REVIEW

Supplemental Substances Derived from Foods as Adjunctive Therapeutic Agents for Treatment of Neurodegenerative Diseases and Disorders[1,2]

Gregory E. Bigford[3] and Gianluca Del Rossi[4]*

[3]The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami, FL; and [4]Department of Orthopedics and Sports Medicine, College of Medicine, University of South Florida, Tampa, FL

ABSTRACT

Neurodegenerative disorders and diseases (NDDs) that are either chronically acquired or triggered by a singular detrimental event are a rapidly growing cause of disability and/or death. In recent times, there have been major advancements in our understanding of various neurodegenerative disease states that have revealed common pathologic features or mechanisms. The many mechanistic parallels discovered between various neurodegenerative diseases suggest that a single therapeutic approach may be used to treat multiple disease conditions. Of late, natural compounds and supplemental substances have become an increasingly attractive option to treat NDDs because there is growing evidence that these nutritional constituents have potential adjunctive therapeutic effects (be it protective or restorative) on various neurodegenerative diseases. Here we review relevant experimental and clinical data on supplemental substances (i.e., curcuminoids, rosmarinic acid, resveratrol, acetyl-L-carnitine, and ω-3 (n–3) polyunsaturated fatty acids) that have demonstrated encouraging therapeutic effects on chronic diseases, such as Alzheimer's disease and neurodegeneration resulting from acute adverse events, such as traumatic brain injury. *Adv. Nutr. 5: 394–403, 2014.*

Introduction

Neurodegenerative disorders and diseases (NDDs)[5] are a rapidly growing cause of disability and death, characterized by progressive pathology and dysfunction. Manifestations of disease states can be chronically acquired in an indiscriminate manner or incited by an acute/singular event. For example, physiologic and functional deficits in chronic neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease, are evident, with these deficits having both primary (intrinsic/hereditary) and secondary (sporadic/nongenetic) components. Similarly, traumatic brain injury (TBI), particularly moderate to severe, initiates a number of biochemical cascades resulting in prolonged and continual neurodegeneration and long-term neurologic deficits associated with cognitive disorders and dementia (1,2), sensorimotor disability, and mortality (3). As such, a single moderate-to-severe TBI represents the beginnings of a chronic disease process. Although the increasing prevalence of cognitive decline and dementia, mainly associated with AD, is emerging as a pervasive health threat to the growing aging population (4,5), TBI represents an increasing cause of chronic disability and mortality in the young (2,6). Thus, NDDs represent a considerable public health concern and socioeconomic burden that necessitates more research to advance our understanding of potential treatment strategies.

Major advancements in our understanding of NDDs revealed several common pathologic features or mechanisms, including oxidative stress and immune-mediated inflammation (5,7). The burden of these biologic mechanisms on degenerative pathophysiology are mutable, influenced by environmental factors and behavioral determinants, such as diet and exercise (8). In fact, there is growing evidence that certain dietary compounds have potential therapeutic applications for numerous neurodegenerative diseases. Research showed that certain polyphenols and endogenous compounds have considerable positive effects on oxidative and inflammatory mechanisms associated with NDDs (4,9) and are capable of countering metabolic abnormalities associated with these disorders (10,11). Here we review 5

[1] No funds were received for this review.

[2] Author disclosures: G. E. Bigford and G. Del Rossi, no conflicts of interest.

[5] Abbreviations used: AD, Alzheimer's disease; ALC, acetyl-L-carnitine; Aβ, β-amyloid; MCI, mild cognitive impairment; NDDs, neurodegenerative diseases and disorders; RA, rosmarinic acid; RCT, randomized placebo-controlled trial; TBI, traumatic brain injury.

* To whom correspondence should be addressed. E-mail:gdelross@health.usf.edu.

©2014 American Society for Nutrition.

AN Advances in Nutrition An International Review Journal

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

types of compounds: 3 dietary polyphenols [i.e., rosmarinic acid (RA), resveratrol, and curcuminoids] and 2 endogenous compounds [i.e., acetyl-L-carnitine (ALC) and ω-3 (n–3) PUFAs]. We selected these compounds to review because of epidemiologic evidence and promising clinical support. We subsequently include data on safety, tolerability, and efficacy when available and include emerging experimental (preclinical) evidence. Finally, we highlight the effect of these compounds in AD and/or TBI because they are emerging NDDs in aged and young populations, respectively. In summary, our underlying intention is to advance the discussion of "therapeutic intervention" in regards to supplemental substances derived from food as therapies for NDDs.

Polyphenol Compounds

RA. RA is the structural ester of caffeic acid and 3,4-dihydroxyphenyllactic acid and a predominant phenol in many well-known herbs in the *Lamiaceae* (mint) family (12), such as rosemary, sage, basil, mint, and thyme. Of the vast genus and species within the RA family, extracts from *Salvia officinalis* (sage), *Salvia lavandulaefolia* (Spanish sage), and *Rosmarinus officinalis* (rosemary) have demonstrated beneficial effects on functional outcome measures with a number of neurologic diseases. Several human studies investigated the potential effects of RA extracts on cognitive function (**Table 1**). Single-dose (25–150 μL) *S. lavandulaefolia* was able to elicit consistent improvements in several cognitive performance tasks and mood assessment in healthy young individuals (13–15), with similar results also observed in healthy aged (>65 y) individuals (16). Dose escalation in the aged study was greater (167–1332 mg) than in the studies involving young individuals, suggesting that the cognitive benefit observed with this sage extract is dose dependent in these distinct populations. Moreover, *S. officinalis* (uncertain dose) administered daily over 4 mo conferred improved cognitive and behavioral function in aged (65–80 y) individuals with clinically diagnosed moderate AD (17). A similar pilot trial of individuals with mild-to-moderate AD that administered dose-escalating *S. lavandulaefolia* (50–150 μL) over 6 wk proved tolerable and safe, and individuals showed improvement in memory and attention (18).

In addition, sage extracts were shown to inhibit acetylcholinesterase in vitro (19–21), long implicated in cholinergic deficits observed in the pathogenesis of AD. To our knowledge, there have been no explicit studies investigating RA and TBI (either clinical or experimental). However, RA was shown to be neuroprotective, attenuating oxidative stress and neuronal cell death in vitro (22–24) and reducing inflammatory responses in experimental models of ischemic stroke (25), all of which are common biologic processes associated with TBI pathology. These further demonstrate their potential as therapeutic agents that may target key pathologic features of NDDs and improve functional outcome measures.

Resveratrol. Resveratrol is the major nonflavonoid polyphenol found in a variety of berries, peanuts, and medicinal plants (26), with the most substantial source of dietary

TABLE 1 Randomized double-blind placebo-controlled trials of polyphenol compounds in cognitive neurodegenerative conditions[1]

Study Design	Location	Dose	Duration	Population	Status/Outcome	Miscellaneous	Reference
Rosmarinic acid							
T, R, TB, PC	Tehran, Iran	Unclear ("fixed" dose)	4 mo	Probable AD or mild-to-moderate dementia	Significantly improved outcome on cognitive function (ADAS-cog; CDR-SB)		16
pR, DB, PC	Newcastle upon Tyne, UK	25–150 μL	Single dose	Healthy young adults	≥50 μL improved immediate word recall		13
R, DB, PC	Newcastle upon Tyne, UK	25–50 μL	Single dose	Healthy young adults	25–50 μL improved acute cognition and mood		13
R, DB, PC, COA	Melbourne, Australia	167–1332 mg	Repeated dose escalation	Healthy aged adults	Dose-specific (333 mg) improvement in working memory		16
R, DB, PC, COA	Newcastle upon Tyne, UK	50 μL	Repeated single dose	Healthy young adults	Improved performance on secondary memory and attention		15
Resveratrol							
R, DB, PC, COA	Newcastle upon Tyne, UK	250–500 mg	Repeated single dose	Healthy young adults	Dose-dependent increase in cerebral blood flow during task performance		33
Curcumin							
T, R, DB, PC	Hong Kong, China	1 or 4 g/d	6 mo	Possible or probable AD	No significant difference in cognitive measures (MMSE) and plasma Aβ concentration	Plus *Gingko* (120 mg/d)	50
T, R, DB, PC	California	2 or 4 g/d	6 mo	Mild-to-moderate AD	No significant difference in cognitive function or plasma and CSF Aβ or τ concentrations		51

[1] AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; Aβ, β-amyloid; CDR-SB, clinical dementia rating scale sum of boxes; COA, crossover assignment non-blinded; CSF, cerebrospinal fluid; DB, double blind; MMSE, mini-mental state examination; PC, placebo controlled; pR, partially blinded; R, randomized; T, treatment; TB, triple blind.

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

resveratrol being grapes and red wine (27). A wide range of biologic properties of resveratrol has been reported, including antioxidant, anti-inflammatory, and anticarcinogenic properties (28,29). Several investigations suggested considerable neuroprotective effects of resveratrol. Human (or clinical) trials investigating resveratrol effects on neurodegenerative disorders have been limited to this point. There were several reviews of clinical trials for resveratrol that investigated the biologic effects in humans by examining variables such as pharmacokinetics, metabolism, safety, tolerance, and bioavailability (27,30,31). These trials include conditions, such as cancer, cardiovascular disease, obesity, and diabetes. Reported studies highlight the relative safety of resveratrol over varying doses (25 mg to 5 g), in either a single dose or multiple doses, with minor or inconsistent side effects in short-term or acute studies. However, to date, there is no substantial data on the toxicity of chronic intake of resveratrol, although data from upcoming and ongoing trials may begin to address this (31,32). To our knowledge, and as currently reported by the NIH (32), there are several clinical trials in progress investigating the potential therapeutic effect of resveratrol on cognitive function and cerebral blood flow in the aging brain, with mild cognitive impairment (MCI) and AD, as well as injury (Table 1). One study reports data showing a dose-dependent (250–500 mg/d) increase in cerebral blood flow in the prefrontal cortex during cognitive tasks (33), illustrating the effect of resveratrol on cerebral hemodynamics. Because cerebral blood flow is pathologically affected in numerous disorders, including AD, this may be 1 area in which resveratrol may prove clinically beneficial.

In vitro, resveratrol was shown to protect neurons against β-amyloid (Aβ)-induced toxicity and cell death (34–36) and to destabilize Aβ fibrils (37,38). Importantly, anti-inflammatory and antioxidative effects of resveratrol were linked to suppressing the activation of NF-κB, sirtuin 1, and MAPK pathways. This was shown to attenuate the release of proinflammatory TNF-α, IL-1β, and NO specifically in microglia (39–41), highlighting a potential role in limiting neurodegenerative pathology. In vivo models of sporadic and transgenic AD and tauopathy demonstrated that resveratrol substantially attenuates oxidative stress, neurodegeneration, and cognitive impairment (42,43), with significant decreases in plaque burden in cortical, striatal, and hypothalamic regions (44). Resveratrol was also shown to reduce oxidative stress and lesion volume after experimental TBI (45) and in in vitro models of glutamate-mediated excitotoxic transmission (46) (a key feature of neuronal damage in TBI). Evidence from these studies and the demonstrated safety and tolerance in human trials should stimulate similar population-based trials directed at examining neurologic outcome measures and hasten the advancement of research into the therapeutic effects of adjunctive resveratrol in NDDs.

Curcuminoids. Curcuminoids are the main polyphenol constituents of turmeric (*Curcuma longa*) and have 3 chemical components, including curcumin (75–80%), demethoxycurcumin (15–20%), and bisdemethoxycurcumin (3–5%). Epidemiologic data suggest that dietary curcumin intake is positively related to cognitive function in healthy elderly individuals (47), with evidence that concentrations of Aβ and tau are lower in populations that consume large amounts of curcumin (48,49). To our knowledge, there are 7 clinical investigations of the safety, tolerance, pharmacokinetics, and treatment effects of curcumin in AD (NIH registry) (Table 1), although observations from 4 of these are still pending. Reported data thus far suggest that discernible differences in cognitive scores and/or biochemical features of AD were absent (50,51), but several limitations to these pilot studies should be mentioned. To properly evaluate clinical relevance, a much larger sample size, followed for a longer duration, will be necessary. Importantly, a better understanding of both effective dose and bioavailability will be fundamental for appropriate evaluation. In fact, evidence for tolerability of curcuminoid formulations of up to 12,000 mg was reported previously (52), and, in this regard, dose escalation studies far exceeding the reported 4 g would be pragmatic. Moreover, the hydrophobic nature of curcuminoids (53) has precipitated research into conjugated curcumin or curcumin-like analogs to increase bioavailability and potential effects and improvement in AD (54,55).

Moreover, a growing scientific literature reports potent antioxidative and anti-inflammatory effects of curcuminoids in neurodegenerative conditions, including AD (56–63) and focal TBI (64–70), accompanied by resultant cognitive improvements. In vitro models of AD show that curcuminoids are sufficient for recovery of Aβ-induced long-term potentiation impairment, and in vivo administration can enhance spatial memory in rodents displaying AD-like neuronal loss (71–73). These effects were linked to the antioxidative (56–60) and anti-inflammatory (61–63) properties of curcuminoids and their capabilities in reducing amyloid plaque burden and disaggregating preformed Aβ fibrils (37,60, 74–76), the pathologic hallmark of AD. Notwithstanding the compelling epidemiologic data, methodologically sound clinical studies are still necessary to accurately evaluate the treatment effect of supplemental curcuminoid administration.

Endogenous Compounds

ALC. ALC is a metabolic intermediate that functions as an important transmitochondrial membrane transporter of long-chain FAs for β-oxidation. ALC is produced through endogenous biosynthesis of lysine and methionine, primarily in the brain, liver, and kidneys, and can also be consumed through foods and supplementation (10,11). Mitochondrial dysfunction associated with metabolic and oxidative stress is a hallmark feature in a number of NDDs. ALC was proposed recently as neuroprotective because of its ability to confer improved mitochondrial function. There were a number of human trials on the use of ALC in mild dementia or MCI that were reviewed previously and well described (**Table 2**) (77,78). Of these studies, the duration varied from 3 mo to 1 y, with ALC dose ranges from 1.5 to 3 g/d. Although several studies report considerable benefits of ALC (vs. placebo) on

AN Advances in Nutrition An International Review Journal

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

TABLE 2 Randomized double-blind, placebo-controlled trials of endogenous compounds in cognitive neurodegenerative conditions[1]

Study Design	Location	Dose	Duration	Population	Status/Outcome	Miscellaneous	Reference
Acetyl-L-carnitine							
R, DB, PC	Italy	2 g/d	6 mo	Probable AD	Improved cognitive performance		82
R, DB, PC	Italy	2 g/d	6 mo	Probable AD	Improved cognitive performance		83
R, DB, PC	Italy	3 g/d	6 mo	Mild dementia	Improved cognitive performance		84
R, DB, PC	Italy	3 g/d	12 wk	Probable AD	Improved cognitive performance		85
R, DB, PC	United Kingdom	2 g/d	6 mo	Mild dementia	Improved cognitive performance		86
R, DB, PC	Italy	2.5 or 3 g/d	6 mo	Mild dementia	Improved cognitive performance		87
R, DB, PC	Italy	3 g/d	6 mo	Mild dementia	Improved cognitive performance		88
R, DB, PC	United States	2.5 or 3g/d	6 mo	Probable AD	Improved cognitive performance		89
R, DB, PC	Italy	2 g/d	16 wk	Probable AD	Improved cognitive performance		90
NR, DB, PC	Pennsylvania	3 g/d	1 y	Probable AD	Improved cognitive performance		91
R, DB, PC	Germany	1.5 g/d	12 wk	Mild-to-moderate AD	Significant difference in ≥1 subgroups of clinical global impression		80
R, DB, PC	United Kingdom	2 g/d	6 mo	Mild-to-moderate AD	No significant difference in cognitive performance		92
R, DB, PC	Germany	3 g/d	1 y	Mild-to-moderate AD	Improved cognitive performance in both treatment and placebo		80
R, DB, PC	Wales	2 g/d	6 mo	Mild AD	Significant difference in ≥1 subgroups of clinical global impression		80
R, DB, PC	United Kingdom	2 g/d	6 mo	Mild AD	No significant difference in cognitive performance		93
R, DB, PC	United States	3 g/d	1 y	Probable AD	No significant difference in cognitive performance		94
R, DB, PC	United States	3 g/d	1 y	Probable AD	No significant difference in cognitive performance		95
R, DB, PC	United States	3 g/d	1 y	Probable AD (subset of younger patients)	Improved cognitive performance		96
ω-3 PUFAs							
R, DB, PC	United States	9 mg/d	6 mo	Healthy individuals with age-related cognitive decline	Improved learning and memory function		124
R, DB, PC	Stockholm, Sweden	1.7 g DHA plus 0.6 g EPA/d	6 mo	Diagnosed AD	Positive effects on cognition (MMSE) in mild AD only		125
R, DB, PC	Taipei, Taiwan	1.8 g/d	6 mo	Mild-to-moderate AD	Significant cognitive improvement (ADAS-cog) in mild AD only		126
R, DB, PC	Portland, Oregon	2 g/d	18 mo	Mild-to-moderate AD	No significant difference in cognitive performance		127
T, R, DB, PC	Portland, Oregon	675 mg DHA plus 975 mg EPA/d	1 y	Probable AD or MCI	Stabilization in cognitive performance (MMSE)	+/− ALA	129

[1] AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; ALA, α-lipoic acid; DB, double blind; MCI, mild cognitive impairment; MMSE, mini-mental state examination; NR, nonrandomized; PC, placebo controlled; R, randomized; T, treatment.

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

clinical and psychometric assessment in study participants with probable AD and/or MCI (79–88), other studies including participants with diagnosed moderate AD progression were less conclusive (89–92) and may indicate a prospective "therapeutic window" in terms of extant disease progression. Additional studies and reviews showed that ALC can slow pathologic decline in young patients with AD, improve clinical features of AD (93,94), and, when administered as a component of a vitamin formula, can delay cognitive decline in both early- and late-stage AD (95,96). In general, although the efficacy of ALC in cognitive decline has not been fully delineated, this may in part reflect variability in study design, methodology, and assessment (77).

Growing preclinical evidence seems to support the aforementioned clinical observations. In rodent models, ALC supplementation improves synaptic transmission and learning capacity in aged rats (97,98) and attenuated age-related mitochondrial decay (99,100). Also, ALC was shown to directly affect the cholinergic system (101), which is substantially impaired in AD (102), and provide beneficial effects in experimental models of AD. In vitro analysis reveals that ALC is neuroprotective against Aβ-induced neurotoxicity (103,104). In genetic models of AD, treatment with ALC (500 mg reported in 1 study) was sufficient to reduce oxidative stress, decrease harmful alterations in mitochondrial structure, and attenuate both spatial and temporal memory and cognitive decline (105–107). This indicates that ALC may be beneficial in delaying the progression of AD-associated cognitive decline. Moreover, ALC treatment (100 mg/kg) was effective in reducing brain lesion volume, improving behavioral outcome after experimental TBI (108), and reducing oxidative stress and preserving mitochondrial membrane potential after glutamate-induced neurotoxicity (109), an established feature of TBI-induced neuronal death. Overall, these experiments support ALC as an effective and clinically applicable therapy.

ω-3 PUFAs. Dysregulated lipid metabolism and signaling are principal components of several NDDs (110,111). ω-3 Essential PUFAs, now well understood to be highly bioactive molecules, were shown to regulate a number of metabolic and inflammatory pathways and exert pleiotropic effects in various central nervous system pathologies. Specifically, DHA, found in high concentrations in the brain [~40% of neural plasma membrane phospholipids (9,112)], is suggested as valuable for underlying neuroprotection. Epidemiologic studies show decreases in DHA with cognitive decline in both healthy aged individuals (113,114) and patients with AD (115,116), as well as age-adjusted decreases in DHA in postmortem samples from AD brains (117). Moreover, in populations with higher dietary intake of DHA (118–120) and higher concentrations of plasma DHA (114,116), there is a lower associated risk of cognitive impairment or AD. As such, there were a substantial number of clinical investigations to evaluate the therapeutic efficacy of ω-3 FA treatment in AD (Table 2). In fact, there were several recent reviews that discussed study outcome in depth. Recent evidence reports that DHA (900 mg/d) administered for 6 mo was able to improve learning and memory function in age-related cognitive decline in healthy adults (121), and several additional human trials examining DHA supplementation (240 mg/d to 1.8 g/d) ranging from 3 to 12 mo report improvement or stabilization of memory and attention as assessed by mini-mental state examination and AD assessment scale (122–124) in individuals with MCI only but not individuals with extant AD. Similarly, a more recent report (125) using DHA (2 g/d) for 18 mo did not find a benefit for patients with diagnosed AD, supporting the previous opinion (126) that posits DHA may be a more beneficial therapy in MCI and may delay the onset of age-related cognitive decline, but not in individuals with already diagnosed AD progression. Interestingly, ω-3 FA treatment given as a component of a combination therapy (i.e., in combination with other dietary compounds or supplements, such as lipoic acid) showed encouraging results, stabilizing or improving memory scores in patients with mild AD (127,128), which may be promising in the application and design of future studies. Despite promising experimental evidence, to our knowledge, there are minimal human studies evaluating the effect of ω-3 FAs in TBI (129–131). One study reported that oral PUFA intake [both ω-3 and ω-6 (n–6) FAs] for 90 d improved cognitive dysfunction in a very small cohort of patients with chronic TBI (123). ω-3 FAs have the potential to target a number of mechanisms involved in secondary injury in TBI, and, because their safety and tolerance is well established (132–135), directed clinical evaluation is warranted.

DHA deficiency was shown to activate caspases in modeled AD (136) and exacerbate age-related decline in glutamatergic transmission in rats (137). Conversely, DHA supplementation was shown to attenuate oxidative stress, specifically lipid peroxidation, and protect against memory loss in various rat models of AD and aging (138–140), as well as reduce interneuronal Aβ and tau accumulation (141–143), hallmarks of AD pathology. Furthermore, several studies showed that animals fed ω-3 FA-enriched diets display substantially greater learning acquisition and memory performance (144–150), with these observations extending to aged animals (146,151,152). Finally, in animal models of TBI, DHA supplementation substantially reduces axonal injury, apoptosis, and memory deficits (153–155) and improves biochemical markers of synaptic transmission and learning ability (156), further reinforcing the concept of introducing DHA as an adjunctive therapy for NDDs.

Discussion and Perspective

There has been a broadening body of scientific evidence supporting the potential application and benefit of dietary and nutritional substances in a number of NDDs. Many of the compounds discussed here exert therapeutic effects by limiting pathologic progression associated with common metabolic, oxidative, and inflammatory processes and merit additional study to properly delineate their utility as a therapeutic intervention. Moreover, because a small number of studies suggested positive combination effects in various

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

conditions, emerging areas of study would benefit from investigating the efficacy of multi-therapeutic treatment in these NDDs. This would bring to light the possibility of synergistic effects on oxidative- and/or inflammatory-related pathology. Given the relative safety and tolerance of the compounds discussed, such advances are realistic and feasible.

Although the purpose of this review is to highlight some of the promising evidence emerging in this area, it would be remiss to omit that several caveats and limitations still remain. Several negative (or null) reports, beyond the few mentioned here, were described for most of the polyphenol and endogenous compounds and in a number of the conditions discussed. Extensive experimental data has not always translated to a singular or definitive clinical effect. Variability in doses, population demographics, study design, and testing measures all contributed to the inconsistencies observed. Furthermore, the purity/quality of the compounds also likely contributed to variability and is a valid concern that must be addressed.

As a final point, the inconsistencies observed may in part reflect shortcomings in research approaches being used in nutritional sciences. Although we focused on discussing evidence primarily from randomized placebo-controlled trials (RCTs), considered the gold standard of research design, there was recent discussion that aimed to reevaluate and advance the evidence-based model for nutritional research (157). In short, it has been debated that the central features of RCTs in evidence-based medicine are not appropriate in the nutritional context. Studies on drug therapy and/or medical interventions are designed to test a single dose–dependent effect in a short timeframe and must be compared with a control/placebo condition. Evaluation is based on a large curative effect on a disease that is not caused by the absence of the intervention. In contrast, the efficacy of nutrients is determined by their ability to prevent dysfunction or disease that is a direct result of their inadequate intake. In general, the effects of nutrients are primarily dependent on the intake amount, and, as such, a "true" placebo cannot be used because a "zero" or nutrient-deficient group is unethical to consider. These highlight the inherent limitations associated with extending the RCT paradigm to clinical nutritional science; therefore, a broader consideration of alternate and/or additional research strategies should be incorporated to evaluate the best available evidence.

In summary, the ability of dietary substances to confer therapeutic effects to neurodegenerative conditions still needs to be critically explored, warranting continued basic research to drive appropriate clinical assessment. Here, we aimed to highlight the importance of continued research in this promising area.

Acknowledgments

Both authors read and approved the final manuscript.

References

1. Lye TC, Shores EA. Traumatic brain injury as a risk factor for Alzheimer's disease: a review. Neuropsychol Rev 2000;10:115–29.
2. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? Nat Rev Neurol 2013;9:211–21.
3. Stoica BA, Faden AI. Cell death mechanisms and modulation in traumatic brain injury. Neurotherapeutics 2010;7:3–12.
4. Joseph J, Cole G, Head E, Ingram D. Nutrition, brain aging, and neurodegeneration. J Neurosci 2009;29:12795–801.
5. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature 2010;464:529–35.
6. Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer's disease. Neurosci Biobehav Rev 2012;36:1376–81.
7. Amor S, Puentes F, Baker D, van der Valk P. Inflammation in neurodegenerative diseases. Immunology 2010;129:154–69.
8. Gomez-Pinilla F. The combined effects of exercise and foods in preventing neurological and cognitive disorders. Prev Med 2011;52(Suppl 1):S75–80.
9. Hashimoto M, Hossain S. Neuroprotective and ameliorative actions of polyunsaturated fatty acids against neuronal diseases: beneficial effect of docosahexaenoic acid on cognitive decline in Alzheimer's disease. J Pharmacol Sci 2011;116:150–62.
10. Jones LL, McDonald DA, Borum PR. Acylcarnitines: role in brain. Prog Lipid Res 2010;49:61–75.
11. Malaguarnera M. Carnitine derivatives: clinical usefulness. Curr Opin Gastroenterol 2012;28:166–76.
12. Petersen M, Simmonds MS. Rosmarinic acid. Phytochemistry 2003;62:121–5.
13. Tildesley NT, Kennedy DO, Perry EK, Ballard CG, Savelev S, Wesnes KA, Scholey AB. Salvia lavandulaefolia (Spanish sage) enhances memory in healthy young volunteers. Pharmacol Biochem Behav 2003;75:669–74.
14. Tildesley NT, Kennedy DO, Perry EK, Ballard CG, Wesnes KA, Scholey AB. Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers. Physiol Behav 2005;83:699–709.
15. Kennedy DO, Dodd FL, Robertson BC, Okello EJ, Reay JL, Scholey AB, Haskell CF. Monoterpenoid extract of sage (Salvia lavandulaefolia) with cholinesterase inhibiting properties improves cognitive performance and mood in healthy adults. J Psychopharmacol 2011;25:1088–100.
16. Scholey AB, Tildesley NT, Ballard CG, Wesnes KA, Tasker A, Perry EK, Kennedy DO. An extract of Salvia (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. Psychopharmacology (Berl) 2008;198:127–39.
17. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther 2003;28:53–9.
18. Perry NS, Bollen C, Perry EK, Ballard C. Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacol Biochem Behav 2003;75:651–9.
19. Perry NS, Houghton PJ, Theobald A, Jenner P, Perry EK. In-vitro inhibition of human erythrocyte acetylcholinesterase by salvia lavandulaefolia essential oil and constituent terpenes. J Pharm Pharmacol 2000;52:895–902.
20. Savelev S, Okello E, Perry NS, Wilkins RM, Perry EK. Synergistic and antagonistic interactions of anticholinesterase terpenoids in Salvia lavandulaefolia essential oil. Pharmacol Biochem Behav 2003;75:661–8.
21. Savelev SU, Okello EJ, Perry EK. Butyryl- and acetyl-cholinesterase inhibitory activities in essential oils of Salvia species and their constituents. Phytother Res 2004;18:315–24.
22. Lee HJ, Cho HS, Park E, Kim S, Lee SY, Kim CS, Kim do K, Kim SJ, Chun HS. Rosmarinic acid protects human dopaminergic neuronal cells against hydrogen peroxide-induced apoptosis. Toxicology 2008;250:109–15.
23. Choi HR, Choi JS, Han YN, Bae SJ, Chung HY. Peroxynitrite scavenging activity of herb extracts. Phytother Res 2002;16:364–7.
24. Qiao S, Li W, Tsubouchi R, Haneda M, Murakami K, Takeuchi F, Nisimoto Y, Yoshino M. Rosmarinic acid inhibits the formation of

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

reactive oxygen and nitrogen species in RAW264.7 macrophages. Free Radic Res 2005;39:995–1003.
25. Luan H, Kan Z, Xu Y, Lv C, Jiang W. Rosmarinic acid protects against experimental diabetes with cerebral ischemia: relation to inflammation response. J Neuroinflammation 2013;10:28.
26. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 2006;5:493–506.
27. Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health–a comprehensive review of human clinical trials. Mol Nutr Food Res 2011; 55:1129–41.
28. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997;275:218–20.
29. Soleas GJ, Diamandis EP, Goldberg DM. Resveratrol: a molecule whose time has come? And gone? Clin Biochem 1997;30:91–113.
30. Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP, Brown K. Clinical trials of resveratrol. Ann N Y Acad Sci 2011;1215:161–9.
31. Vang O, Ahmad N, Baile CA, Baur JA, Brown K, Csiszar A, Das DK, Delmas D, Gottfried C, Lin HY, et al. What is new for an old molecule? Systematic review and recommendations on the use of resveratrol. PLoS One 2011;6:e19881.
32. ClinicalTrials.gov [database on the Internet]. Bethesda (MD). [cited 2014 May 5]. Available from http://www.clinicaltrials.gov/ct2/results?term=resveratrol.
33. Kennedy DO, Wightman EL, Reay JL, Lietz G, Okello EJ, Wilde A, Haskell CF. Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: a double-blind, placebo-controlled, crossover investigation. Am J Clin Nutr 2010;91:1590–7.
34. Jang JH, Surh YJ. Protective effect of resveratrol on beta-amyloid-induced oxidative PC12 cell death. Free Radic Biol Med 2003;34: 1100–10.
35. Han YS, Zheng WH, Bastianetto S, Chabot JG, Quirion R. Neuroprotective effects of resveratrol against beta-amyloid-induced neurotoxicity in rat hippocampal neurons: involvement of protein kinase C. Br J Pharmacol 2004;141:997–1005.
36. Chen J, Zhou Y, Mueller-Steiner S, Chen LF, Kwon H, Yi S, Mucke L, Gan L. SIRT1 protects against microglia-dependent amyloid-beta toxicity through inhibiting NF-kappaB signaling. J Biol Chem 2005;280: 40364–74.
37. Ono K, Naiki H, Yamada M. The development of preventives and therapeutics for Alzheimer's disease that inhibit the formation of beta-amyloid fibrils (fAbeta), as well as destabilize preformed fAbeta. Curr Pharm Des 2006;12:4357–75.
38. Ono K, Yamada M. Antioxidant compounds have potent anti-fibrillogenic and fibril-destabilizing effects for alpha-synuclein fibrils in vitro. J Neurochem 2006;97:105–15.
39. Bi XL, Yang JY, Dong YX, Wang JM, Cui YH, Ikeshima T, Zhao YQ, Wu CF. Resveratrol inhibits nitric oxide and TNF-alpha production by lipopolysaccharide-activated microglia. Int Immunopharmacol 2005; 5:185–93.
40. Meng XL, Yang JY, Chen GL, Wang LH, Zhang LJ, Wang S, Li J, Wu CF. Effects of resveratrol and its derivatives on lipopolysaccharide-induced microglial activation and their structure-activity relationships. Chem Biol Interact 2008;174:51–9.
41. Zhang F, Liu J, Shi JS. Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation. Eur J Pharmacol 2010;636:1–7.
42. Sharma M, Gupta YK. Chronic treatment with trans resveratrol prevents intracerebroventricular streptozotocin induced cognitive impairment and oxidative stress in rats. Life Sci 2002;71:2489–98.
43. Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers JT, Delalle I, Baur JA, Sui G, Armour SM, et al. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. EMBO J 2007; 26:3169–79.
44. Karuppagounder SS, Pinto JT, Xu H, Chen HL, Beal MF, Gibson GE. Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. Neurochem Int 2009;54: 111–8.
45. Ates O, Cayli S, Altinoz E, Gurses I, Yucel N, Sener M, Kocak A, Yologlu S. Neuroprotection by resveratrol against traumatic brain injury in rats. Mol Cell Biochem 2007;294:137–44.
46. Gao ZB, Chen XQ, Hu GY. Inhibition of excitatory synaptic transmission by trans-resveratrol in rat hippocampus. Brain Res 2006;1111: 41–7.
47. Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. Curry consumption and cognitive function in the elderly. Am J Epidemiol 2006;164: 898–906.
48. Subramanian S, Sandhyarani B, Shree AN, Murthy KK, Kalyani K, Kumar SP, Pradeep MJ, Noone MJ, Taly AB. Lower levels of cerebrospinal fluid amyloid beta (Abeta) in non-demented Indian controls. Neurosci Lett 2006;407:121–3.
49. Kandimalla RJ, Prabhakar S, Binukumar BK, Wani WY, Sharma DR, Grover VK, Bhardwaj N, Jain K, Gill KD. Cerebrospinal fluid profile of amyloid beta42 (Abeta42), hTau and ubiquitin in North Indian Alzheimer's disease patients. Neurosci Lett 2011;487:134–8.
50. Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, Lam L, Leung V, Hui E, Ng C, et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. J Clin Psychopharmacol 2008;28:110–3.
51. Ringman J, Cole GM, Tend E, et al. Oral curcumin for the treatment of mild-to-moderate Alzheimer's disease: tolerability and clinical and biomarker efficacy result of a placebo-controlled 24-week study. Proceedings of the International Conference on Alzheimer's Disease 2008 June 24–27; Chicago, IL.
52. Lao CD, Ruffin MT 4th, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, Crowell J, Rock CL, Brenner DE. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006; 6:10.
53. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm 2007;4: 807–18.
54. Mathew A, Fukuda T, Nagaoka Y, Hasumura T, Morimoto H, Yoshida Y, Maekawa T, Venugopal K, Kumar DS. Curcumin loaded-PLGA nanoparticles conjugated with Tet-1 peptide for potential use in Alzheimer's disease. PLoS One 2012;7:e32616.
55. Orlando RA, Gonzales AM, Royer RE, Deck LM, Vander Jagt DL. A chemical analog of curcumin as an improved inhibitor of amyloid Abeta oligomerization. PLoS One 2012;7:e31869.
56. Kumar A, Naidu PS, Seghal N, Padi SS. Effect of curcumin on intracerebroventricular colchicine-induced cognitive impairment and oxidative stress in rats. J Med Food 2007;10:486–94.
57. Ishrat T, Hoda MN, Khan MB, Yousuf S, Ahmad M, Khan MM, Ahmad A, Islam F. Amelioration of cognitive deficits and neurodegeneration by curcumin in rat model of sporadic dementia of Alzheimer's type (SDAT). Eur Neuropsychopharmacol 2009;19:636–47.
58. Reeta KH, Mehla J, Gupta YK. Curcumin is protective against phenytoin-induced cognitive impairment and oxidative stress in rats. Brain Res 2009;1301:52–60.
59. Park SY, Kim HS, Cho EK, Kwon BY, Phark S, Hwang KW, Sul D. Curcumin protected PC12 cells against beta-amyloid-induced toxicity through the inhibition of oxidative damage and tau hyperphosphorylation. Food Chem Toxicol 2008;46:2881–7.
60. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 2001;21:8370–7.
61. Frautschy SA, Hu W, Kim P, Miller SA, Chu T, Harris-White ME, Cole GM. Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol Aging 2001;22:993–1005.
62. Mishra S, Palanivelu K. The effect of curcumin (turmeric) on Alzheimer's disease: an overview. Ann Indian Acad Neurol 2008;11:13–9.
63. Ahmed T, Gilani AH. A comparative study of curcuminoids to measure their effect on inflammatory and apoptotic gene expression in an Abeta plus ibotenic acid-infused rat model of Alzheimer's disease. Brain Res 2011;1400:1–18.

AN Advances in Nutrition An International Review Journal

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

64. Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. Curcumin: from ancient medicine to current clinical trials. Cell Mol Life Sci 2008;65:1631–52.
65. Calabrese V, Cornelius C, Mancuso C, Pennisi G, Calafato S, Bellia F, Bates TE, Giuffrida Stella AM, Schapira T, Dinkova Kostova AT, et al. Cellular stress response: a novel target for chemoprevention and nutritional neuroprotection in aging, neurodegenerative disorders and longevity. Neurochem Res 2008;33:2444–71.
66. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol 2006;197:309–17.
67. Sharma S, Ying Z, Gomez-Pinilla F. A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. Exp Neurol 2010;226:191–9.
68. Wu A, Ying Z, Schubert D, Gomez-Pinilla F. Brain and spinal cord interaction: a dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. Neurorehabil Neural Repair 2011;25:332–42.
69. Sharma S, Zhuang Y, Ying Z, Wu A, Gomez-Pinilla F. Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. Neuroscience 2009;161:1037–44.
70. Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? J Neurochem 2010;113:637–48.
71. Conboy L, Foley AG, O'Boyle NM, Lawlor M, Gallagher HC, Murphy KJ, Regan CM. Curcumin-induced degradation of PKC delta is associated with enhanced dentate NCAM PSA expression and spatial learning in adult and aged Wistar rats. Biochem Pharmacol 2009;77:1254–65.
72. Ahmed T, Enam SA, Gilani AH. Curcuminoids enhance memory in an amyloid-infused rat model of Alzheimer's disease. Neuroscience 2010;169:1296–306.
73. Ahmed T, Gilani AH, Hosseinmardi N, Semnanian S, Enam SA, Fathollahi Y. Curcuminoids rescue long-term potentiation impaired by amyloid peptide in rat hippocampal slices. Synapse 2011;65:572–82.
74. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 2005;280:5892–901.
75. Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. J Neurochem 2007;102:1095–104.
76. Mishra S, Mishra M, Seth P, Sharma SK. Tetrahydrocurcumin confers protection against amyloid beta-induced toxicity. Neuroreport 2011;22:23–7.
77. Hudson S, Tabet N. Acetyl-L-carnitine for dementia. Cochrane Database Syst Rev 2003;(2):CD003158.
78. Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol 2003;18:61–71.
79. Battistin L, Pizzolato G, Dam M, Ponza I, Perlotto N, Bergamo LC, Furlanut M De, Ziliotto R, Bardin G, Chinaglia L, et al. Effects of acetyl-L-carnitine (ALC) treatment in dementia: a mutlicentric, randomized, double-blind study. New Trends Clin Neuropharmacol 1989;3:131–2.
80. Mantero M, Barbero M, Giannini R, Grosso VB, Tomasina C, Iannuccelli M. Acetyl-L-carnitine as a therapeutic agent for mental deterioration in geriatric patients. (Double-blind placebo controlled study). New Trends Clin Neuropharmacol 1989;3:17–24.
81. Passeri M, Cucinotta D, Bonati PA, Iannuccelli M, Parnetti L, Senin U. Acetyl-L-carnitine in the treatment of mildly demented elderly patients. Int J Clin Pharmacol Res 1990;10:75–9.
82. Bellagamba G, Postachini D, Moretti V, Pennachietti L. Acetyl-l-carnitine activity in senile dementia Alzheimer type. Neurobiol Aging 1991;11:345.
83. Livingston G, Sax KB, McClenahan Z, Blumenthal E, Foley K, Willison J, Mann AH, James IM. Acetyl-L-carnitine in dementia. Int J Geriatr Psychiatry 1991;6:853–60.
84. Spagnoli A, Lucca U, Menasce G, Bandera L, Cizza G, Forloni G, Tettamanti M, Frattura L, Tiraboschi P, Comelli M, et al. Long-term acetyl-L-carnitine treatment in Alzheimer's disease. Neurology 1991;41:1726–32.
85. Bianchetti A, Rozzini R, Trabucchi M. Effects of acetyl-L-carnitine in Alzheimer's disease patients unresponsive to acetylcholinesterase inhibitors. Curr Med Res Opin 2003;19:350–3.
86. Sano M, Bell K, Cote L, Dooneief G, Lawton A, Legler L, Marder K, Naini A, Stern Y, Mayeux R. Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease. Arch Neurol 1992;49:1137–41.
87. Costa A, Martignoni E, Blandini F, Petraglia F, Genazzani AR, Nappi G. Effects of etoperidone on sympathetic and pituitary-adrenal responses to diverse stressors in humans. Clin Neuropharmacol 1993;16:127–38.
88. Pettegrew JW, Klunk WE, Panchalingam K, Kanfer JN, McClure RJ. Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease. Neurobiol Aging 1995;16:1–4.
89. Rai G, Wright G, Scott L, Beston B, Rest J, Exton-Smith AN. Double-blind, placebo controlled study of acetyl-l-carnitine in patients with Alzheimer's dementia. Curr Med Res Opin 1990;11:638–47.
90. Bonavita E. Study of the efficacy and tolerability of L-acetylcarnitine therapy in the senile brain. Int J Clin Pharmacol Ther Toxicol 1986;24:511–6.
91. Thal LJ, Carta A, Clarke WR, Ferris SH, Friedland RP, Petersen RC, Pettegrew JW, Pfeiffer E, Raskind MA, Sano M, et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology 1996;47:705–11.
92. Thal LJ, Calvani M, Amato A, Carta A. A 1-year controlled trial of acetyl-l-carnitine in early-onset AD. Neurology 2000;55:805–10.
93. Bowman BA. Acetyl-carnitine and Alzheimer's disease. Nutr Rev 1992;50:142–4.
94. Calvani M, Carta A, Caruso G, Benedetti N, Iannuccelli M. Action of acetyl-L-carnitine in neurodegeneration and Alzheimer's disease. Ann N Y Acad Sci 1992;663:483–6.
95. Chan A, Paskavitz J, Remington R, Rasmussen S, Shea TB. Efficacy of a vitamin/nutriceutical formulation for early-stage Alzheimer's disease: a 1-year, open-label pilot study with an 16-month caregiver extension. Am J Alzheimers Dis Other Demen 2008;23:571–85.
96. Remington R, Chan A, Paskavitz J, Shea TB. Efficacy of a vitamin/nutriceutical formulation for moderate-stage to later-stage Alzheimer's disease: a placebo-controlled pilot study. Am J Alzheimers Dis Other Demen 2009;24:27–33.
97. Barnes CA, Markowska AL, Ingram DK, Kametani H, Spangler EL, Lemken VJ, Olton DS. Acetyl-1-carnitine. 2: Effects on learning and memory performance of aged rats in simple and complex mazes. Neurobiol Aging 1990;11:499–506.
98. Kobayashi S, Iwamoto M, Kon K, Waki H, Ando S, Tanaka Y. Acetyl-L-carnitine improves aged brain function. Geriatr Gerontol Int 2010;10(Suppl 1):S99–106.
99. Ames BN, Liu J. Delaying the mitochondrial decay of aging with acetylcarnitine. Ann N Y Acad Sci 2004;1033:108–16.
100. Pesce V, Fracasso F, Cassano P, Lezza AM, Cantatore P, Gadaleta MN. Acetyl-L-carnitine supplementation to old rats partially reverts the age-related mitochondrial decay of soleus muscle by activating peroxisome proliferator-activated receptor gamma coactivator-1alpha-dependent mitochondrial biogenesis. Rejuvenation Res 2010;13:148–51.
101. Janiri L, Falcone M, Persico A, Tempesta E. Activity of L-carnitine and L-acetylcarnitine on cholinoceptive neocortical neurons of the rat in vivo. J Neural Transm Gen Sect 1991;86:135–46.
102. Anand P, Singh B. A review on cholinesterase inhibitors for Alzheimer's disease. Arch Pharm Res 2013;36:375–99.
103. Forloni G, Angeretti N, Smiroldo S. Neuroprotective activity of acetyl-L-carnitine: studies in vitro. J Neurosci Res 1994;37:92–6.

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

104. Abdul HM, Calabrese V, Calvani M, Butterfield DA. Acetyl-L-carnitine-induced up-regulation of heat shock proteins protects cortical neurons against amyloid-beta peptide 1–42-mediated oxidative stress and neurotoxicity: implications for Alzheimer's disease. J Neurosci Res 2006;84:398–408.
105. Aliev G, Liu J, Shenk JC, Fischbach K, Pacheco GJ, Chen SG, Obrenovich ME, Ward WF, Richardson AG, Smith MA, et al. Neuronal mitochondrial amelioration by feeding acetyl-L-carnitine and lipoic acid to aged rats. J Cell Mol Med 2009;13:320–33.
106. Shenk JC, Liu J, Fischbach K, Xu K, Puchowicz M, Obrenovich ME, Gasimov E, Alvarez LM, Ames BN, Lamanna JC, et al. The effect of acetyl-L-carnitine and R-alpha-lipoic acid treatment in ApoE4 mouse as a model of human Alzheimer's disease. J Neurol Sci 2009;283:199–206.
107. Suchy J, Chan A, Shea TB. Dietary supplementation with a combination of alpha-lipoic acid, acetyl-L-carnitine, glycerophosphocoline, docosahexaenoic acid, and phosphatidylserine reduces oxidative damage to murine brain and improves cognitive performance. Nutr Res 2009;29:70–4.
108. Scafidi S, Racz J, Hazelton J, McKenna MC, Fiskum G. Neuroprotection by acetyl-L-carnitine after traumatic injury to the immature rat brain. Dev Neurosci 2010;32:480–7.
109. Nagesh Babu G, Kumar A, Singh RL. Chronic pretreatment with acetyl-L-carnitine and +/−DL-alpha-lipoic acid protects against acute glutamate-induced neurotoxicity in rat brain by altering mitochondrial function. Neurotox Res 2011;19:319–29.
110. Adibhatla RM, Hatcher JF. Role of lipids in brain injury and diseases. Future Lipidol 2007;2:403–22.
111. Adibhatla RM, Hatcher JF. Altered lipid metabolism in brain injury and disorders. Subcell Biochem 2008;49:241–68.
112. Lauritzen L, Hansen HS, Jorgensen MH, Michaelsen KF. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. Prog Lipid Res 2001;40:1–94.
113. Heude B, Ducimetiere P, Berr C, Study EVA. Cognitive decline and fatty acid composition of erythrocyte membranes–The EVA Study. Am J Clin Nutr 2003;77:803–8.
114. Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 2007;85:1103–11.
115. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids 2000;35:1305–12.
116. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol 2006;63:1545–50.
117. Söderberg M, Edlund C, Kristensson K, Dallner G. Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease. Lipids 1991;26:421–5.
118. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60:940–6.
119. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62:275–80.
120. Noel K, Hoffman J, Ellis L, Yurko-Mauro K, Cella C, Sercus B, Nalysnyk L. DHA and cognitive function in the elderly: a systematic review of the literature. Res Pract Alzheimers Dis 2006;11:381–7.
121. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, Salem N, Jr, Stedman M, Investigators M. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement 2010;6:456–64.
122. Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol 2006;63:1402–8.
123. Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res 2006;56:159–64.
124. Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, Stewart R, Huang SY. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1538–44.
125. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR Jr, Weiner M, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010;304:1903–11.
126. Cole GM, Ma QL, Frautschy SA. Omega-3 fatty acids and dementia. Prostaglandins Leukot Essent Fatty Acids 2009;81:213–21.
127. Shinto L, Quinn J, Motine T, Baldauf-Wagner SB, Bourdette D, Oken DB, Kaye J. Omega-3 fatty acids and lipoic acid in Alzheimer's disease. Neurology 2008;70:A393.
128. Scheltens P, Kamphuis PJ, Verhey FR, Olde Rikkert MG, Wurtman RJ, Wilkinson D, Twisk JW, Kurz A. Efficacy of a medical food in mild Alzheimer's disease: a randomized, controlled trial. Alzheimers Dement 2010;6:1–10.e1.
129. Erdman J, Oria M, Pillsbury L. Nutrition and traumatic brain injury: improving acute and subacute health outcomes in military personnel. National Research Council, Trauma and the Brain Committee on Nutrition, Institute of Medicine. Washington, DC: National Academies Press; 2011.
130. Petraglia AL, Winkler EA, Bailes JE. Stuck at the bench: potential natural neuroprotective compounds for concussion. Surg Neurol Int 2011;2:146.
131. Hasadsri L, Wang BH, Lee JV, Erdman JW, Llano DA, Barbey AK, Wszalek T, Sharrock MF, Wang HJ. Omega-3 fatty acids as a putative treatment for traumatic brain injury. J Neurotrauma 2013;30:897–906.
132. Wohl DA, Tien HC, Busby M, Cunningham C, Macintosh B, Napravnik S, Danan E, Donovan K, Hossenipour M, Simpson RJ Jr. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. Clin Infect Dis 2005;41:1498–504.
133. Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, Ballantyne CM, Ginsberg HN. COMBination of Prescription Omega-3 with Simvastatin (COMBOS) Investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007;29:1354–67.
134. Lien EL. Toxicology and safety of DHA. Prostaglandins Leukot Essent Fatty Acids 2009;81:125–32.
135. Farooqui A. Potential neuroprotective strategies for traumatic brain injury. In: Neurochemical aspects of neurotraumatic and neurodegenerative diseases, 1st ed. New York: Springer; 2010.
136. Calon F, Lim GP, Morihara T, Yang F, Ubeda O, Salem N Jr, Frautschy SA, Cole GM. Dietary n-3 polyunsaturated fatty acid depletion activates caspases and decreases NMDA receptors in the brain of a transgenic mouse model of Alzheimer's disease. Eur J Neurosci 2005;22:617–26.
137. Latour A, Grintal B, Champeil-Potokar G, Hennebelle M, Lavialle M, Dutar P, Potier B, Billard JM, Vancassel S, Denis I. Omega-3 fatty acids deficiency aggravates glutamatergic synapse and astroglial aging in the rat hippocampal CA1. Aging Cell 2013;12:76–84.
138. Hossain MS, Hashimoto M, Gamoh S, Masumura S. Antioxidative effects of docosahexaenoic acid in the cerebrum versus cerebellum and brainstem of aged hypercholesterolemic rats. J Neurochem 1999;72:1133–8.
139. Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, Ishibashi Y, Oka J, Shido O. Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats. J Neurochem 2002;81:1084–91.
140. Hashimoto M, Tanabe Y, Fujii Y, Kikuta T, Shibata H, Shido O. Chronic administration of docosahexaenoic acid ameliorates the impairment of spatial cognition learning ability in amyloid beta-infused rats. J Nutr 2005;135:549–55.

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015

141. Oksman M, Iivonen H, Hogyes E, Amtul Z, Penke B, Leenders I, Broersen L, Lutjohann D, Hartmann T, Tanila H. Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. Neurobiol Dis 2006;23:563–72.
142. Green KN, Martinez-Coria H, Khashwji H, Hall EB, Yurko-Mauro KA, Ellis L, LaFerla FM. Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. J Neurosci 2007;27:4385–95.
143. Lebbadi M, Julien C, Phivilay A, Tremblay C, Emond V, Kang JX, Calon F. Endogenous conversion of omega-6 into omega-3 fatty acids improves neuropathology in an animal model of Alzheimer's disease. J Alzheimers Dis 2011;27:853–69.
144. Yamamoto N, Saitoh M, Moriuchi A, Nomura M, Okuyama H. Effect of dietary alpha-linolenate/linoleate balance on brain lipid compositions and learning ability of rats. J Lipid Res 1987;28:144–51.
145. Jensen MM, Skarsfeldt T, Hoy CE. Correlation between level of (n-3) polyunsaturated fatty acids in brain phospholipids and learning ability in rats. A multiple generation study. Biochim Biophys Acta 1996;1300: 203–9.
146. Suzuki H, Park SJ, Tamura M, Ando S. Effect of the long-term feeding of dietary lipids on the learning ability, fatty acid composition of brain stem phospholipids and synaptic membrane fluidity in adult mice: a comparison of sardine oil diet with palm oil diet. Mech Ageing Dev 1998;101:119–28.
147. Gamoh S, Hashimoto M, Sugioka K, Shahdat Hossain M, Hata N, Misawa Y, Masumura S. Chronic administration of docosahexaenoic acid improves reference memory-related learning ability in young rats. Neuroscience 1999;93:237–41.
148. Greiner RS, Moriguchi T, Hutton A, Slotnick BM, Salem N Jr. Rats with low levels of brain docosahexaenoic acid show impaired performance in olfactory-based and spatial learning tasks. Lipids 1999;34(Suppl):S239–43.
149. Lim SY, Suzuki H. Effect of dietary docosahexaenoic acid and phosphatidylcholine on maze behavior and fatty acid composition of plasma and brain lipids in mice. Int J Vitam Nutr Res 2000;70: 251–9.
150. Lim SY, Suzuki H. Intakes of dietary docosahexaenoic acid ethyl ester and egg phosphatidylcholine improve maze-learning ability in young and old mice. J Nutr 2000;130:1629–32.
151. Gamoh S, Hashimoto M, Hossain S, Masumura S. Chronic administration of docosahexaenoic acid improves the performance of radial arm maze task in aged rats. Clin Exp Pharmacol Physiol 2001;28: 266–70.
152. Lim S, Suzuki H. Changes in maze behavior of mice occur after sufficient accumulation of docosahexaenoic acid in brain. J Nutr 2001; 131:319–24.
153. Bailes JE, Mills JD. Docosahexaenoic acid reduces traumatic axonal injury in a rodent head injury model. J Neurotrauma 2010;27: 1617–24.
154. Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery 2011;68:474–81, discussion 481.
155. Mills JD, Bailes JE, Sedney CL, Hutchins H, Sears B. Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. J Neurosurg 2011;114:77–84.
156. Wu A, Ying Z, Gomez-Pinilla F. The salutary effects of DHA dietary supplementation on cognition, neuroplasticity, and membrane homeostasis after brain trauma. J Neurotrauma 2011;28:2113–22.
157. Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM, Zeisel SH. Evidence-based criteria in the nutritional context. Nutr Rev 2010;68:478–84.

AN Advances in Nutrition An International Review Journal

Downloaded from advances.nutrition.org at ASN Member on August 9, 2015