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Understanding How Exercise Promotes Cognitive Integrity in the Aging Brain

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Abstract

Alterations in the structure and organization of the aging central nervous system (CNS), and associated functional deficits, result in cognitive decline and increase susceptibility to neurodegeneration. Age-related changes to the neurovascular unit (NVU), and their consequences for cerebrovascular function, are implicated as driving cognitive impairment during aging as well as in neurodegenerative disease. The molecular events underlying these effects are incompletely characterized. Similarly, the mechanisms underlying effects of factors that reduce the impact of aging on the brain, such as physical exercise, are also opaque. A study in this issue of *PLOS Biology* links the NVU to cognitive decline in the aging brain and suggests a potential underlying molecular mechanism. Notably, the study further links the protective effects of chronic exercise on cognition to neurovascular integrity during aging.

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Abbreviations: AD, Alzheimer disease; ApoE, apolipoprotein E; BBB, blood–brain barrier; CBF, cerebral blood flow; CNS, central nervous system; NVU, neurovascular unit.

Introduction

Age-associated alterations in the structure and organization of the central nervous system (CNS) result in cognitive impairment [1] and increase susceptibility to individual overt neurodegenerative pathology and clinical disease [2]. Thus, understanding the factors that contribute to age-related changes in structure and function within the CNS may lead to novel approaches to prevent the associated cognitive decline as well as reduce the incidence of neurodegenerative conditions such as Alzheimer disease (AD).

Links between Cerebrovascular Function and Cognitive Function in Aging

Changes in both neuronal and non-neuronal populations within the CNS have been associated with functional deficits in the aging brain. For example, alterations in synaptic morphology and activity of neurons, notably in the hippocampus and prefrontal cortex, have been associated with impairments in cognition during aging [3]. Notably, and perhaps less intuitively, important roles for non-neuronal lineages have also been demonstrated in cognitive decline. Chronic inflammatory changes in resident and invading cells of the innate immune system, such as microglia/monocytes and astrocytes, occur with aging [4] and may predispose to neural pathology in the CNS. In addition, age-related changes to the neurovascular unit (NVU), (Fig 1) and associated cerebrovascular alterations, have also been implicated as impacting neural

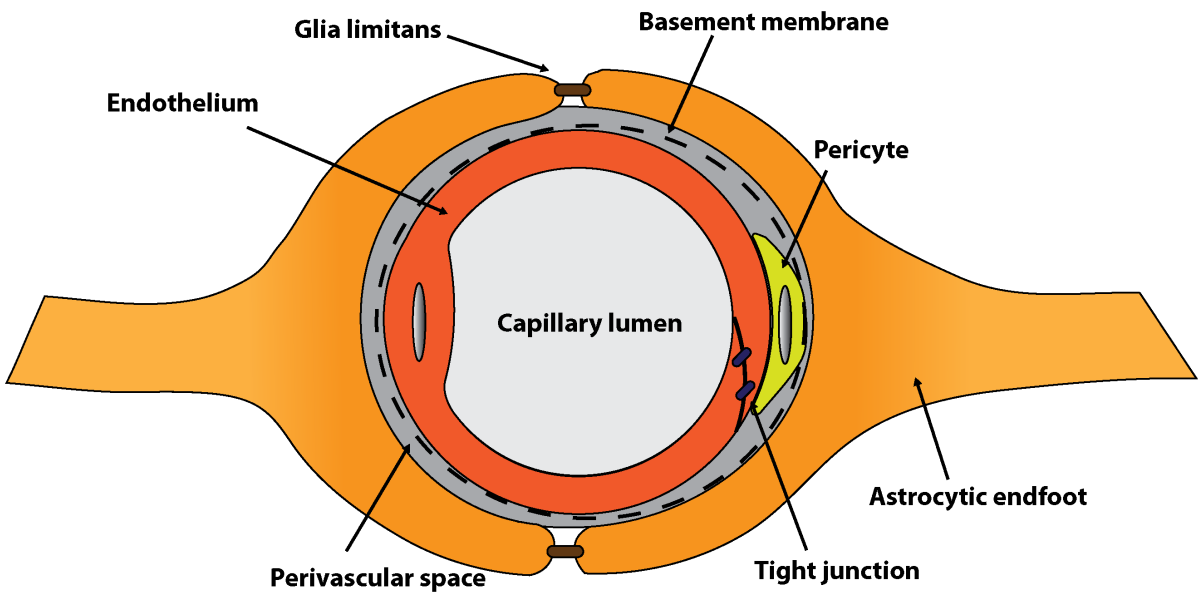

Fig 1. Schematic of the NVU. The NVU comprises the cerebral microvascular endothelium (shown in red), its basement membrane, and associated pericytes (yellow) and astrocytes (orange). The perivascular space exists between the endothelium and astrocytic endfeet. The endothelium provides the structural and functional basis for the blood–brain barrier (BBB), while astrocytes and pericytes control barrier induction and maintenance [7]. Junctional proteins exist between endothelial cells and astrocytes (glia limitans) to help regulate entrance into the CNS parenchyma. *Image credit*: *Gareth R. John & Benjamin M. Laitman*.

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integrity and function [5,6]. However, the relative contribution of alterations of the NVU to these age-related changes in brain structure and function, and the molecular events that drive them, are incompletely characterized. Thus, an important question is how exactly cerebrovascular function, particularly integrity of the NVU, impacts cognitive function during aging. Examination of underlying mechanisms presents an interesting avenue to discover and develop treatments to prevent cognitive decline and/or neurodegeneration.

The NVU comprises the cerebral microvascular endothelium, its basement membrane, and associated pericytes and astrocytes [7,8] (Fig 1). The endothelium provides the structural and functional basis for the blood–brain barrier (BBB), while astrocytes and pericytes control barrier induction and maintenance [7,8]. Notably, defects in the NVU have been linked to cognitive decline in the context of neurodegenerative conditions. For example, vascular defects in mice deficient for the AD risk factor, apolipoprotein E (ApoE), or transgenic for the human *APOE4* isoform, display vascular defects that precede neuronal dysfunction [9]. Furthermore, human *APOE4* carriers may be susceptible to age-dependent breakdown of the BBB prior to the onset of clinical AD deterioration [10].

Studies have also linked neurovascular dysfunction to cognitive decline in aging. Cerebral microvascular pathology together with reductions in cerebral blood flow (CBF) and glucose and oxygen metabolism are known to occur during human aging [11]. Moreover, use of a novel high-resolution MRI technique has also shown that vascular leakage is an early event in the aged human brain, beginning in the hippocampus and correlating with cognitive deficit [12]. These studies, and others like them, suggest that changes in the NVU may be significant in driving deterioration in the structure and organization of the CNS, and therefore cognitive deficits, during aging as well as in neurodegenerative disease.

The Mechanism by Which Exercise Impacts the Aging Brain Is Incompletely Understood

Interestingly, the mechanisms underlying effects of factors that reduce the impact of aging on the brain are similarly opaque. A good example is physical exercise, which is strongly associated with protection against age-related decline in cognitive and sensorimotor function [1,13] (Fig 2). Exercise is known to improve cardiovascular function, and blood flow within the CNS, and is associated with improved cognitive, sensory, and motor test outcomes, angiogenesis,

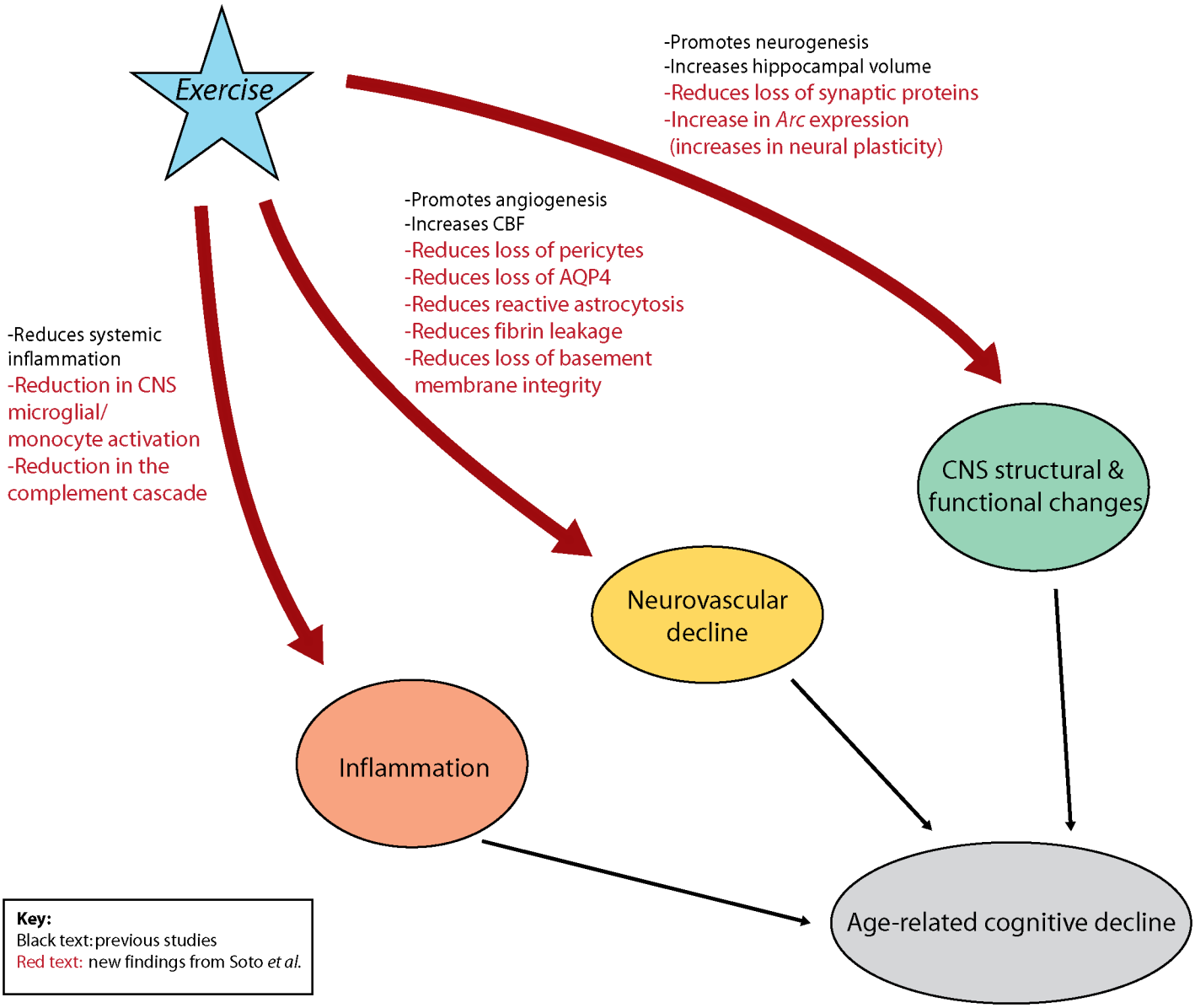

Fig 2. The impacts of exercise on age-related cognitive decline. Three major factors have been implicated in promoting age-related cognitive decline: inflammation, neurovascular changes, and changes in CNS structure and function. Exercise has been shown to be beneficial in impacting these three categories. It has been shown to promote neurogenesis [16], increase CBF and angiogenesis [14], and reduce inflammation [4,17], correlating with improved cognitive performance. Soto et al. adds to this data (red text) by demonstrating that exercise reduces the age-related loss of pericytes, basement membrane components, and astrocyte reactivity at the NVU, and reduces the amount of complement induction in myeloid cells. *Image credit*: *Gareth R. John & Benjamin M. Laitman*.

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and neurogenesis [13–16]. However, the molecular events that drive this protective effect remain incompletely understood.

A study in this issue of *PLOS Biology* by Soto and coauthors builds on these previous findings, linking the NVU to cognitive decline in the aging brain and suggesting a potential underlying molecular mechanism [18]. Notably, the study further links the protective effects of exercise on cognition to neurovascular integrity. The authors present RNA sequencing data from young (4 mo) and aged (21 mo) mice that suggest that aging causes regional compromise of the NVU. They confirm these findings using immunohistochemistry and electron microscopy, which reveals deterioration of neurovascular structures in the aging brain, including basement membrane reduction, loss of pericytes, and astrocyte dysfunction. Importantly, these neurovascular changes result in vascular leakage. Interestingly, these events further correlate with microglial/monocyte activation and complement induction, implicated in age-related cognitive decline in mice [19]. Collectively, these data suggest a connection between neurovascular dysfunction and innate inflammation in the context of cognitive decline in aging. The authors then turn their focus to the long-term impact of aerobic exercise on age-related neurovascular dysfunction. They show that exercise strongly protects against neurovascular decline in aged mice, and that this correlates with improved behavioral outcomes and markers of neuroplasticity and reduced inflammation and complement induction (Fig 2).

What are the molecular mechanisms responsible for these outcomes? Interestingly, the authors' data in the final section of their paper returns us to ground familiar to those in the fields of neurodegeneration and AD. Their findings implicate the AD risk factor ApoE as also regulating neurovascular integrity during aging and, moreover, suggest involvement of ApoE in the protective effects of exercise. They show that astrocytic ApoE decreases in aged mice concomitant with age-related neurovascular decline and complement activation, and that this effect is prevented by exercise. These data extend previous studies showing that ApoE deficiency in mice leads to progressive age-related neurovascular dysfunction [9,20,21] and suggest a potential link between astrocytic ApoE, age-related neurovascular dysfunction, and microglial/monocyte activation. To test this hypothesis, the authors examine the effect of regular exercise from life to old age on ApoE-deficient mice. Importantly, In contrast to wild-type mice, they show that exercise has no effect on age-related neurovascular decline or microglia/monocyte activation in the absence of ApoE.

Future Directions

Collectively, the findings presented by Soto et al. connect the NVU to cognitive decline in the aging brain and suggest that exercise can prevent or attenuate age-related indices of both neurovascular decline and inflammation. They further propose that the beneficial effects of exercise on neurovascular integrity and inflammation, and neuroplasticity, may be mediated at least in part by ApoE. How then might these findings be extended, and what might be the logical next steps in the current work? Several interesting questions spring to mind, some of which are discussed by the authors. For example, do the increases in microglia/monocytes seen in aging mice in the current study occur as a result of proliferation of resident microglia, infiltration of peripheral monocytes, or both? How do these responses impact cognitive function during aging, given that increase of proinflammatory markers in the blood is correlated with poor cognitive performance in older adults? And does complement induction seen in aged mice precede neurovascular decline, or occur as a consequence to it?

An additional point that should be addressed is how this work extends to age-related cognitive decline in humans. While several studies, including Soto et al., provide encouraging evidence of the positive effects of exercise on age-related cognitive decline, findings in humans

have been inconsistent. In a study that examined a combination of dietary changes and aerobic exercise, the authors found exercise only improved cognition when combined with a high flavanol diet [22]. Unexpectedly, the exercise program alone failed to improve cognition. While this same research group has previously demonstrated exercise to be beneficial for human cognitive tasks [16], the authors bring up the possibility that the exercise regimen used in their diet-exercise study was not stringent enough for the older population investigated. The benefit of exercise on age-related cognitive decline is still inconsistent in humans, even if it strongly protects against the cognitive decline in aged rodents. More robust studies in human populations are thus warranted.

However, perhaps the most important questions that the current study suggests are those that are more directly translational. Notably, what is the detailed molecular mechanism of action by which ApoE preserves neurovascular integrity and cognitive function in the aging brain, and can we develop targeted therapies based on those results? Based on recent studies, might neurovascular and cognitive decline in the brain be reduced by pharmacologically targeting the cyclophilin A-nuclear factor κB-matrix metalloproteinase-9 axis, as has been proposed for *APOE4*-mediated neurovascular injury [9]? Furthermore, as noted by the authors, the constitutive ApoE-deficient mice used in the manuscript already displayed a dysfunctional NVU prior to the start of exercise studies, in contrast to wild-type mice. Thus, it would be interesting to repeat these studies using an inducible conditional allele. This may answer the question of whether, in addition to protecting against neurovascular dysfunction in aging mice, exercise might be used as an intervention to repair (or restore) existing neurovascular breakdown. Such findings could be translationally useful, in the prevention or amelioration of age-related and pathologic cognitive decline in the growing geriatric population.

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