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Research report

# Voluntary wheel running, but not a diet containing (−)-epigallocatechin-3-gallate and β-alanine, improves learning, memory and hippocampal neurogenesis in aged mice

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## HIGHLIGHTS

- Old mice were fed EGCG and β-alanine with or without exercise for 40 days.
- We examined changes in behavioral learning and memory.
- We measured brain oxidative stress, gene expression and hippocampal neurogenesis.
- We found that exercise, but not diet, improved memory and neurogenesis.
- EGCG and β-alanine reduced oxidative stress in the brain.

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## ABSTRACT

Aging is associated with impaired learning and memory accompanied by reductions in adult hippocampal neurogenesis and brain expression of neurotrophic factors among other processes. Epigallocatechin-3-gallate (EGCG, a green tea catechin), β-alanine (β-ala, the precursor of carnosine), and exercise have independently been shown to be neuroprotective and to reduce inflammation and oxidative stress in the central nervous system. We hypothesized that EGCG, β-ala supplementation or exercise alone would improve learning and memory and increase neurogenesis in aged mice, and the combined intervention would be better than either treatment alone. Male Balb/cByJ mice (19 months) were given AIN-93M diet with or without EGCG (182 mg/kg/d) and β-ala (417 mg/kg/d). Half of the mice were given access to a running wheel (VWR). The first 10 days, animals received 50 mg/kg bromodeoxyuridine (BrdU) daily. After 28 days, learning and memory was assessed by Morris water maze (MWM) and contextual fear conditioning (CFC). Brains were collected for immunohistochemical detection of BrdU and quantitative mRNA expression in the hippocampus. VWR increased the number of BrdU cells in the dentate gyrus, increased expression of brain-derived neurotrophic factor, decreased expression of the inflammatory cytokine interleukin-1β, and improved performance in the MWM and CFC tests. The dietary intervention reduced brain oxidative stress as measured by 4-hydroxynonenal in the cerebellum, but had no effect on

*Abbreviations:* 4-HNE, 4-hydroxynonenal; β-ala, beta-alanine; CFC, contextual fear conditioning; EGCG, epigallocatechin gallate; MWM, Morris water maze; TLDA, TaqMan low density array; VWR, voluntary wheel running.

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BrdU labeling or behavioral performance. These results suggest that exercise, but not a diet containing EGCG and β-ala, exhibit pro-cognitive effects in aged mice when given at these doses in this relatively short time frame.

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## 1. Introduction

The percentage of the population 60 years of age and older is rapidly growing worldwide [1] (United Nations 2012) and therefore, research investigating therapeutic interventions to combat aging-related pathological changes in the brain has garnered high interest [2–4]. Deterioration of brain function is a consequence of normal aging leading to cognitive impairments that are independent of disease [5–7]. In particular, the functional integrity of the hippocampus is vulnerable to the aging process impacting learning and memory in various animal models and in humans [8–11]. During aging, pathological changes in the brain include increased production of pro-inflammatory cytokines and higher levels of oxidative stress that, in turn, can precipitate a decrease in adult hippocampal neurogenesis and decline in learning and memory. Down regulation of neurotrophic factors, most notably brain-derived neurotrophic factor (BDNF), has been linked to cognitive decline and the age-related decrease in neurogenesis [12–16]. BDNF plays a critical role in synaptic plasticity, learning and memory [17] and promotes hippocampal neuron survival and differentiation [18–20]. The complex interaction of increased pro-inflammatory cytokines, increased oxidative stress, decreased neurotrophin expression and decreased neurogenesis promotes a microenvironment conducive to age-related cognitive decline.

Green tea, a polyphenol-rich beverage has drawn much attention due to its health benefits in cardiovascular disease, diabetes, inflammatory diseases, and its prevention and treatment of cancer [21]. Green tea is rich in flavonoids and contains many catechins, including (−)-epigallocatechin-3-gallate (EGCG), which is the most abundant (~60%) catechin in green tea [22]. Green tea consumption is related to lower prevalence of cognitive impairment in aged humans [23] and, in animals, tea catechins increase adult neurogenesis perhaps by reducing neuroinflammation [24–27]. EGCG reduces microglia activation [24,28], oxidative stress [29,30], and inflammation [31]. Based on these observations, catechins from green tea are thought to act as a general neuroprotective factor helping to prevent neurodegenerative diseases [29].

β-alanine (β-ala) is the β form of the amino acid alanine and is a precursor molecule for carnosine [32]. β-ala supplementation and subsequent increases in muscle carnosine have been shown to improve muscle function and decrease fatigue in high intensity exercise [33]. β-ala is used as a dietary supplement by athletes for this reason. Less is known about the effect of β-ala on learning or memory. A recent study demonstrated an increase in β-ala in the hippocampus of rats at 5 min and 6 h after a Morris water maze probe trial [34], a finding the authors speculate may indicate a role for β-ala in retrieval of spatial memory. β-ala is thought to act as a neurotransmitter in the hippocampus, is a structural intermediate between established amino acid neurotransmitters glycine and γ-aminobutyric acid (GABA), and is recognized by multiple receptors in the central nervous system (CNS) [32]. However, the exact role of β-ala in the CNS is not presently clear. L-Carnosine, a dipeptide of β-ala and L-histidine, has been studied for its effects on cognition. L-Carnosine supplementation improved cognitive flexibility and efficiency as well as reaction time in schizophrenic patients [35]. It is hypothesized that the CNS effects of L-carnosine supplementation are mediated, at least in part, by its potent anti-oxidant effects [36,37]; a theory supported by the protective role of carnosine against cerebral ischemia in animal models [38,39]. However, as with β-ala, the functional role of L-carnosine in the CNS remains poorly defined.

In contrast, a large body of literature has established that regular exercise increases adult neurogenesis in the hippocampus of mice, and this increase has been related to improved spatial memory in the Morris water maze [40,41], radial arm maze [42], and y-maze [43]. Our group has shown that adult hippocampal neurogenesis is required for exercise-induced improvements in spatial memory, as irradiation-induced reduction in neurogenesis was sufficient to eliminate the positive wheel running effect on performance in the Morris water maze [44]. BDNF is thought to play a major role in the increase in neurogenesis and learning/memory as a result of physical exercise [45,46]. Inhibition of the exercise-induced increase in BDNF action in mice abrogates the exercise-related improvements in spatial memory [47]. Importantly, our recent study in older adults demonstrated an exercise training-induced increase in circulating BDNF concomitant with increases in hippocampal volume and performance on memory tasks [48].

Despite the number of studies that have demonstrated that exercise and dietary supplementation with EGCG or β-ala are beneficial for preventing or recovering age-related deficits individually, no research has been conducted that investigates whether additive or synergistic effects between dietary supplementation with EGCG, β-ala and exercise exist for enhancing age-related cognitive loss and reducing oxidative stress and inflammation in the aged brain. Moreover, most studies have utilized long-term (e.g. 6–7 months) administration [49–53] of catechins as a means of *preventing* age-related cognitive loss. It is unclear whether cognitive loss and age-related hippocampal changes can be *reversed* with short-term supplementation with or without exercise. We hypothesized that exercise supplemented with dietary EGCG and β-ala would reduce neuroinflammation, increase the formation of new cells in the dentate gyrus of the hippocampus and improve performance in tests of spatial learning and memory when compared to each treatment (e.g. exercise or EGCG/β-ala) individually and that all interventions would significantly improve all outcomes relative to untreated aged mice.

## 2. Methods

### 2.1. Animals

For all studies, aged (19 month old) male BALB/cByJ mice were utilized. Retired breeder mice (8–10 months old) were purchased from Jackson Labs (Bar Harbor, ME) and aged in our facility. Upon arrival at our facility, all mice were fed 8640 Teklad 22/5 rodent diet (Harlan Teklad, Indianapolis, IN) and autoclaved water ad libitum. Mice were individually housed in polypropylene cages under a reverse 12-h-light/-dark cycle at 24 °C. All procedures were approved by the University of Illinois Institutional Animal Care and Use Committee.

### 2.2. Diets containing EGCG and β-ala

At the start of the intervention (e.g. 18–19 months old), mice received either a control diet (AIN-93M, Research Diets, New Brunswick, NJ) or an experimental diet containing 1.5 mg Teavigo (90% EGCG, DSM Nutritional Products, Basel, Switzerland) and

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