‘Mega Mind’
Maximizing Mental Performance

Gary E. Foresman, MD
June 2012
Credits

- Today’s presentation I give credit to David Perlmutter MD, Neurologist, http://www.perlhealth.com/
- We will use the model for Alzheimer’s disease and other neurodegenerative diseases to discuss methods of diagnosis, analysis, and treatment for giving the best scientific evidence for mental performance optimization.
- **Key concepts**: infectious disease, vitamin D, insulin resistance, functional fats, gluten sensitivity, Nrf-2 activation.
Neurotoxicity by microglia: Mechanisms and potential therapeutic strategy

Hideyuki Takeuchi
Neurotoxicity by microglia: Mechanisms and potential therapeutic strategy

Cytokines/chemokines
TNF-α, IFN-γ, IL-1, IL-5, IL-6, IL-12, IL-18
IL-10, TGF-β
RANTES, MIP-1α, MCP-1, IP-10

Nucleic acids
ATP, UDP

Excitatory amino acids
Glutamate, serine

ROS
NO, ONOO-, O₂⁻

Proteases
MMP, cathepsin

Growth factors
bFGF, HGF

Neurotrophic factors
NGF, BDNF, GDNF, NT3/4
Neurotoxicity by microglia: Mechanisms and potential therapeutic strategy
Hidetoshi Takeuchi

Activated microglia → Glutamate → NMDA receptor → Neuron → Mitochondria → Energy loss → Neuritic beading (axon transport impairment) → Neuronal dysfunction → Excitotoxic neuronal death
2009 Alzheimer’s Disease Facts and Figures

Alzheimer’s disease triples healthcare costs for Americans aged 65 or older

5.3 million people have Alzheimer’s

148 billion dollars in annual costs

9.9 million unpaid caregivers

1 new case every 70 seconds

6th leading cause of death
The Alzheimer’s Disease-Associated Amyloid β-Protein Is an Antimicrobial Peptide

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Abstract

Background: The amyloid β-protein (Aβ) is believed to be the key mediator of Alzheimer’s disease (AD) pathology. Aβ is most often characterized as an incidental catabolic byproduct that lacks a normal physiological role. However, Aβ has been shown to be a specific ligand for a number of different receptors and other molecules, transported by complex trafficking pathways, modulated in response to a variety of environmental stressors, and able to induce pro-inflammatory activities.

Methodology/Principal Findings: Here, we provide data supporting an in vivo function for Aβ as an antimicrobial peptide (AMP). Experiments used established in vitro assays to compare antimicrobial activities of Aβ and LL-37, an archetypal human AMP. Findings reveal that Aβ exerts antimicrobial activity against eight common and clinically relevant microorganisms with a potency equivalent to, and in some cases greater than, LL-37. Furthermore, we show that AD whole brain homogenates have significantly higher antimicrobial activity than aged matched non-AD samples and that AMP action correlates with tissue Aβ levels. Consistent with Aβ-mediated activity, the increased antimicrobial action was ablated by immunodepletion of AD brain homogenates with anti-Aβ antibodies.

Conclusions/Significance: Our findings suggest Aβ is a hitherto unrecognized AMP that may normally function in the innate immune system. This finding stands in stark contrast to current models of Aβ-mediated pathology and has important implications for ongoing and future AD treatment strategies.


Editors: Ashley I. Bush, Mental Health Research Institute of Victoria, Australia

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Competing Interests: Dr Tanzi is a consultant to and holds stock options in Prana Biotechnology.

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Recent studies have shown that while the adaptive immune system has limited access to the brain, the CNS can still mount a robust response to invading pathogens via antimicrobial peptides and the innate immune system.
antimicrobial peptides (AMPs)

AMPs, also called “host defense peptides” function in the brain’s innate immune system. They are potent, broad-spectrum antibiotics that target Gram-negative and Gram-positive bacteria, mycobacteria, enveloped viruses, fungi, protozoans and in some cases, transformed or cancerous host cells. AMPs are also potent immunomodulators that mediate cytokine release.
A large body of data supports a central role for neuroinflammation in AD neuropathology. A number of studies have proposed Ab as the source of AD-associated inflammation. However, a re-evaluation of the role of Ab in inflammation may now be warranted in view of these data suggesting that the peptide functions as an AMP in tissues. Inflammatory response in the immunologically privileged CNS is mediated by the innate immune system. Rather than Ab acting as a sole independent initiator of neuroinflammation, our data raise the possibility that the peptide may be part of a response mounted by the innate immune system.

If the normal function of Ab is to function as an AMP, then an absence of the peptide may result in increased vulnerability to infection.
Semagacestat is an oral agent designed to reduce the body's production of amyloid beta plaques, which scientists believe play an important role in causing Alzheimer's disease.

Patients treated with semagacestat worsened to a statistically significantly greater degree than those treated with placebo.

The company's decision does not affect the ongoing clinical trials of solanezumab, Lilly's other compound in Phase III trials as a potential Alzheimer's treatment. While both drugs focus on amyloid-beta proteins, which are believed to play a critical role in Alzheimer's disease, they have different mechanisms of action. Lilly also has two other compounds in earlier stages of clinical development; those studies are not affected by today's announcement.

In two pivotal Phase III trials, semagacestat was compared with placebo in more than 2,600 patients with mild-to-moderate Alzheimer's disease. Lilly has now reviewed data from a pre-planned interim analysis of semagacestat studies. This interim analysis showed that, as expected, cognition and the ability to complete activities of daily living of placebo-treated patients worsened. However, by these same measures, patients treated with semagacestat worsened to a statistically significantly greater degree than those treated with placebo. In addition, data showed semagacestat is associated with an increased risk of skin cancer compared with those who received placebo.

"This is disappointing news for the millions of Alzheimer's patients and their families worldwide who anxiously await a successful treatment for this devastating illness," said Jan M. Lundberg, Ph.D., Executive Vice President, Science and Technology, and President, Lilly Research Laboratories. "This is a setback, but Lilly's commitment to beating Alzheimer's will not waver."
Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D$_3$

Adrian F. Gombart,*† Niels Borregaard,† and H. Phillip Koeffler*  
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In this study, we show that 1,25-dihydroxyvitamin D3 and three of its analogs induced expression of the human cathelicidin antimicrobial peptide (CAMP) gene.

Our findings reveal a novel activity of 1,25-dihydroxyvitamin D3 in regulation of primate innate immunity.
The Vitamin D–antimicrobial Peptide Pathway and Its Role in Protection against Infection

Adrian F Gombart

Abstract and Introduction

Abstract

Vitamin D deficiency has been correlated with increased rates of infection. Since the early 19th century, both environmental (i.e., sunlight) and dietary sources (cod liver) of vitamin D have been identified as treatments for TB. The recent discovery that vitamin D induces antimicrobial peptide gene expression explains, in part, the 'antibiotic' effect of vitamin D and has greatly renewed interest in the ability of vitamin D to improve immune function. Subsequent work indicates that this regulation is biologically important for the response of the innate immune system to wounds and infection and that deficiency may lead to suboptimal responses toward bacterial and viral infections. The regulation of the cathelicidin antimicrobial peptide gene is a human/primate-specific adaptation and is not conserved in other mammals. The capacity of the vitamin D receptor to act as a high-affinity receptor for vitamin D and a low-affinity receptor for secondary bile acids and potentially other novel nutritional compounds suggests that the evolutionary selection to place the cathelicidin gene under control of the vitamin D receptor allows for its regulation under both endocrine and xenobiotic response systems. Future studies in both humans and humanized mouse models will elucidate the importance of this regulation and lead to the development of potential therapeutic applications.
“Whoa! That was a good one! Try it, Hobbs — just poke his brain right where my finger is.”
The Role of Infections in Neurodegenerative Diseases

• The following slides will present the potential role of various infections, including HSV1, Chlamydia, and Candida in neurodegenerative diseases such as Alzheimer’s, Parkinson’s, and Multiple Sclerosis.

• The synergistic role of Vitamin D deficiency, insulin resistance, systemic inflammation, and obesity in promoting these diseases
"Reactivation of HSV seropositivity is highly correlated with incident AD. HSV chronic infection may therefore be contributive to the progressive brain damage characteristic of AD.

As AD pathology begins many years before the dementia stage, the recurrent reactivation of HSV might act as a potent stimulus to the brain microglia, increasing the level of cytokines and initiating a positive feedback cycle that gives rise to an increasing accumulation of pathological changes."

www.plosone.org 1 November 2008 Volume 3 (11) e3637
Our demonstration of this intrathecal immune response in AD and elderly normals subjects not only confirms that HSV1 is present in human brain but it also reveals that the virus has replicated there, causing an acute, perhaps recurrent, infection.

Younger people were found to lack this HSV1-specific intrathecal immune response. We used in situ PCR to confirm that the brains of AD patients and age-matched controls contain HSV1 DNA and the virus is present in neurons.
APOE-ε4 associated with greater risk of HSV1 virus spread to the brain and viral latency (rodent)

Both acute and chronic HSV1 infection lead to inflammation and oxidative neuronal damage

The virus competed better against apoE ε4- than against apoE ε3-enriched lipoprotein particles for binding to the cell receptor and intracellular internalisation.
Culture of the organism from brain tissue homogenate from one AD patient demonstrated that the organisms were viable and metabolically active in those samples. Immunohistochemical analyses showed that astrocytes, microglia, and neurons all served as host cells for C. pneumoniae in the AD brain, and that infected cells were found in close proximity to both neuritic senile plaques and neurofibrillary tangles.
Chlamydia (Chlamydia) pneumoniae in the Alzheimer’s brain


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% PCR (+) Chlamydia pneumoniae

- non-Alzheimer’s: 0%
- Alzheimer’s: 80%
Vitamin D and the Brain

- membrane-bound antioxidant
- enhances neurotrophins
- increases hippocampal density (rodent)
- suppresses expression of inflammatory cytokines
- antimicrobial
• The findings of many epidemiological studies and a discordance of MS in monozygotic twins suggest that the disorder is acquired.

• The most likely cause is infectious because more than 90% of patients with MS have high concentrations of IgG, manifest as oligoclonal bands, in the brain and CSF.

• Most chronic inflammatory CNS disorders are infectious.
Association of UV radiation with multiple sclerosis prevalence and sex ratio in France

Figure 1: Annual mean ultraviolet B (Wh/m²) radiation in France

Multiple sclerosis prevalence rates (per 100,000) for each Mutualité Sociale Agricole
Association of UV radiation with multiple sclerosis prevalence and sex ratio in France
Table 1: Treatment group vitamin D3 and calcium dosing schedule

<table>
<thead>
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<th>Calcium (mg/d)</th>
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</table>

Graph: Serum calcium (mmol/L) vs. Vitamin D3 dose (IU/d)
annualized relapse rate

(- 41% treatment group vs. control)
Hypovitaminosis D is associated with insulin resistance and β cell dysfunction\(^1-3\)

Ken C. Chiu, Audrey Chu, Vey Liang W Go, and Mohammed F Saad
Vitamin D not only facilitates the biosynthetic capacity of β cells but also accelerates the conversion of proinsulin to insulin.

The data show a positive correlation of 25(OH)D concentration with insulin sensitivity and a negative effect of hypovitaminosis D on β cell function. Subjects with hypovitaminosis D are at higher risk of insulin resistance.
UV-B

7-dehydrocholesterol → Pro-Vitamin D3 → Skin

Skin Cell / Skin Monocyte

Calcidiol (25-D3) → Calcitriol (1,25-D3)

Depakote (Epilepsy Drug):

Cathelicidin

Calcidiol (25-D3)

→ Calcitriol (1,25-D3: Active Vit.D3)

Immune Response (Antimicrobial, inflammation, wound healing)
Serum Vitamin D and the Risk of Parkinson Disease

Paul Knekt, DPH; Annamari Kilkkinen, PhD; Harri Rissanen, MSc; Jukka Marniemi, PhD; Katri Sääksjärvi, MSc; Markku Heliövaara, PhD

**Objective:** To investigate whether serum vitamin D level predicts the risk of Parkinson disease.

**Design:** Cohort study.

**Setting:** The study was based on the Mini-Finland Health Survey, which was conducted from 1978 to 1980, with Parkinson disease occurrence follow-up through the end of 2007. During the 29-year follow-up period, 50 incident Parkinson disease cases occurred. Serum 25-hydroxyvitamin D level was determined from frozen samples stored at baseline. Estimates of the relationship between serum vitamin D concentration and Parkinson disease incidence were calculated using the Cox model.

**Participants:** Three thousand one hundred seventy-three men and women, aged 50 to 79 years and free of Parkinson disease at baseline.

**Main Outcome Measure:** Parkinson disease incidence.

**Results:** Individuals with higher serum vitamin D concentrations showed a reduced risk of Parkinson disease. The relative risk between the highest and lowest quartiles was 0.33 (95% confidence interval, 0.14-0.80) after adjustment for sex, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index, and month of blood draw.

**Conclusions:** The results are consistent with the suggestion that high vitamin D status provides protection against Parkinson disease. It cannot, however, be excluded that the finding is due to residual confounding and further studies are thus needed.

*Arch Neurol.* 2010;67(7):808-811.
Serum Vitamin D and the Risk of Parkinson Disease

- **Relative Risk for Parkinson's**

Quartile 1: Serum 25-Hydroxyvitamin D level
Quartile 2
Quartile 3
Quartile 4

Relative risk decreases as serum 25-Hydroxyvitamin D level increases.
“Sure—but can you make him drink?”
8,776 men and women aged 40-45 years, between 1964 and 1973

- Triceps skin fold measurement
- Average follow up 27 years later
- Risk of Alzheimer’s comparing lowest to highest quintile increased 293%
Decreased bioavailability of vitamin D in obesity

Jacobo Wortsman, Lois Y Matsuoka, Tai C Chen, ZhirenLu, and Michael F Holick

Introduction: Obese subjects had significantly lower basal 25-hydroxyvitamin D concentrations and higher parathyroid hormone concentrations than did age-matched control subjects. Evaluation of blood vitamin D concentrations 24 h after whole-body irradiation showed that the incremental increases in vitamin D were 57% lower in obese than in nonobese subjects. The content of the vitamin D precursor 7-dehydrocholesterol in the skin of obese and nonobese subjects did not differ significantly between groups nor did its conversion to previtamin D$_3$ after irradiation in vitro. The obese and nonobese subjects received an oral dose of 50,000 IU (1.25 mg) vitamin D$_3$. BMI was inversely correlated with serum vitamin D$_3$ concentrations after irradiation ($r = -0.55$, $P = 0.003$) and with peak serum vitamin D$_3$ concentrations after vitamin D$_3$ intake ($r = -0.56$, $P = 0.007$).

Conclusions: Obesity-associated vitamin D insufficiency is likely due to decreased bioavailability of vitamin D$_3$ from cutaneous and dietary sources because of its deposition in body fat compartments.

Subjects and Methods

Subjects

The experimental population was 19 healthy whites (skin types II and III) of normal body weight [body mass index (BMI, in kg/m$^2$) < 25] and 19 healthy obese subjects (skin types II and III, BMI > 30). Subjects were recruited among medical school personnel and had similar socioeconomic status. None of the subjects had a history of hepatic or renal disorders and none were taking vitamin D supplements, anti-inflammation medications, or cortico-steroids. The study was performed during the winter (November through February) and the subjects refrained from sunlight exposure beginning 24 h before the study and during the study. All subjects gave their informed consent and the study was approved by the Jefferson Medical College (Philadelphia) Institutional Review Board.

Key Words: Vitamin D, ultraviolet radiation, tan, bed, obesity, 25-hydroxyvitamin D, parathyroid hormone, obesity, vitamin D$_3$, sunlight, obesity, 25-hydroxyvitamin D, bioavailability.
Systemic inflammation and disease progression in Alzheimer disease

C. Holmes, et al., Neurology, September 2009; 73; 768-774

- **Results**: Acute systemic inflammatory events, found in around half of all subjects, were associated with an increase in the serum levels of proinflammatory cytokine TNF-α and a 2-fold increase in the rate of cognitive decline over a 6-month period. High baseline levels of TNF-α were associated with a 4-fold increase in the rate of cognitive decline. Subjects who had low levels of serum TNF-α throughout the study showed no cognitive decline over the 6-month period.

- **Conclusions**: Both acute and chronic systemic inflammation, associated with increases in serum TNF-α, is associated with an increase in cognitive decline in Alzheimer disease.
In summary, we propose that during events such as stress and peripheral infection, latent HSV1 reactivates (as in the PNS) and causes an acute but localised infection, perhaps a “mild”, variant type of encephalitis, causing greater damage – both direct, and indirect via inflammatory processes – in APOE-ε4 carriers, and eventually, AD.
Alzheimer’s Disease - Functional Medicine Model
Damage to Lipids, Proteins, DNA, and RNA in Mild Cognitive Impairment

Markesbery, W., Arch Neurol. 64(7):954-956; July, 2007

“Better antioxidants and agents used in combination to up-regulate defense mechanisms against oxidation will be required to neutralize the oxidative component of the pathogenesis of AD. It is most likely that to optimize these neuroprotective agents, they will have to be used in the presymptomatic phase of the disease.”
Could lysine supplementation prevent Alzheimer’s dementia? A novel hypothesis

Robert N Rubey

Retired, Red Lodge, Montana, USA
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Lysine treatment of herpes labialis

- HSV-1 requires arginine for replication
- Lysine inhibits HSV-1 replication by competing with arginine
- Lysine is a treatment for the common condition known as herpes labialis caused by HSV-1
- Six randomized, double-blind, placebo-controlled studies have found lysine to be effective in preventing or decreasing outbreaks
- Lysine was found to be effective in reducing outbreaks when serum lysine concentration was greater than 165 nmol/mL
- A dosage of 1,248 mg/day was effective in reducing outbreak frequency. It seems beyond question, then, that lysine in sufficient concentrations relative to arginine suppresses reactivation of HSV-1 in vivo
Lysine treatment of herpes labialis

• The Mediterranean diet emphasizes fruits, vegetables, cheese, yogurt, and fish, all foods high in lysine and low in arginine.
• Perhaps more than any other food, weekly consumption of fish is associated with a lower risk of AD.
• This is generally attributed to omega-3 fatty acids in fish; however, it is also true that fish have a high lysine to arginine ratio.
Insulin Resistance and Cognitive Impairment
The InCHIANTI Study


• Early in type 2 DM:
  progressive insulin resistance
  high fasting blood insulin levels
  normal fasting glucose

The IR syndrome
Insulin Resistance and Cognitive Impairment
The InCHIANTI Study


• 523 participants 70-90 years of age
• MMSE
• Fasting plasma insulin, insulin resistance index, insulin sensitivity index
Glucose tolerance status and risk of dementia in the community
The Hisayama Study
Ohara, T., et al., Neurology September 20, 2011 vol. 77 no. 12 1126-1134

• 15 year study
• 1017 dementia-free subjects ≥ 60 years
• comparison of risk of dementia versus normal, abnormal GTT, or DM
Glucose tolerance status and risk of dementia in the community
The Hisayama Study
Ohara, T., et al., Neurology September 20, 2011 vol. 77 no. 12 1126-1134
Diabetes mellitus and the risk of dementia
– The Rotterdam Study

• 6,370 patients
• RR of Alzheimer’s with diabetes – 1.9X
• RR dementia if using insulin – 4.3X
Glyco-Oxidation

- Advanced Glycosylation End Products (AGE) – Posttranslational modifications of proteins – amino group of protein reacts with monosaccharide
% annual brain volume change

HbA1c (%)

Enzinger, C., et al., Neurology 64: 1704-11; May 24, 2005
Alzheimer’s Disease – Synergistic Effects of Glucose Deficit, Oxidative Stress and Advanced Glycosylation End Products


AGEs are more than just markers of aging since they can exert adverse biological effects on tissues and cells including the activation of intracellular signal transduction pathways, leading to the upregulation of cytokine and free radical production (oxidative stress)
AGE modulated β-Amyloid

- Generates ROS
- Activates NFκB
- Activates microglia
- Enhances production of superoxide radical and nitric oxide
Regulation of Cyclooxygenase-2 Expression in Monocytes by Ligation of the Receptor for Advanced Glycation End Products

Shanmugam, N., et al., The Journal of Biological Chemistry 278 (37): 34834-34844; September 12, 2002

• Human monocytes treated with AGEs or a specific RAGE ligand significantly increases COX-2 mRNA and protein expression, as well as COX-2 product PGE2
Advanced Glycosylated End Products

Nutritional Therapy -

- benfotiamine
- alpha-lipoic acid
- taurine
- resveratrol
- N-acetyl cysteine
- aspirin
- carnosine
- DHA
- low carbohydrate diet
Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease.


Source
Department of Neuroscience, Case Western Reserve University, Cleveland, OH, USA.

Abstract
Recent studies have implicated resveratrol and pterostilbene, a resveratrol derivative, in the protection against age-related diseases including Alzheimer's disease (AD). However, the mechanism for the favorable effects of resveratrol in the brain remains unclear and information about direct cross-comparisons between these analogs is rare. As such, the purpose of this study was to compare the effectiveness of diet-achievable supplementation of resveratrol to that of pterostilbene at improving functional deficits and AD pathology in the SAMP8 mouse, a model of accelerated aging that is increasingly being validated as a model of sporadic and age-related AD. Furthermore, we sought to determine the mechanism of action responsible for functional improvements observed by studying cellular stress, inflammation, and pathology markers known to be altered in AD. Two months of pterostilbene diet but not resveratrol significantly improved radial arm water maze function in SAMP8 compared with control-fed animals. Neither resveratrol nor pterostilbene increased sirtuin 1 (SIRT1) expression or downstream markers of sirtuin 1 activation. Importantly, markers of cellular stress, inflammation, and AD pathology were positively modulated by pterostilbene but not resveratrol and were associated with upregulation of peroxisome proliferator-activated receptor (PPAR) alpha expression. Taken together, our findings indicate that at equivalent and diet-achievable doses pterostilbene is a more potent modulator of cognition and cellular stress than resveratrol, likely driven by increased peroxisome proliferator-activated receptor alpha expression and increased lipophilicity due to substitution of hydroxy with methoxy group in pterostilbene.

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• Importantly, markers of cellular stress, inflammation, and AD pathology were positively modulated by pterostilbene but not resveratrol.

• Taken together, our findings indicate that at equivalent and diet-achievable doses pterostilbene is a more potent modulator of cognition and cellular stress than resveratrol.
Preventable Risk Factors Account for Nearly Half of All Alzheimer’s Disease Cases

Published report: Lancet Neurology, July 18, 2011

“ A 25% reduction in seven risk factors could potentially prevent as many as three million cases of Alzheimer’s disease worldwide.”

- quitting smoking
- increasing physical activity
- increasing mental activity
- controlling blood pressure
- controlling diabetes
- managing obesity
- managing depression
Combination therapy is effective at slowing the advance of Alzheimer's symptoms

A study published in the Journal of the American Medical Association showed that combination therapy with NAMENDA and ARICEPT® (donepezil 5 and 10mg) is more effective at slowing the advance of symptoms than taking ARICEPT alone. Use this guide to talk to your doctor about how adding Namenda can help your loved one.

Learn more
Lack of Evidence for the Efficacy of Memantine in Mild Alzheimer Disease

Lyn S. Schneider, MD, MS; Karen S. Dagerman, MS; Julian P. T. Higgins, PhD; Rupert McShane, MD

Objective: We directly assessed the clinical trials’ evidence for memantine’s efficacy in mild Alzheimer disease (AD). Memantine is indicated in the United States and Europe for moderate to severe AD, which is diagnosed if a patient has a Mini-Mental State Examination (MMSE) score of less than 15 or less than 20, respectively. Yet memantine is very frequently prescribed for mild AD and mild cognitive impairment, and a manufacturer-sponsored meta-analysis claimed its efficacy in mild AD.

Data Sources, Study Selection, and Data Extraction: Manufacturer-sponsored meta-analyses, registries, presentations, and publications were systematically searched for randomized placebo-controlled, parallel-group clinical trials of memantine in patients with mild to moderate AD. The trials’ characteristics and outcomes were extracted by one reviewer and checked by another. Meta-analyses were performed as inverse variance-weighted averages of mean differences using fixed-effects models. Summary results for patients with mild AD were obtained by contrasting the summary results for patients with mild or moderate AD with the summary results for the subset of patients with moderate AD.

Data Synthesis: Three trials were identified that included 431 patients with mild AD (i.e., with MMSE scores of 20-23) and 697 patients with moderate AD (i.e., with MMSE scores of 10-19). There was no significant differences between the placebo and memantine at any outcome for patients with mild AD, either within any trial or when data were combined: mean differences (95% confidence intervals [CIs]) on the ADAS-cog, the Clinician’s Interview-Based Impression of Change plus caregiver input (CIBIC-plus), the Alzheimer Disease Cooperative Study–activities of daily living (ADCS-ADL) scale, and the Neuropsychiatric Inventory (NPI) were -0.17 (95% CI, -1.60 to 1.26), -0.09 (95% CI, -0.30 to 0.12), 0.62 (95% CI, -1.64 to 2.71), and 0.09 (95% CI, -2.11 to 2.29), respectively. For patients with moderate AD, there were small differences on the ADAS-cog and the CIBIC-plus, -1.33 (95% CI, -2.28 to -0.38) and -0.16 (95% CI, -0.32 to 0.00), respectively, but no differences on the ADCS-ADL scale (-0.57 [95% CI, -1.72 to 0.60]) or the NPI (0.25 [95% CI, -1.48 to 1.99]).

Conclusions: Despite its frequent off-label use, evidence is lacking for a benefit of memantine in mild AD, and there is meager evidence for its efficacy in moderate AD. Prospective trials are needed to further assess the potential for efficacy of memantine either alone or added to cholinesterase inhibitors in mild and moderate AD.

Review of ... “all clinical trials of memantine vs placebo that included patients with mild AD.”

Conclusions: Despite its frequent off-label use, evidence is lacking for a benefit of memantine in mild AD, and there is meager evidence for its efficacy in moderate AD.

In the United States, nearly half of the patients with mild Alzheimer’s Disease and a substantial proportion of patients with mild cognitive impairment are receiving memantine despite a lack of evidence that the drug is helpful and some evidence that it is not.
Oh please, oh please...
The Transcription Factor Nrf2 Is a Therapeutic Target against Brain Inflammation

Nadia G. Innamorato,*† Ana I. Rojo,*† Ángel J. García-Yagüe,*† Masayuki Yamamoto,‡ María L. de Ceballos,‡§ and Antonio Cuadrado2*†

Because chronic neuroinflammation is a hallmark of neurodegenerative diseases and compromises neuron viability, it is imperative to discover pharmacologic targets to modulate the activation of immune brain cells, the microglia. In this study, we identify the transcription factor Nrf2, guardian of redox homeostasis, as such target in a model of LPS-induced inflammation in mouse hippocampus. Nrf2 knockout mice were hypersensitive to the neuroinflammation induced by LPS, as determined by an increase in F4/80 mRNA and protein, indicative of an increase in microglial cells, and in the inflammation markers inducible NO synthase, IL-6, and TNF-α, compared with the hippocampi of wild-type littermates. The aliphatic isothiocyanate sulforaphane elicited an Nrf2-mediated antioxidant response in the BV2 microglial cell line, determined by flow cytometry of cells incubated with the redox sensitive probe dihydrodichlorofluorescein diacetate, and by the Nrf2-dependent induction of the phase II antioxidant enzyme heme oxygenase-1. Animals treated with sulforaphane displayed a 2–3-fold increase in heme oxygenase-1, a reduced abundance of microglial cells in the hippocampus and an attenuated production of inflammation markers (inducible NO synthase, IL-6, and TNF-α) in response to LPS. Considering that release of reactive oxygen species is a property of activated microglia, we propose a model in which late induction of Nrf2 intervenes in the down-regulation of microglia. This study opens the possibility of targeting Nrf2 in brain as a means to modulate neuroinflammation. The Journal of Immunology, 2008, 181: 680–689.
Induction of EpRE-dependent transcription by various dietary plant extracts
Common uses for HBOT

Air embolism, decompression illness, burns, carbon monoxide poisoning, cerebral edema, closed head injuries, sickle cell anemia, gangrene, near drowning, severed limbs, smoke inhalation, spinal cord injury, stroke, coma, multiple sclerosis, hearing loss, peripheral neuropathy, radiation myelitis, crush injuries, soft tissue injuries, osteomyelitis (both acute and chronic), non-healing fractures, tendon and ligament injuries, delayed wound healing, soft tissue ulcers from arterial or venous insufficiency, decubitus ulcers, frostbite, diabetic retinopathy, migraine headache, cluster headache, myocardial infarction, chronic fatigue, post-polio syndrome, Crohn's disease, Bell's palsy, Lyme disease, Meniere's disease, reflex sympathetic dystrophy, and osteoradionecrosis.
Hyperbaric Oxygen Therapy

- Multiple sclerosis
- Chronic Lyme disease
- Reflex sympathetic dystrophy
- Cerebral Palsy
- Head injury
- Parkinson’s disease
- Wound healing
- Fibromyalgia
- Post-radiation necrosis
Neuroprotective mechanisms of calorie restriction

**Improved mitochondrial function**
- reduced ROS
- increased energy output (mitochondrial biogenesis)

**Regulation of gene expression**
- decreased pro-apoptotic factors
- decreased inflammatory factors
- increased neuroprotective trophins
- increased molecular chaperones
The French Paradox

- The French eat more saturated than almost any Western country
- Incidence of heart-related death among middle-aged men is less than half of that in America
- Lowest rate in Gascony, the area with the highest fat consumption
People in northern India eat seventeen times more animal fat compared to the south and their incidence of heart disease is seven times lower.
The diet-heart hypotheses (that suggests that high intake of fat and cholesterol causes heart disease) has been repeatedly shown to be wrong, and yet, for complicated reasons of pride, profit and prejudice, the hypothesis continues to be exploited by scientists, fund-raising enterprises, food companies, and even governmental agencies. The public is being deceived by the greatest health scam of the century.
Diet and Alzheimer's disease risk factors or prevention: the current evidence.

Source

- Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy.

Abstract

- Preventing or postponing the onset of Alzheimer's disease (AD) and delaying or slowing its progression would lead to a consequent improvement of health status and quality of life in older age. Elevated saturated fatty acids could have negative effects on age-related cognitive decline and mild cognitive impairment (MCI). Furthermore, at present, epidemiological evidence suggests a possible association between fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; in particular, n-3 PUFA) and a reduced risk of cognitive decline and dementia.
Diet and Alzheimer's disease risk factors or prevention: the current evidence.

• Poorer cognitive function and an increased risk of vascular dementia (VaD) were found to be associated with a lower consumption of milk or dairy products. However, the consumption of whole-fat dairy products may be associated with cognitive decline in the elderly. Light-to-moderate alcohol use may be associated with a reduced risk of incident dementia and AD, while for VaD, cognitive decline and predementia syndromes, the current evidence is only suggestive of a protective effect. The limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supports a protective role of these macronutrients against cognitive decline, dementia and AD.
Only recently, higher adherence to a Mediterranean-type diet was associated with decreased cognitive decline, although the Mediterranean diet (MeDi) combines several foods, micro- and macro-nutrients already separately proposed as potential protective factors against dementia and predementia syndromes. In fact, recent prospective studies provided evidence that higher adherence to a Mediterranean-type diet could be associated with slower cognitive decline, reduced risk of progression from MCI to AD, reduced risk of AD and a decreased all-cause mortality in AD patients.
Diet and Alzheimer's disease risk factors or prevention: the current evidence.

• These findings suggested that adherence to the MeDi may affect not only the risk of AD, but also of predementia syndromes and their progression to overt dementia. Based on the current evidence concerning these factors, no definitive dietary recommendations are possible. However, following dietary advice for lowering the risk of cardiovascular and metabolic disorders, high levels of consumption of fats from fish, vegetable oils, nonstarchy vegetables, low glycemic index fruits and a diet low in foods with added sugars and with moderate wine intake should be encouraged. Hopefully this will open new opportunities for the prevention and management of dementia and AD.

• Solfrizzi V, Panza F, Frisardi V, Seripa D, Logroscino G, Imbimbo BP, Pilotto A.
Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease
A Randomized Trial

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A s the world population ages, the number of older adults living with Alzheimer disease (AD) is estimated to increase from the current 26.6 million to 106.2 million by 2050. If illness onset could be delayed by 12 months, 9.2 million fewer cases of AD would occur worldwide. For this reason, attempts have been made to identify individuals who are at increased risk of AD and to test interventions that might delay the progression of prodromal symptoms to full-blown dementia. The results from observational studies suggest that older people who are free of dementia but report memory decline or show objective evidence of cognitive impairment are more likely to develop AD over time. Seven clinical trials have investigated whether cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), vitamin E, piracetam, and roscovit (a cyclooxygenase 2 inhibitor) can prevent cognitive decline and progression to dementia in older adults with mild cognitive impairment. In a trial by Petersen et al, participants with mild cognitive impairment were randomly assigned to receive 10 mg of donepezil, 2000 IU of vitamin E, or placebo daily for 36 months. By study end, progression to dementia and change in cognitive score did not differ by treatment group. A study of rivastigmine to prevent conversion from mild cognitive impairment to dementia and change in cognitive score did not differ by treatment group.

Author Affiliations and Other Information are listed at the end of this article.

Context Many observational studies have shown that physical activity reduces the risk of cognitive decline; however, evidence from randomized trials is lacking.

Objective To determine whether physical activity reduces the rate of cognitive decline among older adults at risk.

Design and Setting Randomized controlled trial of a 24-week physical activity intervention conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Measurements of cognitive function were blinded to group membership.

Participants We recruited volunteers who reported memory problems but did not meet criteria for dementia. Three hundred eleven individuals aged 50 years or older were screened for eligibility, 89 were not eligible, and 52 refused to participate. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.

Intervention Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.

Main Outcome Measure Change in Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores (possible range, 0-70) over 18 months.

Results In an intent-to-treat analysis, participants in the intervention group improved 0.36 points (95% confidence interval, -0.89 to 0.54), and those in the usual care group deteriorated 1.04 points (95% confidence interval, 0.32 to 1.82) on the ADAS-Cog at the end of the intervention. The absolute difference of the outcome measure between the intervention and control groups was -1.3 points (95% confidence interval, -2.38 to -0.22) at the end of the intervention. At 18 months, participants in the intervention group improved 0.79 points (95% confidence interval, -1.27 to 0.25) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% confidence interval, -0.45 to 0.88). Word list delayed recall and Clinical Dementia Rating sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly.

Conclusions In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.

Trial Registration anzctr.org.au Identifier ACTRN12605001366505
JAMA, 2008;2009;1:1027-1037
www.jama.com

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In summary, the results of this randomized trial indicate that a physical activity program of an additional 142 minutes of exercise per week on average modestly improved cognition relative to controls in older adults with subjective and objective memory impairment.
Walking Slows Progression of Alzheimer’s Disease

• Healthy adults needed 6 miles/week to maintain cognitive function and brain volume, cognitively impaired required 5 miles/week
• MMSE declined 5 points in non-exercising cognitively impaired, 1 point in exercisers

CHICAGO — Walking five miles per week slows cognitive function and brain volume loss in people with Alzheimer’s disease, according to data presented at the annual meeting of the Radiological Society of North America (RSNA).

“We found that walking five miles per week protects the brain structure over 10 years in people with Alzheimer’s disease and MCI, especially in areas of the brain’s key memory and learning centers,” said Cyrus Raji, PhD.

“We also found that these people had a slower decline in memory loss over five years.” Dr. Raji is from the Antibody Discovery Unit, National Institute on Aging, National Institutes of Health.

In addition, patients were given the Mini-Mental State Examination (MMSE) to track cognitive decline over five years. Physical activity levels were then correlated with MRI and MMSE results. The analysis adjusted for age, gender, body fat composition, head size, education, and other factors.

The findings showed across the board that greater amounts of physical activity were associated with greater cognitive integrity.

Dr. Raji and colleagues analyzed the relationship between physical activity and brain structure in 426 people, including 299 healthy adults (mean age, 78) and 127 cognitively impaired adults (mean age, 81), including 83 adults with MCI and 44 adults with Alzheimer’s dementia. Patients were recruited from the Cardiovascular Health Study. The researchers monitored the walking and brain imaging of the patients for five years.

Alzheimer’s disease is a devastating illness, and unfortunately, walking is not a cure,” Dr. Raji said. “But walking can improve your brain’s resistance to the disease and reduce memory loss over time.”
Dietary Omega-3 Fatty Acids Normalize BDNF Levels, Reduce Oxidative Damage, and Counteract Learning Disability after Traumatic Brain Injury

Wu, A., Journal of Neurotrauma 21(10): 1457-1467; October, 2004

DHA

• Signal transduction and gene expression
relative risk of Alzheimer's disease

Omega-3 DHA boosts memory for healthy adults

13-Jul-2009

Related topics: Omega-3, Research, Nutritional lipids and oils, Cardiovascular health, Cognitive and mental function

Daily supplements with the omega-3 fatty acid docosahexaenoic acid (DHA) may improve both memory function and heart health in healthy older adults, according to a new study from Martek.

The results, specific to people with a decline in cognitive function that occurs naturally with age, were presented at the Alzheimer's Association 2009 International Conference on Alzheimer's Disease (ICAD 2009) in Vienna.

Almost 500 people took part in the randomised, double-blind, placebo-controlled, multi-center, six month study, which also recorded improvements in the heart rate of people receiving the DHA supplement. The study was funded by Martek Biosciences.

“In our study, healthy people with memory complaints who took algal DHA capsules for six months had almost double the reduction in errors on a test that measures learning and memory performance versus those who took a placebo,” said Yurko-Mauro, PhD, associate director of clinical research at Martek and lead researcher of the study.

“The benefit is roughly equivalent to having the learning and memory skills of someone three years younger.”

“Results of the MIDAS Trial: Effects of Docosahexaenoic Acid on Physiological and Safety Parameters in Age-Related Cognitive Decline”

Essential fatty acids and the brain: possible health implications


**DHA** plays a pivotal role in:

- Mitochondrial and neuronal membrane fluidity
- Signal transduction
- Neurogenesis
- Gliogenesis
- Synaptogenesis
probiotics

Tying the Matrix Together

- Digestion and Absorption
- Structural/Boundary/Membranes
- Immune Surveillance and Inflammatory Processes
- Detoxification and Biotransformation
- Oxidative/Reductive Homeodynamics (Mitochondrial Function)
- Neurotransmitter Regulation
- Psychological Equilibrium
The realization that microbes produce a wide spectrum of neuroactive compounds extending from GABA to somatostatin suggests that the consequences of such neuroactive compound production, as well as the mechanisms governing such interactions, are yet to be discovered. The recent report describing the ability of probiotics to alleviate psychological distress in human volunteers and anxiolytic-like activity in rats lends further support to the increasing evidence that the gut microbiota can influence nervous system function.
Gluten Sensitivity and the Impact on the Brain

Several years ago, parents of a lovely nine-year-old girl, Karen, brought her to see me because she had poor memory. They indicated that she had difficulty in thinking and focusing, and because of these issues she was falling further and further behind in her school work. Interestingly, they stated that at times she was fine, while clearly at other times her brain function seemed to be different. They indicated that she had difficulty keeping her thoughts together and that she became profoundly frustrated when this would occur.

Because of her significant issues with academic performance, her parents elected to home school her. Her academic testing revealed that she was functioning at or below a third grade level in a variety of areas, including math skills, reading fluency, story recall and overall academic skills. Fortunately, she had no significant medical problems in her past and her overall physical, as well as neurological examinations were entirely normal. Routine, typical blood studies were unrevealing, so I was left to reconsider her history to see if there were any clues as to what might be causing this child’s problems.
Current alcohol consumption and its relationship to incident dementia: results from a 3-year follow-up study among primary care attenders aged 75 years and older.

Source
• Central Institute of Mental Health, Mannheim, Germany.
siegfried.weyerer@zi-mannheim.de

Abstract
OBJECTIVE:
• to investigate prospectively the relationship between current alcohol consumption (quantity and type of alcohol) and incident overall dementia and Alzheimer dementia.

METHOD:
• the study is based on individuals (75+) attending general practitioners in Germany: 3,202 subjects free of dementia were studied at baseline, 1.5 years and 3 years later by means of structured clinical interviews including detailed assessment of current alcohol consumption and DSM-IV dementia diagnoses. Associations between alcohol consumption (in grams of ethanol), type of alcohol (wine, beer, mixed alcohol beverages) and incident dementia were examined using Cox proportional hazard models, controlling for several confounders.
Current alcohol consumption and its relationship to incident dementia: results from a 3-year follow-up study among primary care attenders aged 75 years and older.

RESULTS:
• incident overall dementia occurred in 217 of 3,202 participants over a mean follow-up period of 3 years. Significant relationships were found between alcohol consumption (prevalence at baseline: 50.0%) and incident overall dementia (adjusted hazard ratio (HR) 0.71, 95% CI 0.53-0.96), respectively, incident Alzheimer dementia (adjusted HR 0.58, 95% CI 0.38-0.89). With regard to quantity of alcohol and type of alcohol, all hazard ratios were found to be lower than 1.

CONCLUSION:
• in agreement with meta-analyses that include younger age groups, our study suggests that light-to-moderate alcohol consumption is inversely related to incident dementia, also among individuals aged 75 years and older.

Weyerer S, Schäufele M, Wiese B, Maier W, Tebarth F, van den Bussche H, Pentzek M, Bickel H, Luppa M, Riedel-Heller SG; German AgeCoDe Study group (German Study on Ageing, Cognition and Dementia in Primary Care Patients). Collaborators (27)
Health benefits of wine and alcohol from neuroprotection to heart health

Abstract

• Controversy is common during efforts to define the role of nutrition in health, but few modern reflections of such controversy are as vivid as the debate over wine. There exists no query that chronic alcohol abuse, a leading worldwide problem, causes neuronal dysfunction and brain damage.

• **However**, various epidemiologic studies in recent years have indicated that in comparisons with abstainers or never drinkers, light/moderate alcohol/wine consumers have lower risks of age-dependent cognitive decline and/or dementia, including Alzheimer's disease (AD) Neurodegenerative diseases such as AD and Parkinson's (PD) diseases are defined by a progressive neuronal dysfunction and an ensuing behavioral dysfunction.
Health benefits of wine and alcohol from neuroprotection to heart health

- Epidemiologic studies from numerous disparate populations reveal that individuals with the habit of daily moderate wine consumption enjoy significant reductions in all-cause and particularly cardiovascular and neurodegenerative mortality when compared with individuals who abstain or who drink alcohol in excess.

- Apart from the alcohol present in the wine, other trace compounds and polyphenolic compounds such as resveratrol naturally present in wine and grapes also exert neuroprotective and cardioprotective activities.

Source
- Herbal and Indian Medicine Research Laboratory, Sri Ramachandra University, Chennai-600116, India.
  - Vasanthis HR, Parameswari RP, DeLeiris J, Das DK.
microglial activation  inflammatory cytokines  oxidative stress  mitochondrial failure  neuronal death  decreased acetylcholine

Alzheimer’s Disease - Functional Medicine Model
Low-effort thought promotes political conservatism.

Source
• 1University of Arkansas, Fayetteville, USA.

Abstract
• The authors test the hypothesis that low-effort thought promotes political conservatism.

• In Study 1, alcohol intoxication was measured among bar patrons; as blood alcohol level increased, so did political conservatism (controlling for sex, education, and political identification).

• In Study 2, participants under cognitive load reported more conservative attitudes than their no-load counterparts.
Low-effort thought thought promotes political conservatism.

• In Study 3, time pressure increased participants' endorsement of conservative terms.
• In Study 4, participants considering political terms in a cursory manner endorsed conservative terms more than those asked to cogitate; an indicator of effortful thought (recognition memory) partially mediated the relationship between processing effort and conservatism.
• Together these data suggest that political conservatism may be a process consequence of low-effort thought; when effortful, deliberate thought is disengaged, endorsement of conservative ideology increases.

– Eidelman S, Crandall CS, Goodman JA, Blanchard JC.