Symposium

Nutrition, Brain Aging, and Neurodegeneration

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The onset of age-related neurodegenerative diseases superimposed on a declining nervous system could enhance the motor and cognitive behavioral deficits that normally occur in senescence. It is likely that, in cases of severe deficits in memory or motor function, hospitalization and/or custodial care would be a likely outcome. This means that unless some way is found to reduce these age-related decrements in neuronal function, health care costs will continue to rise exponentially. Applying molecular biological approaches to slow aging in the human condition may be years away. So, it is important to determine what methods can be used today to increase healthy aging, forestall the onset of these diseases, and create conditions favorable to obtaining a "longevity dividend" in both financial and human terms. Recent studies suggest that consumption of diets rich in antioxidants and anti-inflammatory components such as those found in fruits, nuts, vegetables, and spices, or even reduced caloric intake, may lower age-related cognitive declines and the risk of developing neurodegenerative disease.

Introduction

By the year 2050, 30% of the total population will be over 65 years of age. As the aged population expands, the economic burden of care and treatment of those with age-related health disorders also increases, necessitating measures to prevent or even reverse age-related health disorders. One such potential option is the use of nutritional substances such as berry fruit and fatty acids from walnuts and fish oils. Research has recently shown that consumption of the aforementioned substances can dramatically impact the aging brain, possibly leading to improved cognition and motor abilities. It has been postulated that these behavioral and neuronal declines are the result of an increasing vulnerability to oxidative and inflammatory insults, thus creating a "fertile environment" (Yu, 1994; Sadoul, 1998; Gilissen et al., 1999; Joseph et al., 2001) for the subsequent development of age-related neurodegenerative disease such as Alzheimer disease (AD) (Markesbery, 1997; Behl, 1999; Praticò and Delanty, 2000; Sultana et al., 2006). The destructive properties of oxidative stress in the aged brain are evidenced by reductions in redox active iron (Gilissen et al., 1999; Joseph et al., 2001), as well as increases in B-cell lymphoma 2 (Bcl-2) (Sadoul, 1998) and membrane lipid peroxidation (Yu, 1994). Studies have also shown that there are significant increases in cellular hydrogen peroxide (Cavazzoni et al., 1999). Additionally, there is significant lipofuscin accumulation (Gilissen et al., 1999) along with alterations in membrane lipids (Denisova et al., 1998), indicating the involvement of lipid rafts with oxidative stress sensitivity (Shen et al., 2004). Importantly, the consequences of these increases in oxidative stress at several levels may result in reduced calcium homeostasis, alterations in cellular signaling cascades, and changes in gene expression (Dalton et al., 1999; Annunziato et al., 2002), which combine to contribute to the increased vulnerability to oxidative stress seen in the aging population (Halliwell, 2001; Rego and Oliveira, 2003) and which is elevated in AD (Smith et al., 1991; Lovell et al., 1995; Marcus et al., 1998) and Parkinson disease (PD) (Dexter et al., 1994; Spencer et al., 1998). Together, these findings indicate that oxidative stress increases during aging, leading to widespread damage to cellular components, and ultimately manifesting in declines in motor and cognitive abilities.

It is clear that the incidence of many of the major disorders, such as Alzheimer's disease, vascular dementia, and cardiovascular disease, increase as a function of age, and that their etiology may partially involve lifestyle determinants such as obesity, decreased sensitivity to insulin, and the metabolic syndrome. Unfortunately, there is a distinct lack of knowledge of these issues among clinicians and physicians, where nutritional recommendations could be used with traditional approaches in neurogerontology. Research described below suggests that polyphenolic compounds contained in berry fruits, walnuts, curcumin, and fish oils exhibit potent antioxidant and anti-inflammatory activities that may reduce the age-related sensitivity to oxidative stress or inflammation and may alter neurodegeneration. Interestingly, the results found with respect to these nutrients are similar to those seen with caloric restriction and caloric restriction mimetics, suggesting a final common pathway among these various interventions.

Berry fruit polyphenols

All plants, including fruit-, nut-, or spice-bearing plants, synthesize a vast array of chemical compounds that are not necessarily involved in the plant's metabolism but instead serve a variety of functions that enhance the plant's survivability. These include combating oxidative stress and inflammation. In this respect, previous studies have found that crude blueberry (BB) or straw-

Received July 21, 2009; revised July 28, 2009; accepted Aug. 4, 2009.

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DOI:10.1523/JNEUROSCI.3520-09.2009

 0270-6474/09/2912795-07$15.00/0

berry (SB) extracts significantly attenuated age-related motor and cognitive deficits in aged rodents. Thus, these supplementations reversed age-related deficits in neuronal and behavioral (cognitive) function in aged (19 months) Fischer 344 rats (Joseph et al., 1999). The rodents in all diet groups, but not the control group, showed improved working memory (short-term memory) performance in the Morris water maze (MWM). A later study has suggested that, in addition to MWM performance, blueberry supplementation was also effective in reversing cognitive declines in object recognition (Goyarzu et al., 2004). Furthermore, the beneficial effects of BB were seen even when superimposed on an already healthy rodent diet, which was more representative of a balanced human diet (Youdim et al., 2000). BB supplementation also improved performance on tests of motor function that assessed balance and coordination (e.g., rod walking and the accelerating rotarod) (Joseph et al., 1999). Thus far, only blueberry, cranberry (Shukitt-Hale et al., 2005), strawberry (Shukitt-Hale et al., 2006b), Concord grape juice (Shukitt-Hale et al., 2006a), blackberry (Shukitt-Hale et al., 2009), or walnut supplementations (Willis et al., 2009) have been effective in reversing motor behavioral deficits. Rats on the BB diet have generally shown the greatest increases in motor performance, as well as increases in carbachol-stimulated GTPase activity and oxotremorine-enhanced dopamine (DA) release (both markers of muscarinic receptor sensitivity).

Importantly, even though these diets were supplemented based on equal antioxidant activity [as determined by the oxygen radical absorbance capacity (ORAC) assay], they were not equally effective in preventing or reversing age-related changes (Joseph et al., 1999). Therefore, antioxidant activity alone was not predictive in assessing the potency of these compounds against certain disorders affected by aging. In fact, oxidative stress markers (as measured by DCF fluorescence and glutathione levels in the brain) were only modestly reduced by the diets (Joseph et al., 1999), suggesting that berry fruit polyphenols may possess a multiplicity of actions aside from antioxidant activity. Other possible mechanisms for the berry fruit's positive effects include: direct effects on signaling to enhance neuronal communication (Joseph et al., 2003), the ability to buffer against excess calcium (Joseph et al., 2004), enhancement of neuroprotective stress shock proteins (Galli et al., 2006), and reduction of stress signals such as nuclear factor κ B (NF-κB) (Goyarzu et al., 2004). Additionally, the anthocyanins contained in blueberries have been shown to enter the brain, and their concentrations were correlated with cognitive performance (Andres-Lacueva et al., 2005).

Research has demonstrated the involvement of various signaling molecules in the protective effects of berries in both cell culture systems and animal models. BB treatment of dopamine (DA)-exposed COS-7 cells (Joseph et al., 2006) or primary hippocampal neurons (Joseph et al., 2007a) significantly increased protective mitogen activated protein kinase (MAPK) expression. Additionally, BB-supplemented APP/PS1 mice exhibited greater levels of hippocampal extracellular signal regulated kinase (ERK), as well as striatal and hippocampal protein kinase C (PKC) α, than seen in the transgenic mice maintained on the control diet (Joseph et al., 2003). ERK has been shown to be involved in diverse forms of memory, such as: contextual fear conditioning [33]; long-term potentiation (English and Sweatt, 1997); striatum-dependent learning and memory (Mazzucchelli and Brambilla, 2000); hippocampus-dependent spatial memory (Selcher et al., 1999); and inhibitory avoidance (Schafe et al., 1999). PKC has been implicated in the regulation of synaptic plasticity and modulation of short- to long-term memory. Studies have shown that PKC activity is important in spatial memory formation (for review, see Micheau and Riedel, 1999). Research has also shown that BB treatment was effective in protecting against amyloid β ($A\beta_{42}$)- or DA-induced decrements in intracellular calcium clearance (Joseph et al., 2007b) following depolarization in M1 muscarinic receptor (MAChR)-transfected COS-7 cells or neonatal hippocampal neurons. This protection involved increases in phosphorylated MAPK and decreases in PKCγ and phosphorylated cAMP response element binding protein (CREB). Blueberry supplementation has also been shown to impact cell signaling molecule expression *in vivo*. BB supplementation reduced the toxicity of kainic acid on hippocampal cells concomitant with reduced expression of stress signals and increased expression of protective signals (Shukitt-Hale et al., 2008a). These alterations in stress signaling were associated with enhanced behavioral performance (Morris water maze) and reduced microglial activation (Bodles and Barger, 2004). An additional study showed that BB-supplemented aged animals had increased ERK and insulin growth factor-1 (IGF-1) activation in the dentate gyrus that was associated with increased neurogenesis and enhanced cognitive ability (Casadesus et al., 2004). Similar findings were observed with respect to microglial activity, BB and stress signaling wherein BB treatment dose-dependently inhibited the production NO, as well as the cytokines Il-1β and TNF-α in lipopolysaccharide- (LPS-) activated BV2 microglia (Lau et al., 2007). Overall, as shown in Table 1, we have proposed the following schemes for the BB effects on stress and protective signaling.

Table 1. Proposed signal transduction pathways possibly affected by berry fruit polyphenols

1. DA/Aβ_{42} → ROS → PKCγ/PKCα → p38 MAPK → CREB/ NfκB → increased ROS and calcium dysregulation
2. 2 DA/Aβ_{42} → ROS → JNK → p53 → increased ROS and calcium dysregulation)

ROS, Reactive oxygen species.

Subsequent studies in progress have suggested that scheme two may be the pathway most likely to be involved in the DA-induced stress signaling and that BBs appear to be able to act at multiple points in the pathway to prevent calcium dysregulation.

Walnut and fish polyunsaturated fatty acids

In addition to plant derived polyphenols, polyunsaturated fatty acids (PUFAs) represent another potential dietary intervention to forestall age-related neuronal and cognitive decline. PUFAs are critical components of neuronal cell membranes, maintaining membrane fluidity that is essential for synaptic vesicle fusion and neurotransmitter communication within neural networks. In addition, membrane PUFAs serve as precursors for lipid messengers, which can participate in signaling processes to promote neuronal protection or induce neuronal dysfunction (Bazan, 2005). In the aged brain, studies have shown a deficit in the amount of PUFAs in the hippocampus, cortex, and cerebellum, all areas involved in cognitive and motor function (Little et al., 2007). These deficits may be further increased in AD.

Walnuts are well known for their high levels of PUFAs, specifically the ω-6 fatty acid linoleic acid (LA) and the ω-3 fatty acid α-linolenic acid (ALA). LA and ALA can either exist as membrane components or can be metabolized via the arachidonic acid cascade to generate numerous lipid messengers including prostaglandins, eicosapentaenoic acid (EPA), and docosahaenoic acid (DHA), which are ω 3 oils. Indeed, a recent study has shown that walnuts improved cognitive function in aged rodents, much as was seen with respect to berry fruit (Willis et al., 2009). Impor-

tantly, the aged animals on walnuts also showed reduced microglial activity in the hippocampus. In addition to PUFAs, walnuts also contain other bioactive constituents which have been shown to influence brain function, including vitamin E, melatonin, and antioxidant polyphenols such as ellagic acid (Venkatachalam and Sathe, 2006) that could act synergistically with the PUFAs to increase dietary polyphenolic absorption and uptake following consumption (Huo et al., 2007).

PUFAs from fish oils may have similar beneficial effects. A 2005 ω-3 meta-analysis assessing the quality of available epidemiology and preclinical studies concluded clinical trials were warranted (Maclean et al., 2005). To date, nine epidemiological studies associate increased fish consumption with reduced AD, while 8/10 studies associate higher blood n-3 with reduced cognitive decline. Moreover, three studies indicate limited protection in ApoE4 carriers (Cole et al., 2009). Four small completed trials with n-3 (typically fish oil) suggest protection, but only in patients showing mild cognitive impairment (MCI). Two trials with n-3 and other nutrients (α lipoate or B vitamins and uridine-5′-monophosphate, a putative enhancer of DHA incorporation) seem to show some effect in AD (Cole et al., 2009). A larger recently completed 6 month trial (MIDAS, 485 subjects with mild memory complaints) reported improvements in mild memory complaints with 900 mg of DHA (Yurko-Mauro et al., 2009). A National Institutes of Health cooperative DHA trial in mild to moderate AD (Quinn, 2009) reported possible but nonsignificant slowing of progression in ApoE3, but not ApoE4 subjects. Additional trials are in progress.

Similarly, DHA reduced amyloid β 42 (Aβ42) in AD mice (Lim et al., 2005; Oksman et al., 2006; Green et al., 2007; Hooijmans et al., 2007) and production by cultured human neurons (Lukiw et al., 2005). The mechanism involved in the DHA-induced reductions in Aβ42 may be due to multiple effects, such as: changes in lipid raft structure (Stillwell et al., 2005), alterations in APP processing (Ehehalt et al., 2003), induction of anti-amyloidogenic chaperones for APP (Ma et al., 2007), and Aβ transthyretin (Schwarzman et al., 1994; Puskás et al., 2003). As with the polyphenols, proposed neuroprotective mechanisms also include increasing survival signaling. For example, insulin/neurotrophin signaling, defective in AD, protects against Aβ oligomer toxicity (Cole and Frautschy, 2007). AD and preclinical models show synaptic and dendritic loss from a postsynaptic attack by Aβ oligomers, which DHA blocks *in vitro*, consistent with protection of the synaptic protein, drebrin, in APP Tg mice.

Insulin receptor substrate (IRS), an adaptor protein, couples insulin/trophic factor signaling to PI3-K/Akt. Thus, DHA reduces Aβ42 production and protects against its toxicity via multiple mechanisms. This is important since DHA is enriched in neuronal phospholipids where it may be in as high as 35% of phosphatidylethanolamine (Salem et al., 2001). Because archidonic acid (AA) and DHA compete for esterification into the labile SN-2 phospholipid position, DHA reduces proinflammatory AA available for cyclooxygenase and lipoxygenase enzymes, an anti-inflammatory NSAID-like property contributing to interest in DHA and AD prevention (Cole et al., 2009). In summary, it appears that DHA reduces $A\beta_{42}$ production and protects against its toxicity via multiple mechanisms.

Curcuminoids

In addition to the polyphenols found in walnuts and berry fruits, polyphenols (curcuminoids) found in the curry spice turmeric may have similar effects. The biophenolic curcumin was isolated as the active yellow component of turmeric, a food preservative inhibitor of lipid peroxidation with potent anti-inflammatory and anti-cancer activities and a long history of use in Asian traditional medicines (Aggarwal et al., 2007). In AD models, curcumin reduced proinflammatory cytokines, oxidative damage, Aβ42 and cognitive deficits (Frautschy et al., 2001). Like Congo red, it is an amyloid binding dye and direct inhibitor of Aβ oligomer and fibril formation that can enter the brain to directly label plaques and markedly reduce Aβ42 and plaques even in old APP Tg mice, suggesting a possible "vaccine-like" clearance (Cole et al., 2003). Direct evidence for curcumin stimulation of amyloid plaque clearance and dystrophic neurite reduction was provided by elegant *in vivo* imaging before and after curcumin (Garcia-Alloza et al., 2007). Curcumin has other pleiotropic anti-AD activities including limiting the tau kinase JNK (c-Jun N-terminal protein kinase) and stimulating neurogenesis and BDNF (Cole et al., 2007). Cucumin synergized with fish oil in reducing insulin signaling defects in triple Tg AD model mice (Ma et al., 2009). These pleiotropic anti-AD activities led to studies assessing curcumin/DHA combinations in aging tau transgenic mice and positive effects were seen against cognitive deficits. A major obstacle with curcumin in the clinic has been limited bioavailability of supplements, but this problem has been solved with new lipidated formulations (Begum et al., 2008), currently in clinical trials. While there are many new treatment approaches, the major advantages of these nutritional interventions is their safety, broad spectrum utility, low cost, and suitability for prevention, especially in diets that contain polyphenols with more "traditional" antioxidants such as vitamin C and vitamin E. A subset of these studies is described in the next section.

The canine antioxidant diet

In this respect it has been shown (Zandi et al., 2004) that the dietary intake of antioxidants in foods is superior to supplements in human studies on cognition and risk of developing AD (Morris et al., 2002; Barberger-Gateau et al., 2007). Furthermore, the addition of mitochondrial cofactors that target mitochondrial function and reduce reactive oxygen species may enhance the effects of cellular antioxidants such as vitamin E. These considerations led to studies involving administering an antioxidant diet to aged beagles. Dogs are particularly useful because they naturally develop cognitive decline with age, accumulate oxidative damage and AD-like neuropathology, and absorb dietary nutrients in a similar manner as humans (Cotman and Head, 2008).

Aged beagles (between ~8–12 years) were used in this study. An antioxidant-enriched diet was formulated to include a broad spectrum of antioxidants and two mitochondrial cofactors (Milgram et al., 2005), which were well within those used in human clinical trials. The daily doses for each compound were 800 IU or 210 mg/d (21 mg/kg/d) of vitamin E, 16 mg/d (1.6 mg/kg/d) of vitamin C, 52 mg/d (5.2 mg/kg/d) of carnitine, and 26 mg/d (2.6 mg/kg/d) of lipoic acid. Fruits and vegetables were also incorporated at a 1 to 1 exchange ratio for corn, resulting in 1% inclusions of each of the following: spinach flakes, tomato pomace, grape pomace, carrot granules, and citrus pulp. This was equivalent to raising fruits and vegetable servings from 3 to 5–6/d. Vitamin E was increased ~75% by the antioxidant diet in treated dogs (Milgram et al., 2002). A second intervention included a behavioral enrichment condition consisting of: (1) additional cognitive experience (20–30 min/d, 5 d/week), (2) an enriched sensory environment (housing with a kennel-mate, rotation of play toys in kennel once/week), and (3) physical exercise (2×20 min walks/week outdoors) (Milgram et al., 2005).

The dogs were evaluated over a 2.8 year period. Treatment with the antioxidant diet lead to cognitive improvements in

learning that were rapid and within 2 weeks of beginning the diet; aged animals showed significant improvements in spatial attention (landmark task) (Milgram et al., 2002). Subsequent testing of animals with a more difficult complex learning task, oddity discrimination, also revealed benefits of the diet (Cotman et al., 2002). Improved visual discrimination and reversal (frontal function) learning ability was maintained over time with the antioxidant treatment while untreated animals showed a progressive decline (Milgram et al., 2005). Interestingly, the antioxidant diet benefitted from the inclusion of behavioral enrichment and aged dogs receiving both treatments were superior to either treatment alone (Milgram et al., 2004, 2005). As predicted, oxidative damage was reduced in antioxidant-fed dogs and in particular within the group of animals receiving the combination of antioxidants and behavioral enrichment (Opii et al., 2008). Endogenous antioxidant activity was also increased (Opii et al., 2008). Interestingly, behavioral enrichment but not the antioxidant diet protected against neuron loss in the hilus of the hippocampus of treated dogs (Siwak-Tapp et al., 2008). These results suggest that cognitive benefits of cellular antioxidants and mitochondrial cofactors can be further enhanced with the addition of behavioral enrichment due to different yet synergistic mechanisms of action in the brain (reducing oxidative damage, maintaining neuron health). These findings suggest that studies in humans may be more efficacious if combinations of antioxidants are administered and dietary intake of antioxidants considered in treatment protocols.

Caloric restriction

Furthermore, however, as compelling as the data concerning the various antioxidant/anti-oxidant diets may be with respect to reducing behavioral deficits in aging, a large literature exists to support the view that caloric restriction rather than caloric selection may provide an additional approach for reducing age-related behavioral deficits. Epidemiological studies have reported the inverse relationship between caloric intake and risk of AD and PD (Luchsinger et al., 2002; Mattson et al., 2002; Mattson, 2003). These findings fit well within the context of the calorie restriction (CR) paradigm, one of the most robust in gerontology (Weindruch and Sohal, 1997; Weindruch and Walford, 1998; Masoro, 2005; Piper and Bartke, 2008). As demonstrated in numerous animal models, CR has proven to be the most effective means to retard aging, including brain aging. Reducing intake of a nutritious diet by 20–50% can increase lifespan, reduce incidence and retard onset of chronic diseases, enhance stress protection, and maintain youthful behavioral function accommodated by preserved features of neural anatomy and activity (Weindruch and Sohal, 1997; Weindruch and Walford, 1998; Masoro, 2005; Piper and Bartke, 2008). Recent studies in mouse models of AD confirm that restricting caloric intake 30–40% from normal levels can markedly slow pathogenesis of the disease (Qin et al., 2006b; Halagappa et al., 2007). Aβ deposition in squirrel monkeys on a CR regimen is also reduced (Qin et al., 2006a). Similarly long-term studies of rhesus monkeys conducted at the National Institute on Aging and the University of Wisconsin have produced data indicating that CR animals (30% less than controls) are healthier than fully fed counterparts based on reduced incidence of various diseases, on exhibition of better indices of predisposition to disease, and slower rates of aging based on analysis of several biomarkers (Ramsey et al., 2000; Roth et al., 2004; Mattison et al., 2007; Raman et al., 2007). A recent report also indicates a significant increase in survival in CR monkeys as well as attenuation of the age-related declines in brain volume in selected regions (Colman et al., 2009). Thus, in a species closely related to humans, CR has shown promise as an intervention that could retard brain aging and neurodegenerative disease. In fact, recent reports of persons electing to practice CR close to levels applied in nonhuman primate studies have also noted many indices of reduced risk of age-related diseases, such as improved blood lipids, cardiac function, enhanced insulin sensitivity, and reduced measures of inflammation (Fontana et al., 2004; Meyer et al., 2006). Formal clinical studies of CR lasting only 6 months in duration have also documented positive impact on many indices of health and risk factors for chronic disease (Civitarese et al., 2007).

However, it is evident implementation of such a stringent regimen would be problematic due to difficulties of compliance, as well as other quality of life issues impacted by CR (McCaffree, 2004; Dirks and Leeuwenburgh, 2006). This has engendered increased attention on the development of calorie restriction mimetics (CRM) (Hursting et al., 2003; Ingram et al., 2004, 2006; Chen and Guarente, 2007), compounds which can mimic CR by targeting metabolic and stress response pathways affected by CR, but without restricting caloric intake. One of these candidates is resveratrol (Baur and Sinclair, 2006; Knutson and Leeuwenburgh, 2008; Markus and Morris, 2008). This polyphenol is found in high concentrations in red grapes and was noted to activate SIRT2 in invertebrates. SIRT1, its homolog in mammals, has actions similar to that of CR. This class of sirtuins represent NAD-dependent histone deacetylases that regulate a variety of stress responses, including CR (Guarente, 2007; Michan and Sinclair, 2007; Lavu et al., 2008). Knock-out of sirt2 in invertebrates eliminated the lifespan extension induced by CR while overexpression increased lifespan similar to CR (Guarente, 2007; Michan and Sinclair, 2007; Lavu et al., 2008). Results from a variety of recent studies in rodent models show that resveratrol can produce a remarkable range of beneficial effects including protection against high fat diets, neurodegeneration and age-related pathologies, such as cardiac function and cataracts (Baur et al., 2006; Fukuda et al., 2006; Kim et al., 2007; Lu et al., 2008; Pearson et al., 2008), and motor declines (Pearson et al., 2008), but did not significantly increase lifespan in mice on a normal diet (Pearson et al., 2008).

The fact that resveratrol is a naturally occurring polyphenol that is produced in response to fungal attack has created an interesting connection to CR (Sinclair, 2005; Howitz and Sinclair, 2008) since, as described above, diets rich in fruits and vegetables have also been related to enhanced health and longevity in human studies (Ferrari, 2004; Heber, 2004; Stanner et al., 2004), while animal studies demonstrate anti-aging effects of such diets paralleling those observed in CR (Shukitt-Hale et al., 2008b). It may be that the convergence point for CR and polyphnolic research may actually involve hormetic-enhanced stress protection (Gems and Partridge, 2008). Thus, moving beyond their demonstrated actions as antioxidants, plant polyphenols appear to have direct actions on signaling pathways involved in stress protection in neurons as described in other parts of this summary. This view provides further support for the potential for effective nutritional interventions to attenuate brain aging, neurodegeneration, and functional declines.

Conclusions

Together, the findings discussed in the previous sections provide compelling evidence to suggest lifestyle changes involving caloric selection through alterations in berry fruit, nut, fish oil, and curcumin intake, and caloric restriction mimetics may provide ben-

eficial effects in aging and prevent or delay the onset of neurodegenerative diseases such as AD. These changes along with those not discussed in this review, such as environmental enrichment, may provide the most efficacious methods thus far for increasing "health span." Interestingly, while many of the mechanisms for the beneficial effects of these nutritional interventions have yet to be discerned, it is clear that they involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling, and may even involve hormetic effects to protect against the two major villains of aging, oxidative and inflammatory stressors.

References

Aggarwal BB, Sundaram C, Malani N, Ichikawa H (2007) Curcumin: the Indian solid gold. Adv Exp Med Biol 595:1–75.

Andres-Lacueva C, Shukitt-Hale B, Galli RL, Jauregui O, Lamuela-Raventos RM, Joseph JA (2005) Anthocyanins in aged blueberry-fed rats are found centrally and may enhance memory. Nutr Neurosci 8:111–120.

Annunziato L, Pannaccione A, Cataldi M, Secondo A, Castaldo P, Di Renzo G, Taglialatela M (2002) Modulation of ion channels by reactive oxygen and nitrogen species: a pathophysiological role in brain aging? Neurobiol Aging 23:819–834.

Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alpérovitch A (2007) Dietary patterns and risk of dementia: the Three-City cohort study. Neurology 69:1921–1930.

Baur JA, Sinclair DA (2006) Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 5:493–506.

Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, et al. (2006) Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444:337–342.

Bazan NG (2005) Lipid signaling in neural plasticity, brain repair, and neuroprotection. Mol Neurobiol 32:89–103.

Begum AN, Jones MR, Lim GP, Morihara T, Kim P, Heath DD, Rock CL, Pruitt MA, Yang F, Hudspeth B, Hu S, Faull KF, Teter B, Cole GM, Frautschy SA (2008) Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. J Pharmacol Exp Ther 326:196–208.

Behl C (1999) Vitamin E and other antioxidants in neuroprotection. Int J Vitam Nutr Res 69:213–219.

Bodles AM, Barger SW (2004) Cytokines and the aging brain - what we don't know might help us. Trends Neurosci 27:621–626.

Casadesus G, Shukitt-Hale B, Stellwagen HM, Zhu X, Lee HG, Smith MA, Joseph JA (2004) Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats. Nutr Neurosci 7:309–316.

Cavazzoni M, Barogi S, Baracca A, Parenti Castelli G, Lenaz G (1999) The effect of aging and an oxidative stress on peroxide levels and the mitochondrial membrane potential in isolated rat hepatocytes. FEBS Lett 449:53–56.

Chen D, Guarente L (2007) SIR2: a potential target for calorie restriction mimetics. Trends Mol Med 13:64–71.

Civitarese AE, Carling S, Heilbronn LK, Hulver MH, Ukropcova B, Deutsch WA, Smith SR, Ravussin E (2007) Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med 4:e76.

Cole G, Yang F, Lim G, Cummings J, Masterman D, Frautschy S (2003) A rationale for curcuminoids for the prevention or treatment of Alzheimer's disease. Curr Med Chem Immun Endoc Metab Agents 3:15–25.

Cole GM, Frautschy SA (2007) The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease. Exp Gerontol 42:10–21.

Cole GM, Teter B, Frautschy SA (2007) Neuroprotective effects of curcumin. Adv Exp Med Biol 595:197–212.

Cole GM, Ma QL, Frautschy SA (2009) Omega-3 fatty acids and dementia. Prostaglandins Leukot Essent Fatty Acids 81:213–221.

Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R (2009) Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325:201–204.

Cotman CW, Head E (2008) The canine (dog) model of human aging and disease: dietary, environmental and immunotherapy approaches. J Alzheimers Dis 15:685–707.

Cotman CW, Head E, Muggenburg BA, Zicker S, Milgram NW (2002) Brain aging in the canine: a diet enriched in antioxidants reduces cognitive dysfunction. Neurobiol Aging 23:809–818.

Dalton TP, Shertzer HG, Puga A (1999) Regulation of gene expression by reactive oxygen. Annu Rev Pharmacol Toxicol 39:67–101.

Denisova NA, Erat SA, Kelly JF, Roth GS (1998) Differential effect of aging on cholesterol modulation of carbachol-stimulated low-K(m) GTPase in striatal synaptosomes. Exp Gerontol 33:249–265.

Dexter DT, Holley AE, Flitter WD, Slater TF, Wells FR, Daniel SE, Lees AJ, Jenner P, Marsden CD (1994) Increased levels of lipid hydroperoxides in the parkinsonian substantia nigra: an HPLC and ESR study. Mov Disord 9:92–97.

Dirks AJ, Leeuwenburgh C (2006) Caloric restriction in humans: potential pitfalls and health concerns. Mech Ageing Dev 127:1–7.

Ehehalt R, Keller P, Haass C, Thiele C, Simons K (2003) Amyloidogenic processing of the Alzheimer beta-amyloid precursor protein depends on lipid rafts. J Cell Biol 160:113–123.

English JD, Sweatt JD (1997) A requirement for the mitogen-activated protein kinase cascade in hippocampal long term potentiation. J Biol Chem 272:19103–19106.

Ferrari CK (2004) Functional foods, herbs and nutraceuticals: towards biochemical mechanisms of healthy aging. Biogerontology 5:275–289.

Fontana L, Meyer TE, Klein S, Holloszy JO (2004) Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A 101:6659–6663.

Frautschy SA, Hu W, Kim P, Miller SA, Chu T, Harris-White ME, Cole GM (2001) Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol Aging 22:993–1005.

Fukuda S, Kaga S, Zhan L, Bagchi D, Das DK, Bertelli A, Maulik N (2006) Resveratrol ameliorates myocardial damage by inducing vascular endothelial growth factor-angiogenesis and tyrosine kinase receptor Flk-1. Cell Biochem Biophys 44:43–49.

Galli RL, Bielinski DF, Szprengiel A, Shukitt-Hale B, Joseph JA (2006) Blueberry supplemented diet reverses age-related decline in hippocampal HSP70 neuroprotection. Neurobiol Aging 27:344–350.

Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ (2007) Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. J Neurochem 102:1095–1104.

Gems D, Partridge L (2008) Stress-response hormesis and aging: "that which does not kill us makes us stronger". Cell Metab 7:200–203.

Gilissen EP, Jacobs RE, Allman JM (1999) Magnetic resonance microscopy of iron in the basal forebrain cholinergic structures of the aged mouse lemur. J Neurol Sci 168:21–27.

Goyarzu P, Malin DH, Lau FC, Taglialatela G, Moon WD, Jennings R, Moy E, Moy D, Lippold S, Shukitt-Hale B, Joseph JA (2004) Blueberry supplemented diet: effects on object recognition memory and nuclear factor-kappa B levels in aged rats. Nutr Neurosci 7:75–83.

Green KN, Martinez-Coria H, Khashwji H, Hall EB, Yurko-Mauro KA, Ellis L, LaFerla FM (2007) Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. J Neurosci 27:4385–4395.

Guarente L (2007) Sirtuins in aging and disease. Cold Spring Harb Symp Quant Biol 72:483–488.

Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, Laferla FM, Mattson MP (2007) Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiol Dis 26:212–220.

Halliwell B (2001) Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. Drugs Aging 18:685–716.

Heber D (2004) Vegetables, fruits and phytoestrogens in the prevention of diseases. J Postgrad Med 50:145–149.

Hooijmans CR, Rutters F, Dederen PJ, Gambarota G, Veltien A, van Groen T, Broersen LM, Lütjohann D, Heerschap A, Tanila H, Kiliaan AJ (2007) Changes in cerebral blood volume and amyloid pathology in aged Alzheimer APP/PS1 mice on a docosahexaenoic acid (DHA) diet or cholesterol enriched Typical Western Diet (TWD). Neurobiol Dis 28:16–29.

Howitz KT, Sinclair DA (2008) Xenohormesis: sensing the chemical cues of other species. Cell 133:387–391.

Huo T, Ferruzzi MG, Schwartz SJ, Failla ML (2007) Impact of fatty acyl composition and quantity of triglycerides on bioaccessibility of dietary carotenoids. J Agric Food Chem 55:8950–8957.

Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC (2003) Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. Annu Rev Med 54:131–152.

Ingram DK, Anson RM, de Cabo R, Mamczarz J, Zhu M, Mattison J, Lane MA, Roth GS (2004) Development of calorie restriction mimetics as a prolongevity strategy. Ann N Y Acad Sci 1019:412–423.

Ingram DK, Zhu M, Mamczarz J, Zou S, Lane MA, Roth GS, deCabo R (2006) Calorie restriction mimetics: an emerging research field. Aging Cell 5:97–108.

Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC (1999) Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci 19:8114–8121.

Joseph J, Shukitt-Hale B, Denisova NA, Martin A, Perry G, Smith MA (2001) Copernicus revisited: amyloid beta in Alzheimer's disease. Neurobiol Aging 22:131–146.

Joseph JA, Denisova NA, Arendash G, Gordon M, Diamond D, Shukitt-Hale B, Morgan D (2003) Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model. Nutr Neurosci 6:153–162.

Joseph JA, Fisher DR, Carey AN (2004) Fruit extracts antagonize Abeta- or DA-induced deficits in Ca^{2+} flux in M1-transfected COS-7 cells. J Alzheimers Dis 6:403–411; discussion 443–9.

Joseph JA, Fisher DR, Carey AN, Neuman A, Bielinski DF (2006) Dopamine-induced stress signaling in COS-7 cells transfected with selectively vulnerable muscarinic receptor subtypes is partially mediated via the i3 loop and antagonized by blueberry extract. J Alzheimers Dis 10:423–437.

Joseph JA, Carey A, Brewer GJ, Lau FC, Fisher DR (2007a) Dopamine and abeta-induced stress signaling and decrements in Ca^{2+} buffering in primary neonatal hippocampal cells are antagonized by blueberry extract. J Alzheimers Dis 11:433–446.

Joseph JA, Shukitt-Hale B, Brewer GJ, McGuigan KA, Kalt W, Fisher DR (2007b) Differential protection among fractionated blueberry polyphenolic families against DA-, LPS- or Abeta-induced decrements in Ca^{2+} buffering in primary hippocampal cells. Soc Neurosci Abs 33:256.20.

Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers JT, Delalle I, Baur JA, Sui G, Armour SM, Puigserver P, Sinclair DA, Tsai LH (2007) SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. EMBO J 26:3169–3179.

Knutson MD, Leeuwenburgh C (2008) Resveratrol and novel potent activators of SIRT1: effects on aging and age-related diseases. Nutr Rev 66:591–596.

Lau FC, Bielinski DF, Joseph JA (2007) Inhibitory effects of blueberry extract on the production of inflammatory mediators in lipopolysaccharide-activated BV2 microglia. J Neurosci Res 85:1010–1017.

Lavu S, Boss O, Elliott PJ, Lambert PD (2008) Sirtuins–novel therapeutic targets to treat age-associated diseases. Nat Rev Drug Discov 7:841–853.

Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem N Jr, Frautschy SA, Cole GM (2005) A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci 25:3032–3040.

Little SJ, Lynch MA, Manku M, Nicolaou A (2007) Docosahexaenoic acid-induced changes in phospholipids in cortex of young and aged rats: a lipidomic analysis. Prostaglandins Leukot Essent Fatty Acids 77:155–162.

Lovell MA, Ehmann WD, Butler SM, Markesbery WR (1995) Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease. Neurology 45:1594–1601.

Lu KT, Ko MC, Chen BY, Huang JC, Hsieh CW, Lee MC, Chiou RY, Wung BS, Peng CH, Yang YL (2008) Neuroprotective effects of resveratrol on MPTP-induced neuron loss mediated by free radical scavenging. J Agric Food Chem 56:6910–6913.

Luchsinger JA, Tang MX, Shea S, Mayeux R (2002) Caloric intake and the risk of Alzheimer disease. Arch Neurol 59:1258–1263.

Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, Serhan CN, Bazan NG (2005) A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. J Clin Invest 115:2774–2783.

Ma QL, Teter B, Ubeda OJ, Morihara T, Dhoot D, Nyby MD, Tuck ML, Frautschy SA, Cole GM (2007) Omega-3 fatty acid docosahexaenoic acid increases SorLA/LR11, a sorting protein with reduced expression in sporadic Alzheimer's disease (AD): relevance to AD prevention. J Neurosci 27:14299–14307.

Ma QL, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ, Chen PP, Hudspeth B, Chen C, Zhao Y, Vinters HV, Frautschy SA, Cole GM (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. J Neurosci 29:9078–9089.

Maclean CH, Issa AM, Newberry SJ, Mojica WA, Morton SC, Garland RH, Hilton LG, Traina SB, Shekelle PG (2005) Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. Evid Rep Technol Assess (Summ) 114:1–3.

Marcus DL, Thomas C, Rodriguez C, Simberkoff K, Tsai JS, Strafaci JA, Freedman ML (1998) Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease. Exp Neurol 150:40–44.

Markesbery WR (1997) Oxidative stress hypothesis in Alzheimer's disease. Free Rad Biol Med 23:134–147.

Markus MA, Morris BJ (2008) Resveratrol in prevention and treatment of common clinical conditions of aging. Clin Interv Aging 3:331–339.

Masoro EJ (2005) Overview of caloric restriction and ageing. Mech Ageing Dev 126:913–922.

Mattison JA, Roth GS, Lane MA, Ingram DK (2007) Dietary restriction in aging nonhuman primates. Interdiscip Top Gerontol 35:137–158.

Mattson MP (2003) Will caloric restriction and folate protect against AD and PD? Neurology 60:690–695.

Mattson MP, Chan SL, Duan W (2002) Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. Physiol Rev 82:637–672.

Mazzucchelli C, Brambilla R (2000) Ras-related and MAPK signalling in neuronal plasticity and memory formation. Cell Mol Life Sci 57:604–611.

McCaffree J (2004) What you should know about calorie restriction. J Am Diet Assoc 104:1524–1526.

Meyer TE, Kovács SJ, Ehsani AA, Klein S, Holloszy JO, Fontana L (2006) Long-term caloric restriction ameliorates the decline in diastolic function in humans. J Am Coll Cardiol 47:398–402.

Michan S, Sinclair D (2007) Sirtuins in mammals: insights into their biological function. Biochem J 404:1–13.

Micheau J, Riedel G (1999) Protein kinases: which one is the memory molecule? Cell Mol Life Sci 55:534–548.

Milgram NW, Head E, Muggenburg B, Holowachuk D, Murphey H, Estrada J, Ikeda-Douglas CJ, Zicker SC, Cotman CW (2002) Landmark discrimination learning in the dog: effects of age, an antioxidant fortified food, and cognitive strategy. Neurosci Biobehav Rev 26:679–695.

Milgram NW, Head E, Zicker SC, Ikeda-Douglas C, Murphey H, Muggenberg BA, Siwak CT, Tapp PD, Lowry SR, Cotman CW (2004) Long-term treatment with antioxidants and a program of behavioral enrichment reduces age-dependent impairment in discrimination and reversal learning in beagle dogs. Exp Gerontol 39:753–765.

Milgram NW, Head E, Zicker SC, Ikeda-Douglas CJ, Murphey H, Muggenburg B, Siwak C, Tapp D, Cotman CW (2005) Learning ability in aged beagle dogs is preserved by behavioral enrichment and dietary fortification: a two-year longitudinal study. Neurobiol Aging 26:77–90.

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Wilson RS, Scherr PA (2002) Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. Jama 287:3230–3237.

Oksman M, Iivonen H, Hogyes E, Amtul Z, Penke B, Leenders I, Broersen L, Lütjohann D, Hartmann T, Tanila H (2006) Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. Neurobiol Dis 23:563–572.

Opii WO, Joshi G, Head E, Milgram NW, Muggenburg BA, Klein JB, Pierce WM, Cotman CW, Butterfield DA (2008) Proteomic identification of brain proteins in the canine model of human aging following a long-term treatment with antioxidants and a program of behavioral enrichment: relevance to Alzheimer's disease. Neurobiol Aging 29:51–70.

Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, Swindell

WR, Kamara D, Minor RK, Perez E, Jamieson HA, Zhang Y, Dunn SR, Sharma K, Pleshko N, Woollett LA, Csiszar A, Ikeno Y, Le Couteur D, Elliott PJ, et al. (2008) Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. Cell Metab 8:157–168.

Piper MD, Bartke A (2008) Diet and aging. Cell Metab 8:99–104.

Praticò D, Delanty N (2000) Oxidative injury in diseases of the central nervous system: focus on Alzheimer's disease. Am J Med 109:577–585.

Puskás LG, Kitajka K, Nyakas C, Barcelo-Coblijn G, Farkas T (2003) Short-term administration of omega 3 fatty acids from fish oil results in increased transthyretin transcription in old rat hippocampus. Proc Natl Acad Sci U S A 100:1580–1585.

Qin W, Chachich M, Lane M, Roth G, Bryant M, de Cabo R, Ottinger MA, Mattison J, Ingram D, Gandy S, Pasinetti GM (2006a) Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (*Saimiri sciureus*). J Alzheimers Dis 10:417–422.

Qin W, Yang T, Ho L, Zhao Z, Wang J, Chen L, Zhao W, Thiyagarajan M, MacGrogan D, Rodgers JT, Puigserver P, Sadoshima J, Deng H, Pedrini S, Gandy S, Sauve AA, Pasinetti GM (2006b) Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. J Biol Chem 281:21745–21754.

Quinn J (2009) A clinical trial of docosahexaenoic acid (DHA) for the treatment of Alzheimer's disease. Paper presented at the Alzheimer's Association International Conference on Alzheimer's Disease, Vienna, July.

Raman A, Ramsey JJ, Kemnitz JW, Baum ST, Newton W, Colman RJ, Weindruch R, Beasley MT, Schoeller DA (2007) Influences of calorie restriction and age on energy expenditure in the rhesus monkey. Am J Physiol Endocrinol Metab 292:E101–E106.

Ramsey JJ, Colman RJ, Binkley NC, Christensen JD, Gresl TA, Kemnitz JW, Weindruch R (2000) Dietary restriction and aging in rhesus monkeys: the University of Wisconsin study. Exp Gerontol 35:1131–1149.

Rego AC, Oliveira CR (2003) Mitochondrial dysfunction and reactive oxygen species in excitotoxicity and apoptosis: implications for the pathogenesis of neurodegenerative diseases. Neurochem Res 28:1563–1574.

Roth GS, Mattison JA, Ottinger MA, Chachich ME, Lane MA, Ingram DK (2004) Aging in rhesus monkeys: relevance to human health interventions. Science 305:1423–1426.

Sadoul R (1998) Bcl-2 family members in the development and degenerative pathologies of the nervous system. Cell Death Differ 5:805–815.

Salem N Jr, Litman B, Kim HY, Gawrisch K (2001) Mechanisms of action of docosahexaenoic acid in the nervous system. Lipids 36:945–959.

Schafe GE, Nadel NV, Sullivan GM, Harris A, LeDoux JE (1999) Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase. Learn Mem 6:97–110.

Schwarzman AL, Gregori L, Vitek MP, Lyubski S, Strittmatter WJ, Enghilde JJ, Bhasin R, Silverman J, Weisgraber KH, Coyle PK (1994) Transthyretin sequesters amyloid beta protein and prevents amyloid formation. Proc Natl Acad Sci U S A 91:8368–8372.

Selcher JC, Atkins CM, Trzaskos JM, Paylor R, Sweatt JD (1999) A necessity for MAP kinase activation in mammalian spatial learning. Learn Mem 6:478–490.

Shen HM, Lin Y, Choksi S, Tran J, Jin T, Chang L, Karin M, Zhang J, Liu ZG (2004) Essential roles of receptor-interacting protein and TRAF2 in oxidative stress-induced cell death. Mol Cell Biol 24:5914–5922.

Shukitt-Hale B, Galli R, Meterko V, Carey A, Bielinski D, McGhie T, Joseph JA (2005) Dietary supplementation with fruit polyphenolics ameliorates age-related deficits in behavior and neuronal markers of inflammation and oxidative stress. AGE 27:49–57.

Shukitt-Hale B, Carey A, Simon L, Mark DA, Joseph JA (2006a) The effects of Concord grape juice on cognitive and motor deficits in aging. Nutrition 22:295–302.

Shukitt-Hale B, Cheng V, Bielinski D, Carey AN, Lau FC, Seeram NP, Heber D, Joseph JA (2006b) Differential brain regional specificity to blueberry and strawberry polyphenols in improved motor and cognitive function in aged rats. Soc Neurosci Abstr 32:81.15.

Shukitt-Hale B, Lau FC, Carey AN, Galli RL, Spangler EL, Ingram DK, Joseph JA (2008a) Blueberry polyphenols prevent kainic acid-induced decrements in cognition and alter inflammatory gene expression in rat hippocampus. Nutr Neurosci 11:172–182.

Shukitt-Hale B, Lau FC, Joseph JA (2008b) Berry fruit supplementation and the aging brain. J Agric Food Chem 56:636–641.

Shukitt-Hale B, Cheng V, Joseph JA (2009) Effects of blackberries on motor and cognitive function in aged rats. Nutr Neurosci 12:135–140.

Sinclair DA (2005) Toward a unified theory of caloric restriction and longevity regulation. Mech Ageing Dev 126:987–1002.

Siwak-Tapp CT, Head E, Muggenburg BA, Milgram NW, Cotman CW (2008) Region specific neuron loss in the aged canine hippocampus is reduced by enrichment. Neurobiol Aging 29:39–50.

Smith CD, Carney JM, Starke-Reed PE, Oliver CN, Stadtman ER, Floyd RA, Markesbery WR (1991) Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease. Proc Natl Acad Sci U S A 88:10540–10543.

Spencer JP, Jenner P, Daniel SE, Lees AJ, Marsden DC, Halliwell B (1998) Conjugates of catecholamines with cysteine and GSH in Parkinson's disease: possible mechanisms of formation involving reactive oxygen species. J Neurochem 71:2112–2122.

Stanner SA, Hughes J, Kelly CN, Buttriss J (2004) A review of the epidemiological evidence for the 'antioxidant hypothesis'. Public Health Nutr 7:407–422.

Stillwell W, Shaikh SR, Zerouga M, Siddiqui R, Wassall SR (2005) Docosahexaenoic acid affects cell signaling by altering lipid rafts. Reprod Nutr Dev 45:559–579.

Sultana R, Perluigi M, Butterfield DA (2006) Protein oxidation and lipid peroxidation in brain of subjects with Alzheimer's disease: insights into mechanism of neurodegeneration from redox proteomics. Antioxid Redox Signal 8:2021–2037.

Venkatachalam M, Sathe SK (2006) Chemical composition of selected edible nut seeds. J Agric Food Chem 54:4705–4714.

Weindruch R, Sohal RS (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. N Engl J Med 337:986–994.

Weindruch R, Walford RL (1998) The retardation of aging and disease by dietary restriction. Springfield, IL: Charles C. Thomas.

Willis LM, Shukitt-Hale B, Cheng V, Joseph JA (2009) Dose-dependent effects of walnuts on motor and cognitive function in aged rats. Br J Nutr 101:1140–1144.

Youdim KA, Shukitt-Hale B, Martin A, Wang H, Denisova N, Bickford PC, Joseph JA (2000) Short-term dietary supplementation of blueberry polyphenolics: beneficial effects on aging brain performance and peripheral tissue function. Nutr Neurosci 3:383–397.

Yu BP (1994) Cellular defenses against damage from reactive oxygen species [published erratum appears in Physiol Rev 1995 Jan;75(1):preceding 1]. Physiol Rev 74:139–162.

Yurko-Mauro K, McCarthy D, Bailey-Hall E, Nelson EB, Blackwell A (2009) Results of the MIDAS trial: effects of docosahexaenoic acid on physiological and safety parameters in age-related cognitive decline. Paper presented at Alzheimer's Association International Conference on Alzheimer's Disease, Vienna, July.

Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC (2004) Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 61:82–88.