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Editorial

Special Issue: Peripheral Factors and Neural Plasticity

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There is accumulating evidence that exercise improves brain function and may delay or prevent the onset neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Studies in humans show that physical activity can enhance or maintain gray and white matter volume, improve cerebral blood flow, cognition and mood. In rodent models, voluntary wheel running as well as forced treadmill training result in upregulation of adult neurogenesis, neurotransmitters, neurotrophins, angiogenesis, mitochondrial biogenesis, especially in the hippocampus a brain area important for learning and memory. In addition, exercise reduces neural oxidative stress and neuroinflammation. Moreover, multiple aspects of memory function in rodents such as spatial navigation, object recognition and pattern separation are enhanced by running [1]. However, the underlying mechanisms remain elusive. In particular, the role of peripheral factors in brain function have only recently begun to be addressed and are the topic of this Special Issue.

Linking the circulation of an aged mouse to that of a young mouse, results in reduced adult neurogenesis, whereas an infusion of plasma derived from exercising young or aged mice into their sedentary counterparts improves adult neurogenesis and memory function [2, 3]. Multiple peripheral organs, including muscle (myokines), liver (hepatokines), adipose tissue (adipokines), bone and gut, secrete factors (e.g., growth factors, cytokines, metabolites, enzymes, exosomes) may mediate neural plasticity. In particular, exercise-induced activation results in the release of molecules that mediate homeostatic adaptation to exercise and affect brain function. At least a dozen peripheral factors have been identified that affect neurotrophin levels, adult neurogenesis, inflammation, synaptic plasticity and memory function. In the coming years likely many more systemic molecules relevant to the brain will be discovered and may provide a basis for novel therapeutic approaches to neurodegenerative diseases [3].

In this Special Issue of *Brain Plasticity* we are very pleased to publish three innovative research papers and five excellent review articles on this important topic. The research articles are focused on two factors that are important for neural plasticity, myokine Cathepsin B (CTSB) [4, 5] and brain-derived neurotrophic factor (BDNF) [6]. The first paper addresses the effects of acute exercise on serum CTSB levels. Previous research showed an elevation of plasma CTSB after 4-6 months of exercise training [4, 5]. The current findings are one of the first to report that high intensity (80% VO2max and VO2max) acute aerobic exercise elevates circulating CTSB in young adults immediately post exercise. The authors also show that human skeletal muscle tissue expresses both message and protein of CTSB and BDNF, and that BDNF is

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highly expressed in glycolytic skeletal muscle fibers [7]. The second research paper also pertains to circulating CTSB. In this study it was found that the latency of event related potentials an electrophysiological correlate of a cognitive task, the Flanker task, was inversely correlated with performance on the task. Thus, this study reports the novel finding that CTSB may play a role in cognitive control by modulating processing speed [8]. The final research paper pertains to effects of moderate-intensity exercise and high-intensity interval exercise on serum BDNF levels and working memory in young adult females. The authors report that both exercise interventions increase serum BDNF levels and benefit memory performance on the backward digit span test of working memory [9].

The five outstanding review articles in the Special Issue cover inter-organ crosstalk between muscle, liver, adipose tissue, the gut microbiome and the brain. The article by Rai and Demontis reviews in great detail the myokines and myometabolites, and other signals that mediate muscle-brain and muscle-retina communication that affect neurogenesis, neurotransmitter synthesis, proteostasis, autophagy, mood, sleep, cognition, feeding behavior following exercise. They also describe their discovery of the amylase Amyrel as a myokine in drosophila, which plays a neuroprotective role in the retina and prevents brain aging. Moreover, the authors raise the possibility of the existence of detrimental myokines resulting from inactivity and muscle disease states, that could become novel focus for therapeutic intervention [10]. The next review paper addresses the issue of biological sex and exercise. The authors provide detailed information pertaining to differences in the biological responses to physical activity in men and women and in their vulnerability to the onset, progression and outcome of neurodegenerative diseases. They suggest that sex-specific regulatory mechanisms might differentially modulate the benefits of exercise, given that muscle gene expression, immune system composition and the anti-inflammatory response to exercise differ between males and females [11]. The third review article, by Formolo and colleagues pertains to the crosstalk between adipose tissue and the brain. Their focus is on an adipocyte secreted hormone, adiponectin, a cytokine that can cross the blood-brain barrier, with anti-inflammatory, -atherosclerotic, -carcinogenic, -depressant, neuroprotective, neurotrophic and pro-cognitive properties. Adiponectin has been shown to improve neuronal function in animal models of obesity, diabetes, and Alzheimer's disease. The authors also describe the beneficial effects on the brain of AdipoRon a synthetic, orally active small molecule that agonizes both adiponectin receptors [12].

The fourth review article, by Guzetta et al., is focused on the accumulating evidence that adult hippocampal neurogenesis can be regulated by gut microbiome. The authors describe lifestyle factors such as stress, diet, environmental enrichment and exercise that are well-known to influence adult hippocampal neurogenesis, and that also affect the composition of the gut microbiome. For instance, a diet that is high in fat and sugars decreases adult neurogenesis, BDNF levels, and hippocampus-dependent behavior in rodents, and this could possibly be mediated via systemic and/or vagus nerve signaling pathways between the gut and brain. The review addresses in detail whether such lifestyle factors which influence both hippocampal neurogenesis and the gut microbiota may be mechanistically linked [13]. The final review article pertains to the effects of exercise and diet on hippocampal BDNF signaling and proposes that harnessing the beneficial effects of this neurotrophin will be an optimal approach to treatment of neurodegenerative conditions [14]. Altogether, we are very pleased to share this exciting Special Issue of *Brain Plasticity* with our readers.

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