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The role of astrocytes on the effects of exercise on episodic memory function

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This review discusses the potential role that glial cells may play in influencing the relationship between exercise and episodic memory function. A narrative review methodology is employed. Herein, the different types of glial cells, their implications in subserving episodic memory function, and how exercise can modulate glial cell activity, particularly astrocyte functionality, are discussed. Although additional experimental work is needed, astrocytes appear to play an important role in the exercise–memory interaction. Exercise may increase astrocytic size, attenuate astrogliodegeneration, improve astrocytic aquaporin-4 expression, and increase astrocytic transporter levels. These effects, in turn, may help to increase the number of synapses that neurons form, increase the number of synaptic structures, and increase presynaptic function and postsynaptic receptor localization. Ultimately, these effects may help influence long-term potentiation and episodic memory function.

Keywords: astrocyte, cognition, glial, long-term potentiation, physical activity, synaptic plasticity

Introduction

Emerging research demonstrates that both acute and chronic exercise may help to subserve implicit memory (26), semantic memory (25), emotional memory (29), and episodic memory function (16, 19, 30, 31, 37, 40–42, 46), with the latter focusing on the retrospective recall of past events/episodes in a spatiotemporal context. This work, and the research discussed herein, has mostly focused on aerobic exercise, unless stated otherwise. We have previously discussed the potential mechanisms through which exercise may influence episodic memory function (15, 27, 28, 32), which includes, e.g., induction of neuronal excitability, neurogenesis, growth factor production [e.g., brain-derived neurotrophic factor (BDNF) (28) and insulin-like growth factor-1 (IGF-1) (24)], and long-term potentiation (LTP). LTP refers to the function connectivity of neurons, which is considered a key correlate of episodic memory.

In the exercise neurophysiology field, much less focus, however, has been on the potential role of glial cell function in the exercise-related enhancement of episodic memory, which was the purpose of this brief primer. Figure 1 provides a schematic illustration of the role that glial cells play in the exercise–memory interaction. In addition to their passive, supportive role, glial cells also actively survey the brain for damage and infection and help to facilitate any necessary restorative processes. As discussed below, glial cells, and astroglia in particular, play a critical role in memory formation (11, 48). Glia cells can be evaluated with various techniques, including microsensors (10) and imaging instruments (13, 36).

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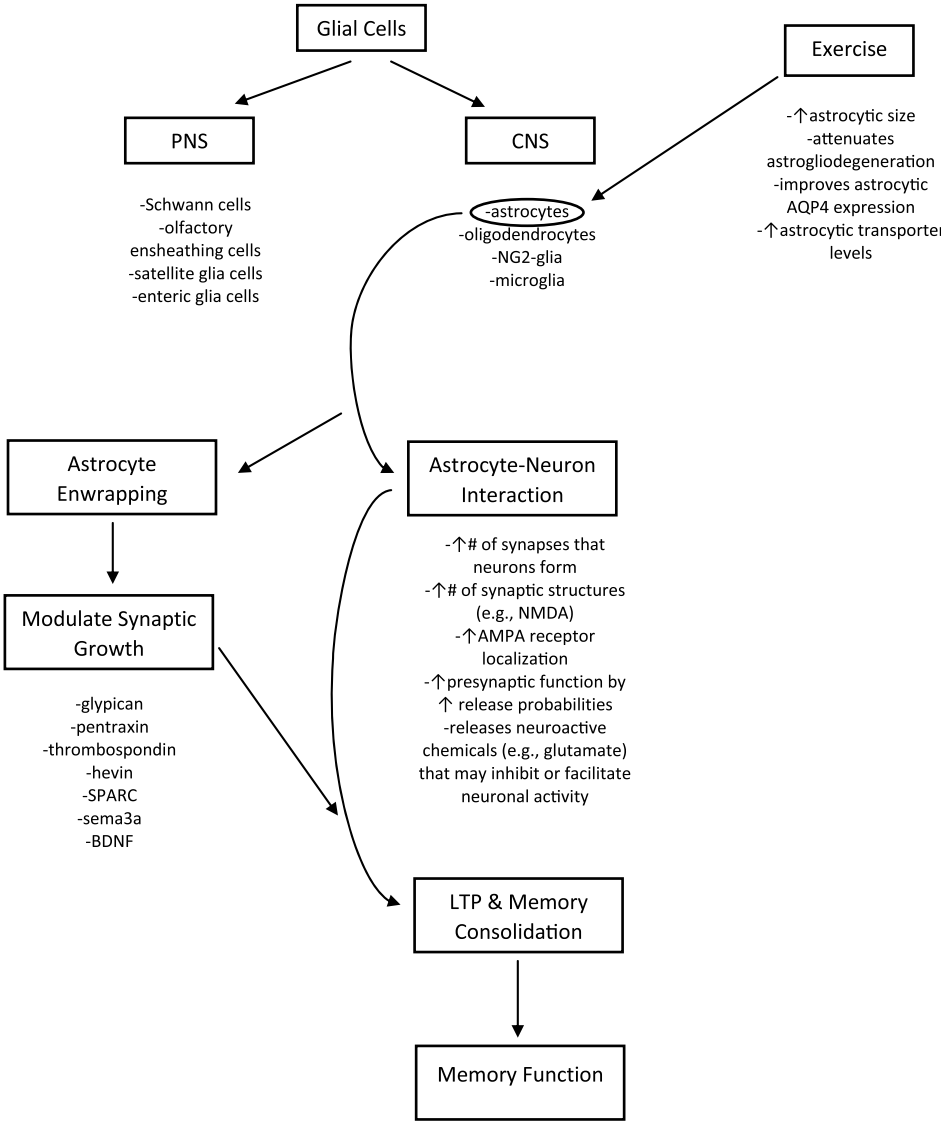

Fig 1. Schematic illustration of potential mechanisms through which astrocytes may influence the exercise–memory interaction

Glial Cell Types

Glial cells account for approximately half of the brain's volume, which includes multiple cellular types. Neuroanatomists recognize four broad types of glial cells in the central nervous system (CNS) and four in the peripheral nervous system (PNS) (20). The four neuroglial cells include astrocytes, oligodendrocytes, neuron-glia antigen 2 (NG2-glia), and microglia (20). Other glial-like cells of the CNS include tanycytes, which line the third ventricle and play major roles in hypothalamic regulation of body weight and energy balance (6). The four glial cells in the PNS include Schwann cells, olfactory ensheathing cells, satellite glia cells, and enteric glia cells.

Glial Cell Functions

Each glial cell type plays an important role in the health and function of the nervous system. Briefly, and constituting nearly half the number of brain cells, astrocytes are star-shaped glia and are the focal glial cell of this paper. Astrocytes sense when neurons become active, as the K^+ released from neurons depolarizes the astrocyte. This uptake of excess K^+ may help maintain the efficiency of signaling between neurons, as excess extracellular K^+ may interfere with neuronal signaling. The astrocyte can fulfill a variety of other roles, including regulating the development and permeability of the blood–brain barrier (BBB), contributing to information processing in the CNS, regulating levels of neurotransmitters (e.g., glutamate) in the CNS, removing/disposing old/damaged organelles (e.g., mitochondria), and nourishing surrounding neurons by releasing growth factors. Oligodendrocytes are small cells with relatively few processes. They produce myelin sheaths by tightly winding their membranous processes around the axon in a spiral fashion. Each cell envelops from 1 to 30 axonal segments. These myelin sheaths help facilitate neuronal transmission, increase the speed of the electrical signal, and help prevent the action potential from escaping the neuron. NG2-glia, a signaling protein expressed by some neuroglia, helps facilitate the differentiation and migration of oligodendrocyte precursor cells as well as it helps facilitate the formation of glutamatergic and GABAergic (gamma-amino butyric acid) synapses. Microglia [yolk sac-derived cells (18)] are macrophage-like cells that play an important role in the immunological surveillance of the CNS, e.g., by reacting to foreign invaders and engulfing pathogens. Schwann cells are like oligodendrocytes but reside in the PNS. Each cell envelops a single segment of one axon. Similar to oligodendrocytes, Schwann cells, upon myelination, enhance signal conduction. Olfactory ensheathing cells unsheathe unmyelinated primary olfactory axons and facilitate the regeneration of olfactory axons. Satellite glia cells may help facilitate signal processing/transmission of sensory ganglia. Finally, enteric glia cells modulate gastrointestional function. Thus, each of these glial cells plays an important role in the functioning of the nervous system. Astrocytes, in particular, play a critical role in neuronal communication, a necessary step for episodic memory function.

Astrocytes on Neuronal Communication

Neuron-to-neuron communication is a critical component subserving episodic memory function. Astrocyte cells can help contribute to the formation of neural networks by inducing synapse formation. For example, astrocytes secrete factors (e.g., thrombospondins) that increase the number of synapses that neurons form. For example, astrocytes increase the number of synaptic structures (e.g., N-methyl-D-aspartate receptors), increase postsynaptic activity by inducing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor localization, and enhance presynaptic function by increasing release probabilities. Indeed, research by Adamsky et al. (1) shows that stimulation of astrocytes potentiates synaptic transmission and facilitates behavioral performance in memory tasks. Neurotransmitters released from neurons may activate signaling cascades within the astrocyte and in turn, the astrocyte may release neuroactive (gliotransmitters) chemicals (e.g., glutamate) that can either inhibit or facilitate neuronal activity (bidirectional astrocyte-neuron signaling). Critically, however, this gliotransmission process may be a pharmacological phenomenon rather than a physiological process (14).

Furthermore, synapses do not just consist of pre- and postsynaptic neurons. Glial cells, and in particular, astrocytes, have projections that envelope the synapse, leading to a multipartite synapse. The multipartite synapse includes multiple components, such as the presynaptic terminal, postsynaptic element, perisynaptic process of the astrocyte, neighboring microglial, and the extracellular matrix (a structural element of the BBB that serves as an anchor of the endothelium) (45). A single human hippocampal astrocyte may associate with approximately two million synapses (48). Astrocyte enwrapping may play a critical role in memory consolidation by modulating synapse growth during memory consolidation. During memory consolidation of Pavlovian threat conditioning, astrocytic processes have been shown to retract from the synapse to allow for structural synaptic changes (synaptic enlargement) (48). Thus, in addition to facilitative mechanisms, astrocytes may hinder synaptic remodeling, and in turn, memory formation.

Relatedly, retraction of the astrocytic membrane from the synapse plays a key role in the homeostatic control of the synaptic cleft, including the removal of neurotransmitters (e.g., glutamate) and ions (e.g., potassium) from the extracellular space (9). Relatedly, microglia may facilitate synaptic pruning and in turn facilitate synaptic maturation, plasticity, and function. Astrocytes also play an important role from an energetic perspective. Glycogen, which is the only substrate stored in the CNS, is present predominately, if not exclusively, in astrocytic cells. In addition to energy metabolism within the neuron (pyruvate provided to the mitochondria via glycolysis), astrocytes may take up glucose (or pyruvate or lactate from glucose) to facilitate the energy demands of astrocytic and neuronal processes (48).

Thus, via the formation of the synapse, as well as the potential for the astrocyte cells to modulate the functional connectivity of the neurons, astrocytes may play a key role in the underlying mechanism (LTP) of episodic memory. Astrocytes also play an important role in controlling the movement across the BBB and thus may serve as a gatekeeper in facilitating the role of other key parameters (e.g., IGF-1) in crossing the BBB to ultimately influence hippocampal LTP. For example, astrocytic end feet express specialized molecules, such as aquaporin-4 (AQP4), that regulates BBB ionic concentrations. Astrocytes also facilitate the development and maintenance of the BBB through the release of growth factors, such as vascular endothelial growth factor, glial cell line-derived neurotrophic factor, basic fibroblast growth factor, and angiopoietin-1 (35).

Astrocytes, Neurogenesis, and Exercise

In addition to influencing synaptic formation and communication, glial cells may also play an important role in the development of new neurons (i.e., neurogenesis). As noted above, astrocytes provide a supportive environment to neurons, ultimately creating a microenvironment permissive for neurogenesis and potential inhibition of apoptosis. For example, using a purified retinal ganglion cell (RGC) culture, research has shown that RGC neurons grown in the absence of astroglia form few synapses (9). Specifically, research demonstrates that astrocytes may regulate hippocampal neurogenesis through ephrin-B signaling (2). In addition, astrocytes also help regulate synaptogenesis by expressing glypican, causing pentraxin release and in turn, stabilizing neurotransmitters on the postsynaptic membrane. Various other astrocyte-expressed molecules help regulate synapse formation, including thrombospondin, hevin, secreted protein acidic and rich in cysteine, sema3a, and BDNF (4).

Research by Uda et al. (44) has shown that chronic treadmill running stimulates the proliferation of astrocytes in the subgranular zone of the dentate gyrus, suggesting a cellular basis for mediating both exercise-induced hippocampal neurogenesis and exercise-induced improvements in learning and memory. Induction of neurogenesis, particularly prior to encoding a memory, may help to facilitate memory function via increased neural network capacity and avoidance of interference effects. Exercise-related alterations in astrocytes may, in part, be responsible for the commonly observed neurogenesis effects from exercise (34). Furthermore, BDNF is an important neurogenic factor that has been hypothesized to help mediate the relationship between exercise and memory and specifically may mediate the effects of exercise on hippocampal neurogenesis (28). Moreover, BDNF may also help increase astrocyte-specific binding proteins as well as increase the production of myelin basic proteins in oligodendrocytes (17). Astrocytes, themselves, may also increase the production of BDNF (38). In addition to BDNF, IGF-1 may play a critical role in episodic memory function and also may be activated via exercise (24), including resistance exercise. Exercise-induced activation of IGF-1 may also have astrocyte implications as IGF-1 has been shown to play an important role in protecting neurons against oxidative damage (3). Research by Lloyd et al. (23) has shown that aerobic exercise can increase mTOR signaling in astrocytes (resistance exercise has also been shown to increase mTOR signaling), which plays an important role in learning and memory, as well as cell growth, proliferation, and survival.

Exercise-Specific Effects on Astrocytes

Relatedly, exercise has been shown to increase the size and complexity of astrocytes (39). This is a noteworthy finding as glial changes may precede neuronal alterations in the progression of Alzheimer's disease (AD) (5). Thus, exercise may serve as an appropriate strategy to reverse these effects. For example, in a mouse model of AD, both voluntary running and an enriched environment led to an increase in the surface and volume of glial fibrillary acidic protein (GFAP)-positive profiles (39). Furthermore, these stimuli also reversed atrophic changes observed in AD-like pathology (39). Thus, exercise may help to attenuate astrogliodegeneration induced by AD. Similar findings in diabetic rats have been observed in that exercise reversed spatial memory impairment induced by diabetes and increased the density of GFAP-positive astrocytes (12). Other work in AD models also suggests that voluntary wheel running accelerates glymphatic clearance, improves astrocytic AQP4 expression and polarization, and protects mice against synaptic dysfunction and spatial memory decline (21). Recent animal work also demonstrates that exercise increases BDNF, hippocampal neurogenesis, and memory in an Alzheimer's model (8). Exercise may also help to prevent Aβ seeding by activating microglia cells (47).

Neurons generate energy (adenosine triphosphate) primarily through oxidative phosphorylation, whereas astrocytes exhibit relatively high levels of glycolysis. Increased oxidation of lactate within the mitochondria may enhance neuronal oxidative phosphorylation and thus astrocyte-produced lactate may be an energetic source for neurons. As an example, this astrocyte-produced lactate can be shuttled to the neuron via the astrocyte–neuron lactate shuttle (ANLS) system, which has been shown to fuel the brain during exhaustive exercise to maintain endurance capacity (33). This ANLS system may also influence long-term memory formation. Exercise may help to increase levels of astrocytes (7) as well as the effectiveness of the ANLS by upregulating astrocytic lactate transporter levels (43). In addition to its effects on this

astrocyte shuttle system, exercise may help to attenuate age-associated astrocyte hypertrophy/reactivity (22), a characteristic of brain aging.

Conclusions

In conclusion, this brief primer highlights the role of astrocytes in subserving memory function and the role astrocytes may play in mediating the relationship between exercise and episodic memory function. Although additional experimental work is needed, astrocytes appear to play an important role in the exercise–memory interaction. For example, exercise may increase astrocytic size, attenuate astrogliodegeneration, improve astrocytic AQP4 expression, and increase astrocytic transporter levels. These effects, in turn, may help to increase the number of synapses that neurons form, increase the number of synaptic structures, and increase presynaptic function and postsynaptic receptor localization. Ultimately, these effects may help influence LTP and episodic memory function. Future work should continue to experimentally evaluate the complex interactions between exercise, glial cell function, and other key molecular mediators (e.g., BDNF and IGF-1) of episodic memory function. Such work should also evaluate whether there is an optimal intensity and duration of exercise to elicit these potential beneficial effects.

Conflict of interest

There are no conflicts of interest and no funding was used to prepare this manuscript.

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