



On the Run for Hippocampal Plasticity

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Accumulating research in rodents and humans indicates that exercise benefits brain function and may prevent or delay onset of neurodegenerative conditions. In particular, exercise modifies the structure and function of the hippocampus, a brain area important for learning and memory. This review addresses the central and peripheral mechanisms underlying the beneficial effects of exercise on the hippocampus. We focus on running-induced changes in adult hippocampal neurogenesis, neural circuitry, neurotrophins, synaptic plasticity, neurotransmitters, and vasculature. The role of peripheral factors in hippocampal plasticity is also highlighted. We discuss recent evidence that systemic factors released from peripheral organs such as muscle (myokines), liver (hepatokines), and adipose tissue (adipokines) during exercise contribute to hippocampal neurotrophin and neurogenesis levels, and memory function. A comprehensive understanding of the body–brain axis is needed to elucidate how exercise improves hippocampal plasticity and cognition.

There is a global increase in physical inactivity (Guthold et al. 2008; Dumith et al. 2011; Hallal et al. 2012; Kohl et al. 2012). Sedentary behavior is associated with increased risk of cognitive decline, whereas exercise boosts brain function (Duzel et al. 2016). Moreover, multiple neurological and neurodegenerative diseases, and conditions such as stroke, traumatic brain injury, and substance addiction, which lack effective medications, are ameliorated by exercise (Table 1). Research into the underlying cellular mechanisms has shown that in rodents running results in structural, neurochemical, mitochondrial, and vascular changes in the brain (Neeper et al. 1996; Eadie et al. 2005; Stranahan et al. 2007; Dietrich et al. 2008; van Praag, 2008; Duzel et al. 2016). In this review, we will focus on the hippocampus, a brain area that is essential

for learning and memory and exhibits extensive functional plasticity in response to exercise. In the dentate gyrus (DG) of the hippocampus, the production of new neurons is increased by voluntary wheel running in rodents in association with enhanced synaptic plasticity and memory function (van Praag et al. 1999a,b; Vivar et al. 2013; Voss et al. 2013). We will discuss local factors in the hippocampus such as neurotrophins and neurotransmitters as well as distal peripheral components (myokines, hepatokines, and adipokines) that may mediate changes in neural plasticity as a result of exercise (Fig. 1).

EXERCISE AND THE HIPPOCAMPUS

The hippocampus is critical for the acquisition of new memories (Squire 1992; Riedel et al. 1999;

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Table 1. Exercise and neurological disorders across humans and animal model studies, with focus on the hippocampus

Disease	Humans	Animals	Hippocampus	References
Alzheimer's disease	↑ Global cognition	↑ Learning and memory ↓ Anxiety ↑ Sensorimotor function ↑ Exploratory behavior	↓ Aβ load, APP ↓ or ↔ Tau AT 100 epitope ↓ IL-1β, TNF-α ↑ LTP ↑ Neurogenesis	Heyn et al. 2004; Adlard et al. 2005; Lautenschlager et al. 2008; Baker et al. 2010; Belarbi et al. 2011; Garcia-Mesa et al. 2011; Liu et al. 2011; Rodriguez et al. 2011; Marlatt et al. 2013; Zhao et al. 2015
Anxiety	↓ State anxiety ↑ Sleep quality	↓ Anxiety-like behaviors ↓ Fear relapse ↓ Corticosterone response ↓ Social avoidance behavior ↓ Learning impairments ↓ Sympathetic nervous system activation Improved diurnal rhythms	↑ Glucocorticoid receptors ↑ BDNF ↑ Inhibitory interneuron mechanisms (ventral hippocampus) ↓ Melanin-concentrating hormone ↓ Serotonin responsiveness to stressors	Oldridge et al. 1991, 1995; Dishman 1997; Broocks et al. 1998; Russo-Neustadt et al. 1999; Bandelow et al. 2000; Greenwood et al. 2003, 2008, 2013; Fulk et al. 2004; Broman-Fulks and Storey 2008; Smits et al. 2008; Carmeli et al. 2009; Wedekind et al. 2010; Herring et al. 2011, 2015; Goldin et al. 2012; Jazaieri et al. 2012; Goldin et al. 2013; Hovland et al. 2013; Schoenfeld et al. 2013; Patki et al. 2014; Mika et al. 2015; Otsuka et al. 2015; Pan-Vazquez et al. 2015; Kim and Han 2016
Autism	↓ Stereotypic behavior ↑ Cognition and attention ↑ or ↔ Social-emotional functioning	↓ Aggressive tendencies ↑ Spatial learning ↑ Motor coordination and balance	↑ Neurogenesis ↑ Reelin ↑ BDNF ↑ LTP	Kern et al. 1982; Levinson and Reid 1993; Rosenthal-Malek and Mitchell 1997; Prupas and Reid 2001; Bass et al. 2009; Pan 2010; Nicholson et al. 2011; Oriol et al. 2011; Rosenblatt et al. 2011; Bahrami et al. 2012; Gabriels et al. 2012; Kim et al. 2013; Movahedi et al. 2013; Seo et al. 2013; Ward et al. 2013
Alcoholism	↓ Drinking days and heavy drinking days ↑ Days abstinent ↓ and ↔ Depression, anxiety, and abstinence self-efficacy ↓ Blood cortisol and ACTH compared with controls	↓ Alcohol preference and consumption ↓ Alcohol withdrawal score ↓ Blood cortisol	↑ BDNF ↑ Neurogenesis	Sinyor et al. 1982; Crews et al. 2004; Vedamurthachar et al. 2006; Coiro et al. 2007; Brown et al. 2009, 2014b; Ehringer et al. 2009; Klintsova et al. 2012; Motaghinejad et al. 2014, 2015; Gallego et al. 2015

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Table 1. Continued

Disease	Humans	Animals	Hippocampus	References
Dementia	↑ Balance	↓ Cognitive impairment	↑ Neurogenesis	Van de Winckel et al. 2004; Cristofolletti et al. 2008; Eggermont et al. 2009a,b; Conradsson et al. 2010; Hwang and Choi 2010; Kemoun et al. 2010; Venturelli et al. 2011; Volkers and Scherder 2011; Forbes et al. 2015; Telenius et al. 2015a,b; Choi et al. 2016
	↓ Agitation/aggression/disinhibition		↑ BDNF	
	↓ Apathy			
	↑ or ↔ Cognitive function			
Depression	↑ Ability to perform activities of daily living			Craft and Landers 1998; Stathopoulou et al. 2006; Daley 2008; Foley et al. 2008; Rethorst et al. 2009; De Zeeuw et al. 2010; Forsman et al. 2011; Krogh et al. 2011; Kiuchi et al. 2012; Cooney et al. 2013; Danielsson et al. 2013; Lee et al. 2013; Silveira et al. 2013; Josefsson et al. 2014; Lu et al. 2014; Sadeghi et al. 2016a,b
	↓ or ↔ Depressive symptoms	↓ Depressive symptoms (↓ immobility time in forced swim test; ↑ sucrose preference)	↓ Toll-like receptor 4	
	↓ Depression symptoms		↓ IL-1β and IL-18	
	↑ Coping strategies		↑ Neurogenesis	
	↑ Episodic memory		↑ VEGF, BDNF	
			↔ 5-HT	
Epilepsy	↑ Seizure threshold	↓ Seizure frequency	↑ PV+ interneurons	Gotze et al. 1967; Nakken et al. 1990; Eriksen et al. 1994; Arida et al. 1999; McAuley et al. 2001; Heise et al. 2002; Arida et al. 2004, 2007, 2008, 2009, 2010; Rambo et al. 2009; Reiss et al. 2009; Tutkun et al. 2010; Eom et al. 2016
	↓ or ↔ Seizure frequency	↓ Seizure intensity	↓ CA1 hyper-responsiveness	
	↓ EEG epileptiform discharges	↓ Susceptibility to kindling and chemically induced seizures	↑ ITP	
	↓ Seizures during mental and physical activity			
	↓ Comorbidities (depression, anxiety)			
	↑ Vigilance and attention			
Huntington's disease	~ ↑ Motor function (gait speed and balance) and coordination	↑ Corticostriatal connectivity	↓ Neurogenesis	Pang et al. 2006; van Dellen et al. 2008; Cepeda et al. 2010; Potter et al. 2010; Renoir et al. 2012; Busse et al. 2013; Harrison et al. 2013; Khalil et al. 2013; Kloos et al. 2013
	↑ Cognitive measures	↑ or ↓ Gait function and motor coordination		
		↑ or ↓ Cognitive dysfunction		
		Delays circadian dysfunction		

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Table 1. Continued

Disease	Humans	Animals	Hippocampus	References
Multiple sclerosis	↔ or Moderately ↓ relapse rates ↔ Markers of immune function ↓ Physical disability progression ↓ MRI brain lesion volumes ↑ Neuroperformance (walking speed and endurance) ↑ Motor function (gait, balance, strength) Improved mood ↓ or ↔ Depressive symptoms ↑ Spatial and verbal working memory ↑ Attention and processing speed ↓ Sleep disturbance (insomnia + daytime sleepiness)	Delay disease onset ↓ Demyelination ↓ Duration of relapse ↓ Physical disability ↔ or ↓ Inflammatory response ↓ Dendritic spine loss ↓ Synaptic deficits ↑ NGE, BDNF ↓ Pain hypersensitivity ↓ Oxidative stress ↓ Spatial learning deficits ↔ Spatial memory ↑ Motor function		Le Page et al. 1994, 1996; Motl and Snook 2008; Motl et al. 2008; Rossi et al. 2009; Motl and Pilutti 2012; Patel and White 2013; Benson et al. 2015; Pryor et al. 2015; Alvarez-Saavedra et al. 2016; Souza et al. 2016
Parkinson's disease			↑ Neurogenesis	Cruise et al. 2011; Shulman et al. 2013; Tomlinson et al. 2013; Nascimento et al. 2014; Park 2014; Uc et al. 2014; Canning et al. 2015; Dashipour et al. 2015; David et al. 2015; Klein et al. 2016
Posttraumatic stress disorder (PTSD)	↓ PTSD symptoms ↓ Depressive symptoms	↓ Acoustic startle response ↑ Stress resilience ↑ Elevated plus maze activity ↑ Spatial learning ↓ Plasma corticosterone ↓ Depressive-like behavior ↓ Anxiety-like behavior	↑ BDNF ↑ Neuropeptide Y ↑ Phosphorylated δ-opioid receptor ↑ Neurogenesis	Kim and Seo 2013; Mitchell et al. 2014; Patki et al. 2014; Van Der Kolk et al. 2014; Hoffman et al. 2015; Powers et al. 2015; Rosenbaum et al. 2015a,b

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Table 1. Continued

Disease	Humans	Animals	Hippocampus	References
Schizophrenia	↑ Neurocognitive function	↓ Behavioral abnormalities and deficits	↑ or ↔ hippocampal volume	Beebe et al. 2005; Acil et al. 2008; Pajonk et al. 2010; Scheewe et al. 2012, 2013a,b; Battaglia et al. 2013; Falkai et al. 2013; Kim et al. 2014a,b; Park et al. 2014; Vancampfort et al. 2014; Kimhy et al. 2015, 2016
	↑ Serum BDNF	↑ NMDA receptor and BDNF expression	↑ N-acetylaspartate to creatine ratio	
	↑ Short-term memory		↑ NMDA receptor expression	
	↓ Positive and negative symptoms			
Stroke	↓ Anxiety, ↓ or ↔ depression			
	↑ Mental and physical QoL			
	↓ Psychotic symptom severity			
	↑ QoL and ability to perform activities of daily living	↑ Spatial memory recovery	↑ Blood flow	Stummer et al. 1994; Lee et al. 2003; Ding et al. 2004; Sim et al. 2004, 2005; Ploughman et al. 2005; Quaney et al. 2009; Rand et al. 2010; Chen and Rimmer 2011; Graven et al. 2011; Cumming et al. 2012; Dean et al. 2012; Zedlitz et al. 2012; Billinger et al. 2014; Moore et al. 2014; Ahn et al. 2016; Himi et al. 2016
	↓ Comorbid cardiovascular disease risk	↓ Ischemia-induced cell death	↑ Neurogenesis	
	↓ Depressive symptoms		↑ BDNF	
	↑ Executive function and memory		↓ Myelin damage	
Substance abuse	↓ Poststroke fatigue		↓ Microvessel damage	
	↑ Cognition			
	↓ Risk of daily smoking	↓ Drug (amphetamine, cocaine, nicotine) intake	↑ Bcl-2	Kanarek et al. 1995; Smith et al. 2008; Korhonen et al. 2009; Zlebnik et al. 2010, 2012; Terry-McElrath and O'Malley 2011; Miladi-Gorji et al. 2014; Mokhtari-Zaer et al. 2014; Wang et al. 2014; Sobieraj et al. 2016
	↓ Risk of illicit drug use	↓ Drug-seeking behavior during extinction and reinstatement	↑ LTP	
		↑ Cognitive function		
Traumatic brain injury	↑ Mood	↓ Withdrawal signs		
	↑ Gait	↓ Susceptibility to seizures	↑ BDNF	Charrette et al. 2016; Mychasiuk et al. 2016; Setkowicz et al. 2016; Weinstein et al. 2016
	↑ Ambulatory status	↑ Motor function		
	↑ Aerobic endurance	↑ Cognitive function		

β , Amyloid β ; APP, amyloid precursor protein; IL, interleukin; TNF- α , tumor necrosis factor α ; LTP, long-term potentiation; BDNF, brain-derived neurotrophic factor; ACTH, adrenocorticotrophic hormone; VEGF, vascular endothelial growth factor; 5-TH, 5-hydroxytryptamine (serotonin) receptors; PV, parvalbumin; CA1, Cornu Ammonis 1; NGF, nerve growth factor; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder; NMDA, N-methyl-D-aspartate; QoL, quality of life; Bcl-2, B-cell lymphoma 2.

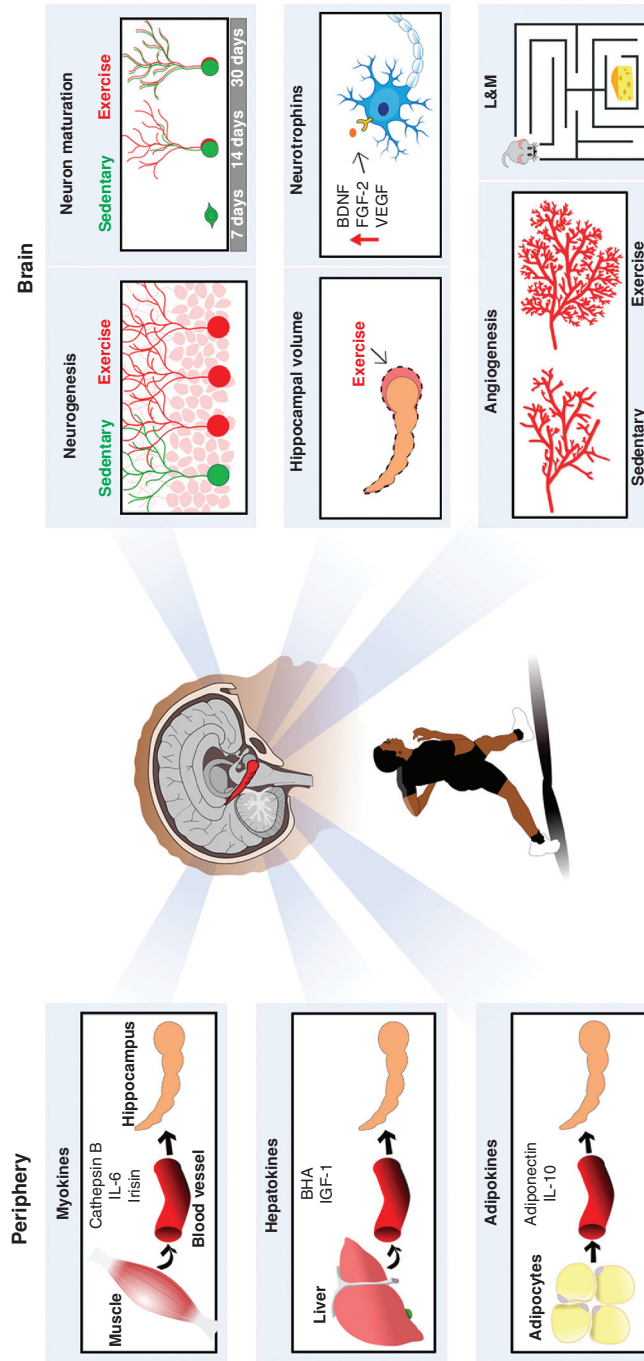


Figure 1. Running induces structural and functional plasticity in the hippocampus. Illustration summarizing how running enhances neurogenesis, accelerates new neuron maturation, augments hippocampal volume (in humans), and promotes angiogenesis. Enhanced neural plasticity and improved memory function may be supported by central and peripheral factors. Increased levels of growth factors in the brain may result, in part, from systemic factors secreted by muscle (myokines), liver (hepatokines), and fat cells (adipokines). BHA, β -Hydroxybutyrate; BDNF, brain-derived neurotrophic factor; FGF-2, fibroblast growth factor 2; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; IL-10, interleukin 10; L&M, learning and memory; VEGF, vascular endothelial growth factor.

Scoville and Milner 2000) and is affected by aging and age-related cognitive disorders, including progressive atrophy of hippocampal volume in humans (Hackert et al. 2002; Raji et al. 2009; Duzel et al., 2016), a process that may be attenuated or ameliorated by exercise (Erickson et al. 2009, 2011, 2014). Higher fitness levels are associated with larger hippocampal volume, and better performance on memory tests (Erickson et al. 2009, 2011; Voss et al. 2013). Intervention studies show that aerobic training 3 days per week for at least 3 months to 1 year can prevent and/or reverse the age-related decline in hippocampal volume (Erickson et al. 2011; Maass et al. 2015; ten Brinke et al. 2015). Interestingly, the exercise-induced increase in grey matter volume seems to occur in the hippocampus (Maass et al. 2015; Duzel et al. 2016), entorhinal (Whiteman et al. 2016), and prefrontal cortex (Erickson et al. 2014), with no change in the thalamus or caudate nucleus (Erickson et al. 2011).

The hippocampus consists of three subfields: area CA1, area CA3, and the DG; each play a role in memory function. Area CA1 is considered to encode memories (Nakazawa et al. 2004), whereas area CA3 is thought to mediate retrieval of complete memories from partial information (pattern completion) (Nakazawa et al. 2002, 2003). The DG is deemed important for spatial pattern separation, the process by which similar incoming information or stimuli is transformed into distinct nonoverlapping experiences (Leutgeb et al. 2007; McHugh et al. 2007; Kesner and Rolls 2015). The DG is unique because it can generate new neurons in the adult brain (Altman and Das 1965), which are considered to play a functional role in spatial memory and pattern separation (Fig. 2) (Vivar et al. 2013). Residual stem cells located in the DG inner granule cell layer continue to proliferate and differentiate in mammals, including humans (Kuhn et al. 1996; Eriksson et al. 1998; Spalding et al. 2013). The stem/progenitor cells consist of quiescent type-1 radial glia-like cells that express glial fibrillary acidic protein (GFAP), nestin and Sox2, and type-2 cells expressing Sox-2 that can generate both astrocytes as well as rapidly proliferating

neuronal progenitor cells (NPCs) that differentiate into mature granule cells over several weeks (Kronenberg et al. 2003; Kempermann et al. 2004; Bonaguidi et al. 2011; Encinas et al. 2011; Gebara et al. 2016). The proliferation, survival, and integration of new neurons can be up- or down-regulated by intrinsic factors, pathological events, and activity (for review, see Zhao et al. 2008; Hsieh and Zhao 2016).

Running increases neurogenesis in the DG of the hippocampus (for review, see van Praag 2008; Vivar et al. 2013; Voss et al. 2013; Patten et al. 2015). The neurogenic response to running results in an ~2–3-fold increase in new neurons, depending on genetic background (Clark et al. 2011; Gregoire et al. 2014), age (van Praag et al. 2005; Kronenberg et al. 2006; Kannangara et al. 2011; Marlatt et al. 2012), running wheel type (Creer et al. 2010), labeling method used (bromodeoxyuridine [BrdU], retroviral vector [Vivar et al. 2016], or doublecortin [DCX] [Kuhn et al. 2016]), and distance run (Clark et al. 2011). Running-induced neurogenesis is localized to the dorsal rather than the ventral DG (Bolz et al. 2015; Vivar et al. 2016). The dorsal aspect of the hippocampus is considered important for spatial navigation (Moser et al. 1995), whereas the ventral hippocampus seems to be more attuned to changes in mood (Henke 1990; Kjelstrup et al. 2002). Consistently, running is associated with improved spatial memory function (van Praag et al. 1999b; Anderson et al. 2000; van der Borght et al. 2007; Clark et al. 2008; Patten et al. 2015). New neurons are also considered to play a role in DG-mediated pattern separation (Clelland et al. 2009; Sahay et al. 2011), the ability to differentiate similar information (Aimone et al. 2011). Running improves fine discrimination (Creer et al. 2010; Bolz et al. 2015) as does enhancement of adult neurogenesis in a mouse model with conditional ablation of *BAX*-dependent programmed cell death in neural progenitors (Sahay et al. 2011). It has also been suggested that increasing neurogenesis by running may cause forgetting by weakening preexisting memories in mice (Akers et al. 2014; Epp et al. 2016). A recent study in rats, however, could not replicate these results,

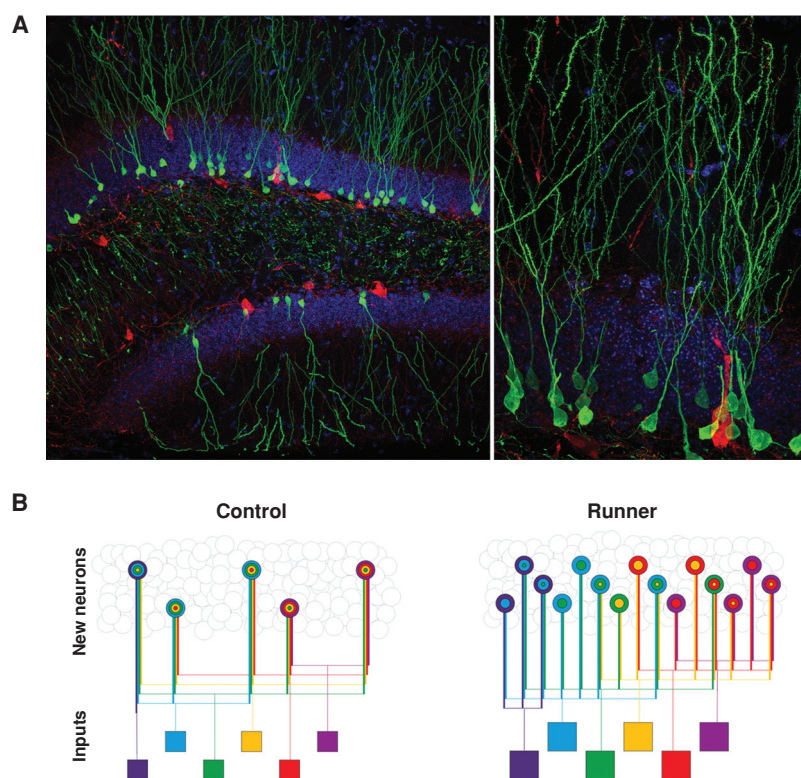


Figure 2. Neurogenesis in the adult mouse dentate gyrus (DG) of the hippocampus and a diagram of modification of new neuron network by running. (A) Photomicrographs of new neurons (green) in a coronal mouse brain section; a mouse 2 months after injection with retrovirus-expressing green fluorescent protein (GFP) in the DG. Section was stained for GFP (green) and GABAergic inhibitory interneuron marker parvalbumin (red), and nuclei were labeled with 4',6-diamidino-2-phenylindole (DAPI, blue). (B) Diagram illustrating how running reorganizes the network of new hippocampal neurons (Vivar et al. 2016). One month of running in male C57Bl/6 mice enhanced DG neurogenesis (threefold). Afferent input (squares) was also increased, but less so (twofold). The resulting change in new neuron connectivity may promote sparse encoding of information and result in a more robust memory-processing system. The expansion of the neural network and enhanced distribution of information over new DG cells may provide more structural redundancy in which failure of one pathway can be compensated for by another.

casting doubt on this hypothesis (Kodali et al. 2016).

Although a running-induced increase in new neuron number may underlie, in part, the benefits for cognitive function, qualitative changes in maturation, morphology, and connectivity are likely also important. Running may shorten the cell cycle of rapidly amplifying progenitor cells (Farioli-Vecchioli et al. 2014; see, however, Fischer et al. 2014) and accelerate neuronal maturation of adult-born DG neurons (Zhao et al. 2006; Piatti et al. 2011; Steib et al. 2014). In particular, retroviral labeling studies

(van Praag et al. 2002; Zhao et al. 2006) have shown that running promotes spine formation in the outer molecular layer of adult-born dentate granule cell dendrites (Zhao et al. 2014). In addition, dendritic spine motility, total dendritic length, branch points, dendritic complexity, and mitochondria density are significantly higher in runners' adult-born DG neurons for up to 3 weeks post-retroviral injection (Zhao et al. 2006; Dietrich et al. 2008; Steib et al. 2014). However, by the fourth week, dendritic morphology and mitochondria content are indistinguishable from adult-born DG neurons



in the sedentary brain (Zhao et al. 2006, 2014; Steib et al. 2014). Similar observations were made in a live imaging study in mice housed in an enriched environment containing running wheels (Gonçalves et al. 2016). Accelerated maturation in runners may vary along the temporal axis, with dorsal aspect exhibiting the fastest maturation (Piatti et al. 2011).

Running also alters the circuitry into which new neurons integrate (Vivar et al. 2016). Analysis of the direct afferent inputs to 1-month-old newly born neurons using a dual-virus selective neuroanatomical tracing approach (Vivar et al. 2012) showed that running expanded the number of afferent cells synapsing onto newborn neurons. Running recruited presynaptic inputs from the entorhinal cortex, mammillary nuclei, and medial septum (Vivar et al. 2016). These brain regions are important for relaying content and context of experiences (Knierim et al. 2014; Knierim 2015; Kropff et al. 2015), spatial-temporal information processing (Vann 2010; Dillingham et al. 2015), and initiating hippocampal theta rhythms (Thinschmidt et al. 1995; Vertes et al. 2004). Within the hippocampus, running reduced the ratio of inhibitory interneurons and glutamatergic mossy cell innervation to new neurons (Vivar et al. 2016). However, inhibitory synaptic transmission onto newborn neurons was not affected, and excitatory synaptic transmission showed only a small decrease in amplitude but not frequency (Vivar et al. 2016). Achieving the same excitatory and inhibitory drive with less afferent input per neuron may result in more efficient integration of new neurons. Moreover, the overall ratio of afferent cells to newborn neurons was decreased (Vivar et al. 2016). A reduction in inputs converging onto individual neurons may be conducive to pattern separation by facilitating sparse activation (Fig. 2).

NEUROTRANSMITTERS

The elaborate network connectivity of newly born neurons with structures throughout the brain is consistent with involvement of multiple neurotransmitters in the development and integration of newly born neurons (for review, see

Suh et al. 2009). Glutamate and γ -aminobutyric acid (GABA) are the primary excitatory and inhibitory neurotransmitters, respectively, in the brain. Both regulate the integration and survival of newly born neurons (Ge et al. 2006; Tashiro et al. 2006). Glutamate is also important for exercise-induced changes in DG synaptic plasticity. Running enhances DG long-term potentiation (LTP), a form of synaptic plasticity that is considered a cellular model for learning and memory (Bliss and Collingridge 1993), in vivo and in vitro (van Praag et al. 1999a; Farmer et al. 2004; Vasuta et al. 2007; Bruel-Jungerman et al. 2009; O'Callaghan et al. 2009; Liu et al. 2011), potentially by lowering the LTP induction threshold. Indeed, weak theta-patterned stimulation that did not produce LTP in the DG of controls, elicited long-lasting LTP in rats housed with a running wheel (Farmer et al. 2004). Acutely, voluntary movement and sensory stimulation can elicit theta pattern activity in the hippocampus (Bland 1986; Czurko 1999; Bland and Oddie 2001), specifically in the CA1 and DG. Thus, exercise may “prime” the network to learn by initiating oscillations that promote plasticity (Greenstein et al. 1988; Pavlides et al. 1988; Christie and Abraham 1992; Abraham et al. 2001; Orr et al. 2001). The contribution of new neurons to running-induced DG plasticity is supported by recordings from individual newly born neurons in slices derived from mice housed under running enrichment conditions, which exhibited increased LTP (Schmidt-Hieber et al. 2004). Running elevates DG gene expression of glutamate receptor subunits NR2A, NR2B, and glutamate receptor 5 (Farmer et al. 2004). The NR2B *N*-methyl-D-aspartate (NMDA) receptor subunit is highly expressed in new neurons (Ge et al. 2007; Kheirbek et al. 2012) and NR2B overexpression facilitates LTP induction (Tang et al. 1999, 2001).

Running also modulates inhibitory neurotransmission. Recent research shows increased expression levels of GABA receptor subunits and GAD67 in hippocampal subfields, including the DG (Hill et al. 2010). In addition, exercise elevated ventral DG extracellular GABA release and vesicular GABA transporter expression. Enhanced local inhibition reduced DG

expression of immediate early genes (Schoenfeld et al. 2013). Increased inhibition may attenuate anxiety and improve cognition. Indeed, reduced inhibitory tone in the DG–CA3 area has been associated with aging-related memory deficits (Bakker et al. 2012). Running has also been shown to alter various other neurotransmitters and neuromodulators (for a review, see Basso and Suzuki 2017), such as monoamines (dopamine, serotonin, norepinephrine) (Chaouloff 1989; Dishman 1997), endocannabinoids (Dietrich and McDaniel 2004; Fuss and Gass 2010; Tantimonaco et al. 2014), and opioids (Sforzo 1989), which can contribute to changes in hippocampal synaptic plasticity. The serotonergic (5-HT) system plays an important role in the exercise-induced increase in adult neurogenesis (Klempin et al. 2013). Recent research has identified 5-HT₃ receptor subunit signaling as an underlying mechanism. Ablation of the 5-HT₃ receptor subunit abolishes running-induced neurogenesis and reduces antidepressant effects (Kondo et al. 2015). Learning, measured by contextual fear conditioning, was intact, consistent with a study in which adult neurogenesis was ablated by X-irradiation in runners (Clark et al. 2008).

BRAIN-DERIVED NEUROTROPHIC FACTOR

Neurotrophins play a significant role in brain plasticity (Intlekofer and Cotman 2013). One of the first growth factors associated with exercise was brain-derived neurotrophic factor (BDNF). In animal models, running increases BDNF expression levels in the hippocampus (Neeper et al. 1995; Kobilov et al. 2011a; Marlatt et al. 2012; Abel and Rissman 2013), in association with improvements in hippocampal plasticity, spatial memory, and object recognition (Vaynman et al. 2004; Griffin et al. 2009; Cassilhas et al. 2012; Gomes da Silva et al. 2012). In humans, exercise-induced increases in BDNF serum levels are associated with changes in hippocampal volume (Erickson et al. 2011). Conversely, reduced BDNF serum levels are observed with age-related decline in hippocampal volume (Erickson et al. 2010). BDNF promotes synaptic plasticity through

downstream targets, cAMP-response element-binding (CREB) protein, synapsin I, and synaptophysin, while simultaneously increasing its own messenger RNA (mRNA) and its receptor tyrosine kinase B (TrkB) (Vaynman et al. 2003, 2006). Blocking hippocampal BDNF in rats precludes exercise-induced cognitive enhancement and hippocampal plasticity (Vaynman et al. 2004). In addition, ablation of the TrkB receptor in neural progenitor cells abolishes the neurogenic response to running (Li et al. 2008). Analysis of the hippocampal subfields shows that exercise increases BDNF mRNA levels in the DG rather than in area CA1 (Farmer et al. 2004).

Exercise-induced changes in neurotrophin levels are likely mediated by several neural cell types. Astrocytes are closely associated with new neuron dendrites (Vivar et al. 2012) and support their development (Sultan et al. 2015). Astrocytes synthesize BDNF and contain TrkB receptors (Zafra et al. 1992; Miklič et al. 2004). Running may up-regulate hippocampal astrocyte number (Li et al. 2005; Saur et al. 2014), lengthen their processes and increase cell body size (Saur et al. 2014; Brockett et al. 2015), and elevate TrkB expression levels (Fahimi et al. 2016). Other nonneuronal cell types may also play a role. Macrophage migration inhibitory factor is a cytokine that is up-regulated by exercise and can induce BDNF expression (Moon et al. 2012). Microglia number is down-regulated by running (Gebara et al. 2013). However, ablation of hippocampal microglia impairs exercise-induced neurogenesis (Vukovic et al. 2012), indicating that cytokines produced by microglia may be required to maintain neurogenic processes (Walton et al. 2006; Ziv et al. 2006; Speisman et al. 2013).

(Epi)genetic factors also play an important role in the function of this neurotrophin. A single-nucleotide polymorphism of the BDNF gene (Val/Met polymorphism) that occurs in 20% to 30% of Caucasians decreases activity-dependent BDNF secretion (Egan et al. 2003; Chen et al. 2004) and is associated with increased susceptibility to depression and anxiety-related disorders (Sen et al. 2003; Verhagen et al. 2010), reduced memory function (Egan et al. 2003; Soliman et al. 2010), and impaired

neural plasticity that is resistant to antidepressants (Bath et al. 2012). In addition, the effect of exercise on hippocampal volume in human subjects is attenuated in Met carriers as compared with Val/Val subjects (Brown et al. 2014a). More recent evidence shows that in adult mice with this polymorphism the running-induced increase in BDNF and neurogenesis are attenuated (Ieraci et al. 2016). These results suggest that exercise may support cognition, in part, through BDNF. The exercise-induced increase in BDNF may also be mediated through epigenetic changes (Gomez-Pinilla et al. 2011; Abel and Rissman 2013). Histone H3 acetylation is increased by exercise and associated with enhanced gene transcription, and can specifically up-regulate BDNF gene expression (Gomez-Pinilla et al. 2011; Ieraci et al. 2015). Hippocampal histone deacetylase (HDAC), on the other hand, can be down-regulated by exercise (Abel and Rissman 2013), and thereby up-regulate BDNF expression (Intlekofer and Cotman 2013; Sleiman et al. 2016).

CEREBROVASCULAR PLASTICITY

Exercise modulates the cerebrovasculature, which may allow for better perfusion, delivery of oxygen, nutrients, neurotrophins, and other factors that may promote brain function. Acute bouts of walking and running increase cerebral blood flow (CBF) in several regions within the animal brain, including the hippocampus (Osborne 1997; Nakajima et al. 2003; Nishijima and Soya 2006; Nishijima et al. 2012, 2016), cortex (Delp et al. 2001; Gu et al. 2003), and striatum (Osborne 1997), but not the olfactory bulb (Nishijima et al. 2012) or hypothalamus (Delp et al. 2001), suggesting region-specific control of CBF by exercise. In the rat hippocampus, CBF is increased soon after walking initiation and returns to baseline levels right afterward (Nakajima et al. 2003). Longer bouts resulted in prolonged CBF elevation after cessation of running (10–20 min) (Nishijima and Soya 2006). Thus, exercise duration and intensity differentially modulate CBF. Neuronal activity may drive regional hippocampal CBF increased by exercise. Infusion of tetrodotoxin

(TTX), NMDA receptor antagonist (MK-801), and NO synthase inhibitor (L-NAME) suppressed the increase in hippocampal CBF induced by walking (Nishijima et al. 2012). In humans, exercise also increases CBF (Querido and Sheel 2007; Secher et al. 2008; Ogoh and Ainslie 2009) and counteracts age-related decline in CBF (Ainslie et al. 2008; Viboolvorakul and Patumraj 2014) and cerebrovascular reactivity (Barnes et al. 2013; Murrell et al. 2013). In addition, gadolinium contrast imaging in humans revealed hippocampal perfusion changes after long-term exercise in young (Pereira et al. 2007) and older adults (Maass et al. 2015).

Prolonged exercise training improves cerebrovascular plasticity in rodents (Lange-Aschenfeldt and Kojda 2008; Tarumi and Zhang 2014; Barnes 2015), likely by increasing angiogenesis in several brain regions, including the hippocampus (van Praag et al. 2005; Clark et al. 2009; van der Borght et al. 2009), striatum (Clark et al. 2009), cerebellum (Black et al. 1990; Lopez-Lopez et al. 2004), and cortex (Swain et al. 2003; Viboolvorakul and Patumraj 2014). The increase in angiogenesis is preserved in aged animals (Ding et al. 2006). Vascular endothelial growth factor (VEGF) may mediate exercise-induced vascular plasticity, adult neurogenesis, and communication between peripheral tissues and brain (Carmeliet 2003; Fabel et al. 2003; Cotman et al. 2007; Udo et al. 2008). VEGF is involved in blood vessel formation (Prior et al. 2003; Gavin et al. 2004; Kraus et al. 2004) and can attenuate the aged-related decline in neurogenesis (Licht et al. 2016). The importance of VEGF for neurogenesis was first shown in songbirds. A seasonal increase in neurogenesis in the higher vocal center of male canaries involves a testosterone-linked VEGF to BDNF signaling pathway (Louissaint et al. 2002). In rodents, overexpression of VEGF enhanced blood vessel proliferation in the hippocampus in association with an increase in hippocampal neurogenesis (Cao et al. 2004; Licht et al. 2011). VEGF may be required for exercise-induced hippocampal neurogenesis. Using a systemic pharmacological inhibitor of VEGF, Fabel et al. (2003) showed that VEGF is necessary for voluntary running-enhanced hip-

pocampal neurogenesis, supporting the link between physical activity, angiogenesis, and neurogenesis (Trejo et al. 2001; Voss et al. 2013).

PERIPHERAL ORGANS AND BRAIN FUNCTION

Parabiosis studies between young and aged animals have provided evidence that factors in blood can regulate vascular remodeling, CBE, and adult neurogenesis (Villeda et al. 2011; Katsimpardi et al. 2014). Peripheral organs such as skeletal muscle, adipose tissue, and liver secrete various molecules and vesicles into circulation to promote systemic homeostasis during exercise (Hansen et al. 2011; Pedersen and Febbraio 2012). Indeed, glucose and lipid metabolic adaptations to exercise are widely studied in these peripheral tissues. However, the effects of exercise-induced system metabolic changes on behavior and cognition as well as the underlying cellular mechanisms have largely remained unexplored. Below, we describe recent research that has begun to reveal metabolic energy metabolism pathways that may elicit and coordinate the adaptive responses to exercise in the brain.

Muscle

Skeletal muscle releases myokines (Pedersen and Febbraio 2008; Hawley et al. 2014) that may be linked to neural plasticity. This putative link is supported by clinical and basic research. For instance, children with Duchenne muscular dystrophy have cognitive deficits (Scheinfeld 1950; Black 1973; Florek and Karolak 1977; Bushby 1992; Lenk et al. 1993; Hinton et al. 2000). In addition, mdx (X-linked muscular dystrophy) mice have impaired memory function (Vaillend et al. 1995; Anderson et al. 2002). An important “master regulator” of muscle physiology is AMP-activated protein kinase (AMPK) (Hardie 2011). Activation of AMPK with an agonist, AICAR, decreased fat mass, increased oxygen consumption, and increased running endurance in sedentary mice by reprogramming muscle fibers to a type I phenotype in a PPAR δ -dependent manner (Narkar et al.

2008; Guerrieri et al. 2017). To determine whether the effects on endurance extended to brain function, we treated mice with AICAR and spatial memory was tested (Kobilo et al. 2011b, 2014). The observed enhancement of memory function by AICAR was precluded by muscle-specific AMPK α 2-subunit deficiency (Kobilo et al. 2014), supporting a link between muscle and cognition. Based on these findings, we set out to find the underlying mechanisms by treating L6 muscle cells with AICAR in culture and analyzing the conditioned media. Proteomic analysis led to identification of a novel myokine, cathepsin B (Ctsb), as a mediator of exercise-induced hippocampal plasticity (Moon et al. 2016).

Ctsb is a lysosomal thiol proteinase that has been implicated in a variety of physiological and pathological processes, including proteolytic maturation of proinsulin (Docherty et al. 1984; Steiner et al. 1984) and proalbumin (Judah and Quinn 1978; Quinn and Judah 1978; Matsuda et al. 1986), as well as cancer progression (Koblinkski et al. 2002). The role of Ctsb in the brain has been mainly studied under disease conditions, with contradictory results. In a nonhuman primate model of transient ischemia, treatment with a Ctsb inhibitor prevented neuronal cell death (Yoshida et al. 2002). In Alzheimer’s disease (AD) mouse model studies, some researchers report that Ctsb increased pathological processes (Hook et al. 2008) or was neuroprotective with antiamyloidogenic functions (Mueller-Steiner et al. 2006; Wang et al. 2012; Embury et al. 2016). In our recent study, Ctsb was increased in plasma by exercise across mammalian species, including mice, monkeys, and humans (Moon et al. 2016). In adult hippocampal progenitor cell cultures, Ctsb application enhanced the expression of neurotrophin BDNF and DCX, a marker for neuronal differentiation. In Ctsb knockout mice, impaired spatial memory function and dentate granule cell physiology was observed. In addition, the neurogenic and cognitive response to exercise was blunted in the Ctsb-deficient mice as compared with their littermates. It is noteworthy that Ctsb deficiency did not affect general locomotor activity or mood-related behaviors such



as sucrose preference and elevated T-maze. A role for *Ctsb* in cognition was also found in humans. The exercise-induced change in fitness was positively associated with performance on a complex-figure recall task that is considered to be hippocampus dependent (Vargha-Khadem et al. 1997; Maass et al. 2015). It will be of interest to determine in future studies whether there is a positive association between *Ctsb* levels and pattern separation performance.

Support for the idea that muscle energy metabolism affects brain function also comes from recent studies in mice that overexpress peroxisome proliferator-activated receptor γ coactivator (PGC-1 α) in muscle (Wrann et al. 2013; Agudelo et al. 2014). Exercise activates this transcriptional coactivator (Pilegaard et al. 2003; Finck and Kelly 2006), and in muscle-specific PGC-1 α -KO mouse, activity and maximal exercise capacity are reduced (Geng et al. 2010). Overexpression of PGC-1 α in muscle increased production of fibronectin type III domain containing 5 (FNDC5), which is cleaved and is secreted as irisin, a myokine that is involved in oxygen consumption, transition of white fat into brown fat, and thermogenesis (Boström et al. 2012). FNDC5 is primarily expressed in the brain (Teufel et al. 2002), including the hippocampus. FNDC5 deficiency impairs neuronal development (Hashemi et al. 2013). Thirty days of voluntary exercise increased FNDC5 mRNA in the quadriceps and hippocampus, but not the whole brain. Increased FNDC5 expression in cortical neuron cultures enhanced BDNF levels. In addition, peripheral up-regulation of FNDC5 increased hippocampal BDNF gene expression (Wrann et al. 2013). Exercise also elevates irisin in human plasma (Jedrychowski et al. 2015). A link to cognitive function remains to be determined. In another study, overexpression of PGC-1 α in mouse muscle regulated the kynurenine pathway and thereby protected these mice from stress-induced reduction of synaptic plasticity proteins in the brain, as well as from exhibiting depression-like behaviors (Agudelo et al. 2014).

Interleukin (IL)-6 is a cytokine with various physiological roles (Erta et al. 2012). IL-6 plasma level is significantly increased during exer-

cise, partially from contracting skeletal muscles (Pedersen et al. 2001; Rasmussen et al. 2011). Exercise-induced IL-6 from skeletal muscle can increase glycogenolysis in the liver to maintain blood glucose levels during exercise (Keller et al. 2001; Pedersen et al. 2001). IL-6 also plays a major role in energy homeostasis in the central nervous system (CNS). Studies with IL-6-deficient mice indicate that IL-6 can regulate appetite, energy expenditure, and is related to the development of obesity (Wallenius et al. 2002). IL-6 peripheral administration can be absorbed into the cerebrospinal fluid (CSF) (Banks et al. 1994). In addition, IL-6 is increased in the adult mouse brain after exercise (Nybo et al. 2002; Rasmussen et al. 2011). IL-6 levels are reportedly elevated in mood-related disorders, such as depression (Bob et al. 2010), which are generally improved by exercise (Cooney et al. 2013). The role of IL-6 in neurogenesis is still controversial. Chronic astrocytic production of IL-6 reduces hippocampal neurogenesis in the subgranular zone (SGZ) of the DG in adult mice (Vallières et al. 2002). On the other hand, IL-6 increased differentiation in human fetal NPCs in the SGZ (Sarder et al. 1996). In addition, proliferation of neuronal cells is reduced and hippocampus-dependent learning is impaired in IL-6-deficient mice (Baier et al. 2009; Bowen et al. 2011). Thus, the role of IL-6 in mediating exercise-induced neurogenesis and improvement of brain function is still elusive. Further studies are needed to determine whether IL-6 is a critical factor in the improvement of cognitive function during exercise. Altogether, these studies suggest that myokines such as *Ctsb*, irisin, and IL-6 may modulate brain function during exercise. Because these myokines have various roles in different physiological and pathological conditions, care must be taken when extrapolating their role to brain function.

Adipose Tissue

Adipose tissue-derived cytokines, called adipokines, are also affected by exercise (Golbidi and Laher 2014). Adiponectin is involved in regulation of energy metabolism, immune systems,

and brain functions, similar to exercise (Pedersen and Hoffman-Goetz 2000; Vu et al. 2007). Adiponectin increases fatty acid oxidation and glucose uptake in skeletal muscle (Yamauchi et al. 2014). In addition, it increases anti-inflammatory cytokines such as IL-10 in the macrophage (Moschen et al. 2012) and has beneficial effects on cardiovascular function (Han et al. 2007; Wang et al. 2009). In addition, adiponectin can enhance adult hippocampal neurogenesis in mice and in cell culture models (Zhang et al. 2011, 2016). Accordingly, Yau et al. (2014) suggest that adiponectin can cross the blood–brain barrier and that increased adiponectin levels may modulate hippocampal neurogenesis and ameliorate mood. Running-induced neurogenesis and antidepressant-like behavior was not detected in adiponectin knockout mice (Yau et al. 2014). Overall, the discovery of adipokines, such as adiponectin, has led to important research showing that there is direct cross talk between adipose and brain tissues. Prospective studies should consider the potential secondary effects of adipokines on brain function, such as regulation of inflammation and reactive oxygen species (ROS) production during exercise.

Liver

Like adipose tissue and skeletal muscle, the liver releases proteins, termed hepatokines, for glucose and lipid homeostasis (Stefan and Häring 2013). Different kinds of hepatokines are known to be involved in organ cross talk during exercise (Hansen et al. 2011; von Holstein-Rathlou et al. 2016). Insulin-like growth factor 1 (IGF-1) consists of 70 amino acids and is mainly in the liver as an endocrine hormone, and has a molecular structure similar to insulin. Circulating IGF-1 binds to IGF-1 receptors and insulin/IGF-1 heteroreceptors, which activate the AKT signaling pathway enhancing insulin action (Moses et al. 1996). IGF-1 is a critical hormone in carbohydrate metabolic reactions, and administration of IGF-1 lowers glucose levels in humans (Guler et al. 1987). IGF-1 crosses the blood–brain barrier (Pardridge 1993; Pan and Kastin 2000) and mediates neu-

roplasticity and neuroprotection. Indeed, IGF-1 gene mutations cause microcephaly, sensorineural deafness, as well as mental retardation (Woods et al. 1996). Activation of the IGF-1 signaling cascade can regulate amyloid precursor protein (APP) metabolism through increasing levels of insulin-degrading enzyme, a thiol metalloendopeptidase able to degrade amyloid β (Wang et al. 2015).

During physical exercise, IGF-1 levels in skeletal muscle are rapidly up-regulated (Berg and Bang 2004). Increased levels of circulating IGF-1 also result in elevated IGF-1 levels in the brain (Carro et al. 2000). Intracerebroventricular injection of IGF-1 enhances cognitive function in old rats (Markowska et al. 1998). Peripheral administration of IGF-1 can increase the number of newborn neurons in the DG of rat hippocampi (Aberg et al. 2000). Blockade of circulating IGF-1 using antiserum inhibits the exercise-induced increase in adult hippocampal neurogenesis, indicating that circulating IGF-1 may be a critical factor for exercise-induced changes in the adult rat brain (Carro et al. 2000; Trejo et al. 2001). Despite these encouraging findings, it may be premature to state that IGF-1 is the systemic link between physical activity and brain function. In a meta-analysis of 115 research studies, >50% of studies found no difference in total circulating IGF-1 as a result of exercise (Orenstein and Friedenreich 2004). In addition, depletion of IGF-1 apparently has a protective role (Cohen et al. 2009; Gontier et al. 2015) in mouse models of Alzheimer's disease.

The formation of ketones has recently been shown to play an important role in the effects of exercise on the brain. Acetyl-CoA induced by β -oxidation enters the citric acid cycle with oxaloacetate in the mitochondria (Newman and Verdin 2014). However, oxaloacetate is mainly involved in the gluconeogenic system in the liver during chronic exercise by hydrogenating into malate (Shimazu et al. 2013; Newman and Verdin 2014). The remaining acetyl-CoA is redirected into formation of ketone bodies, such as acetoacetate and β -hydroxybutyrate (BHA) (Laffel 1999). These ketone bodies are released from liver and used in other tissues as an energy source during cellular starvation (Feldman and



Nelson 2004). BHA protects against oxidative stress by inhibiting class I HDACs, which regulate gene expression and chromatin structure involved in glucose metabolism and diabetes (Gregoretta et al. 2004). BHA has neuroprotective effects in various neurodegenerative diseases affecting the dopaminergic system (Tieu et al. 2003; Lim et al. 2011) and increases BDNF levels in cortical cells (Marosi et al. 2016). Recently, Sleiman and colleagues found that exercise-induced BHA can increase BDNF expression through HDAC2/HDAC3 inhibition and histone H3 acetylation in the hippocampus. They further showed that BHA can increase neurotransmitter release via TrkB receptors. Although their study did not include behavioral analyses after BHA administration, their findings suggest that peripheral BHA can link exercise and brain function through BDNF (Sleiman et al. 2016). Thus, in various physiological and pathological conditions, hepatokine levels are altered. These hepatokines have multiple roles and are particularly important for energy homeostasis. Further research will be needed to elucidate the interactions between hepatokines and exercise, and to understand their role in brain function.

CONCLUSION

Regular exercise has profound benefits for body and brain health. Emerging data suggests that the underlying mechanisms involve various physiological adaptations, including neural, immunological, vascular, and metabolic systems. However, caution should be used when extrapolating factors modulated by exercise to potential therapeutic interventions. For instance, IGF-1, when delivered systemically, has a potent proliferative action that promotes cancer (Arnaldez and Helman 2012) and decreases life span in animal models (Junnala et al. 2013). Thus, exercise may be most beneficial as a precision delivery tool that can distribute and up- or down-regulate important substrates with impeccable temporal and spatial resolution. Evidently, exercise stimulates neuronal activation in brain regions important for learning and memory, while engaging cross talk between peripheral organs (skeletal muscle, adipose tissue,

liver) to supply critical substrates for brain health. The mechanisms by which different modes of exercise may affect brain function remain to be elucidated. To achieve this, specified intensity and time lines of exercise training paradigms as well as systematic analyses of brain function and adaptations will be needed.

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