RESEARCH HIGHLIGHT

An exercise infusion benefits brain function

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There is increasing evidence that exercise improves brain function and may prevent the onset of neurodegeneration; however, the underlying mechanisms remain unclear. New research by de Miguel et al. in *Nature* shows that runner mouse plasma contains factors, in particular, clusterin, that recapitulate the stimulating effects of exercise on hippocampal cell genesis and memory, and reduce neuroinflammation when administered to sedentary controls.

What if while watching our favorite athletes exert themselves on television or in a stadium, we would be able to reap the benefits of exercise for cognition and mood[1,2] for our own brains. Unfortunately, decades ago, researchers showed that if a rat observes another rat performing activities, it does not acquire the same changes in brain structure and biochemistry as the engaged animal.[3] However, recent research suggests that active participation may not be required if blood is harvested from exercisers and administered to inactive recipients. Evidence provided by de Miguel et al.[4] in an elegant set of experiments, shows that an infusion of plasma derived from running mice (runner plasma, RP) into their sedentary counterparts can confer several of the positive outcomes of physical activity for brain function (Fig. 1).

The effects of exercise on the brain are particularly apparent in the hippocampus, a brain area essential for learning and memory and among the first to be affected by aging and Alzheimer's Disease (AD). In rodents, running increases hippocampal neurogenesis, synaptic plasticity, neurotrophin and neurotransmitter levels, vascularization and reduces neuroinflammation.[1] In humans, physical activity maintains hippocampal volume, may delay or prevent aging-related neurodegeneration and improves memory function.[2] The underlying mechanisms, however, remain under investigation. In particular, the role of peripheral factors in brain function is becoming increasingly apparent. Parabiosis studies between young and aged animals have provided evidence that factors in blood can regulate adult neurogenesis and memory function.[5] During exercise, peripheral organs such as skeletal muscle, adipose tissue, and liver secrete molecules and vesicles into circulation (exerkines) that mediate systemic homeostasis. In recent years, about a dozen exerkines have been identified that may affect neural function, synaptic plasticity and behavior.[6,7]

In the study by de Miguel et al.,[4] RP or control plasma (CP) was collected from mice that were housed with or without a running wheel for four weeks, a timeline consistent with running-induced increases in adult hippocampal neurogenesis.[8] RP was administered to 3-month-old sedentary male C57Bl/6 mice via intra-orbital infusion every three days for 28 days. Upon testing in the Morris water maze and fear conditioning tests, the RP-treated mice displayed improved retention of contextual and spatial memory. In addition, within the hippocampus the number of neural progenitor cells, doublecortin-expressing immature neurons and astrocytes was increased. To begin to understand how RP influences the brain and behavior, the researchers first analyzed changes in hippocampal gene expression. RP treatment resulted in 1952 significantly differentially expressed genes, of which 61% were downregulated (cell migration, adhesion and, most significantly, the inflammatory response) and 39% were upregulated (learning, plasticity, immune system). Moreover, following lipopolysaccharide (LPS) treatment, a mouse model of acute neuroinflammation, treatment with RP was found to reverse LPS-induced changes in hippocampal gene expression.

Using mass spectrometry of CP and RP, the authors found 235 unique proteins across CP and RP; of these, 23 were downregulated and 26 were upregulated in RP. Proteins of the complement and coagulation pathways represented 26% of the significantly changed proteins, including clusterin (CLU), complement factor H (FH), and complement 1 inhibitor (C1INH). In particular, depleting RP of CLU precluded the anti-inflammatory effects observed in LPS-exposed male mice that had undergone RP treatment. CLU has been associated with cell death, cancer and neurodegeneration, but also with proteostasis, cell survival, differentiation and complement inhibition.[9] Secreted CLU in the present study[4] is reportedly derived from the liver and heart, and binds to the receptor LRP8 which is highly expressed in brain endothelial cells (BECs). Indeed, treatment with recombinant CLU in mice exposed to LPS or in AD animals reversed upregulation of twenty overlapping transcripts, relevant to aberrant interferon and cytokine signaling in BECs. These findings are consistent with the role of exercise in sustaining the integrity of the neurovascular unit and blood–brain barrier.[1]

It is of interest that CLU is a Janus-faced molecule, a property it shares with several other exerkines. For instance, IL-6, the first described myokine, is associated with inflammation and appetite regulation.[6] Additionally, in rodents, circulating hepatokine IGF is positively associated with neurogenesis, but reducing IGF in AD is considered neuroprotective and may extend lifespan.[2] Furthermore, myokine Cathepsin B (CTSB) is linked to neurogenesis, and elevated plasma levels are correlated with improved hippocampus-dependent memory in young and aged adults;[10] however, this molecule has also been implicated as a cause of amyloid accumulation and is expressed at high levels in malignancies. Similarly, CLU reportedly is highly expressed in the brains of AD patients and plays a role in cancer proliferation.[9] However, in the current study the role of CLU is consistent with the beneficial effects of exercise on the brain, especially in the reduction of hippocampal neuroinflammation. Moreover, plasma CLU was found to be elevated in elderly humans with cognitive impairment after a six-month exercise intervention[4] and this might be linked to improved memory function. In future

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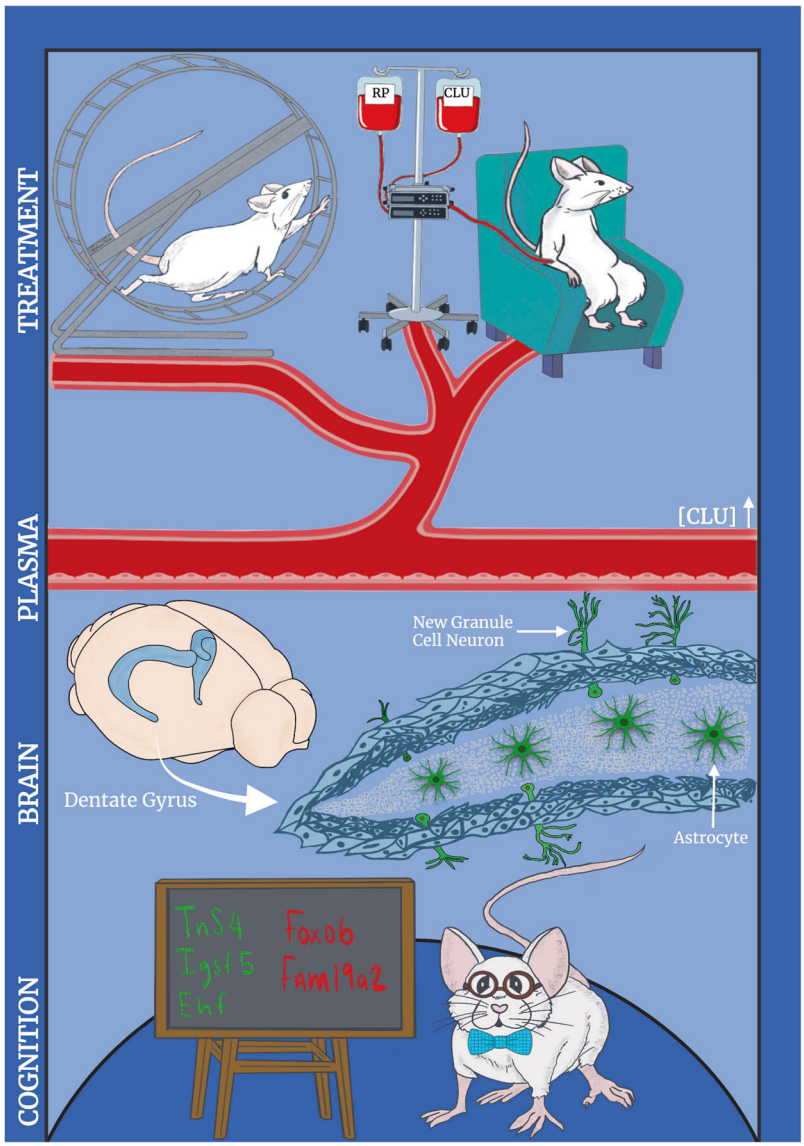

Fig. 1 Effects of runner plasma (RP) on neurogenesis, neuroinflammation and memory. RP administration to sedentary control mice resulted in increased hippocampal neurogenesis and gliogenesis, improved memory retention, and enhanced expression of genes important for learning and memory in the hippocampus. Clusterin (CLU) in RP reduced hippocampal neuroinflammation and may mediate beneficial effects of RP for brain function.

studies it will be important to further understand the complex nature of these exercise molecules so as to harness the potential therapeutic and diagnostic value of their effects on the brain.

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ADDITIONAL INFORMATION

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