Review

Neuroplastic Effect of Exercise Through Astrocytes Activation and Cellular Crosstalk

Fengwu Li1,2, Xiaokun Geng1,3,4*, Ho Jun Yun4, Yazeed Haddad4, Yuhua Chen2, Yuchuan Ding4*

1China-America Institute of Neuroscience, Luhe Hospital, Capital Medical University, Beijing, China.
2Department of Developmental Cell Biology, Key Laboratory of Cell Biology, Ministry of Public Health, and Key Laboratory of Medical Cell Biology, Ministry of Education, China Medical University, Shenyang, China.
3Department of Neurology, Beijing Luhe Hospital, Capital Medical University, China.
4Department of Neurosurgery, Wayne State University School of Medicine, Detroit, MI, USA.

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ABSTRACT: Physical exercise is an effective therapy for neurorehabilitation. Exercise has been shown to induce remodeling and proliferation of astrocyte. Astrocytes potentially affect the recruitment and function of neurons; they could intensify responses of neurons and bring more neurons for the process of neuroplasticity. Interactions between astrocytes, microglia and neurons modulate neuroplasticity and, subsequently, neural circuit function. These cellular interactions promote the number and function of synapses, neurogenesis, and cerebrovascular remodeling. However, the roles and crosstalk of astrocytes with neurons and microglia and any subsequent neuroplastic effects have not been studied extensively in exercise-induced settings. This article discusses the impact of physical exercise on astrocyte proliferation and highlights the interplay between astrocytes, microglia and neurons. The crosstalk between these cells may enhance neuroplasticity, leading to the neuroplastic effects of exercise.

Key words: rehabilitation, neuroplasticity, neuron, microglia, interaction

1. Introduction

Neuroplasticity is a process characterized by enhanced neurogenesis, synaptogenesis, angiogenesis and release of various neurotrophic factors [1]. The brain changes its functional and structural properties of neuroplasticity, which commonly occurs during learning or acquiring new skills. Evidence suggests that physical exercise facilitates neuroplasticity in certain areas of the brain, promoting cognitive and motor functions [2, 3]. Studies have shown potential mechanisms by which exercise could influence neuroplasticity, including neurogenesis, growth factor production, alteration of neuronal excitability and axonal outgrowth [4-6]. For instance, astrocytes exhibit plasticity via changes in their morphology and functional modification in response to stimuli [7]. They play a critical role in recovery from nerve injuries by interacting with blood vessels and microglia [8]. Numerous evidences highlights the roles of astrocytes in neural circuits of developing long-term adaptations under various physiological and pathological conditions [9, 10].

Despite astrocytes being shown to be activated after physical exercise [11], their roles or interactions with neurons and microglia, and any subsequent neuroplasticity have not been extensively studied in exercise-induced settings [11]. Without knowing the...
mechanisms of the exercise-induced neuroplasticity, it still remains challenging to establish optimal exercise programs for rehabilitation [4]. This article reviews the related studies, and provides descriptions outlining the role of astrocytes in exercise settings. Particularly, the interplay between astrocyte, microglia and neuron is emphasized. Understanding the roles of astrocytes in physical exercise and the effects on neuroplasticity could provide opportunities to improve long-term recovery from central nervous system (CNS) injuries.

2. Physical Exercise Enhances Neuroplasticity

Exercise therapy has long been considered a reliable strategy to ameliorate physical disabilities by inducing neuroplasticity [12, 13]. Physical exercise is beneficial for those with neurodegenerative disorders [14] and neurovascular injuries [15], because it improves their behavioral function by promoting blood flow and neurogenesis [16]. Exercise increases the rate of newborn cell numbers, the fraction differentiating into neurons, and the proportion that incorporates into neuronal circuits; these can be beneficial for functional motor outcomes [16]. Physical exercise - particularly balance and coordination movements - facilitates synaptic plasticity and angiogenesis in the brain [17, 18]. Involuntary, voluntary, and forced exercises have been found to induce high expressions of synaptic plasticity molecules, such as postsynaptic density 95 (PSD-95), synapsin I (SYN), and angiogenesis proteins, such as vascular endothelial cell growth factor (VEGF). This upregulation in the hippocampus or cortex surrounding ischemic regions ultimately results in enhanced cognition and better functional rehabilitation [19].

Synaptic plasticity is the capacity of neurons to undergo activity-dependent changes in their intensity and efficacy of synaptic transmission. This process, presumably the major mechanism of neuroplasticity, is responsible for learning and memory as well as development and response of the brain to injuries [20]. Studies involving animals with stroke show increased brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I) and nerve growth factor (NGF) after physical exercise [17, 21, 22]; these factors all contribute to reduction of neurons loss and growth of synaptic connections in multiple brain regions [11]. Physical exercise regulates numerous supporting systems of neuroplasticity, including neurogenesis, synaptogenesis, cerebral metabolism and angiogenesis [23]. Various forms of exercise may be beneficial for neuroplasticity and applied especially for those suffering from cerebrovascular injuries and neurodegenerative disorders [24, 25].

3. Astrocytes Activation and Crosstalk Underlying Exercise-Induced Neuroplasticity

Astrocytes, characterized by their intricate arborization have multiple receptors, transporters, and molecules; this feature enables them to sense neurons [26, 27]. Astrocytes release a variety of molecules at synaptic sites, including glutamate, d-serine, ATP, adenosine, lactate, and other soluble or contact factors that participate in the formation, stabilization, and remodeling of astrocyte-neuron or neuron-neuron crosstalk [28, 29]. Furthermore, astrocytes induce microglial activation and control their cellular functions. This astrocyte-microglia crosstalk is created through the release of a variety of molecules, including neurotransmitters, lipocalin proteins, inflammatory cytokines, and growth factors. It can be concluded that astrocyte activation and interactions in neural circuits after physical exercise can play a critical role in developing functional outcomes and neuroplasticity [30, 31].

3.1 Exercise Induces Astrocytes Activation

Studies have shown that physical exercise stimulates astrocytes proliferation, laying a cellular basis for mediating exercise-induced neurogenesis and improvements in cognitive function [32, 33]. Increasing evidences demonstrate that astrocytes can control the growth and differentiation of adult-born granule cells by releasing various trophic factors and gliotransmitters [34, 35]. In addition, they could supply energy, such as lactate, an essential component for neurogenesis [36]. The proliferation of astrocytes as well as their link to improved behavioral outcomes and neurogenesis may depend on releasing cytokines in GFAP-positive astrocytes, such as BDNF [37].

Astrocytes increase their overall arborization and distal-to-proximal span following continuous exercise [38, 39]. Additionally, astrocytes activated by physical exercise can affect the changes in neural activity by altering messenger RNA transcript expression. The expression of GFAP, thrombospondin 2 (Thbs2), leukemia inhibitory factor (Lif), and interleukin 6 (IL-6) are associated with astrocytes’ function during exercise. Physical exercise activates astrocytic gene expression by transcribing the different mRNA, which ultimately render the differences in astrocytic structure and function [40].

Exercise-induced astrocytic activation is thought to provide vascular protection against cerebral injuries, such as stroke, via vascular remodeling [41, 42]. Moreover, the astrocytic activation diminishes blood-brain barrier (BBB) dysfunction and promotes cerebral angiogenesis [43]. Overall, the aforementioned functions of astrocyte denote its role as a central component to exercise-induced
neuroplasticity in many neurodegenerative and neurovascular disorders.

3.2 Exercise Induces Astroocyte-Neuron Crosstalk

A single astrocyte can be involved in hundreds of thousands of synapses [44]. This morphological feature is critical for the tight functional astrocyte-neuron crosstalk. Astrocytes regulate neurons by maintaining the crosstalk and delivering metabolic substrates to neurons [45]. In fact, physical exercise increases the level of astrocytes in the hippocampus, prefrontal cortex, striatum, and entorhinal cortex, and induces changes in their morphology [46]. These changes produce beneficial effects on neuronal activity and plasticity [39]. For instance, long-term exercise is found to induce the proliferation of astrocytes and improvements in learning and memory [47]. Increasing neural networks can promote brain recovery from cerebral injuries via neuroplasticity; alterations in astrocytes induced by physical exercise may be responsible for this effect [11]. Additionally, astrocytes express a variety of receptors for typical neurotransmitter molecules, including glutamate, acetylcholine, ATP, gamma-aminobutyric acid (GABA), norepinephrine, and release retrograde messengers such as endocannabinoids, which sense neural activity [29]. Neurotrophic factors and lactate are the primary source mediating astrocyte-neuron communication among a variety of molecules [29].

Figure 1. Exercise-induced astrocytes activation and crosstalk with neuron and microglia.
Exercise enhances astrocyte-neuron crosstalk by regulating neurotrophic factors [11], such as IGF-1 and BDNF. Astrocytes derived IGF-1 shows a protective effect on neurons through suppressing oxidative stress. In fact, the activation of IGF-1 by physical exercise initiates the involvement of astrocytes [48, 49]. In addition, physical exercise leads to an upregulation astrocyte expression of BDNF, thereby improving hippocampal neuroplasticity [50]. By acting on these neurotrophic factors derived from astrocyte, physical exercise mediates neural growth, proliferation, and survival, eventually enhancing neuroplasticity in numerous CNS disease [51].

Physical exercise also regulates energy metabolism of astrocytes to modify neuron activity, underlying its mechanism to the astrocyte-neuron crosstalk [52, 53]. Neurons generate energy mainly via oxidative phosphorylation, while astrocytes utilize glycolysis [54]. Lactate oxidation in mitochondria increases oxidative phosphorylation in neurons; lactate derived from astrocytes serves to promote the oxidative phosphorylation [55]. Lactate from astrocytes is delivered to neurons via the astrocyte-neuron lactate shuttle (ANLS) system, which has been reported to supply energy to the brain during physical exercise [56]. Moreover, physical exercise augments the effectiveness of the ANLS by upregulating astrocytic lactate transporter levels [57], suggesting a potential role of exercise in mediating astrocyte-neuron signal pathways. Figure 1 shows numerous ways that astrocytes and neurons interact and how they can impact neuroplasticity.

3.3 Exercise Induces Astrocyte-Microglia Crosstalk

Physical exercise has shown to affect numerous CNS pathologies by regulating astrocytes, microglia and glial activation [58-60]. There is growing evidence demonstrating that glial cells play a multifaceted role in ischemia and neurodegeneration; recent studies explain supportive effects of astrocytes and microglia on neural cell proliferation and survival [61]. Indeed, physical exercise results in increasing activation and crosstalk of microglia and astrocyte [62].

Emerging evidence indicates the bidirectional crosstalk between astrocytes and microglia occurs via their secreted molecules, including neurotransmitters, lipocalin proteins, inflammatory cytokines, and growth factors [63]. The molecular conversation between these cells plays a pivotal role in brain development, functions, and homeostasis [58]. A neurotransmitter, such as BDNF, derived from astrocyte, controls microglial activation, and reduces neurodegeneration [64]. Lipocalin proteins and inflammatory cytokines released from astrocyte regulate neuroplasticity via the relevant receptor-mediated signaling in microglia [65, 66]. Physical exercise mediates the crosstalk between astrocytes and microglia with regulatory effects on these molecules and cytokines to enhance neuroplasticity. Additionally, astrocytes and microglia are found to play beneficial roles in patient outcomes in certain neurological pathologies and even aid in brain development [58]. As Figure 1 illustrates, astrocyte-microglia interaction builds the foundation for the exercise-induced neuroplasticity. Nevertheless, this interplay is complex, thus, any detailed mechanism demands further investigations at this point.

3.4 Exercise Induces Microglia-Neuron Crosstalk

There are reciprocal and bidirectional crosstalk between microglia and neurons. Generally, microglial activation occurs is associated with dysfunctional neurons; physical exercise suppresses this detrimental effect by regulating microglia, neurons and their crosstalk [67, 68]. In addition to their role as an immune sentinel in the brain, microglia express a large variety of neurotransmitter receptors which influences the key microglial functions, such as cytokines production, cellular motility and phagocytosis [69]. Neurons also express receptors that are activated by the molecules from microglia [63]. Physical exercise triggers communications between microglia and neurons through microglial activation, neural regeneration and cytokine secretion. For instance, CD200-CD200R, ATP, and CX3CL1-CX3CL1R interaction pathways are shown to be enhanced by exercise [70, 71].

Microglial activation occurs with dysfunctional neurons. The ability of microglia to engulf dysfunctional neural synapses is impaired in a pathological state [72]. Physical exercise could ameliorate this abnormality by activating neurons whose axons provide synaptic contacts with pyramidal cell dendrites [73]. Current studies indicate the microglia-neuron crosstalk is induced by exercise and plays as an important contributing factor to neuroplasticity as illustrated in Figure 1.
transmission, activities of neurons, and neuroplasticity [75]. Physical exercise could mediate astrocyte activation and astrocyte-neuron crosstalk by regulating glutamate release [52, 78] (Fig. 2). It has been found that physical exercise improves neuroplasticity by increasing the density of GFAP positive astrocytes, glutamine secreted from astrocyte [79], and NMDAR expression in neurons [80]; these changes indicate potential role of astrocyte on regulating neurons and there crosstalk.

**Figure 2. Signal pathway underlying astrocyte-neuron crosstalk**

D-serine, a neurotransmitter released by the astrocytes, has shown to play a role in the classical NMDAR-dependent long-term potentiation (LTP) [81, 82] (Fig. 2). D-serine takes an important part in forms of neuroplasticity by integrating adult-born granule neurons into the hippocampal circuitry, which affects local neural circuit performance in memory processes and mood control [34, 83]. Exercise induces the release of D-Serine from astrocytes, and this may explain the underlying astrocyte-neuron interactions [84].

**Lactate.** Lactate from astrocytes has shown to play a vital role in LTP at neural synaptic sites [85, 86] (Fig. 2). In an active metabolic state, glycogen from astrocytes are converted to lactate and delivered to neurons [85, 87]. Lactate affects neurons in many ways [88, 89]. It activates NMDAR and stimulates neuronal molecules, such as the cell-surface lactate receptor GPR8139-41 [90]. Physical exercise has been reported to increase the astrocyte-neuron metabolic shuttle by upregulating the astrocytic lactate transporter levels to induce neuroplasticity [57]. Exercise increased glutamate concentration and decreased lactate levels hence demonstrating lactate transport from astrocytes to neurons; these studies underly the increasing astrocyte-neuron crosstalk induced by exercise.

**Tumor Necrosis Factor-α (TNFα).** Astrocytes modulate synapses and neuroplasticity with immune mediators that are produced in physiological and pathological inflammatory reactions [91, 92]. For instance, TNFα induces synaptic remodeling by incorporating AMPA receptor subunits in excitatory synapses [93] and influences the neuron activity by regulating the release of glutamate from astrocytes [94] (Fig. 2). Studies indicate physical exercise improves neural function and reduces neuron damage by regulating the activation of astrocytes and release of TNF-α [95]. Therefore, TNFα derived from astrocyte have potency to
mediate neurons and an inflammatory response to be a potential source altering neuroplasticity.

**Figure 3. Signaling pathways underlying astrocyte-microglia crosstalk.**

### 4.2 Signals Pathway Underlying Astrocyte-Microglia Crosstalk

Microglia, the immune cell of the CNS, exert neurotoxic and neuroprotective effects and regulate astroglial function and neuroplasticity [96]. Microglia affect neurotransmissions and appear to be necessary for neuronal reorganization in the adult brain [63]. Microglia build the neuronal network by inducing synapses with astrocytes [58]. Although the interplay between astrocytes and microglia remains unclear, several molecules responsible for the astrocyte-microglia crosstalk have been elucidated in Figure 3.

**Neurotransmitters.** Increasing numbers of studies indicate that targeting the microglia-astrocyte crosstalk has a therapeutic potential [58]. Numerous membrane receptors enable microglia to communicate with astrocytes while mediating neuronal activity and synaptic transmission [97]. For instance, microglia release ATP that could induce astrocytes to release glutamate, indicating the astrocyte-mediated regulation of excitatory neurotransmission [98]. Physical exercise is reported to increase the proportion of anti-inflammatory M2 microglia with induced ATP synthesis [43]. These findings point out a potential role of exercise on astrocyte by regulating microglia release of ATP. Additionally, glial-cell line-derived neurotrophic factor (GDNF), cerebral dopamine neurotrophic factor (CDNF), and BDNF are some of the important astrocyte molecules that are involved in the modulation of the microglial activation [58, 99]. Physical exercise is reported to save neurons as well as induce microglia activation by increasing the astrocyte-derived BDNF and GDNF levels [50]; these denote the potential neuroplastic effect of physical exercise with the neurotrophic factors from the microglia-astrocyte interaction (Fig. 3).

**Lipocalin Proteins.** Studies have shown that astrocyte-derived orosomucoid-2 (ORM2) and lipocalin-2 (LCN2) induce the microglial activation [66, 100]. Mainly secreted by astrocytes, ORM2 binds to the microglial C-C chemokine receptor type 5 (CCR5) and inhibits the CXCL4-CCR5 interaction, which is critical for the microglial activation [101]. LCN2 is found in astrocytes whereas the LCN2 receptors (LCN2R) are mainly expressed on microglia [102]. The distribution of LCN2 and LCN2R suggests that the astrocyte-derived LCN2 could act on microglia [100]. In fact, a series of experiments show that astrocytes in the hippocampus interact with microglia by secreting LCN2 in the rodent brains [66]. According to previous studies, physical exercise upregulates ORM level [103, 104] and LCN2 [105, 106]. Improving neuroplasticity and behaviors are found in lipocalin 2-null mice after exercise [107]; these findings note a potential effect of exercise on neuroplasticity by ORM2 or LCN2 from the astrocyte-microglia interaction (Fig. 3).

**Inflammatory Cytokine.** Interleukin-33 (IL-33) is a vital IL-1 family member as a cellular alarmin especially
after tissue damage, such as spinal cord injuries, stroke, and Alzheimer’s disease (AD) [108-110]. In addition to its roles in inflammation, IL-33 promotes brain tissue development and remodeling [111, 112]. In the brain, astrocytes are the primary source of IL-33 and microglia mainly express ST2 receptors [113, 114]. Studies demonstrate that astrocyte-derived IL-33 promotes microglial synapse engulfment and neural circuit development via the ST2 receptor-mediated signaling in microglia [113]. The increasing levels of IL-33 and ST2 are also found after physical exercise in normal people or those with ischemic heart disease [115]; these findings suggest that exercise-induced IL-33/ST2 maybe associated with astrocyte-microglia crosstalk (Fig. 3).

CXCL12 and CXCR4 are found to be expressed in astrocytes and microglia respectively, implying the CXCL12/CXCR4 axis may be involved in the astrocyte-microglia crosstalk [116]. Studies indicate that crosstalk between astrocytic CXCL12 and microglial CXCR4 are related to the development of neuropathic disease. Furthermore, CXCL12 and CXCR4 are upregulated in rats that have undergone constrained exercise on a treadmill [117]. Physical exercise is found to regulate the neural stem cell proliferation and migration via the CXCL12-CXCR4 pathway in rats after ischemic stroke [118]. This evidence suggests a potential role of physical exercise on the astrocyte-microglia crosstalk through the CXCL12-CXCR4 signaling (Fig. 3).

Microglia regulate the astrocyte activation by releasing IL-1 whose receptors are mainly expressed on astrocytes [119]. Microglia activates astrocytes by secreting IL-1 which promotes neuronal survival, outgrowth and neuroplasticity in various human neurodegenerative diseases [97]. Physical exercise has a strong effect on the immune system and induces the production of IL-1 [120] and IL-1 receptors [121]. These studies denote that physical exercise may modify the astrocyte-microglia crosstalk through IL-1. Additionally, exercise-induced inflammatory molecules mediating the microglia-astrocyte crosstalk also include C3, MCP-1, TNFα and C1q [122-125] (Fig. 3).

![Figure 4. Signals underlying crosstalk between microglia and neuron.](image-url)

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**Li F., et al.**

**Exercise-induced astrocyte activation and cellular crosstalk**

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**Aging and Disease • Volume 12, Number 7, October 2021**

1650
4.3 Signals Underlying Exercise-Induced Crosstalk Between Microglia and Neuron

Microglia can directly influence neuronal activity and neuroplasticity through many signals [63, 126] (Figure 4). Interactions between microglia and neurons play an important role in many neurological disorders with altered neural network excitability [127]. Advanced understanding in the neurobiology field has revealed active roles of microglia in modulating neuron activities, glial function, the crosstalk between neurons and microglia [70]. Anti-inflammatory microglia are found to enhance neuronal growth, suggesting microglia’s concomitant growth-promoting properties [63].

CX3CL1 is one of the critical chemokines released from neurons and binds to microglial receptors, CX3CR1 [128, 129]. Studies have indicated that decreased microglia-neuron communication caused by reduction of CX3CR1/CX3CL1 signaling, is critical for the loss of the homeostatic microglial function [63]. Physical exercise is believed to improve the cognitive function and neuroplasticity through the CX3CL1-CX3CR1 signal mediated by microglia [130]. Studies address that physical exercise could modulate stress-evoked neuronal-microglial responses by altering the CX3CL1-CX3CR1 axis, which results in activation and proliferation of microglia and neuroplasticity [70]. These findings suggest that exercise-induced microglial-neuron communications somehow depend on the CX3CL1-CX3CR1 axis (Fig. 4).

Microglia modulate neuron activities and refine neural circuits through the complement system [131]. Complement and microglia are found to mediate early loss of synapsis in neurodegenerative disorders [132]; inhibiting C3, C1q, or the microglial complement receptor, CR3 decreases the extend of early synaptic loss and the number of microglia [133]. Microglia-mediated neurotoxic effects in neurodegenerative diseases could be explained by astrocytes activation induced by cytokines and C1q [97]; this mechanism implies that microglia may indirectly affect neurons with reactive astrogrodes. Long-term physical exercise has been reported to prevent pathological neurovascular changes by reducing C1q+ microglia and increasing neuroplasticity [134]; these findings indicate that physical exercise may induce microglial-neuron communication through complement molecules (Fig. 4).

Neuron-microglia crosstalk also occurs through interaction between a neuronal glycoprotein, CD200, and a microglial receptor, CD200R, leading to a formation of CD200-CD200R complex [135, 136]. Interaction of neuronal CD200 and microglial CD200R are associated with neurodegenerative changes. Alteration in the activation of CD200 and microglia in those with depression have been observed after treatment with physical exercise [130]. Studies have established that exercise prevents dopaminergic neuronal loss by suppressing brain inflammation and microglial activation and increasing expressions of CD200 and CD200 receptor [71]. These findings suggest physical exercise could mediate the neuron-microglia crosstalk via the CD200-CD200R signaling (Fig. 4). Additionally, more pathways mediated by exercise are demonstrated to address the communications between neurons and microglia [137-148].

5. Exercise-Induced Astrocyte Activation/Crosstalk in Nervous System Disease

Physical exercise improves brain functions by regulating glial activation in numerous CNS diseases, including AD, Parkinson’s Diseases and ischemic stroke [60, 149, 150]. Physical exercise could activate cellular and molecular pathways contributing to neuroplasticity [4, 151]. Glial cells play a multifaceted and complex role in CNS diseases with their supportive effects on cell proliferation and brain plasticity [61]. Neuroplasticity is found to be enhanced in the absence of microglia T cell interaction and microglia activation after exercise [62]. Physical exercise inhibits neuroinflammation and microglial activation and modulates dopaminergic damages [60, 149].

6. Conclusion

This article highlights the neuroplastic effects of exercise on astrocytes and their interplays with microglia and neurons. Physical exercise promotes the astrocytic proliferation, astrocytic transporter levels, and interaction between glial cells and neurons. These effects help to increase the number of synapses, neural structures, and pre- and postsynaptic receptor localization. Future studies are needed for further clarification on the complex interactions between exercise, glial cell functions, and other key molecular mediators.

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Disclosure statement

The authors declare no conflicts of interest.
References

[1] Hotting K, Roder B (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev, 37:2243-2257.

[2] Xing Y, Bai Y (2020). A Review of Exercise-Induced Neuroplasticity in Ischemic Stroke: Pathology and Mechanisms. Mol Neurobiol, 57:4218-4231.

[3] Zhang H, Lee JY, Borlongan CV, Tajiri N (2019). A brief physical activity protects against ischemic stroke. Brain Circ, 5:112-118.

[4] Nicolini C, Fahnestock M, Gibala MJ, Nelson AJ (2020). Understanding the Neuropsychological and Molecular Mechanisms of Exercise-Induced Neuroplasticity in Cortical and Descending Motor Pathways: Where Do We Stand? Neuroscience.

[5] Luo L, Li C, Du X, Shi Q, Huang Q, Xu X, et al. (2019). Effect of aerobic exercise on BDNF/proBDNF expression in the ischemic hippocampus and depression recovery of rats after stroke. Behav Brain Res, 362:323-331.

[6] Trinchero MF, Herrero M, Schinder AF (2019). Rejuvenating the Brain With Chronic Exercise Through Adult Neurogenesis. Front Neurosci, 13:1000.

[7] Li K, Li J, Zheng J, Qin S (2019). Reactive Astrocytes in Neurodegenerative Diseases. Aging Dis, 10:664-675.

[8] Allen NJ, Eroglu C (2017). Cell Biology of Astrocyte-Synapse Interactions. Neurosci, 96:697-708.

[9] Khakh BS, Sofroniew MV (2015). Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci, 18:942-952.

[10] Chen J, Poskanzer KE, Freeman MR, Monk KR (2020). Live-imaging of astrocyte morphogenesis and function in zebrafish neural circuits. Nat Neurosci, 23:1297-1306.

[11] Loprinzi PD (2019). The role of astrocytes on the effects of exercise on episodic memory function. Physiol Int, 106:21-28.

[12] Johansson H, Hagstromer M, Grooten WJA, Franzen E (2020). Exercise-Induced Neuroplasticity in Parkinson's Disease: A Metasynthesis of the Literature. Neural Plast, 2020:8961493.

[13] Mellow ML, Goldsworthy MR, Coussens S, Smith AE (2020). Acute aerobic exercise and neuroplasticity of the motor cortex: A systematic review. J Sci Med Sport, 23:408-414.

[14] Gronen P, Balko S, Gronen J, Zajac A, Maszczynk A, Celka R, et al. (2019). Physical Activity and Alzheimer's Disease: A Narrative Review. Aging Dis, 10:1280-1292.

[15] Terashi T, Otsuka S, Takada S, Nakanishi K, Ueda K, Sumizono M, et al. (2019). Neuroprotective effects of different frequency preconditioning exercise on neuronal apoptosis after focal brain ischemia in rats. Neuron Res, 41:510-518.

[16] Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW (2013). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol, 12:716-726.

[17] Li F, Geng X, Khan H, Pandy JT, Jr., Peng C, Li X, et al. (2017). Exacerbation of Brain Injury by Post-Stroke Exercise Is Contingent Upon Exercise Initiation Timing. Front Cell Neurosci, 11:311.

[18] Dornbos D, 3rd, Zwagerman N, Guo M, Ding JY, Peng C, Esmail F, et al. (2013). Preischemic exercise reduces brain damage by ameliorating metabolic disorder in ischemia/reperfusion injury. J Neurosci Res, 91:818-827.

[19] Pan R, Cai J, Zhan L, Guo Y, Huang RY, Li X, et al. (2017). Buyang Huanwu decoction facilitates neurorehabilitation through an improvement of synaptic plasticity in cerebral ischemic rats. BMC Complement Altern Med, 17:173.

[20] De Pitta M, Brunel N, Volterra A (2016). Astrocytes: Orchestrating synaptic plasticity? Neuroscience, 323:43-61.

[21] Chen Z, Hu Q, Xie Q, Wu S, Pang Q, Liu M, et al. (2019). Effects of Treadmill Exercise on Motor and Cognitive Function Recovery of MCAO Mice Through the Caveolin-1/VEGF Signaling Pathway in Ischemic Penumbra. Neurochem Res, 44:930-946.

[22] King M, Kelly LP, Wallack EM, Hasan SMM, Kirkland MC, Curtis ME, et al. (2019). Serum levels of insulin-like growth factor-1 and brain-derived neurotrophic factor as potential recovery biomarkers in stroke. Neurol Res, 41:354-363.

[23] Emrich HM, Dose M, von Zerssen D (1985). The use of sodium valproate, carbamazepine and oxcarbazepine in patients with affective disorders. J Affect Disord, 8:243-250.

[24] de Sousa Fernandes MS, Ordonez TF, Santos GCJ, Santos LER, Calazans CT, Gomes DA, et al. (2020). Effects of Physical Exercise on Neuroplasticity and Brain Function: A Systematic Review in Human and Animal Studies. Neural Plast, 2020:8856621.

[25] Sandroff BM, Jones CD, Baird JF, Motl RW (2020). Systematic Review on Exercise Training as a Neuroplasticity-Inducing Behavior in Multiple Sclerosis. Neurorehabil Neural Repair, 34:575-588.

[26] Stogsdill JA, Ramirez J, Liu D, Kim YH, Baldwin KT, Enustun E, et al. (2017). Astrocytic neurologin-4 controls astrocyte morphogenesis and synaptogenesis. Nature, 551:192-197.

[27] Cohen-Salmon M, Slauoi L, Mazare N, Gilbert A, Oudart M, Alvear-Perez R, et al. (2020). Astrocytes in the regulation of cerebrovascular functions. Glia.

[28] Rosskothen-Kuhl N, Hildebrandt H, Birkenhager R, Illing RB (2018). Astrocyte Hypertrophy and Microglia Activation in the Rat Auditory Midbrain Is Induced by Electrical Intracochlear Stimulation. Front Cell Neurosci, 12:43.

[29] Durkee CA, Araque A (2019). Diversity and Specificity of Astrocyte-neuron Communication. Neuroscience, 396:73-78.

[30] Dallerac G, Zapata J, Rouach N (2018). Versatile control of synaptic circuits by astrocytes: where, when and how? Nat Rev Neurosci, 19:729-743.
[31] Farhy-Tselnicker I, Allen NJ (2018). Astrocytes, neurons, synapses: a tripartite view on cortical circuit development. Neural Dev, 13:7.

[32] Fahimi A, Baktir MA, Moghadam S, Mojabi FS, Sumanth K, McNerney MW, et al. (2017). Physical exercise induces structural alterations in the hippocampal astrocytes: exploring the role of BDNF-TrkB signaling. Brain Struct Funct, 222:1797-1808.

[33] Belaya I, Ivanova M, Sorvari A, Illic M, Loppi S, Koivisto H, et al. (2020). Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease. J Neuroinflammation, 17:271.

[34] Sultan S, Li L, Moss J, Petrelli F, Casse F, Gebara E, et al. (2015). Synaptic Integration of Adult-Born Hippocampal Neurons Is Locally Controlled by Astrocytes. Neuron, 88:957-972.

[35] Araki T, Ikgaya Y, Koyama R (2020). The effects of microglia- and astrocyte-derived factors on neurogenesis in health and disease. Eur J Neurosci.

[36] Alvarez Z, Hyrossova P, Perales JC, Alcantara S (2016). Neuronal Progenitor Maintenance Requires Lactate Metabolism and PEPCK-M-Directed Cataplerosis. Cereb Cortex, 26:1046-1058.

[37] Quesseveur G, David DJ, Gaillard MC, Pla P, Wu MV, Nguyen HT, et al. (2013). BDNF overexpression in mouse hippocampal astrocytes promotes local neurogenesis and elicits anxiolytic-like activities. Transl Psychiatry, 3:e253.

[38] Tatsumi K, Okuda H, Morita-Takemura S, Tanaka T, Isonishi A, Shinjo T, et al. (2016). Voluntary Exercise Induces Astrocytic Structural Plasticity in the Globus Pallidus. Front Cell Neurosci, 10:165.

[39] Saur L, Baptista PP, de Senna PN, Paim MF, do Nascimento P, Ilha J, et al. (2014). Physical exercise increases GFAP expression and induces morphological changes in hippocampal astrocytes. Brain Struct Funct, 219:293-302.

[40] Lundquist AJ, Parizher J, Petzinger GM, Jakowec MW (2019). Exercise induces region-specific remodeling of astrocyte morphology and reactive astrocyte gene expression patterns in male mice. J Neurosci Res, 97:1081-1094.

[41] Wang X, Zhang M, Feng R, Li WB, Ren SQ, Zhang J, et al. (2014). Physical exercise training and neurovascular unit in ischemic stroke. Neuroscience, 271:99-107.

[42] Bonsack B, Borlongan MC, Lo EH, Arai K (2019). Brief overview: Protective roles of astrocyte-derived pentraxin-3 in blood-brain barrier integrity. Brain Circ, 5:145-149.

[43] Lu Y, Dong Y, Tucker D, Wang R, Ahmed ME, Brann D, et al. (2017). Treadmill Exercise Exerts Neuroprotection and Regulates Microglial Polarization and Oxidative Stress in a Streptozotocin-Induced Rat Model of Sporadic Alzheimer's Disease. J Alzheimers Dis, 56:1469-1484.

[44] Oheim M, Schmidt E, Hirrlinger J (2018). Local energy on demand: Are 'spontaneous' astrocytic Ca(2+) microdomains the regulatory unit for astrocyte-neuron metabolic cooperation? Brain Res Bull, 136:54-64.

[45] Cali C, Tauffenberger A, Magistretti P (2019). The Strategic Location of Glycogen and Lactate: From Body Energy Reserve to Brain Plasticity. Front Cell Neurosci, 13:82.

[46] Bernardi C, Tramontina AC, Nardin P, Biasibetti R, Costa AP, Vizueti AF, et al. (2013). Treadmill exercise induces hippocampal astroglial alterations in rats. Neural Plast, 2013:709732.

[47] Uda M, Ishido M, Kami K, Masuhara M (2006). Effects of chronic treadmill running on neurogenesis in the dentate gyrus of the hippocampus of adult rat. Brain Res, 1104:64-72.

[48] Ayadi AE, Zigmond MJ, Smith AD (2016). IGF-1 protects dopamine neurons against oxidative stress: association with changes in phosphokinasps. Exp Brain Res, 234:1863-1873.

[49] Lu Y, Sareddy GR, Wang J, Zhang Q, Tang FL, Prapat UP, et al. (2020). Neuron-Derived Estrogen Is Critical for Astrocyte Activation and Neuroprotection of the Ischemic Brain. J Neurosci, 40:7355-7374.

[50] Palasz E, Niewiadomski W, Gasiorowska A, Mietelska-Porowska A, Niewiadomska G (2019). Neuroplasticity and Neuroprotective Effect of Treadmill Training in the Chronic Mouse Model of Parkinson's Disease. Neural Plast, 2019:8215017.

[51] Lloyd BA, Hake HS, Ishiwata T, Farmer CE, Loetz EC, Fleshner M, et al. (2017). Exercise increases mTOR signaling in brain regions involved in cognition and emotional behavior. Behav Brain Res, 323:56-67.

[52] Diener GA, Rothman DL (2020). Reevaluation of Astrocyte-Neuron Energy Metabolism with Astrocyte Volume Fraction Correction: Impact on Cellular Glucose Oxidation Rates, Glutamate-Glutamine Cycle Energetics, Glycogen Levels and Utilization Rates vs. Exercising Muscle, and Na(+)/K(+) Pumping Rates. Neurochem Res, 45:2607-2630.

[53] Diener GA, Rothman DL (2019). Glycogenolysis in Cerebral Cortex During Sensory Stimulation, Acute Hypoglycemia, and Exercise: Impact on Astrocytic Energetics, Aerobic Glycolysis, and Astrocyte-Neuron Interactions. Adv Neurobiol, 23:209-267.

[54] Garcia-Caceres C, Ballard E, Prevot V, Luquet S, Woods SC, Koch M, et al. (2019). Role of astrocytes, microglia, and tanyocytes in brain control of systemic metabolism. Nat Neurosci, 22:7-14.

[55] Ivanov AI, Malkov AE, Waseem T, Mukhtarov M, Buldakova S, Gubkina O, et al. (2014). Glycology and oxidative phosphorylation in neurons and astrocytes during network activity in hippocampal slices. J Cereb Blood Flow Metab, 34:397-407.

[56] Matsui T, Omuoro H, Liu YF, Soya M, Shima T, McEwen BS, et al. (2017). Astrocytic glycogen-derived lactate fuels the brain during exhaustive exercise to maintain endurance capacity. Proc Natl Acad Sci U S A, 114:6358-6363.

[57] Tsai SF, Chen PC, Calkins MJ, Wu SY, Kuo YM (2016). Exercise Counteracts Aging-Related Memory Impairment: A Potential Role for the Astrocytic Metabolic Shuttle. Front Aging Neurosci, 8:57.
Jha MK, Jo M, Kim JH, Suk K (2019). Microglia-Astrocyte Crosstalk: An Intimate Molecular Conversation. Neuroscientist, 25:227-240.

Luo D, Zhang Y, Yuan X, Pan Y, Yang L, Zhao Y, et al. (2019). Oleoylthanolamide inhibits glial activation via modulating PPARalpha and promotes motor function recovery after brain ischemia. Pharmacol Res, 141:530-540.

Reall CC, Doorduin J, Kopschina Feltes P, Vallez Garcia D, de Paula Faria D, Britto LR, et al. (2019). Evaluation of exercise induction of glial activation and dopaminergic damage in a rat model of Parkinson's disease using [(11)C]PBR28 and [(18)F]FDOPA PET. J Cereb Blood Flow Metab, 39:989-1004.

Ekldahl CT, Kokaia Z, Lindvall O (2009). Brain inflammation and adult neurogenesis: the dual role of microglia. Neuroscience, 158:1021-1029.

Olah M, Ping G, De Haas AH, Brouwer N, Meerlo P, Van Der Zee EA, et al. (2009). Enhanced hippocampal neurogenesis in the absence of microglia T cell interaction and microglia activation in the murine running wheel model. Glia, 57:1046-1061.

Marinelli S, Basilico B, Marrone MC, Ragazzino D (2019). Microglia-neuron crosstalk: Signaling mechanism and control of synaptic transmission. Semin Cell Dev Biol, 94:138-151.

Rocha SM, Cristovao AC, Campos FL, Fonseca CP, Baltazar G (2012). Astrocyte Crosstalk: An Intimate Molecular Mechanism among Neuron, Astrocyte, Microglia, and Glial Cells. Front Physiol, 3:195.

Sheridan GK, Murphy KJ (2013). Neuron-glia crosstalk in health and disease: fractalkine and CX3CR1 take center stage. Open Biol, 3:130181.

Kim JH, Ko PW, Lee HW, Jeong JY, Lee MG, Kim JH, et al. (2017). Astrocyte-derived lipocalin-2 mediates hippocampal damage and cognitive deficits in mice with models of vascular dementia. Glia, 65:1471-1490.

Littlefield AM, Setti SE, Priester C, Kohman RA (2015). Voluntary exercise attenuates LPS-induced reductions in neurogenesis and increases microglia expression of a proneurogenic phenotype in aged mice. J Neuroinflammation, 12:138.

Nakanishi K, Sakakima H, Norimatsu K, Otsuka S, Takada S, Tani A, et al. (2021). Effect of low-intensity motor balance and coordination exercise on cognitive functions, hippocampal Abeta deposition, neuronal loss, neuroinflammation, and oxidative stress in a mouse model of Alzheimer's disease. Exp Neurol, 337:113590.

Hayashi Y, Nakanishi H (2013). [Synaptic plasticity and synaptic reorganization regulated by microglia]. Nihon Shinkei Seishin Yakurigaku Zasshi, 33:211-216.

Fleshner M, Greenwood BN, Yirmiya R (2014). Neuronal-glial mechanisms of exercise-evoked stress robustness. Curr Top Behav Neurosci, 18:1-12.

Sung YH, Kim SC, Hong HP, Park CY, Shin MS, Kim CJ, et al. (2012). Treadmill exercise ameliorates dopaminergic neuronal loss through suppressing microglial activation in Parkinson's disease mice. Life Sci, 91:1309-1316.

Sellgren CM, Gracias J, Watmuff B, Biag JD, Thanos JM, Whittredge PB, et al. (2019). Increased synapse elimination by microglia in schizophrenic patient-derived models of synaptic pruning. Nat Neurosci, 22:374-385.

Andoh M, Shibata K, Okamoto K, Onodera J, Morishita K, Miura Y, et al. (2019). Exercise Reverses Behavioral and Synaptic Abnormalities after Maternal Inflammation. Cell Rep, 27:2817-2825 e2815.

Santello M, Toni N, Volterra A (2019). Astrocyte function from information processing to cognition and cognitive impairment. Nat Neurosci, 22:154-166.

Savitchouk I, Volterra A (2018). Gliotransmission: Beyond Black-and-White. J Neurosci, 38:14-25.

Yang J, Vitery MDC, Chen J, Osei-Owusu J, Chu J, Qiu Z (2019). Glutamate-Releasing SWELL1 Channel in Astrocytes Modulates Synaptic Transmission and Promotes Brain Damage in Stroke. Neuron, 102:813-827 e816.

Li F, Eriksen J, Finer-Moore J, Chang R, Nguyen P, Bowen A, et al. (2020). Ion transport and regulation in a synaptic vesicle glutamate transporter. Science, 368:893-897.

Swiatkiewicz M, Fiederowicz M, Orzel J, Welniak-Kaminska M, Bogorodzki P, Langfort J, et al. (2017). Increases in Brain (1)H-MR Glutamine and Glutamate Signals Following Acute Exhaustive Endurance Exercise in the Rat. Front Physiol, 8:19.

de Senna PN, Bagatini PB, Galland F, Bobermin L, do Nascimento PS, Nardin P, et al. (2017). Physical exercise reverses spatial memory deficit and induces hippocampal astrocyte plasticity in diabetic rats. Brain Res, 1655:242-251.

Okutsu S, Hatakeyama H, Kanzaki M, Tsubokawa H, Nagatomi R (2008). Electric pulse stimulation induces hippocampal astrocyte plasticity in diabetic rats. Brain Res, 1231:79-89.

Neame S, Safory H, Radziszhevsky I, Touitou A, Marchesani F, Marchetti M, et al. (2019). The NMDA receptor activation by d-serine and glycine is controlled by an astrocytic Phgdh-dependent serine shuttle. Proc Natl Acad Sci U S A, 116:20736-20742.

Bodner O, Radziszhevsky I, Foltyn VN, Touitou A, Valenta AC, Rangel IF, et al. (2020). D-Serine Signaling and NMDAR-Mediated Synaptic Plasticity Are Regulated by System A-Type of Glutamate/D-Serine Dual Transporters. J Neurosci, 40:6489-6502.

Henneberger C, Papouin T, Oliet SH, Rusakov DA (2010). Long-term potentiation depends on release of D-serine from astrocytes. Nature, 463:232-236.

Lalo U, Bogdanov A, Pankratov Y (2018). Diversity of Astroglial Effects on Aging- and Experience-Related Cortical Metaplasticity. Front Mol Neurosci, 11:239.

Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, et al. (2011). Astrocyte-neuron lactate transport is required for long-term memory formation. Cell, 144:810-823.
Exercise-induced astrocyte activation and cellular crosstalk

[86] Hertz L, Chen Y (2018). Glycogenolysis, an Astrocyte-Specific Reaction, is Essential for Both Astrocytic and Neuronal Activities Involved in Learning. Neuroscience, 370:27-36.

[87] Dienel GA (2017). Lack of appropriate stoichiometry: Strong evidence against an energetically important astrocyte-neuron lactate shuttle in brain. J Neurosci Res, 95:2103-2125.

[88] Magistretti PJ, Allaman I (2018). Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci, 19:235-249.

[89] Jimenez-Blasco D, Busquets-Garcia A, Hebert-Chabalain E, Serrat R, Vicente-Gutierrez C, Ioannidou C, et al. (2020). Glucose metabolism links astroglial mitochondria to cannabinoid effects. Nature, 583:603-608.

[90] Clasadonte J, Scenes E, Wang Z, Boison D, Haydon PG (2017). Connexin 43-Mediated Astroglial Metabolic Contributions to the Regulation of the Sleep-Wake Cycle. Neuron, 95:1365-1380 e1365.

[91] Levin SG, Godukhin OV (2017). Modulating Effect of Cytokines on Mechanisms of Synaptic Plasticity in the Brain. Biochemistry (Mosc), 82:264-274.

[92] Bialas AR, Stevens B (2013). TGF-beta signaling regulates neuronal C1q expression and developmental synaptic refinement. Nat Neurosci, 16:1773-1782.

[93] Lewitus GM, Priibiag H, Duseja R, St-Hilaire M, Stellwagen D (2014). An adaptive role of TNFalpha in synaptic refinement. Nat Neurosci, 16:1782-1784.

[94] Bedner P, Steinhauser C (2019). TNFalpha-Driven Astrocyte Purinergic Signaling during Epileptogenesis. Trends Mol Med, 25:70-72.

[95] Zhang Q, Zhang J, Yan Y, Zhang P, Zhang W, Xia R (2017). Proinflammatory cytokines correlate with early exercise attenuating anxiety-like behavior after cerebral ischemia. Brain Behav, 7:e00854.

[96] Rozzano R (2017). [Astrocytes and microglia: active players in synaptic plasticity]. Med Sci (Paris), 33:1071-1078.

[97] Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. Nature, 541:481-487.

[98] Pascual O, Ben Achour S, Rostaing P, Triller A, Bessis A (2012). Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. Proc Natl Acad Sci U S A, 109:E197-E205.

[99] Xu R, Wu J, Lang L, Hu J, Tang H, Xu J, et al. (2020). Implantation of glial cell line-derived neurotrophic factor-expressing adipose tissue-derived stromal cells in a rat Parkinson's disease model. Neuron Res, 42:712-720.

[100] Lee S, Jha MK, Suk K (2015). Lipocalin-2 in the Inflammatory Activation of Brain Astrocytes. Crit Rev Immunol, 35:75-84.

[101] Jo M, Kim JH, Song GJ, Seo M, Hwang EM, Suk K (2017). Astrocytic Orosomucoid-2 Modulates Microglial Activation and Neuroinflammation. J Neurosci, 37:2878-2894.

[102] Chen X, Qiu F, Zhao X, Lu J, Tan X, Xu J, et al. (2020). Astrocyte-Derived Lipocalin-2 Is Involved in Mitochondrion-Related Neuronal Apoptosis Induced by Methamphetamine. ACS Chem Neurosci, 11:1102-1116.

[103] Carlson LA, Tighe SW, Kenefick RW, Dragon J, Westcott NW, Leclaire RJ (2011). Changes in transcriptional output of human peripheral blood mononuclear cells following exercise resistance. Eur J Appl Physiol, 111:2919-2929.

[104] Kohler M, Walpurgis K, Thomas A, de Marie M, Mester J, Schanzer W, et al. (2010). Effects of endurance exercise on the urinary proteome analyzed by 2-D PAGE and Orbitrap MS. Proteomics Clin Appl, 4:568-576.

[105] Wolyniec R, Ratkowski W, Urbanski R, Bartoszewicz M, Siluk D, Wolyniec Z, et al. (2018). Urinary Kidney Injury Molecule-1 but Not Urinary Neutrophil Gelatinase Associated Lipocalin Is Increased after Short Maximal Exercise. Nephron, 138:29-34.

[106] Silva D, Moreira R, Beltrao M, Sokhatska O, Montanha T, Pizarro A, et al. (2019). What is the effect of a Mediterranean compared with a Fast Food meal on the exercise induced adipokine changes? A randomized cross-over clinical trial. PLoS One, 14:e0215475.

[107] Ferreira AC, Novais A, Sousa N, Sousa JC, Marques F (2019). Voluntary running rescues the defective hippocampal neurogenesis and behaviour observed in lipocalin 2-null mice. Sci Rep, 9:1649.

[108] Gadani SP, Walsh JT, Smirnov I, Zheng J, Kipnis J (2015). The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. Neuron, 85:703-709.

[109] Luo Y, Zhou Y, Xiao W, Liang Z, Dai J, Weng X, et al. (2015). Interleukin-33 ameliorates ischemic brain injury in experimental stroke through promoting Th2 response and suppressing Th17 response. Brain Res, 1597:86-94.

[110] Fu AK, Hung KW, Yuen MY, Zhou X, Mak DS, Chan IC, et al. (2016). IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. Proc Natl Acad Sci U S A, 113:E2705-2713.

[111] Molofsky AB, Savage AK, Locksley RM (2015). Interleukin-33 in Tissue Homeostasis, Injury, and Inflammation. Immunity, 42:1005-1019.

[112] Wang Y, Fu WY, Cheung K, Hung KW, Chen C, Geng H, et al. (2021). Astrocyte-secreted IL-33 mediates homeostatic synaptic plasticity in the adult hippocampus. Proc Natl Acad Sci U S A, 118.

[113] Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, et al. (2018). Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science, 359:1269-1273.

[114] Nguyen PT, Dorman LC, Pan S, Vainchtein ID, Han RT, Nakao-Inoue H, et al. (2020). Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. Cell, 182:388-403 e315.

[115] Raygan F, Sayyah M, Janes Samsari SM, Nikoueinejad H, Sefat M (2017). Effects of
Submaximal Aerobic Exercise on Regulatory T Cell Markers of Male Patients Suffering from Ischemic Heart Disease. Iran J Allergy Asthma Immunol, 16:14-20.

Luo X, Tai WL, Sun L, Pan Z, Xia Z, Chung SK, et al. (2016). Crosstalk between astrocytic CXCL12 and microglial CXCR4 contributes to the development of neuropathic pain. Mol Pain, 12:205-1215.

Evidence for the involvement of the CXCL12 system in the adaptation of skeletal muscles to physical exercise. Cell Signal, 28:1205-208.

Physical exercise regulates neural stem cells proliferation and migration via SDF-1alpha/CXCR4 pathway in rats after ischemic stroke. Neurosci Lett, 578:203-208.

Murata Y, Sugimoto K, Yang C, Harada K, Gono R, Harada T, et al. (2020). Activated microglia-derived macrophage-like cells exacerbate brain edema after ischemic stroke correlate with astrocytic expression of aquaporin-4 and interleukin-1 alpha release. Neurochem Int, 140:104848.

Radak Z, Suzuki K, Higuchi M, Balogh L, Boldogh I, Koltai E (2016). Physical exercise, reactive oxygen species and neuroprotection. Free Radic Biol Med, 98:187-196.

Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. Exerc Immunol Rev, 21:8-25.

Lian H, Litvinchuk A, Chiang AC, Aithmitti N, Jankowsky JL, Zheng H (2016). Astrocyte-Microglia Cross Talk through Complete Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. J Neurosci, 36:577-589.

Kano SI, Choi EY, Dohi E, Agarwal S, Chang DJ, Wilson AM, et al. (2019). Glutathione S-transferases promote proinflammatory astrocyte-microglia communication during brain inflammation. Sci Signal, 12.

Peake JM, Della Gatta P, Suzuki K, Nieman DC (2015). Microglia mediate early synapse loss in Alzheimer mouse models. Science, 352:712-716.

Microglia-mediated neurodegeneration in a mouse model of Alzheimer's disease. J Neuroinflammation, 13:e1002279.

Mihrshahi R, Brown MH (2010). Downstream of tyrosine kinase 1 and 2 play opposing roles in CD200 receptor signaling. J Immunol, 185:7216-7222.

Wang L, Liu Y, Yan S, Du T, Fu X, Gong X, et al. (2020). Disease Progression-Dependent Expression of CD200R1 and CX3CR1 in Mouse Models of Parkinson's Disease. Aging Dis, 11:254-268.

Chen Z, Zhong D, Li G (2019). The role of microglia in viral encephalitis: a review. J Neuroinflammation, 16:76.

Ativie F, Komorowska JA, Beins E, Albayram O, Zimmer T, Zimmer A, et al. (2018). Cannabinoid 1 Receptor Signaling on Hippocampal GABAergic Neurons Influences Microglial Activity. Front Mol Neurosci, 11:295.

Regulation of Physical Microglia Activity: an immune perspective. Front Psychiatry, 4:3.

Shi Y, Yamada K, Liddelow SA, Smith ST, Zhao L, Luo W, et al. (2017). ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of taulopathy. Nature, 549:523-527.

Kaewmool C, Udomruk S, Phitak T, Pothacharoen P, Kongtawelert P (2020). Cyanidin 3-Caffeoylquinic Acid Protects PC12 Cells Against Neuronal Apoptosis Mediated by LPS-Stimulated BV2 Microglial Activation. Neurotox Res, 37:111-125.

Podbielska M, Das A, Smith AW, Chauhan A, Ray SK, Inoue J, et al. (2016). Neuron-microglia interaction evidence for the role of microglia in synaptic pruning in health and disease. Curr Opin Neurobiol, 36:128-134.

Spinal Inflammation and Neuroprotection by Exercise Prevents Aging Neurovascular Dysfunction and Complement Induction. PLoS Biol, 13:e1002279.
induced bi-directional cytotoxicity associated with calpain activation. J Neurochem, 139:440-455.

[145] Willis EF, MacDonald KPA, Nguyen QH, Garrido AL, Gillespie ER, Harley SBR, et al. (2020). Repopulating Microglia Promote Brain Repair in an IL-6-Dependent Manner. Cell, 180:833-846 e816.

[146] Todd L, Palazzo I, Suarez L, Liu X, Volkov L, Hoang TV, et al. (2019). Reactive microglia and IL1beta/IL1R1-signaling mediate neuroprotection in excitotoxin-damaged mouse retina. J Neuroinflammation, 16:118.

[147] Miao H, Li R, Han C, Lu X, Zhang H (2018). Minocycline promotes posthemorrhagic neurogenesis via M2 microglia polarization via upregulation of the TrkB/BDNF pathway in rats. J Neurophysiol, 120:1307-1317.

[148] Cattaneo A, Capsoni S (2019). Painless Nerve Growth Factor: A TrkA biased agonist mediating a broad neuroprotection via its actions on microglia cells. Pharmacol Res, 139:17-25.

[149] Mee-Inta O, Zhao ZW, Kuo YM (2019). Physical Exercise Inhibits Inflammation and Microglial Activation. Cells, 8.

[150] Ahn JH, Shin MC, Park JH, Kim IH, Cho JH, Lee TK, et al. (2017). Effects of longterm postsischemic treadmill exercise on gliosis in the aged gerbil hippocampus induced by transient cerebral ischemia. Mol Med Rep, 15:3623-3630.

[151] Wang Q, Wills M, Han Z, Geng X, Ding Y (2020). Mini Review (Part I): An Experimental Concept on Exercise and Ischemic Conditioning in Stroke Rehabilitation. Brain Circ, 6:242-247.