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Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions

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Abstract

Alzheimer's disease (AD) and cardiovascular disease (CVD) are syndromes of aging that share analogous lesions and risk factors, involving lipoproteins, oxidative damage and inflammation. Unlike in CVD, in AD, sensitive biomarkers are unknown, and high-risk groups are understudied. To identify potential prevention strategies in AD, we have focused on pre-clinical models (transgenic and amyloid infusion models), testing dietary/lifestyle factors strongly implicated in reducing risk in epidemiological studies. Initially, we reported the impact of non-steroidal anti-inflammatory drugs (NSAIDs), notably ibuprofen, which reduced amyloid accumulation, but suppressed few inflammatory markers and without reducing oxidative damage. Safety concerns with chronic NSAIDs led to a screen of alternative NSAIDs and identification of the phenolic anti-inflammatory/anti-oxidant compound curcumin, the yellow pigment in turmeric that we found targeted multiple AD pathogenic cascades. The dietary omega-3 fatty acid, docosahexaenoic acid (DHA), also limited amyloid, oxidative damage and synaptic and cognitive deficits in a transgenic mouse model. Both DHA and curcumin have favorable safety profiles, epidemiology and efficacy, and may exert general anti-aging benefits (anti-cancer and cardioprotective.)

Keywords: Docosahexaenoic acid; Curcumin; Alzheimer's; Prevention; Anti-oxidant; Anti-inflammatory

1. Introduction

Alzheimer's disease (AD) resembles cardiovascular disease (CVD) since both show age-dependent accumulation of lipophilic material in multicellular plaque lesions, which involves a macrophage lineage (microglial) inflammatory response, oxidative damage and injury to surrounding cells. The genetic (ApoE alleles) and environmental (high homocysteine, statin use/cholesterol/inflammatory markers/dietary fats/fish/wine/type II diabetes, low exercise, etc.) risk factors for AD and CVD show strong overlap, suggesting that prevention approaches for reducing CVD may be relevant to AD. Studies with CVD in both animal models and the clinic have identified relevant epidemiological risk factors that can be applied to development of successful prevention of CVD. Two major advantages for CVD prevention have been adequate biomarkers (blood lipid profiles) and the opportunity to conduct prevention trials in at-risk patients with secondary cardiovascular "events" as endpoints. Unfortunately, the lack of suitable biomarkers, "second events" and the cost and time involved in conducting prevention trials for AD have prohibited testing prevention in clinical trials; most testing has been in AD patients. Clinical trials in AD patients with vitamin E, and several NSAIDs (naproxen, cyclo-oxygenase-2 (COX-2) inhibitors) have shown mostly minimal or no effects on cognitive decline and AD progression. These failures emphasized the need for better screening in preclinical animal models (expressing familial AD genes or after amyloid peptide infusion into the central nervous system, CNS) using drugs with

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good epidemiology and proven safety. Amyloid models have permitted testing interventions limiting β-amyloid and associated oxidative damage and inflammation. Similar studies in tau transgenics to limit tau/tangle pathology are underway.

CNS inflammation in AD is characterized by reactive microglia and elevated IL-1 and complement factors [3]. Aβ aggregates can stimulate oxidation in multiple ways: including neuronal H_2O_2 production [4], radical production via iron or copper binding [22] and pro-inflammatory stimulation of peroxynitrite or superoxide. Both oxidative damage [4,24,28] and inflammation [3] begin early in AD accompanying amyloid accumulation and neurodegeneration. AD risk is reduced by anti-oxidant [20,34] and non-steroidal anti-inflammatory drug (NSAID) [11] intake suggesting these might be useful prevention methods.

We initially tested the NSAID (ibuprofen) that had the strongest epidemiological rationale. With low dosing designed to model apparently protective chronic NSAID consumption in populations with reduced AD risk, ibuprofen suppressed amyloid accumulation in APPsw transgenic mice [16] but reduced a surprisingly limited subset of inflammatory markers, notably IL-1β and downstream murine ACT mRNA, but not iNOS, macrosialin or CD11c mRNA [19]. Further, some NSAIDs including ibuprofen (but not naproxen and COX-2 inhibitors) selectively lowered Aβ1–42 production without inhibiting Aβ1–40 or NOTCH in vitro or in vivo [8,32]. Although ibuprofen has the strongest rationale for use in AD prevention, it has not been tested (side-effect concerns halted COX-2 inhibitor and naproxen prevention trials in 2004). Efficacy (and possibly even safety) issues with Vitamin E leaves us with few viable approaches to chronic control of oxidative damage and inflammation in AD and other diseases of aging.

2. Phenolic anti-oxidants

Many potent dietary anti-oxidants occur in plant fruiting bodies, seeds or roots and contain one or more phenol groups that contribute to potent anti-oxidant activities presumably selected to protect the plant germ line. Grapes, apples, many types of berries, pomegranates, green tea and many other plant sources are rich sources of these anti-oxidant compounds that often have potent anti-oxidant and anti-inflammatory properties and related health benefits. Notable among these are resveratrol from red wine, the green tea catechins and the turmeric extract curcumin which have received intensive study for potential disease prevention or treatment and are worthy of consideration for AD.

3. Curcumin is a combined polyphenolic anti-oxidant/NSAID that targets AD pathogenesis at multiple sites

Chronic oxidative damage and inflammation occur in AD and likely contribute to neurodegeneration. Although other groups have some evidence for protection, in our hands, neither ibuprofen nor Vitamin E supplements reduced protein carbonyls, one marker for oxidative damage. In contrast, a polyphenolic tumeric component, diferulomethane (curcumin) lowered F2 isoprostanes and carbonyls as measures of oxidative damage, reduced IL-1β, iNOS and CD11b as markers of activated microglia and limited cognitive deficits, postsynaptic marker loss and amyloid accumulation [9,15].

Curcumin has the potential to suppress the AD pathogenic cascade at multiple sites. Curcumin's structure is two methoxyphenol groups separated by a β-diketone bridge that confers iron and other metal chelating activity. Metals have been implicated in Aβ aggregation and toxicity. Thus, while curcumin is a direct radical scavenger, it is a more potent anti-oxidant and inhibitor of lipid peroxidation, particularly metal catalyzed peroxidation [29]. Curcumin is also a good inhibitor of expression of inflammatory cytokines, COX-2, and iNOS by virtue of inhibition of JNK/AP-1 and NFκ-B-mediated gene transcription [1]. All of these factors (IL-1, TNFα, COX-2, iNOS, JNK, NFκ-B) have been implicated in Aβ toxicity or Aβ-induced AD pathogenesis in different AD models, indicating potential as a multi-target intervention. Beyond this, curcumin has other anti-amyloid activities. Because curcumin is a good inhibitor of cytokines, it may also limit inflammatory and oxidative damage induction of BACE1, the β-secretase enzyme that makes the initial step in amyloid production [12]. Our data suggest that, under conditions of elevated oxidative damage and inflammation, curcumin can reduce BACE1 expression in vivo. Curcumin is not simply immunosuppressive, but immunomodulatory, simultaneously inhibiting cytokine and microglial activation indices related to neurotoxicity, but increasing mRNA and immunostaining for both CD11c and macrosialin, markers for microglial phagocytosis that may clear amyloid [Cole and Morihara, unpublished data]. As previously, reviewed, curcumin's hydroxyls provide polar groups 19 Å apart, resembling chrysamine G and the amyloid binding dye Congo red. Thus, curcumin binds and labels plaques in vitro and in vivo and inhibits amyloid aggregation in vitro and amyloid accumulation in vivo [33]. Curcumin also inhibits neurotoxic Aβ oligomer formation and oligomer-dependent Aβ toxicity in vitro [33]. Curcumin's multiple anti-amyloid activities may contribute to the suppression of amyloid in vivo and it's anti-amyloid activity remains effective in aged mice, even after amyloid deposits are well established. Since this compound has multiple direct and indirect anti-amyloid actions including metal chelating, phagocytosis enhancing, anti-oxidant and cholesterol-lowering activity (reviewed in refs. [15,33] and possible suppression of BACE1 induction, it is likely that no one mechanism is involved. Curcumin also inhibits known amyloid response pathways including JNK kinase and iNOS expression in vitro [5,12,23] and in vivo [10,13] and in CNS (our data). Thus, curcumin should be able to suppress not only Aβ but key aspects of the response to Aβ that are JNK- and iNOS-dependent including LTP inhibition [30], reported to depend on JNK, iNOS, and microglial radicals