



The influence of vitamins E and C and exercise on brain aging



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ARTICLE INFO

Article history:

Received 30 September 2016
Received in revised form 1 December 2016
Accepted 7 December 2016
Available online 9 December 2016

Keywords:

Exercise
Antioxidants
Brain function
Vitamin E
Vitamin C
Aging
Cognition
Motor function

ABSTRACT

Age-related declines in motor and cognitive function have been associated with increases in oxidative stress. Accordingly, interventions capable of reducing the oxidative burden would be capable of preventing or reducing functional declines occurring during aging. Popular interventions such as antioxidant intake and moderate exercise are often recommended to attain healthy aging and have the capacity to alter redox burden. This review is intended to summarize the outcomes of antioxidant supplementation (more specifically of vitamins C and E) and exercise training on motor and cognitive declines during aging, and on measures of oxidative stress. Additionally, we will address whether co-implementation of these two types of interventions can potentially further their individual benefits. Together, these studies highlight the importance of using translationally-relevant parameters for interventions and to study their combined outcomes on healthy brain aging.

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1. Introduction

Aging is associated with a decline in neurophysiological functions including but not limited to motor coordination and activity, memory, cognitive flexibility, and problem-solving ability (Rusinek et al., 2003; Seidler, 2006; Seidler et al., 2010). While the underlying mechanisms associated with declining motor and cognitive function remain unclear, it is known that the brain is particularly vulnerable to oxidative stress due to its high aerobic metabolism rate, abundance of redox modifiable substrates like iron and polyunsaturated fatty acids, relatively low antioxidant capacity, and limited cell turnover and neuroplasticity (Evans, 1993; Klempin and Kempermann, 2007). While some controversy has emerged (Perez et al., 2009), the oxidative stress theory remains an active explanation of the mechanisms underlying aging processes in multiple species and systems (Ferguson and Bridge, 2016; Huang et al., 2015; Sohal and Forster, 2014). In humans and in rodents, studies have provided evidence of increased oxidative stress and oxidative damage in the aging brain (Grimm et al., 2011; Perluigi et al., 2010), and that damage accumulation varied in different regions of the brain (Dubey et al., 1996). Furthermore, protein oxidative damage in the cerebral cortex and in the cerebellum of old mice was found to vary directly with the severity of their cognitive (water maze acquisition) and motor (bridge walking) impairments, respectively (Forster et al., 1996). More recent experiments have used shifts in the redox state of glutathione

(GSH:GSSG; reduced glutathione:oxidized glutathione) as a more sensitive indicator of cellular oxidative stress (Sohal and Orr, 2012), and have indicated progressive pro-oxidizing shifts in several brain regions that began as early as 6 months of age (Rebrin et al., 2007). This degree of pro-oxidizing shift seems sufficient to produce redox-dependent cellular dysfunction (Droge and Schipper, 2007), leading to age-related declines in brain function.

According to this hypothesized mechanism, an intervention capable of reducing the oxidative burden or the pro-oxidizing shift would also prevent or delay age-related functional deficits. One dietary intervention that has received extensive scrutiny over several decades and has been shown to reduce oxidative stress and improve brain function is caloric restriction (CR). While these observations have been extensively found in rodents and other species (Dubey et al., 1996; Ingram, 1991), the benefits of CR remain contradictory in humans and non-human primates (Gillette-Guyonnet et al., 2013; Ingram et al., 2007). Additional studies of CR in humans and non-human primates are undergoing and are needed to fully determine the efficacy of CR to improve brain aging. Whereas CR is a promising intervention, its practicality and popularity remain questionable and has led researchers to seek out alternate strategies, such as other lifestyle changes, to improve brain function during aging. Popular interventions such as antioxidant intake and moderate exercise are often recommended to attain healthy brain aging. Both types of intervention have the ability through both shared and independent mechanisms to reduce oxidative stress and improve brain function.

While many antioxidants have been studied, this review will focus primarily on vitamins C and E, as they are readily available, affordable,

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frequently taken as supplements and have been used, alone or in combination, in many studies of brain aging. Furthermore, they have other advantages when used together: (i) they each protect a different cellular fraction (membrane vs. cytosol), and (ii) there exists a recycling mechanism in which oxidized vitamin E is reduced by vitamin C. The effects of moderate exercise on age-related declines in motor and cognitive function will also be described. Finally, this review will highlight the current findings on the outcomes of combining antioxidant intake with moderate exercise and whether precautions should be taken when implementing interventions to delay age-related declines in motor and cognitive function.

2. Antioxidant intake and moderate exercise as interventions against brain aging

2.1. Single antioxidant supplementation

Vitamin E, or α -tocopherol (the most commonly used form), is the most potent antioxidant found in the cellular membrane capable of stopping the propagation of lipid peroxidation, and has been shown to accumulate in brain tissues upon supplementation (Sumien et al., 2003). Over the years, studies of vitamin E supplementation have led to the overall conclusion that vitamin E alone does not infer much protection against brain aging and neurodegenerative diseases. However, it is important to highlight that differences in studies may explain the disparities in outcomes, and the lack of translation in randomized clinical trials (RCTs). In rodents, differential outcomes may be explained by the use of different isoforms of α -tocopherol (synthetic (Sumien et al., 2004) vs. natural (Shetty et al., 2014)), and by the age at which the supplementation was started. Indeed, when vitamin E is introduced in younger subjects and maintained into advanced age, improvements in cognitive and motor performance as well as decrease in oxidative stress were observed (Joseph et al., 1998); however senescence-initiated vitamin E supplementation did not reverse oxidative damage or improve brain function (Sumien et al., 2004). In human studies, the outcomes of vitamin E supplementation were also disappointing with little to no effect reported in RCTs (Gilgun-Sherki et al., 2001). However, with advancement in the understanding of the biochemistry and roles of vitamin E (Joshi and Pratico, 2012), along with reconsidering basic interventional studies parameters (use of translational relevance in setting dosage and timing), more studies will be needed prior to reaching a final conclusion on the usability of vitamin E to improve brain function.

Vitamin C, or ascorbic acid, a potent water-soluble antioxidant found in the cytosol, is responsible for quenching different types of radicals, has the capability to regenerate other antioxidants such as vitamin E and glutathione, and is highly concentrated in the brain (Harrison et al., 2014). Studies on the effects of vitamin C on oxidative stress and brain function in aging and neurodegenerative diseases have also led to inconclusive data on its suitability as an intervention to delay age-related decline in brain function. In rodents, studies have suggested that ascorbic acid supplementation can facilitate learning and memory in old mice (Arzi et al., 2004), and models of Alzheimer's disease (Harrison et al., 2009a; Harrison et al., 2009b). While ascorbic acid's role as an antioxidant has been under scrutiny due to its potential to become a pro-oxidant by means of the Fenton reaction in the presence of metal ions, *in vivo* studies have vastly supported an antioxidant role (Carr and Frei, 1999; Halliwell, 1996). Animal and human studies have supported that a deficiency in ascorbic acid was associated with increased oxidative stress (Harrison et al., 2014). Epidemiological studies remain inconclusive on whether dietary intake might affect cognitive status, with some studies showing delay in development of Alzheimer's disease and others reported no effect. The inconclusive nature of these studies is in part due to the unreliability of the vitamin C intake reports, as most are self-reported and do not reflect lifetime dietary habits, and might be affected by recall ability which is diminished by age and presence of neurodegenerative diseases (Harrison et al., 2014). Further

studies on the association of ascorbic acid with cognitive and motor status will require more reliable measurements of vitamin C intake, such as plasma and cerebrospinal fluid (CSF) levels. CSF:plasma ratio has been predictive of cognitive declines in Alzheimer's disease patients, and more research will be needed to determine the factors influencing the brain's capacity to keep this ratio high and delay functional declines (Bowman, 2012).

Whereas results with individual antioxidant compounds have been relatively disappointing, supplementation involving multiple antioxidants or antioxidant-rich food has consistently yielded positive outcomes (Joseph et al., 2009; Willis et al., 2009). Even combinations of just two or three antioxidants have led to increased beneficial outcomes on learning and to decreased oxidative stress (McDonald et al., 2005; Shetty et al., 2014) when compared to each antioxidant alone. The basic rationale for combining vitamin E and vitamin C stems from their different mechanisms and loci of action, and their interaction within a redox network. Alpha-tocopherol (vitamin E) is found in all biological membranes and is involved in a chain-breaking mechanism to prevent further lipid peroxidation by scavenging peroxy radicals. In the process, α -tocopherol becomes oxidized to α -tocopheroxyl radical, which can in turn become very damaging. Based on redox potential and availability of the radical located at the membrane water interface, ascorbate, a lipophilic co-antioxidant, can reduce back the tocopheroxyl radical to tocopherol. Ascorbate is then oxidized and is recycled with the help of enzyme systems using NADH or NADPH (Buettner, 1993). The plasma concentrations of vitamins C and E, along with other antioxidants, were found to be depleted in patients with mild cognitive impairments and with Alzheimer's disease (Rinaldi et al., 2003). In rodents, the combination of vitamins C and E has been shown to prevent homocysteine-induced functional impairments (Reis et al., 2002), to reduce age-associated impairments in cognitive function (Arzi et al., 2004), to decrease oxidative stress in the brain of old diabetic rats (Naziroglu et al., 2011), and to protect against intermittent cold exposure-induced oxidative stress in the hypothalamus and cortex of old rats (Asha Devi and Manjula, 2014; Asha Devi et al., 2012). While these studies demonstrated that the combination of the two vitamins is effective in improving brain function and decreasing oxidative stress, most do not systematically compare the stand alone intervention with their combination and therefore do not provide evidence of an additive or synergistic effect. More studies are needed to determine the nature of the interactions between antioxidants on cellular redox state and resulting brain function during aging.

2.2. Physical exercise

The World Health Organization has recommended that older individuals exercise for at least 150 min at moderate intensity or 75 min at vigorous intensity per week to obtain overall health benefits (WHO, 2012). More recently, attention has shifted toward its potential to offer protection against motor and cognitive declines associated with aging. Rodent studies have consistently shown that motor and cognitive declines can be delayed or reversed with regular physical activity. In rodents, exercise has been associated with enhanced muscular function, increased strength, delayed age-related muscular decline, improved cognitive function (Boveris and Navarro, 2008; Merritt and Rhodes, 2015), and enhanced neural plasticity (Cotman et al., 2007). Meta-analyses on exercise outcomes have suggested that endurance and/or strength training improve physical and cognitive functions in elderly adults (Heyn et al., 2004, 2008). Other studies have associated hippocampal plasticity and reversal of the age-related loss of hippocampal volume with exercise training (Duzel et al., 2016; Erickson et al., 2011). Whereas high individual variations are inherent to the response to exercise, most studies have reported that exercise can attenuate motor and cognitive declines associated with aging and dementia (Ahlskog et al., 2011; Kramer et al., 2006; Lautenschlager et al., 2012). While most of these studies have focused on aerobic training, other

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