Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: informahealthcare.com/journals/iern20

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To cite this article: Shibu M Poulose, Amanda N Carey & Barbara Shukitt-Hale (2012) Improving brain signaling in aging: could berries be the answer?, Expert Review of Neurotherapeutics, 12:8, 887-889, DOI: 10.1586/ern.12.86

To link to this article: https://doi.org/10.1586/ern.12.86

Published online: 09 Jan 2014.

Improving brain signaling in aging: could berries be the answer?

Expert Rev. Neurother. 12(8), 887–889 (2012)

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"…as the incidences of neurological diseases are skyrocketing in tandem with the economic burden of long-term care for the elderly, interest in the aging brain is growing."

As the lifespan of humans is increasing, the quest for 'healthy aging' is increasingly becoming a focus of the media and people. This trend is important, as the population of people older than 65 years worldwide is expected to triple by the mid-century [1]. Although healthy aging may have previously been regarded as preventing wrinkles or reducing heart disease risk, as the incidences of neurological diseases are skyrocketing in tandem with the economic burden of long-term care for the elderly, interest in the aging brain is growing. Dementia is one consequence of brain aging, with concomitant behavioral deficits in motor and cognitive function. Therefore, there is a need to improve neuronal communication in the brain in aging, which is habitually destabilized by enhanced oxidative stress, inflammation and toxic protein accumulation. These factors can ultimately lead to death of neurons, disease pathologies and behavioral deficits.

Neurodegeneration is highly debilitating in nature, and the underlying brain pathology may go undetected prior to the presentation of symptoms or diagnosis [2]. Even with significant advancement in many areas of neuroscience, we are far away from a therapeutic remedy to impede or cease the root causes of age-related neurological decline and pathological disease. Much of the research pertaining to combating age-related neurological dysfunction focuses on treatment after disease onset, but fewer studies have focused on preventative measures. One of the preventative strategies that has been gaining support over the past decade is boosting the brain's endogenous defenses through supplementation with phytochemical-rich fruits and vegetables.

The loss of brain function with advancing age, at least in part, has been attributed to waning protective neuronal signaling that normally thwarts damage to brain cell structures and function [3]. The interaction between oxidative stress and damage to neural structures has been well documented. As the brain consumes more than one-fifth of total oxygen in the body and accounts for more than 20% of the metabolic rate, the environment is conducive to the generation of reactive oxygen and/or nitrogen species [4]. The shift in equilibrium toward a greater amount of reactive oxygen and/or nitrogen species production than endogenous antioxidant defenses in the brain has been reported to induce alterations in the membrane microenvironment by increasing oxidation of proteins and lipids, altered calcium buffering, accumulation of damaged organelles and protein structures, reduced neurotransmitter release and dystrophy and death of neurons [3,5]. Inflammatory response by innate immune cells such as glia is also thought to be a key player in age-related brain pathology. Glial cell activation is the hallmark of inflammation in the brain; these cells release inflammatory molecules such as growth factors, complement proteins and proinflammatory cytokines such as IL-1, IL-6 and TNF-α [6]. The question is: can berries directly or indirectly improve protective signaling in the brain?

Colorful fruits such as blueberries, strawberries, raspberries and blackberries

Keywords: aging • berry • cognition • flavonoids • fruit • signaling

EXPERT REVIEWS

  ISSN 1473-7175

have been shown to contain countless phytochemicals, which are produced by plants for self-defense to thwart pests and diseases, and possess powerful antioxidant and anti-inflammatory properties [5]. Berries are packed with various phytochemicals, but the most notable is a large class of polyphenols, of which phenolic acids and flavonoids are members, which are potent antioxidant/anti-inflammatory substances in nature. A subset of flavonoids, called anthocyanidins, not only has the potency to discharge or negate free radical effects in the brain, but also has been demonstrated to affect intraneural signaling [3] and inhibit lipid peroxidation and the inflammatory mediators COX-1 and 2 [7]. Flavonoids are also known to be involved in the transcriptional regulation of antioxidant enzymes related to glutathione synthesis and/or glutathione, mediated via ERK1 and 2 [8]. It has been well established that ERK plays a critical role in diverse forms of memory, such as contextual fear conditioning, long-term potentiation, striatum-dependent learning and memory, hippocampus-dependent spatial memory, inhibitory avoidance and increased neurogenesis [9–11]. In addition, the brains of aged rats fed a blueberry-supplemented diet showed increases in carbachol-stimulated GTPase activity in the striatum and improved G protein–muscarinic receptor coupling/uncoupling, an indicator of muscarinic receptor function and subsequent cognitive performance [12]. All the emerging evidence converges at the transcriptional level, indicating that the effects of these phytochemicals are beyond their traditional antioxidant activities [3,5,13]. It appears that berry fruits can have a multiplicity of significant effects on signaling cascades. Now the question is: can these berry-induced alterations observed at the cellular level translate into the prevention of age-related behavioral decline?

> "One of the preventative strategies that has been gaining support over the past decade is boosting the brain's endogenous defenses through supplementation with phytochemical-rich fruits and vegetables."

Much of this research has been accomplished in aging animals or animal models of neurological disease. Dietary supplementation with berries improves motor, memory and cognitive functions with age. Experiments in our laboratory showed that aged rats, maintained for 2 months on a diet supplemented with 2% blueberry, strawberry or blackberry, displayed improved spatial memory in the Morris water maze (a cognitive test in which rats repeatedly locate a submerged platform in a pool of opaque water) [12,14,15]. A 4-month supplementation of diet with blueberry has also been shown to enhance novel object recognition memory and decrease NF-κB, a transcription factor indicative of oxidative stress, in aged rats [16]. In mice, blueberry intake improved memory retention in a step-down passive avoidance task [17]. Furthermore, young rats that consumed a diet containing 2% blueberry for 8 weeks were protected from bilateral microinfusion of a neurotoxin (kainic acid) into the CA3 region of the hippocampus on subsequent performance in the Morris water maze. The brains of the rats fed the berry diet demonstrated increases in the expression of the neuroprotective trophic factor IGF-1, suggesting berries are potent regulators of brain signaling that is correlated to enhancements in cognitive function [18]. Berries have been successful at allaying age-related cognitive decline in rodent models; however, this leaves us with the question: can berries prevent age-associated decline in human brain function?

Data compiled from an array of studies indicate that the polyphenols present in brightly colorful fruits like berries may forestall the onset of dementia and improve memory indices in humans [19], but this has only recently been investigated. Blueberries and strawberries have been shown to counteract peripheral proinflammatory signaling, which may mitigate risk factors for neurodegeneration [20,21]. Moreover, participants with age-related mild cognitive impairment who consumed blueberry juice for 12 weeks showed improved performance on a word recall task and the Verbal Paired Associates Test [22].

> "Berries have been successful at allaying age-related cognitive decline in rodent models; however, this leaves us with the question: can berries prevent age-associated decline in human brain function?"

Evidence on the capacity of dietary berry fruits in the prevention of age-related decline in behavior and brain function is accumulating; however, many questions remain unanswered. Currently, researchers possess an incomplete picture of the bioavailability of different phytochemical components in berry fruits. Furthermore, the most efficacious intake levels and the optimal duration of consumption to prevent or allay age-related cognitive decline in humans have yet to be determined. Future research also needs to identify critical periods during which berry consumption is most effective and the longevity of the beneficial effects, in addition to transitioning preclinical evidence into human studies. As the population begins to focus more on ways to 'age healthfully,' prevention becomes key. Dietary intervention with berry fruits is a promising avenue for further research, but many questions remain to be answered before we can draw a definitive conclusion about the extent to which their consumption can protect the aging brain.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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