused rapid and sustained anti-depression effect by enhancing cortical serotonin receptor [110,111]. CBD stimulated serotonin receptor and inhibited serotonin re-uptake [112,113]. CBD protected neuronal death by preventing the release of glutamate by activating anandamide, one of the ligands of endocannabinoid system, which stimulates endocannabinoid receptor (CB1R) that acts as an antagonist of glutamate receptor (NMDAR) [114,115].

CBD also plays an important role in reducing the progression of AD. For example, CBD reduces gliosis, neuroinflammation, and phosphorylation of tau protein. It reverses and prevents cognitive deficits in rodent AD model, and protects against beta-amyloid-induced death of cholinergic neurons [116]. Excessive release of glutamate causes hyperactivity and can lead to neuronal death. CBD inhibits glutamate release, neuronal apoptosis, and production of Neurofibrillary Tangles (NFT) [114]. These effects of CBD are like those produced by the micronutrient mixture; however, they are caused by different mechanisms. Therefore, the combination of two may produce at least additive benefits.

CONCLUSION

Since the discovery of pathological features of dementia by Dr. Alzheimer himself, several biochemical internal risk factors which participate in the development and progression of Alzheimer's disease (AD) have been identified. They include increased oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, autophagic dysfunction, progressive loss of acetylcholine, oxidation of omega-3 fatty acids, increased production of beta-amyloids, hyperphosphorylation of tau protein, loss of collagen, impaired glucose metabolism in cases of insulin resistance, intestinal dysbiosis, and expression of behavior abnormalities in advanced AD. This review suggests that addressing one of these cellular risk factors such as beta-amyloids alone may not be sufficient for the prevention or improved treatment of current therapy. This review proposes a prevention plan which includes changes in diet, lifestyle, and reduce exposure to environmental toxins, and supplementation with a micronutrient mixture which would reduce oxidative stress, chronic neuroinflammation, improve mitochondrial and autophagic functions, protect cholinergic neurons from oxidative and inflammatory damages, prevent oxidation of omega-3 fatty acids, and reduce production of beta-amyloids by decreasing the activity of gamma-secretase, and prevent hyperphosphorylation of tau protein. Micronutrient mixture alone cannot affect intestinal dysbiosis, loss of collagen, reduced glucose uptake in cases of insulin resistance, behavior abnormalities associated with AD. Therefore, this review suggests that supplementation with probiotics with prebiotics which would reverse intestinal dysbiosis in favor of beneficial bacteria, collagen peptides which would restore the loss of collagen and increase the levels of collagen type VI which acts as a neuroprotective agent, and omega

3 which improve glucose uptake by directly activating insulin receptor linked AKT. Activation of AKT causes translocation of Glucose Transporter-4 (GLUT-4) from the cytoplasm to the cell surface membrane which then allows the entry of glucose inside the neurons for generating energy. It also proposes that combining drugs with the prevention plan may prolong the effectiveness of drugs, and possibly reduce their potential toxicity. Since the patients with advanced AD exhibit abnormal behaviors, supplementation with CBD together with drugs and prevention plan may improve behavior and quality of life of these patients.

Cleavage of Amyloid Precursor Protein (APP) to produce beta-amyloids (Aβ1-42)

↓

β- secretase and γ secretase

↓

Beta amyloid (insoluble)

↓

Aggregation of beta amyloids

↓

Produces free radicals.

↓

Damage or kill cholinergic neurons.

↓

Alzheimer's disease (AD)

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