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REVIEWS: CURRENT TOPICS

Potential of tocotrienols in the prevention and therapy of Alzheimer's disease

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Abstract

Currently there is no cure for Alzheimer's disease (AD); clinical trials are underway to reduce amyloid generation and deposition, a neuropathological hallmark in brains of AD patients. While genetic factors and neuroinflammation contribute significantly to AD pathogenesis, whether increased cholesterol level is a causative factor or a result of AD is equivocal. Prenylation of proteins regulating neuronal functions requires mevalonate-derived farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). The observation that the levels of FPP and GGPP, but not that of cholesterol, are elevated in AD patients is consistent with the finding that statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, reduce FPP and GGPP levels and amyloid β protein production in preclinical studies. Retrospective studies show inverse correlations between incidence of AD and the intake and serum levels of the HMG CoA reductase-suppressive tocotrienols; tocopherols show mixed results. Tocotrienols, but not tocopherols, block the processing and nuclear localization of sterol regulatory element binding protein-2, the transcriptional factor for HMG CoA reductase and FPP synthase, and enhance the degradation of HMG CoA reductase. Consequently, tocotrienols deplete the pool of FPP and GGPP and potentially blunt prenylation-dependent AD pathogenesis. The antiinflammatory activity of tocotrienols further contributes to their protection against AD. The mevalonate- and inflammation-suppressive activities of tocotrienols may represent those of an estimated 23,000 mevalonate-derived plant secondary metabolites called *isoprenoids*, many of which are neuroprotective. Tocotrienol-containing plant foods and tocotrienol derivatives and formulations with enhanced bioavailability may offer a novel approach in AD prevention and treatment.

Keywords: Tocotrienol; Alzheimer's; Mevalonate; HMG CoA reductase; Prenylation; Inflammation

1. Introduction

The socioeconomic burden of Alzheimer's disease (AD) coupled with lack of a clear understanding of its molecular mechanism and effective treatments call for more in-depth investigations of this debilitating disease with novel approaches. Here, we first summarize the risk factors including genetic variation, heredity, age and neuroinflammation and follow up with the fundamentals of AD pathogenesis. The ambiguous link between AD and cholesterol levels in plasma, serum and brain tissues stands in contrast with a notable observation that intermediates of the mevalonate pathway by which cholesterol is synthesized are elevated in AD patients; these intermediates support prenylation of proteins regulating neuronal function. The preclinical studies of statins that inhibit the biosynthesis of these mevalonate-derived intermediates, albeit with equivocal clinical outcomes, lend support to the preventive and therapeutic potentials of mevalonate-suppressive tocotrienols, vitamin E molecules with structures and biological activities distinct from those of the more commonly studied tocopherols. Emerging literature also reveals a variety of neuroprotective activity of tocotrienols. We delineate potential mechanisms of tocotrienols based on their impact on the mevalonate pathway that, when coupled with their antiinflammatory activity, renders them — and potentially the broad class of dietary phytonutrients they represent — promising candidates in protection against AD.

2. Risk factors for AD

Risk factors associated with AD have been identified through their functional and physical interaction with neuropathological proteins of

Abbreviations: Aβ, amyloid β protein; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; BACE1, β-secretase; CI, confidence interval; CN, cognitively normal; FPP, farnesyl pyrophosphate; FTI, farnesyl transferase inhibitor; GGPP, geranylgeranyl pyrophosphate; GGTI, geranylgeranyl transferase inhibitor; GRAS, Generally Recognized As Safe; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDLR, low-density lipoprotein receptor; LLA, lipid-lowering agent; LPS, lipopolysaccharide; MCI, mild cognitive impairment; NFκB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; OR, odds ratio; PS, presenilin; ROS, reactive oxygen species; SREBP, sterol regulatory element binding protein; TPA, 12-O-tetradecanoyl phorbol-13-acetate; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TREM2, triggering receptor expressed on myeloid cells 2; WML, white matter lesion.

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AD, amyloid β protein (Aβ) and Tau. Age and greater inflammation are well-established risk factors, and multiple genes have been found to facilitate the disease onset and progression.

2.1. Genetic variation

Genetic and neuropathologic evidence suggests that AD is caused in part by the overproduction and lack of clearance of Aβ [1,2], accompanied by enhanced neuroinflammation [3]. Detrimental mutations in genes encoding presenilin 1 and 2 (PS1 and PS2) and amyloid precursor protein (APP) alter APP processing mediated by β-secretase (BACE1) and γ-secretase (a.k.a. PS1/2) [4–6], leading to an increased ratio of Aβ42/Aβ40 and to early onset familial AD. A beneficial mutation in APP reduces Aβ production and protects against the onset of sporadic AD [7].

Genetic analysis of risk factors reveals that one or two aberrant copies of the apolipoprotein E (ApoE) ε4 alleles are a major risk factor for late-onset sporadic AD. The risk factor gene ApoE has three major isoforms, ApoEε2, ε3, and ε4. ApoEε3 is found in the majority of the healthy population; ApoEε2 allele is found to be protective from incidence of AD, and ApoEε4 allele is the strongest known risk factor for AD. The major receptor for all forms of ApoE is the low-density lipoprotein receptor (LDLR) that regulates amyloid plaque deposition, and overexpression of the LDLR enhances blood–brain barrier-mediated ApoEε2, ε3 and ε4 clearance, thus leading to reduced Aβ accumulation [8]. Brains of sporadic AD patients carrying the ApoEε4 allele were found to have an increased density of Aβ deposits and a limited capability to clear Aβ [3]. The AddNeuroMed Project, a multicenter European longitudinal study, examined the biomarkers for AD; assessment of 168 AD patients, 166 subjects with mild cognitive impairment (MCI), and 187 cognitively normal (CN) people found that the percentages of subjects carrying any ApoEε4 allele were 52%, 41% and 29%, respectively, in these three groups, suggesting a potential correlation between neurodegeneration and ApoEε4 [9].

2.2. Heredity

The majority of AD cases are sporadic in nature, and a small percentage of AD patients are familial cases. Currently, only three genes, PS1, PS2 and APP, are known to cause AD. Autosomal dominant mutations in PS1, PS2 and APP lead to early onset, familial AD and mutant PS1 accounts for the majority of these inherited cases. Interestingly, PS1/PS2 is the enzyme called *γ-secretase* that cleaves the precursor to generate Aβ, and APP is the precursor of Aβ [4–6]. Therefore, mutations in either enzyme or precursor of Aβ initiate onset of disease in all familial cases.

2.3. Age and inflammation

Epidemiological studies reveal that aging is the single most significant risk factor contributing to AD. Among elderly at 65 years old and above, 5% of them have sporadic or familial AD. This number dramatically increases to 50% in elderly over 85 years old. Many factors associated with aging directly or indirectly contribute to the pathogenesis of AD. As imbalanced Aβ homeostasis is an upstream event of neuroinflammation and neurodegeneration, enhanced microgliosis and astrocytosis are directly associated with neuronal loss. Previous studies have shown that some microglia cells originate from the bone marrow. These cells can migrate toward Aβ plaques, mainly because of attraction by Aβ42. These microglia cells are able to eliminate Aβ by phagocytosis, which provides a novel therapeutic opportunity for bone marrow stem cells to remove Aβ deposit in brains of AD patients [10]. Genetic mutations found in several genes lead to changes to immune molecules and reduce Aβ uptake. Mutations in the microglial receptor TREM2 (triggering receptor expressed on myeloid cells 2) triple a person's risk for AD [11,12]. CD33 is another gene linked to AD and functions to suppress Aβ uptake and clearance. AD risk variants reduce expression of CD33 [13,14]. Systemic analysis of hundreds of AD brains reveals changes in networks related to immunologic molecules and microglial cells, including microglial protein TYROBP that binds TREM2 and may regulate CD33 [15].

Physiological alteration provides manifestation of risk factors associated with AD pathogenesis. Many responses characteristic of AD are in part triggered by Aβ. Interleukin-1β is implicated in AD and inflammatory disorders. When microglia cells engulf extracellular aggregates such as Aβ, they trigger inflammasomes [such as NOD-like receptor family pyrin domain-containing 3 (NLRP3)], activate caspases and promote IL-1β release [16]. This pathway was validated in AD transgenic mice where NLRP3 was shown to contribute to AD-like pathology in mouse brains [17]. Recent studies have shown that Aβ can bind to scavenger receptors expressed on microglia such as CD36 — a central regulator of immune responses that drives inflammatory diseases [18] — enter microglia and activate inflammation. Another scavenger receptor Scara1 functions similarly to CD36 and clears extracellular Aβ [19].

3. AD pathology

3.1. Plaques and tangles

Neuritic plaques and neurofibrillary tangles (NFTs) are two characteristic hallmarks in brains of AD patients. Neuritic plaques are composed of heterogeneous Aβ peptides. Biochemical/Immunohistochemical findings have revealed neurotoxic properties of different Aβ isoforms in brain. Compared to shorter Aβ peptides like Aβ40 and Aβ38, the 42-residue Aβ42 enhances aggregation propensity [20], leading to accelerated formation of small (low-n) Aβ oligomers (oAβ) [21]. It has been documented that the oligomeric form of Aβ seems to be the most toxic species of Aβ as well as the precursor to the fibrillary Aβ found in senile plaques [1,21–24].

The second hallmark of AD is NFT. Hyperphosphorylated Tau is the main component of NFT. Phosphorylated Tau appears early in neurons from subjects suffering MCI and accumulates in neurofibrillary neurons as AD progresses. They localize to the dystrophic neurites, a change correlating with synaptic and cognitive deficits. Phosphorylated Tau gradually loses normal function to promote microtubule assembly and becomes highly stable and prone to aggregation.

3.2. Role of cholesterol and mevalonate pathway in causing plaques and tangles

Preclinical studies suggest the cholesterol-AD connection, though evidence for whether elevated cholesterol level is a causative factor or a casualty of AD is equivocal. A hypercholesterolemic diet increased the Aβ load in a transgenic mouse model [25]. Dietary cholesterol induced a two-fold increase in Aβ concentration in rabbit hippocampal cortices [26], and accumulation of Aβ can be reversed by removing cholesterol from diet [27]. Early studies using partially purified γ-secretase complex were carried out to understand the effect of cholesterol on its activity. When different levels of cholesterol were presented in membrane vesicles composed of a known content of phospholipids such as phosphotidylethanolamine and phosphotidylcholine, efficacy of γ-secretase cleavage of its substrate to generate Aβ40 and Aβ42 was either dramatically increased or decreased depending on the composition of phospholipids. However, there is no direct relationship between the amount of cholesterol and the level of phospholipids such as phosphotidylethanolamine and phosphotidylcholine. Statins, competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A