Brain Plasticity 4 (2018) 17–52
DOI 10.3233/BPL-180069
IOS Press

Review

The Neuroprotective Effects of Exercise: Maintaining a Healthy Brain Throughout Aging

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Accepted: 2 September 2018
Published: 6 October 2018

Abstract. Physical activity plays an essential role in maintaining a healthy body, yet it also provides unique benefits for the vascular and cellular systems that sustain a healthy brain. While the benefit of exercise has been observed in humans of all ages, the availability of preclinical models has permitted systematic investigations into the mechanisms by which exercise supports and protects the brain. Over the past twenty-five years, rodent models have shown that increased physical activity elevates neurotrophic factors in the hippocampal and cortical areas, facilitating neurotransmission throughout the brain. Increased physical activity (such as by the voluntary use of a running wheel or regular, timed sessions on a treadmill) also promotes proliferation, maturation and survival of cells in the dentate gyrus, contributing to the process of adult hippocampal neurogenesis. In this way, rodent studies have tremendous value as they demonstrate that an 'active lifestyle' has the capacity to ameliorate a number of age–related changes in the brain, including the decline in adult neurogenesis. Moreover, these studies have shown that greater physical activity may protect the brain health into advanced age through a number of complimentary mechanisms: in addition to upregulating factors in pro-survival neurotrophic pathways and enhancing synaptic plasticity, increased physical activity promotes brain health by supporting the cerebrovasculature, sustaining the integrity of the blood–brain barrier, increasing glymphatic clearance and proteolytic degradation of amyloid beta species, and regulating microglia activation. Collectively, preclinical studies demonstrate that exercise initiates diverse and powerful neuroprotective pathways that may converge to promote continued brain health into old age. This review will draw on both seminal and current literature that highlights mechanisms by which exercise supports the functioning of the brain, and aids in its protection.

INTRODUCTION

Regular exercise plays essential role in maintaining a healthy lifestyle. It bolsters the cardiovascular, and immune and metabolic systems and in addition, modulates the internal milieu of the brain [1–6]. Both acute, high-intensity activity and regular, moderate aerobic exercise have been reported to increase levels of circulating neurotrophic factors and enhance neurotransmission, exerting beneficial effects on mood and cognitive functions in individuals of all ages [7–16]. In young adults, an acute bout of high-intensity cycling induced an increase in serum levels of brain-derived neurotrophic factor (BDNF) that correlated with blood lacate [7], as did long-term

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ISSN 2213-6304/18/$35.00

exercise of moderate intensity (i.e. 5 weeks of cycling, 3 times per week, at intensities below the ventilatory threshold) [8]; both regimens correlated with improved cognitive performance. Adults over 65 years of age that participated in regular exercise (e.g. walking, hiking, biking, weight-training, stretching, or others) score higher on common memory tests and have been shown to be at a reduced risk for dementia and impairment in executive functions associated with advancing age [17–21]. These benefits often correlated with measures such as frequency and/or intensity of exercise, and caloric expenditure. Exercise such as walking, aerobic exercise, and strength training, was also shown to improve executive functions and cognition in individuals already suffering from early stages of dementia [18, 22–24]. To this end, the importance of exercise in supporting continued brain health in the aging brain, even individuals affected by the early stages of neurodegeneration, is gaining recognition. Moreover, because studies suggest that physical activity can reduce the risk of cognitive decline, an active lifestyle can be thought of as a 'preventative' strategy to ameliorate the deterioration of brain health much as it is with cardiovascular dysfunction.

In humans, age-related changes in the brain commonly underlie cognitive decline; these may include progressive reductions in neurotrophic levels, alterations in the cerebrovasculature, and declining neurogenesis [25–34]. The hippocampus is particularly vulnerable to age-related morphological and functional alterations [34–39]. Similar age-related alterations have been observed in rodents, making them an ideal model for identifying changes that occur on a cellular level and for investigating interventional or preventative strategies [40–43]. As in humans, rodent models have shown age–related reductions in hippocampal volume [38, 44, 45]. This is, in part, a consequence of a decline in cell proliferation [46, 47] and morphologic changes in the rodent brain, such as reductions in dendritic branching, spine densities, and fibres projecting into the hippocampus [38, 42, 43, 45, 48–51]. In addition, advanced age in both rodents and humans have been associated with a reduction in trophic support to the brain, such as declining levels of BDNF and its full-length receptor, tropomyosin receptor kinase B (TrkB) [35, 37, 42]. The loss of neurotrophic support is concomitant with attenuated neuronal survival and synaptic plasticity [29, 36, 43, 48, 50, 52, 53]. Importantly, age-related neurological changes correlate with functional decline, particularly in hippocampus-dependent learning and memory tasks, and navigational strategies [5, 54–59].

Notably, though the hippocampus is known to be a principle site of mammalian adult neurogenesis [60], there has been some discrepancy as to whether this occurs in humans [61–65]. A recent paper by Sorrells and colleagues found no evidence for neurogenesis beyond youth [64], while Boldrini et al. published a paper shortly thereafter showing that neurogenesis did in fact persist into adulthood, with a small age-related decline [61], in keeping with previous studies [62, 65]. Indeed, numerous studies have suggested that adult-born neural stem cells may be stimulated to form distinct populations of neurons and though these cells may lose proliferative potential and become quiescent with age, they can be reactivated upon stimulation, including running [63, 66–71].

Over two decades ago, mice living in enriched cages were showed to have elevated neurogenesis in the dentate gyrus, an effect that is most remarkable in young rodents; these cages were larger, housed many mice and contained a number of accessories (including a running wheel) [56, 72, 73]. Subsequent studies dissociated the different elements of the enriched environment, and demonstrated that voluntary running alone is sufficient to increase cell proliferation and survival in the hippocampus, enhance synaptic plasticity and improve cognitive performance [54, 56, 57, 74, 75]. In young mice, treadmill training and voluntary wheel running has been consistently associated with enhanced performance on hippocampal-dependent memory tasks such as the Y-Maze and Morris water maze [54, 56, 57, 74, 76], as well as tasks that do not specifically depend on the learning or consolidation of spatial memory (i.e. contextual fear conditioning, passive avoidance learning, and novel object recognition) [75, 77–81]. In aging rodents, exercise attenuates the age-related decline in cell proliferation and differentiation [41, 54, 57]. Moreover, just one month of voluntary running ameliorates many neurological and behavioural deficits associated with aging [41, 54, 57, 82, 83]. Notably, even short bouts of mild-intensity exercise (4–6 minutes on 5 consecutive days, for 5 weeks) initiates pro-survival pathways in aged rats [82]. In addition, mice that underwent long-term voluntary running throughout middle-age exhibited improved performance on spatial memory tasks later in life, which correlated with an increase in BDNF levels and enhanced neurogenesis in the dentate gyrus [41, 54, 76].

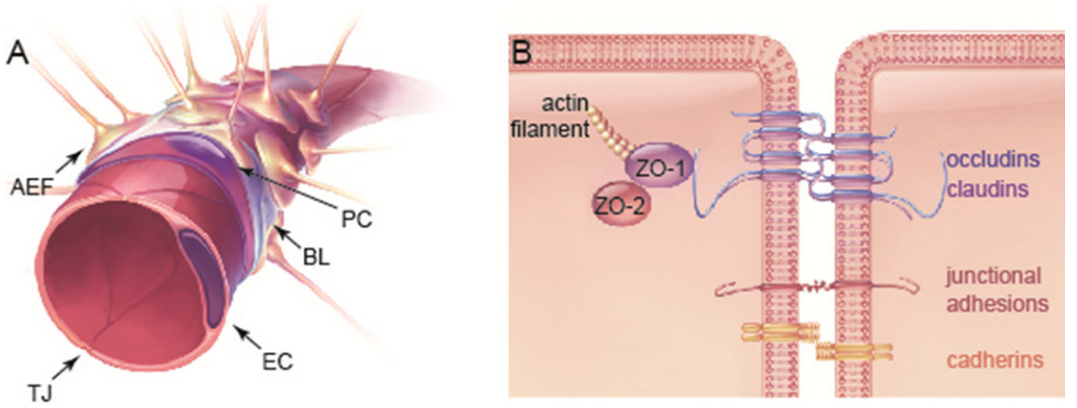

Fig. 1. The anatomy of the blood–brain barrier (BBB). (A) The BBB is comprised of astrocytic endfeet (AEF) and pericytes (PC), which surround a single layer of endothelial cells. Endothelial cells secrete extracellular matrix proteins, forming the basal lamina (BL). Endothelial cells are connected by tight junctions (TJ) that form a highly selective semi-permeable membrane, separating the brain's parenchyma from the circulatory system. (B) TJs anchor endothelial cells close together through a number of transmembrane proteins (e.g. occludin, claudins and junctional adhesion molecules). These TJ proteins interact with cytoplasmic scaffolding proteins such as zonula occludens (ZO), as well as with the actin cytoskeleton. Other integral membrane proteins and cell adhesion molecules, such as cadherins and integrins, are also found at cell-cell junctions [105]. Exercise has been shown to increase the expression of claudins, as well as the co-expression of proteins from the ZO and occludin family at the plasma membrane.

Rodent models have shown that short-term periods of increased physical activity are sufficient to upregulate central and peripheral factors that support the brain, and promote synaptic plasticity [4, 5, 12, 84–86] (Table 1). Nerve growth factor (*Ngf*), *Bdnf* and *TrkB* messenger RNA (mRNA) levels are upregulated in the hippocampus of adult rats after 3 days of free access to a running wheel, as are genes related to synaptic trafficking and signal transduction [85]. In addition, exercise promotes trophic support to the vasculature, including increased central and circulating levels of insulin-like growth factor 1 (IGF-1), which has also been shown to support neurotransmission and neuronal survival [1, 2, 56, 87–90]. The greater, systemic benefits of exercise and their relation to brain health cannot be understated, as the neuroprotective effects of exercise extend beyond the promotion of neurotrophic pathways and hippocampal neurogenesis. Voluntary wheel running has been shown to upregulate tight-junction (TJ)–associated proteins of the blood-brain barrier (BBB), which protects the brain from circulating molecules that might contribute to toxicity, inflammation, or pathogenesis [91–93]. Running has also been shown to reduce microglia activation and cytokine levels in the hippocampus of aged mice, representing another mechanism by which exercise may protect the neurovascular unit and in turn, the brain from insult [6, 94, 95]. In models of advanced aging and Alzheimer's disease (AD), exercise reduces soluble amyloid-beta (Aβ) load and plaque formation, in part mediated by glymphatic clearance and proteolytic degradation [76, 94, 96–99]. Voluntary exercise has also been shown to delay white matter atrophy and protect cerebral vasculature in mouse models of AD, correlating with improved performance on spatial memory tasks [100–102].

The remainder of the review will survey preclinical literature reporting the neuroprotective benefits of exercise, with special attention paid to the mechanisms by which exercise supports a healthy aging brain*. Exercise, as it pertains to these animal studies, will be defined as a greater degree of physical activity than is otherwise permitted in a control home cage either by granting free access to a running wheel, or through timed session on a treadmill. Drawing from both seminal and recent literature, the mechanisms by which exercise promotes the maintenance of BBB integrity, clearance of Aβ peptides, and upregulation of neurotransmitters and neurotrophic factors (principally, BDNF) will be discussed.

*Please note that the specific effects of exercise on the cerebrovasculature, and on neurogenesis in animal models of AD, are the subjects of other focused reviews found within this issue (see papers by Barnes, J.N. and Corkery, A.T.,"*Exercise improves vascular function, but does this translate to the brain*"; Llorens-Martin, M. "*Exercising new neurons to vanquish Alzheimer's Disease"*) . While these topics are of relevance to the discussion here and will be briefly mentioned, please refer to those articles for greater detail. In this review, general topics surrounding AD will be discussed as they pertain to the neuroprotective effect of exercise, such as exercise-facilitated clearance of Aβ species.

Table 1
Summary of the effects of increased physical activity on the rodent brain. The neuroprotective benefits of physical activity are noted in a variety of ages; 'age at onset' describes the age, if specified, at which the activity paradigm (whether it be acute or chronic) is commenced. (The specific effects on vasculature are not included in this table.) Please see abbreviation listed below the table

System affected by increased activity	Age at onset, Species, Sex	'Exercise' duration and protocol	Details
Blood-brain barrier/Neurovascular unit	7-8 weeks; 13 weeks, mice (male)	5 weeks; 2 weeks (respectively), VWR	Reduced pro-inflammatory cytokines and methamphetamine-induced oxidative stress in cerebral vasculature; enhanced expression and/or co-localisation of tight junction proteins (e.g. claudin-5, occludin and ZO-1) [91, 93]
	12 weeks, mice (male)	5 weeks, VWR	Maintained BBB integrity (enhanced expression and/or co-localisation of tight junction proteins claudin-5, occludin and ZO-1) in a mouse model of early brain metastasis; limited tumour extravasation [132]
	adult, rats (male)	3 consecutive days, TR • 30 min, speeds increasing from 5 m/min to 12 m/min, 0° incline	Reduced the expression of MMP, and mitigated BBB disruption (specifically, the reduction of occludin) following middle cerebral arterial occlusion in ischemia model of stroke (TR within 24 hrs) [130]
	12 months, mice (female)	6 months, VWR	VWR from middle to early old-age attenuated age-related deterioration of neurovascular structures and vascular leakage (shown by extravasation of fibrin[ogen]), microglial activation, and decline in astrocytic ApoE; the benefit to the NVU was not seen in exercised ApoE deficient mice [92]
Glymphatic System	9 weeks, mice (female)	5 weeks, VWR (averaged 6.7 km per night)	Glymphatic influx (as measured by fluorescent tracer) increased in awake, exercised mice as compared to mice that had been sedentary; overall tracer influx was impaired during acute running (measured in awake running mice); history of daily running increased CSF flux in widespread brain regions (primarily in hypothalamus and ventral parts of the cortex) [145]
	14–16 months, mice (male)	6 weeks, VWR	Increased expression of AQP4 on astrocytic endfeet; accelerated clearance of tracer and decreased Aβ accumulation; increased dendrites, dendritic spines and postsynaptic density protein (PSD95); improved spatial memory [94]
Neurotrophins			
BDNF	8 weeks, mice (male)	Acute session, TR • 120 min, at 15 m/min, with an incline of 5% • mice were acclimated to motorized TR running for 3 days (5 min/day,15 m/min, 5%); acute session began 72 hrs after acclimatisation	Obese, glucose-intolerant mice (fed high-fat diet) shown to have a reduction in BDNF levels, as well as reduction in TrkB phosphorylation and CREB activation in the prefrontal cortex; 2 hrs following an acute session of TR, levels of phosphorylated TrkB and CREB significantly elevated over sedentary mice fed the same high fat diet [347]
	2 – 5 months, mice and rats	3 days – 4 weeks, VWR	BDNF consistently upregulated with VWR, along with proteins associated with BDNF signalling cascade; most notably increased in dentate gyrus, CA1, CA3, and CA4 of the hippocampus, and in the most caudal third of cortex (examples: [4, 5, 85, 86, 186, 190, 348, 349])

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Table 1
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	2 months, rats (male)	3 days, VWR (against 100 g resistance)	Positive correlation between exercise and hippocampal protein levels of [synaptic proteins] synapsin I and synaptophysin mRNA; synapsin I correlated with the amount of exercise (i.e. running distance); blocking TrkB (BDNF signalling) abolished the upregulation of both proteins [86]
	3 months, rats (male)	1 week, VWR (against 100 g resistance) • minimum of 100 m/day	Increased BDNF, concomitant with improved performance on MWM; inhibiting the action of BDNF blocked cognitive enhancement following exercise, as well as downstream proteins involved in synaptic plasticity (CREB and synapsin I); best performance (learning and recall) associated with highest expression of BDNF and CREB mRNA levels [5]
	9 months, mice (female)	8 months, VWR (note: same animals underwent behavioural testing at 1 *and* 6-months)	VWR throughout middle-age (i.e. 8 months total) increased BDNF protein levels in the hippocampus of 15 month-old runners compared to age-matched controls; reduced age-related cognitive decline [48]
	8 *or* 12 months, mice (male)	5 *or* 8 weeks, TR • began at 10 m/min, 20 min for the first day and increased 10 min/day until 60 min/day reached; intensity increased to maintain 70% of animals' VO_2 max; speed increased to 11 m/min in final week	Increased proliferation and maturation in dentate gyrus, and restored age-dependent decline in BDNF and TrkB [350]
	24 months, rats (female)	1 week habituation + 4 weeks exercise regimen, TR (4 consecutive days/week) • daily regimen: warm-up (3 min, 2 m/min), two bouts of running (4–6 min, 10 m/min) with 1 min interval between	In aging rats, shorts bouts of mild-intensity exercise increased muscle oxygen consumption by soleus and heart; lactate levels remained stable throughout 4 weeks (levels indicative of mild-moderate intensity exercise); reversed age-related spatial learning and memory impairment; increased *Bdnf* mRNA and protein in hippocampus; increased levels of phosphorylated AKT and phosphorylated CREB protein in the hippocampus; results suggest even short bouts of exercise effective at facilitating hippocampal plasticity [82]
	4 weeks, mice (male)	4 weeks	Increased production of DBHB, a ketone body produced in the liver and capable of crossing the BBB, which in turn induced activity of BDNF promotors in the hippocampus via HDAC2/HDAC3 inhibition; increase in neurotransmitter release, dependent upon TrkB signalling [192]
NGF	3 – 4 months, rats (male)	2, 4 or 7 days, VWR • mice acclimated to wheel for 3 days, then removed for 10 before testing [3, 190]	NGF is increased in the acute/short-term phase, reported in the hippocampus at 2 – 3 days and in the cortex, from 2 – 7 days [3, 85, 190]
	3 – 4 months, rats (male)	4, 7 and 28 days, VWR • 1 week acclimation • at least 5 km/day [85]	

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IGF-1	adult, rats (male)	5 days, VRW (against 100 g resistance)	5 days VWR increased hippocampal levels of IGF-1, but not IGF-2; improved performance on MWM Blocking hippocampal IGF-1 receptors during 5-day exercise period blocked the uptake of circulating IGF-1 into the hippocampus and in turn, diminished the upregulation of BDNF and its precusor, pro-BDNF; diminished rate of acquisition and abolished preference for probe quadrant in MWM; eliminated exercise-facilitated upregulation of *synapsin I* mRNA and protein in the hippocampus [1]
	adult, rats (male)	2 weeks, TR • 60 minutes, 17 m/min • rats assigned to both sedentary group and exercise familiarised to treadmill	In response to exercise, IGF-1 participates in neuronal stimulation and c-fos expression in hippocampus; subcutaneous administration of IGF-1 to sedentary animals increased number of new neurons in the hippocampus; infusion of IGF-1 anti-serum blocked uptake of circulating IGF-1 into hippocampus, which abolished increase in new neurons; infusion of IGF-1 anti-serum throughout exercise period abolished both short-term and long-term survival of new cells in hippocampus [89] *Note*: Physical activity produces increase in IGF-1 levels in circulation and hippocampus; uptake of circulating IGF-1 into hippocampus involved in both exercise-induced elevation in BDNF and neurogenesis; infusion of IGF-1 increases glutamate receptor subunits (particularly NR2A and NR2B) in aged mice; IGF-1 levels correlated with vascular density [1, 29, 43, 200, 215, 219, 220]
Neurotransmitters			
DA	young, rats (male)	young rats: 6 months 'endurance training', TR • progressive treadmill test performed on an 18° incline, correlated to peak oxygen consumption [254]	Increased radioligand ([3H]SP) binding to D2 receptors in the striatum and increased "synaptic coupling ratio" (defined as the "specific DA binding/DOPAC concentration") [254]; in aged rats, regular exercise attenuated age-associated increases in DA metabolites (which can be associated oxidative stress), and increased D2 receptor binding [351]
		► 18 months, rats (male) ► aged rats: 12 weeks, TR [351]	
	8 weeks, mice (males)	2 or 4 weeks, TR • 10 m/min for 20–60 min per day (increased at an increment of 10 min per day), 5 days/week the first week; 60 min/day at the same speed, 10 m/min, 5 days/week for additional 1 or 3 weeks • both mice assigned to exercise and sedentary groups underwent 1 week of habituation training on the treadmill (9 m/min, 10 min/day for 5 days)	TR regimen (meant to replicate moderate exercise in humans) completely protected against LPS-induced dopaminergic neuronal loss in the substantia nigra and attenuated motor impairment following 4 weeks of running; neuroprotection in the nigrostriatal pathway was dependent on the activation of the BDNF-TrkB signalling pathway rather than modulation of microglial activation or cytokine/chemokine levels; intrastriatal perfusion of BDNF alone was sufficient to counteract LPS-induced DA neuron loss; protection not observed after 2 weeks of running [246]

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	3 months *vs* 23 months, rats (female)	9 weeks, TR • 5 days/week, intensity adjusted to approximately 70% of their peak oxygen consumption (time, grade and speed increased as weeks progressed, and differed for each age group)	TH mRNA, TH immunoreactivity, and TH activity showed age-related decline in the hypothalamus; endurance training significantly elevated all TH parameters in the hypothalamus of old animals ($p < 0.05$), but there was no significant change in young animals following training [259] *Note:* DA neurotransmission has been shown to increase BDNF production, as well as surface expression and phosphorylation of TrkB (*in vitro* and *in vivo*); TrkB signalling shown to increase expression of D1 and D3 receptors (*in vitro* and *in vivo*) [246–248, 259]
NA	3 months, rats (male)	3 days, VWR	BDNF mRNA upregulated in CA1, CA2, CA3, CA4 and detate gyrus; modest increase in BDNF mRNA with antidepressant, tranylcypromine, CA3 and dentate gyrus only; β-adrenergic receptor blockade significantly blunted BDNF mRNA elevations in response to exercise, and inhibited modest elevations resulting from antidepressant treatment in CA3 [189]
	young, rats (sex not specified) • age not specified, 146 +/– 2 g at start of study	5 days/week, 2 weeks (TR) (1 hour, 25 m/min, 3% slope) • workload corresponded to 70% VO_2 max • 4 day break, in which microdialysis probe implanted + recovery • Acute session of 1 *or* 2 hrs	Increased levels of NA centrally and peripherally following 1 and 2 hr exercise sessions; the peak of NA concentration in the cortex is higher with 2 hours of exercise, and levels remain elevated for longer periods as compared to a 1-hour session [266] (see also [265])
	adult, rats (male) • age not specified, 220 g on arrival	5 days, VWR (against 100 g resistance)	Blocking the β-adrenergic receptors with propranolol (β-blocker that crosses the BBB) but not nadolol (peripherally acting, does not cross the BBB) before each of five consecutive nights of exercise reversed the exercise-induced improvement in learning and memory in rat [271] (see also [270])
5-HT	adult,rats (male) • age not specified, 300 +/– 15 g at start of study	Acute session, 120 min, TR • trained 6 – 7 times prior to experiment day, gradually accustomed to run at 25 m/min; 2 days before experimentation, ran 30 min at a speed of 25 m/min	Hippocampal and cortical 5-HT levels significantly increased by 90 min of intense aerobic exercise (collected by microdialysis); maximal levels in the cortex, 30 min after exercise cessation and in the hippocampus, 60 min after cessation; hippocampal levels remained elevated at least 90 minutes after cessation; cortical 5-HT levels rapidly decrease when hippocampal levels still maximal [352]
	6 weeks *vs* 3 months *vs* 1 year, mice (female) • *Tph2 -/-* and controls	6 days, VWR	*Tph2*-deficient mice have normal baseline hippocampal neurogenesis but impaired proliferation in response to increased physical activity; serotonergic deficits results in alterations in Sox2-positive precusor cells; serotonergic signalling required for proproliferative effect on physical activity, in young and aged animals [292] (see also: [293])

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Glutamate	28 – 40 days, mice (sex not specified)	7 – 10 days, VWR averaged 4 km/day	Synaptic plasticity in dentate gyrus examined *in vitro*: LTP significantly greater in slices prepared from runners than control animals; LTP significantly reduced by NR2B subunit antagonists in both groups; LTP blocked by an antagonist with higher affinity for NR2A (NVP-AAM077) in running groups, with only slight depression in controls; NVP-AAM077 completely blocked LTD in runners but not controls [236]
	3 months, rats (male)	3, 7 *or* 28 days, VWR (against 100 g resistance) • VWR followed 1 week habituation at least 5 km/day • Similar results seen with TR, 3, 7, 15 or 30 days (40 minutes daily, 10 m/min)	Increased synaptic glutamate receptors (mRNA and/or protein levels) in several brain regions including, but not limited to, the hippocampus, motor cortex, sensory cortex, and striatum; mRNA expression of NMDAR subunits modulated in hippocampus after 3 days of VMR (NR2A and NR2B); AMPA receptors modulated after 10 days of VWR or 30 days of TR [85, 186, 353]
	3 months, rats (male)	3 *or* 7 days, VWR at least 5 km/day (against 100 g resistance)	Blocking NMDAR (MK-801, delivered unilaterally by microsphere into hippocampus) was sufficient to fully abrogate exercise-induced increases in *Bdnf, TrkB, CREB,* and *Synapsin I*, suggesting an interaction between BDNF and glutamate signalling may be necessary for increased transcription of genes modulating synaptic plasticity [4]
GABA	5–6 weeks, mice (male)	10 days, VWR	GABAergic transmission excitatory in the first two weeks and becomes inhibitory as granule cells mature and integrate into networks; involved in initial integration of adult-born neurons [354] Young, 1-week old progenitor cells receive input from inhibitory GABAergic interneurons and cholinergic input from the septum, as well as multiple intra-hippocampal glutamatergic cells types, all of which have been implicated in the maturation and integration of new neurons [296]; exercise enhances new dentate granule cell number, arborization and morphological complexity but only NMDA-mediated glutamatergic inputs shown to be modified by running [296] Electrophysiological recordings from slices taken from exercised mice suggest that alternations to glutamatergic inputs, rather than GABAergic inputs, are predominately responsible for increased morphological complexity in new neurons [296]
	5–6 weeks, mice (male)	40 days, VWR	In new neurons, ratio of interneuron inputs to new neurons was reduced, but GABAergic inhibitory synaptic transmission was not changed by running; in mature granular cells in the outer molecular layer, synaptic inhibition was strongly increased, (possibly due to interneuron sprouting of axonal collaterals onto these cells) [297]

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	young, rats (males), • age not specified, 140 – 160 g on arrival	4 weeks, VWR • ran 5 – 9 km per night • began running 1 week after arrival	Gene expression of various $GABA_A$ receptor subunits as well as the GABA-synthesising enzyme glutamic acid decarboxylase-67 (GAD67) altered in the forebrain of runners (*in situ* hybridisation histochemistry): region-specific decreases in mRNA expression of $\alpha 2$, $\beta 3$ and $\gamma 2$ $GABA_AR$ subunits and region-specific increases in $\beta 1$ subunit; $\alpha 5$ and δ subunits showed differential increases in mRNA expression levels; GAD67 mRNA increased in many forebrain regions, including all hippocampal cell layers, peri-paraventricular nucleus, bed nucleus stria terminalis, nucleus accumbens core and motor cortex [241]
	6 weeks, mice (male)	6 weeks	During cold water swim stress, increased expression of the protein products of the immediate early genes c-fos and arc in granular neurons (new and mature) of sedentary mice but not runners Runners showed enhanced local inhibitory mechanisms in the hippocampus during stress test: increased in stress-induced activation of hippocampal interneurons, expression of vesicular GABA transporter, and extracellular GABA release [355]
ACh	adult, rats (male)	5 minutes, walking on treadmill (2.3 m/min, 0° incline)	Increased ACh (as well as NA and 5-HT) levels in cerebral cortex, sampled from freely-behaving animals by microdialysis [226, 227, 356]
	3–4 months, rats (male)	30 seconds *or* 3 minutes, walking on treadmill (4 cm/s, 0° incline)	Increased ACh in hippocampus; increased regional blood flow; abolished by AChR antagonists; various degrees of physical activity shown to elevate ACh levels in cortex and hippocampus [357]
	►26–29 months, 'healthy aged' rats (male)	► 30 seconds *or* 3 minutes, walking on treadmill (2, 4, or 8 cm/s, 0° incline)	►Similarly, increased ACh release in hippocampus of aged rats (likely cholinergic fibres that originate in the septal complex of forebrain and project to hippocampus); increased regional blood flow [237].
	adult, mice (male)	15 consecutive days, TR (30 min, 5 m/min, 0° incline)	In scopolamine-treated mice, a pharmacological model of amnesia, treadmill exercise ameliorated short-term memory impairment, suppressed AChE expression, and enhanced angiogenesis [239] *Note:* An increased concentration of ACh in the hippocampus supports the generation of theta oscillations, which serves to facilitate synaptic plasticity, learning and memory [240, 324, 325].

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Neurogenesis	3 weeks, mice (female)	40 days in enriched environment (tunnels, toys and running wheel; 3 mice per cage) ►second group survived 68 days total (after 40 days in enriched or control environments, tested on MWM for 5 consecutive days, then returned to assigned environments for an additional 23 days)	Housing in enriched environments, which included running wheels, induced neurogenesis: when mice were sacrificed 1 day after final BrdU injection (daily, 12 days), no significant difference between two groups suggesting little influence on proliferative activity of progenitor cells in dentate gyrus; when mice sacrificed 4 weeks after last injection, a significantly higher number of BrdU+ cells in the dentate gyrus of mice living in enriched environments, suggesting a survival-promoting effect on proliferating neuronal precursors; studies in mice of an alternative background (129/SvJ rather than C57BL/6) did show a significant increase in the number of progenitor cells under similar conditions [72, 73]
	3 months, mice (female)	12 days, 40 days, VWR (*vs* other conditions in enriched environments)	Running is sufficient to increase hippocampal neurogenesis: an increase in both proliferating cells (measured 1 day after last BrdU injection, injected daily for 12 days) as well surviving neurons, after an additional 4 weeks of VWR, seen in running group and enriched environment groups only LTP and spatial learning in mice [56]
	3 months, mice (female)	2 months *or* 4 months, VWR 1+ months	Improved performance on MWM, increased cell proliferation (as measured by BrdU+ cells) and enhanced LTP in the dentate gyrus.
	3 months *vs* 19 months, mice (male)	45 days, VWR	Faster acquisition and better retention on MWM than sedentary age-matched controls; age-related decline in neurogenesis ameliorated (compared to young and aged controls); fine morphology of new neurons did not differ between young and aged runners; perimeter and surface area of blood vessel increased in young runners but not aged mice; angiogenesis was not a rate-limiting factor for neurogenesis (angiogenesis not increased in this study, although reported to be increase in motor cortex, cerebellum and hippocampus following running in other studies) [57]
	3 months *vs*, 12 and 24 months, mice (male)	6 months VWR (young mice) *vs* 10 days VWR (aged)	Chronic (i.e. long-term) running starting at 3 months of age attenuated age-dependent decline in precursor cell proliferation measured at 9 months; short-term running reduced age-related decline in cell proliferation at 12 and 24 months, but did not return net neurogenesis to 'young levels' in this study [41]

ACh – acetylcholine; AChE – acetylcholinesterase; AKT – Protein kinase B; BDNF – brain derived neurotrophic factor; BrdU – bromodeoxyuridine; CA – cornu Ammonis (i.e. hippocampal subfield); CREB – cAMP response element-binding protein; CSF – cerebrospinal fluid; DA – dopamine; DCX – doublecortin; DOPAC – 3,4-Dihydroxyphenylacetic acid (a dopamine metabolite); DRN – dorsal raphe nucleus; HDAC – histone deacetylase; 5-HT – serotonin; IGF-1 – insulin growth factor 1; LPS – Lipopolysaccharide; LTD – long-term depression; LTP – long-term potentiation; MMP – matrix metalloproteinases; MWM – Morris Water Maze; NA – noradrenaline; NMDAR – N-methyl-D-aspartate receptor; NR2A/2B – NMDAR subunits 2A and 2B; NGF – neurotrophic growth factor; TR – treadmill running (controlled for duration and speed); VWR – voluntary wheel running (animals are freely behaving); ZO-1 – zonula occludens 1.

EXERCISE MAINTAINS THE BBB AND SUPPORTS THE NEUROVASCULAR UNIT

The BBB in health and disease

The BBB is a highly selective semi-permeable membrane at the interface between the circulatory system and brain parenchyma, formed of specialised endothelial cells that compose the walls of all cerebral blood vessels (Fig. 1). The endothelial cells are in turn encased by a layer of pericytes, astrocytic endfoot processes and neurons. Together, these cells comprise the neurovascular unit, communicating with one another to tightly regulate cerebral blood-flow and maintain a homeostatic chemical environment within the brain [103, 104].

TJs between adjacent endothelial cells set the brain's vasculature apart from most other blood vessels in the body. They are primarily formed by transmembrane proteins (occludins, claudins, and junctional adhesion molecules) that interact with cytoplasmic scaffolding proteins (i.e. zonula occludens [ZO] proteins and the actin cytoskeleton), and other membrane-associated proteins (i.e. kinases, GTPases, and G proteins) [105–108]. The integrity of TJs is critical to forming the protective barrier of the BBB, which selectively limits the passage of molecules between the circulating blood and the extracellular fluid in the brain [104, 108] (Fig. 1). Both meta-analyses of human subjects and animal models have revealed an association between normal aging and BBB deterioration [109–111]. Injury or disease may contribute to BBB dysfunction, and can be associated with the presence inflammatory markers; if this state is prolonged or persistent, a compromised BBB can permit the extravasation of circulating molecules, including those that are neurotoxic [112–120].

Exercise protects the neurovascular unit

In animal models of aging, habitual long-term (or, 'chronic') aerobic activity has been shown to protect the neurovascular unit and maintain the integrity of the BBB. Soto and colleagues demonstrated that daily voluntary running (at an average of 3 km per night) from midlife (12 months of age) to early old age (18 months of age) reduced age-related neurovascular dysfunction in mice, leading to a 'younger-like' brain. Long-term voluntary running, representing an 'active' lifestyle, was shown to preserve the basement membrane of the neurovascular unit and to prevent the neurovascular deterioration and leakage observed in sedentary mice at 18 months: a significant reduction in fibrin levels was found in aged runners compared to sedentary age-matched controls, with levels more closely resembling those seen in 12-month-old mice [92]. Aged runners also showed higher levels and coverage of cortical and hippocampal pericytes, as well as a reduction in astrocytic and microglial activation. Notably, running prevented an age-related decline in astrocytic ApoE, an anti-inflammatory protein important in cerebrovascular maintenance and pericytic signalling [92, 121, 122]. Running was not, however, associated with a significant effect in aging ApoE-deficient mice, suggesting that ApoE may partially mediate the beneficial effect of exercise on the neurovascular unit [92]. As allelic variations in *APOE* are associated with decreased longevity and the development of familial forms of AD [123, 124], this is a relevant observation for translational research. It is possible that exercise may offer greater BBB protection in some individuals than others, however this would not diminish the other neuroprotective and health benefits promoted by exercise. For instance, voluntary running and treadmill training were also shown to decrease microglial and astrocytic activation in aged rodents (with some sex- and region-specific effects), which may aid in the protection of the neurovascular unit from damage [90, 94, 95].

Exercise maintains the BBB

Animal models of disease and toxicity, with injury to the BBB, can provide additional insight into the benefits of an active lifestyle. Spontaneously hypertensive rats (SHR) have been shown to have greater BBB permeability and increased angiotensin II (Ang II) in the brain parynchema (both locally-produced and circulating), which not only alters neurovascular coupling and dysregulates cerebral perfusion, but permits the extravasation of circulating inflammatory cells [125]. In a recent study, the maximal aerobic capacities of individual SHR and Wistar Koyoto (control) rats were determined at the start of experimentation, and used to ensure rats with identical capacities were allocated to both the trained and sedentary groups [125]. Rats in the exercise group then underwent aerobic treadmill exercise for 2 months, set to 50–60% of their own maximal exercise capacity (performed 5 days/week, 1 hour/day). The marked fluorescein isothiocyanate dextran (FITC, 10 kD) leakage seen in the autonomic areas of the

sedentary SHR group was significantly diminished after just 2 weeks of treadmill training. Although regional Ang II content was not directly measured, authors of the study suggest that regular treadmill running may reduce Ang II content in autonomic areas, as simultaneous intracerebroventricular Ang II infusion abrogated training effects on both FITC leakage and microglia activation. This interpretation is supported by studies demonstrating that pharmacological blockage of the Ang II receptor, AT1, reduced BBB permeability in autonomic regions of hypertensive rats; AT1 receptor blockade has also been shown to reduce BBB permeability in the hippocampus and cortex [125–129].

Physical activity may support or strengthen the BBB by modulating the expression of TJ-proteins, and in the same way, aid in its recovery following injury. Started 24 hours following middle cerebral artery occlusion in rats, short-term treadmill running (30 minutes per day for 3 days) attenuated an ischemia-induced reduction in occludin, reduced disruption of the BBB, and diminished expression of matrix metalloproteinases (MMPs) [130]. Similar results were observed in rats undergoing a pre-ischemia treadmill program (30 min per day, 5 days/week, 3 weeks) [131]. Rats that had been exercised prior to ischema showed reduced infarction size and reduced Evan's Blue extravasation; moreover, exercised rats show enhanced expression of proteins associated with the basal lamina such as collagen IV, a major component of the basement membrane of cerebral microvessel. In a murine model of brain metastasis, mice that ran for 5 weeks prior to tumor cell infusion showed enhanced expression of claudin-5 and occludin [132]. Furthermore, while tumor cells target ZO-1 to increase BBB permeability, prior running resulted in a reduction in tumor cell extravasation at both 48-hour and 3-week time points.

As an interventional strategy, exercise was reported to be protective in a mouse model of drug–induced damage to the BBB. Methamphetamine (METH) exposure has been shown to reduce the expression of claudin-5, occludin and ZO-1, and disrupt the co-localisation of occludin and ZO-1 in the plasma membrane [91, 93]. Two weeks of voluntary running following exposure to METH enhanced the expression of TJ proteins, stabilised the BBB, and attenuated a METH-induced increase in systemic pro-inflammatory cytokines. Furthermore, exercise significantly increased the number cells co-labelled with bromodeoxyuridine (BrdU) and NeuN, a neuronal nuclear antigen, compared to sedentary mice following METH administration. This demonstrated that, in addition to its effects on the BBB, exercise can attenuated the suppression of neurogenesis associated with METH-toxicity [91, 93].

Together, these studies indicate that engagement in regular sessions of aerobic physical activity has the capacity to strengthen the BBB by upregulating TJ-associated proteins, and in this way, protects the brain from circulating insults. Reductions in BBB permeability were reported whether exercise programs was administered prior to or following an injury (such as that imposed by ischemia or drug toxicity), with a rapid increase in TJ proteins observed after just 3–14 days of scheduled treadmill running or voluntary wheel running (respectively) [91, 130].

EXERCISE PROMOTES GLYMPHATIC CLEARANCE IN AGED MICE

The glymphatic system is defined by a space between the vessel basement membrane and glial limitans formed around pre- and post-capillary vessels, in which the cerebrospinal fluid exchanges with interstitial fluid. The astrocytic endfeet that line the paravascular space express astrocyte water channel aquaporin 4 (AQP4), a bidirectional channel believed to facilitate influx and efflux of molecules between these fluids. Glympathic influx delivers glucose and signalling molecules to the cerebrospinal fluid; efflux, conversely, has an important role in the clearance of waste products and compounds in the interstitial fluid (including Aβ and tau), and eventually drains into the subarachnoid space and cervical lymph nodes [133]. Glymphatic activity has been found to be increased in sleep, and decreased in traumatic brain injury, stroke, and subarachnoid hemorrhage [134–136]. In addition, glymphatic transport is reduced with age and certain diseases, such as small vessel disease [134, 137–141]. Furthermore, glymphatic dysfunction has implications in disorders characterised by accumulation of abnormal proteins, such as AD. For example, the accumulation of $A\beta_{40}$ and cerebral amyloid angiopathy (CAA) can result in Aβ deposits in the basement membrane drainage pathways, in turn impeding the glymphatic elimination of Aβ and interstitial fluid from the brain [141–143]. Since the glymphatic system is believed to be under immune surveillance by blood-borne macrophage and T cells, it serves as an important bridge between the brain and rest of the body [138]. Nonetheless, it is worth noting that our understanding of the mechanisms of the glymphatic system, or a similar sort of fluid filtration system, still requires refinement [144].

In middle-aged mice, 6 weeks of voluntary running has been shown to accelerate efficiency of glymphatic clearance, assessed using intracisternal injections of a paravascular tracer. The expression of AQP4 was increased in runners, as was its distribution to astrocytic endfeet, while BBB permeability was unaltered [94, 145]. Running mice also showed reduced intraneuronal $A\beta_{1\text{-}40}$ accumulation in the cortex as well as reduced $A\beta_{1\text{-}42}$ deposition outward of vessel. Furthermore, access to a voluntary wheel running reduced activation of astrocytes and microglial [94], an important observation given recent focus on the relationship between the BBB and a glymphatic system [133, 139, 144]. Although research pertaining to glymphatic clearance of neurotoxins is relatively young, these studies suggest that such a system may participate in the neuroprotective benefits of increased physical activity.

EXERCISE FACILITATES CLEARANCE AND DEGRADATION OF SOLUBLE Aβ

Regular, long-term aerobic activity that commences in the pre-plaque stage has been shown to inhibit hippocampal and cortical Aβ deposition in several mouse models [76, 99, 146, 147]. TgCRND8 mice who underwent voluntary running for 3–5 months have shown reduced Aβ load, and CAA pathology [76, 99, 146]. Similar reductions in the number of plaques have been reported in Tg2576 mice [98, 148]. Ten weeks to 5 months of treadmill training in APP/PS1 trangenic mice (beginning at 3 months of age) also inhibited the expression of AD-like pathology, including robust reductions in both Aβ deposition and tau phosphorylation [147, 149, 150]. Recent work has shown that housing animals in enriched environments (equipped with activity wheels) is effective at ameliorating memory deficits related to Aβ toxicity, as induced by intra-hippocampus infusions of $A\beta_{25\text{-}35}$ [151]. When housed in an enriched environment prior to the introduction of Aβ, which provides both voluntary access to physical activity and cognitive stimulation, rats showed improved performance on short– and long–term novel object recognition challenges. Exercised rats also presented lower lipid peroxidation, showing that physical activity may protect against Aβ-induced cellular damage [151].

Recent studies have focused on the mechanisms by which exercise attenuates the build-up of Aβ in the brain [96, 97, 101, 150, 152–154]. The supportive role of exercise in glymphatic clearance of toxic molecules, including Aβ, was described in the previous section. A 2017 study showed that exercise can also decrease Aβ production in NSE/APPsw mice, by biasing the processing of amyloid precursor protein (APP) toward a non-amyloidogenic pathway [96]. This effect was mediated by enhancement of the sirtuin-1 pathway. Authors demonstrated that treadmill running reduced levels of the β-site APP cleaving enzyme (BACE-1), which is responsible for the first cleavage step in the transformation of APP into Aβ. In addition, exercise enhanced expression of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM-10), which cleaves APP in a nonamyloidogenic pathway [96]. These changes correlated with reductions in cortical $A\beta_{40}$ and $A\beta_{42,}$ reduced cortical markers of cell death, and improved performance on the Morris water maze [96].

Moore and colleagues used Tg2576 mice, which normally develop amyloid plaques around 9 months of age, to determine if the preventative effects of exercise are 'dose dependent' using two different exercise regimens [97]. Animals engaged in either low-intensity training or high-intensity treadmill training, where soleus muscle citrate synthesis was increased by 39% and 71% relative to sedentary mice, respectively. In both in the cortex and hippocampus, treadmill training from 3 to 6 months of age reduced soluble $A\beta_{40}$ and $A\beta_{42}$ in an exercise-training dose-dependent manner. Moreover, there was an upregulation of 5 proteins involved in Aβ clearance (or efflux) and degradation: neprilysin, insulin-degrading enzyme (IDE), matrix metallopeptidase 9 (MMP9), low-density lipoprotein-related receptor 1 (LRP1) and heat-shock protein 70 (HSP70). Upregulation of these proteins was also dependent on training intensity [97]. The intensity-dependent reduction of Aβ is an interesting observation, as it is consistent with the positive correlation between duration and/or intensity of exercise and BDNF production noted in both humans and animals.

The studies described here demonstrate that exercise protects against Aβ build-up when commenced in a pre-plaque period and in this way, it can be considered in the context of a greater preventative strategy. In genetic animal models, the effects on Aβ load could not be recapitulated when exercise was commenced *after* plaque onset [155], however studies of AD patients in nursing homes have reported positive cognitive effects on cognition and behaviour that can likely be attributed to some of the other factors positively affected by exercise [22, 156, 157].

EXERCISE PRODUCES A RAPID UPREGULATION OF NEUROTROPHIC FACTORS

BDNF

Growth and neurotrophic factors, as well as hormones produced both in the brain and periphery, are essential for the growth and maturation, survival, and function of cells in the brain [1, 20, 89, 158–160]. BDNF, the most widely distributed neurotrophin in the brain, participates in neurogenesis, synaptogenesis and dendritogenesis, and also initiates signalling cascades that upregulate transcription of pro–survival genes [55, 161–168]. In addition, BDNF-mediated pathways promote the induction of hippocampal long-term potentiation (LTP) [161, 169]. Conditional TrkB knockout mice show age and region–specific reductions in spine density as well as altered spine morphologies in the hippocampus, which are linked to impaired LTP [38, 45]. Moreover, disruption of hippocampal BDNF/TrkB signalling — genetical or pharmacological — has been shown to result in a variety of memory deficits in rodent models, demonstrating the functional relationship between BDNF and cognition [5, 153, 159, 169–172]. In humans, BDNF and full-length TrkB are reduced with age and in early stages of AD, where decreased BDNF/TrkB signalling has associated with both cognitive decline and the presence of oligomeric $A\beta_{1\text{-}42}$ [35, 37, 173–178]. Reductions in BDNF and full-length TrkB have also been described in aging rodents, and correlate to AD-like pathology, aberrant spine morphology, and impaired signalling pathways [42, 45, 174, 179].

BDNF is known to be elevated by physical activity. In healthy human participants, BDNF has been reported to be elevated in blood serum both after one acute session of moderate to intense (anaerobic) exercise as well as by chronic aerobic training, such as 5 weeks of training on a stationary bike, 3 times per week, where workload was gradually increased to maintain 60% of maximal oxygen consumption (VO_2 max) for 60 minutes [8, 9, 180, 181]. However, meta-analyses revealed that regular exercise augments the effect of any single exercise session on serum levels of BDNF, and that only aerobic exercise had an effect on resting BDNF levels [182, 183]. And while BDNF is robustly up-regulated in contracting muscle fibres, analyses of the arterial-to-internal jugular venous difference in plasma BDNF levels suggest that neurotrophin produced and released from the brain contributes 70–80% of circulating levels following 4 hours of aerobic exercise [9].

As in humans, increased physical activity in rodents elicits a rapid elevation in the transcription and translation of BDNF and TrkB in the hippocampus. Indeed, a positive correlation between levels of hippocampal BDNF and the activation of gene transcription pathways has been described after only 6 hours of voluntary running in mice (during which they ran approximately 6 km), mimicking an acute session of exercise in humans [184]. (Note: Six days earlier, mice had been exposed to the wheel for 48 hours to habituate them to the wheel). In rats, the upregulation of *Bdnf* mRNA has been well-characterised after 2 days of voluntary wheel running and *TrkB*, after 7 days [3–5, 85, 185–190]. The upregulation of *Bdnf* mRNA is region-specific, demonstrated by *in situ* hybridisation in rats aged 3 and 22 months; changes are most notable in the dentate gyrus, CA1, CA3, and CA4 of the hippocampus, and in the most caudal third of cortex, though less robust in the aged cohort [188, 191].

The uptake of peripherally circulating factors, released in greater quantities during exercise, contribute to central increases in BDNF production [1, 85, 192] (Fig. 3). Blocking hippocampal uptake of circulating IGF-1 or the IGF-1 receptor significantly blunts the exercise-induced increase in *Bdnf* mRNA and protein, as well as that of it precursor protein [1, 75, 193]. Recently, β-hydroxybutyrate (DBHB), a BBB-permeable ketone body produced in the liver, has been shown to accumulate and stimulate production of BDNF in the hippocampus following exercise [192]. There, it acts as both an energy source and an inhibitor of class I histone deacetylases to enhance BDNF expression. It has also been shown to attenuate stress-induced behavioural and hippocampal neuroinflammation [194]. Notably, exercise-associated increases of hippocampal BDNF are replicated by direct ventricular application of DBHB [192]. And while there is an age–related decline in the transport of DBHB into the brain, studies have suggested that exercise has the capacity to regulate the expression of the monocarboxylate transporters that mediate its passage [195–199]. Together, these studies demonstrate that the production of BDNF, and in turn its effects upon neuronal survival/plasticity, can be modulated by circulating factors. As many of these factors decline with age, exercise may serve to enhance their presence and, in turn, their ability to reach the brain [29, 43, 192, 198, 200].

Notably, prolonged periods of exercise (i.e. 3 weeks to 8 months of voluntary running) produce

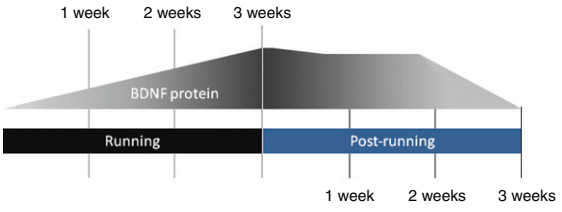

Fig. 2. Regular physical activity produces a progressive and sustained increase in the expression of brain-derived neurotrophic factor (BDNF). Elevation of intraparenchymal BDNF protein levels are graded with the duration (or total period) of regular sessions of physical activity, with profound mRNA increases detectable starting from 2–3 days. Cessation of exercise is followed by a gradual decline of BDNF protein level though it has been shown to remain significantly higher than baseline levels for up to 2 weeks. Notably, a return to exercise results in a rapid reinstatement of elevated protein levels, more quickly than is typical of exercise-naïve rodents [201, 202].

progressive elevations of *Bdnf* transcription and protein translation in rodents [54, 57, 185, 201–203] (Fig. 2). In one experiment, mice who ran daily for 2, 4, 7, 14, 28 and 90 days showed a progressive increase in BDNF protein levels in the hippocampus; the results were mirrored in mice who ran on alternating days rather than daily [201, 202]. Furthermore, protein levels have been shown to remain elevated over control levels beyond the period of exercise: following a 3 week period of daily voluntary running, hippocampal levels of BDNF were reported to be elevated for at least 2 weeks [201]. Moreover, a history of exercise has also been describe as a "molecular primer" for BDNF production, where a brief exposure to running can rapidly increase hippocampal levels following a period of rest [202]. For example, in rats returning to exercise after a week-long sedentary period, 2 days of running produced BDNF levels comparable to those requiring several weeks of running in mice who were exercise naïve. The potentiation of BDNF upregulation was comparable between animals that ran daily and those who ran on alternate days (though the post-exercise decay was shorter in the latter group), suggesting that alternative exercise regimens can provide similar benefits [202]. Recent studies have addressed whether workload, in the absence of added stress, leads to greater *Bdnf* transcription by comparing rats assigned to 7 days of no exercise, voluntary running, or voluntary running on a loaded 'resistance' wheel [204]. One week of running on a loaded wheel demonstrated a positive correlation between BDNF production and "workload", as measured by energy expenditures calculated by distance, resistance and body weight; no change was seen in TrkB between groups. These animal studies are valuable as they are consistent with observations in human studies of acute high-intensity exercise and aerobic exercise, and establish similarities between species in the required 'work' to produced elevated BDNF levels. More specifically, they demonstrate a variety of exercise regimens are capable of producing increased BDNF levels, on a similar time-course, in both rodents and humans, and that regular exercise is required for prolonged elevations. This provides good rationale for using rodents to establish the molecular effectors downstream of activity-induced elevations in BDNF.

Neural growth factor

While some studies have reported upregulation of *Ngf* mRNA after physical activity, its role in supporting exercise-mediated neurogenesis and neuroprotection is less well-defined. A study of middle cerebral artery stroke in rats showed that forced treadmill running for 12 weeks (but not 4 or 8 weeks) increased cortical *Ngf* expression and reduced the volume of infarction [205]. In contrast, when mice were exposed to 10 days of treadmill 'rehabilitation' intervention beginning 4 days after stroke induction, NGF/Trk-A signally was not elevated; instead, BDNF/TrkB signalling was increased and associated with repair processes [206]. Previously, analyses had shown that voluntary running mediated only a transient increase in *Ngf* expression in the hippocampus, with levels elevated in after 3 days but not beyond [85], though it remained elevated in the caudal cortex when measured after 7 days of running [190]. Topographical differences within the hippocampus were found with *in situ* hybridisation, with a modest but significant increase in *Ngf* mRNA after 7 days of running in the dentate gyrus and CA4 regions, as well as in the caudal cortex [190]. The local and temporal differences in NGF versus BDNF upregulation in response to exercise suggests that they likely play different roles in the neuroprotection of the aging brain.

Insulin-like growth factor-1

The protective effects of exercise also involves trophic factors that are produced peripherally, such as such as IGF-1 and vascular endothelial growth factor (VEGF) [1, 2, 16, 147, 207–209]. Peripheral factors can aid in neuroprotection by supporting angiogenesis and modulation of energy metabolism [1, 6, 89, 180, 181, 210]. Stimulated by circulating growth hor-

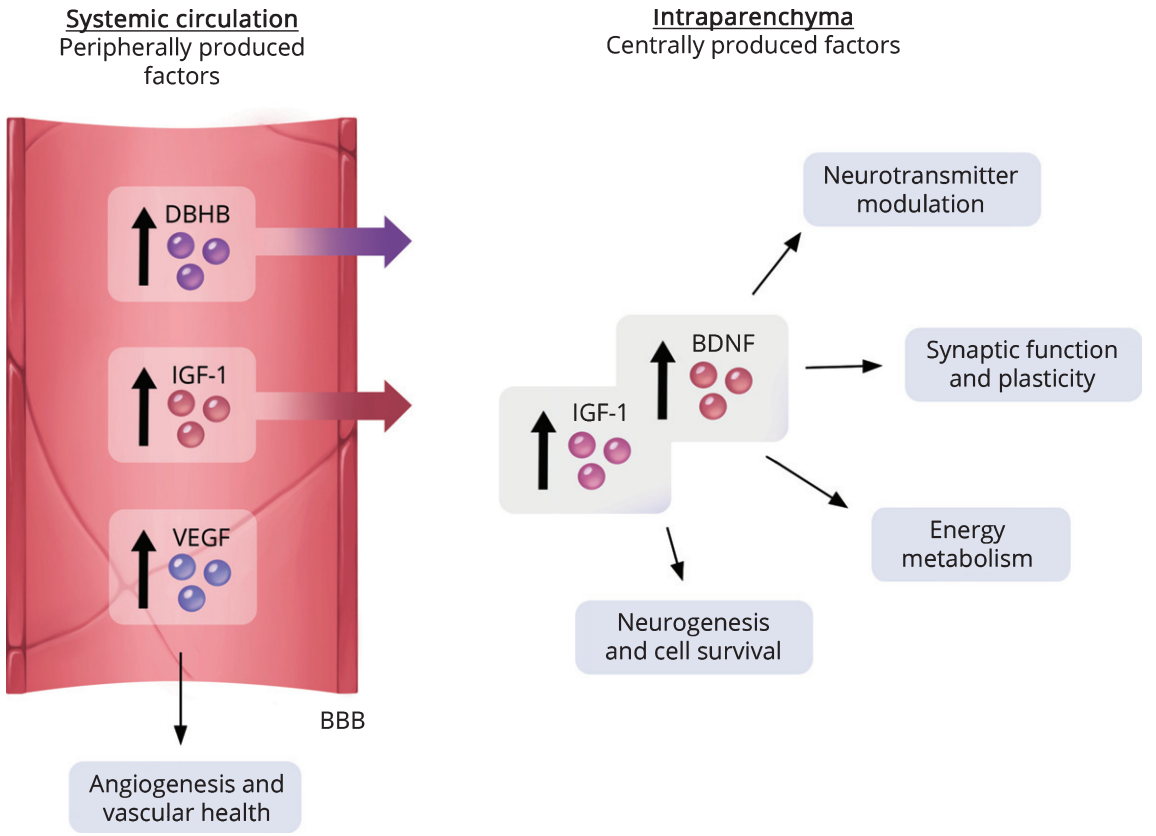

Fig. 3. Both circulating and central factors participate in exercise-facilitated protection of the brain. Exercise can increase both peripheral and central factors that co-operate in sustaining brain health. Systemic circulating factors that are elevated by exercise include beta-hydroxybutyrate (DBHB), vascular epithelial growth factor (VEGF) and insulin growth factor-1 (IGF-1). Some circulating factors, such as DBHB and IGF-1, are capable of crossing the blood-brain barrier (BBB) and may contribute to the upregulation of BDNF [16, 19, 20, 192, 209].

mone (GH), IGF-1 is produced by the liver before being released into the circulatory system [211]. It is also derived and stored in peripheral tissue, such as skeletal muscle, from which it can be rapidly released; transient increases in circulating IGF-1 following acute, high-intensity (anaerobic) exercise are believed to be muscle-derived, and are independent of GH levels [29, 193, 212–214]. However, studies have suggested that muscle-derived IGF-1 may also be an important source of circulating levels following periods of more moderate, regular exercise [193, 213, 215].

Circulating IGF-1 is BBB-permeable and thus able to reach the brain parenchyma. It is widely expressed centrally, where it is believed to modulate and support both cells and cerebrovasculature. In the brain, glial cells are known to have a role in mediating neuroprotective properties of IGF-1 and have been particularly well-studied in models of hypoxia, where IGF-1 treatment reduced oligodendrocyte loss and neuronal death [216–219]. Importantly, both GH and IGF-1 levels decline with age, coincident with neurological and vascular changes [28, 29, 43, 211, 220]. In 32 month-old rats, 2–4 weeks of IGF-1 treatment enhanced both neurogenesis and vascular density and ameliorated age–related declines in the performance of tasks involving working memory (e.g. repeated acquisition task and novel object recognition) [29, 88, 200, 220]. In 28 month-old rats, 4 weeks of continuous [mini-pump] IGF-1 infusion into the lateral ventricle reversed an age-related decreases in hippocampal glutamatergic N-methyl-D-aspartate ionotropic (NMDA) receptor subunits NR2A and NR2B ($NMDAR_{2A}$ and $NMDAR_{2B}$, respectively), subunits that are well-connected to learning and memory [200, 220]. Recent studies have also shown IGF-1 to protect cultured hippocampal cells (under stressful conditions) against NMDA-mediated excitotoxicity by modifying the phosphorylation of $NMDA_{2B}$ [221].

Rats undergoing 15 days of treadmill running show that regular training elevated the level of circulat-

ing IGF-1 taken up into the hippocampus, where it is believed to modulate the effects of exercise [89]. Blocking hippocampal IGF-1 receptors during exercise significantly attenuated elevations in the transcription and translation of BDNF as well as that of its precursor, pro-BDNF. It also abrogated the signalling cascade downstream of BDNF/TrkB, including the phosphorylation of CaMKII and MAPK-II, paralleled by a dampened upregulation of proteins regulating synaptic function, such as synapsin I [1, 20]. In addition, inhibiting the uptake of circulating IGF-1 with subcutaneous infusion of anti-serum blocked exercised-induced increases in the number of new granular cells in rats undergoing treadmill training [89]. Finally, while blocking IGF-1 did not affect exercise-enhanced learning acquisition, it attenuated the benefit to memory recall [1]. These studies suggest that while IGF-1 and BDNF co-operate to facilitate neurogenesis and synaptic plasticity, they may each play unique roles [1, 2, 89, 200].

EXERCISE INCREASES NEUROTRANSMITTER LEVELS IN THE CENTRAL NERVOUS SYSTEM

Alterations in neurotransmission as a result of age or pathology is a well-known contributor to impairments in learning and memory. Acute bouts of moderate to high intensity aerobic exercise (20 to 120 minutes) have been shown to influence a number of different neurotransmitter systems implicated in cognitive function and mood, including dopamine (DA), serotonin (5-HT), noradrenaline (NA), acetylcholine (ACh), glutamate, and gamma-aminobutyric acid (GABA) (Table 1; see reviews: [16, 222]). In this way, acute sessions of physical activity may enhance cognitive performance by increasing both blood flow and tissue content of neurotransmitters associated with cortical arousal, such as glutamate, NA and ACh [223–231]. Moreover, evidence suggests that increases in central neurotransmitters may co-operate with neurotrophins to promote beneficial long-term neuronal adaptations [222]. Indeed, a reciprocal relationship exists between several neurotransmitters and BDNF in the hippocampus [189, 203, 232–235]. These studies suggest that increases in neurotransmission and BDNF/TrkB signalling may converge to enhance neuronal survival, synaptic plasticity and neurogenesis, such as that observed to be coincident with increased physical activity [4, 5, 236]. The following discussion of neurotransmitters is limited to those that have been most closely linked to BDNF in the pro-survival and signal transduction pathways; however, it should be noted that other transmitters, including ACh and GABA, have also been linked to the neuronal adaptations, cerebrovascular effects, and cognitive improvements associated with exercise [166, 227, 228, 237–241].

Dopamine

Positron emission tomography (PET) and post-mortem biochemical analyses have revealed declines in DA synthesis, receptor binding, and receptor levels in the aging human brain [242–245]. These alterations may hold significance not only for mood and motor functions, well-known to be under dopaminergic governance, but from the perspective of neuroprotection in the aging brain.

Dopaminergic neurotransmission has been associated with enhanced BDNF signalling, a relationship well-described *in vitro* [246–248]. In embryonic neurons, D_1 receptor agonism transactivates TrkB and several factors in its signalling pathway, accelerating morphological maturation, differentiation, and neurite outgrowth [248]. Similarly, pharmacological stimulation of the D_1-D_2 receptor hetero-oligomer was shown to increase BDNF production via a calcium signalling cascade in cultured striatal neurons and the adult rat brain [247]. In turn, BDNF originating from cortical neurons can elicit long-term adaptations by influencing the response of targets cells to DA, in part by controlling the expression of select DA receptor subtypes. This has been demonstrated *in vivo* using lesioning and gene–targeting experiments: mice lacking TrkB showed a global reduction in D_1 mRNA [249], while BDNF-null mice and 6-hydroxydopamine (6-OHDA) lesioning of cortical dopaminergic neurons show BDNF to be necessary for normal expression of D_3 receptor in the nucleus accumbens [250].

In both human and animals studies, moderate aerobic exercise such as treadmill running has been reported to increase DA synthesis, DA receptor expression and neurotransmission in a variety of structures, including the striatum, hippocampus, midbrain, pons-medulla and prefrontal cortex [210, 225–227, 251–259]. Some of these effects may be more profound in aged rodents, or under pathological conditions. For example, 8 weeks of was shown to upregulate the expression and activity of tyrosine hydroxylase, the rate-limiting enzyme in

the synthesis of catecholamines, in aged mice but not in young mice, representing a reversal of its age-related decline [259]. In a neurotoxicity model of Parkinsonian dopaminergic cell loss, 28-days of intensive treadmill running enhanced DA bioavailability and neurotransmission both by increasing DA release and, by modulating the expression of its transporter, the time DA resides in the extracellular space [260]. These studies demonstrate that regular physical activity has the capacity to promote adaptive changes that facilitate dopaminergic transmission which might otherwise be compromise due to age or disease.

By enhancing both DA neurotransmission and BDNF production, exercise may promote neuroprotection of dopaminergic cells via a co-operative activation of pro-survival pathways. A 4-week history of treadmill running at speeds that incrementally built to the equivalent of a moderate intensity session (60 minutes/day, 5 days per week) was shown to completely protect against inflammation-induced dopaminergic neuronal loss in the substantia nigra and attenuated motor impairment in freely-behaving mice [246]. Neuroprotection in the nigrostriatal pathway was dependent on the activation of the BDNF-TrkB signalling pathway rather than modulation of microglial activation or cytokine/chemokine levels [246]. In contrast to the 4-week regimen, 2 weeks of exercise prior to the inflammatory challenge was insufficient to provide significant protection, which could be indicative of a minimal requirement for adequate exercise-facilitated BDNF translation to rescue neuronal loss in the striatum.

Noradrenaline

NA modulates a wide variety of brain functions, including attention, memory consolidation and memory retrieval [261–263]. Following both session of both moderate and intense exercise, tissue content of NA and its metabolites has been reported to be widely elevated throughout the brain (i.e. striatum, cortex, hippocampus, pons-medulla, and amygdala) as well as in the blood [226, 264–268]. Early microdialysis experiments showed that following 2 weeks of training on a treadmill (5 days per week, 1 hour at 25 m/min, 3% slope; workload equivalent to 70% of VO_2 max), rats that exercised for 1 to 2 hours showed increased levels of NA in both brain microdialysate and blood plasma (note: there was a 4 day rest after the initial, 2-week training for surgery and recovery) [266]. While both 1 and 2 hours were sufficient to significantly increase cortical NA levels within 40 minutes of the onset of treadmill running, the magnitude and duration of change was not equivalent: the maximal increase seen in a 1 hour session was fivefold over baseline, still evident 30 minutes after running cessation, while 2 hours of running increased NA levels 6.5 times over basal levels, with significant elevations lasting for 70 minutes [266].

Notably, exercise-induced upregulation of *Bdnf* is dependent on the activation of the transcription factor, cyclic AMP response element binding protein (CREB), which is in part facilitated by increased neurotransmission via the cAMP second messenger pathway [184, 269]. Selectively blocking β-adrenergic receptors throughout 3 days of voluntary wheel running abolishes *Bdnf* mRNA elevations within the hippocampus, suggesting noradrenergic signalling plays an important role in its upregulation [189]. Noradrenergic receptor antagonism was also found to blunt the exercise-mediated enhancement of learning and memory in rodents, as assessed by performance in contextual fear conditioning [270] and the Morris water maze [271]. In addition, activation of noradrenergic G protein-coupled receptors has been shown to transactivate BDNF/TrkB pathways, representing another means by which NA signalling participates in neuronal adaptations associated with exercise (Fig. 4A) [184, 189, 272–274].

Interestingly, noradrenergic signalling has also been shown to protect against Aβ toxicity, achieved both through the transactivation of TrkB [275] and by facilitating increased expression of *Bdnf* [269]. It is possible that this represents an additional mechanism by which exercise-facilitated alterations in neurotransmission can confer neuroprotection. The NA system may also protect the brain by modulating the central inflammatory response, including that in response to Aβ, via adrenergic receptors on astrocytes and microglia [224, 276–278]. Selective lesioning of NA fibres has been shown to impair microglial migration and phagocytosis, reducing clearance of Aβ in the hippocampus and frontal cortex [277]. This is a particularly interesting observation considering that degeneration of noradrenergic cells within the locus coeruleus has been associated not only with the severity of cognitive disturbance but with the cortical correlates of AD, including Aβ plaque load and neurofibrillary tangles [277, 279, 280]. Noradrenergic lesioning also exacerbates lipopolysaccharide (LPS)-induced systemic inflammation, which is positively correlated to levels of hippocampal pro-inflammatory cytokines

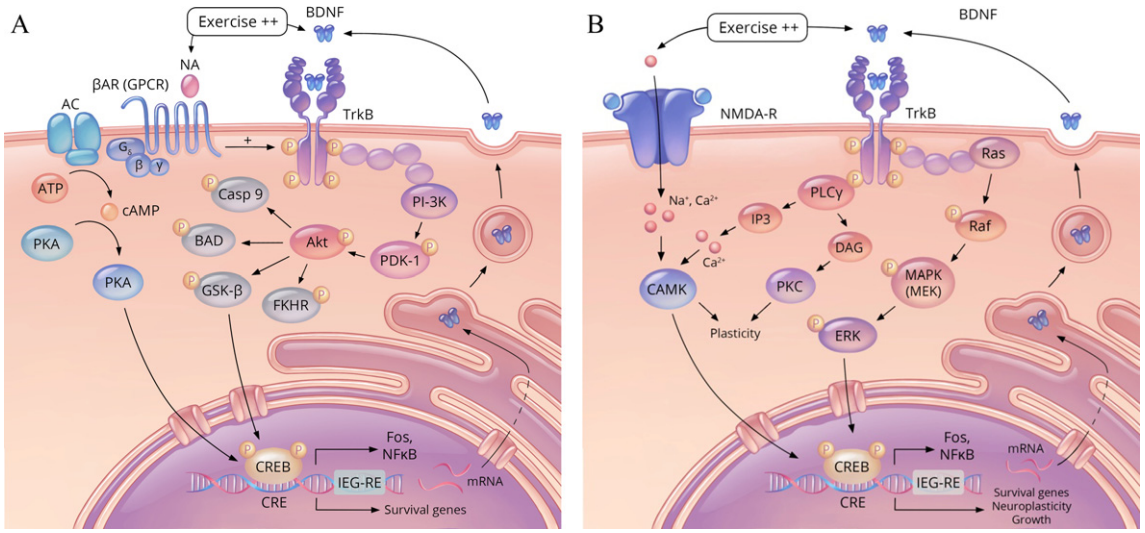

Fig. 4. Exercise-activated pathways regulating growth, survival, and neuroplasticity. (A) Schematic representation of the effect of increased noradrenaline (NA)–signalling and brain-derived neurotrophic factor (BDNF) / tropomyosin receptor kinase B (TrkB) signalling. Noradrenaline binds to the β-adrenergic receptor (βAR), a G protein–coupled receptor (GPCR) which can initiate a cyclic adenosine monophosphate (cAMP) pathway to phosphorylate (and activate) the transcription factor cAMP response element-binding protein (CREB). In addition, NA–mediated signalling can augment BDNF signalling pathways by transactivating its receptor, TrkB. Phosphorylation of TrkB initiates the phosphatidylinositol-3 kinase (PI-3K) pathway to activate protein kinase B (Akt), which phosphorylates glycogen synthase kinase 3-β (GSK-β), deactivating it, in turn increasing CREB activity. Phosphorylated CREB transcribes a number of pro-survival genes, such as Immediate-Early Gene-Regulatory Element (IEG-RE), and nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB). In addition, it acts to further promote the transcription of BDNF and TrkB. Proteins that are deactivated by Akt include a number of pro-apoptotic factors (i.e. Casp 9, FKHR, and BAD) (shown in dark grey). Activated proteins and kinases are shown in pinks and blue, and activated CREB, in yellow. *Additional abbreviations*: adenosine triphosphate (ATP); Bcl-2-associated death promoter (BAD); cAMP response element (CRE); caspase 9 (Casp 9); forkhead transcription factor (FKHR); protein kinase A (PKA); phosphoinositide-dependent protein kinase-1 (PDK-1). (B) Two additional exercise-facilitated pathways involved in the growth, survival and plasticity pathways are the mitogen-activated protein kinases/extracellular signal-regulated kinases pathway (MAPS/ERK) and the phospholipase Cγ/Ca2 + /calmodulin-dependent protein kinase II (PLCγ/CaMKII) pathway. Glutamate NMDA receptors activity also facilitates the effect of exercise on CREB activation. These pathways, like the PI-3K pathway, have also been shown to be involved BDNF/TrkB activation in promoting genes involved in survival and neuroplasticity. Activated proteins and kinases are shown in pinks and blue, and activated CREB, in yellow. *Additional abbreviations*: Ca^{2+} /calmodulin-dependent protein kinase (CAMK), diacyl-glycerol (DAG), Mitogen-activated protein kinase kinase (MEK), inositol trisphosphate (IP3), protein kinase C (PKC) [184, 287, 345, 346].

and microglial activation in aged rats [281]. Serum and BDNF levels were reduced in rats who were pre-treated with a selective noradrenergic toxin prior to receiving LPS [281]. Collectively, NA has been shown to play a number of important neuroprotective roles, both by transactivating TrkB and participating in the clearance of toxic peptides by microglia. It is possible that exercise may support these roles by facilitating NA neurotransmission.

Serotonin

Declines in the serotonergic system have been described in the aging human brain, and include decreased levels of 5-HT_2 receptor in the prefrontal cortex as well as reduced binding capacity [245, 282]. In addition, post-mortem analyses of patients with mild cognitive impairment have revealed a global reduction in 5-HT_{1A} and 5-HT_{2A} receptors [283]. Activation of 5-HT_{1A} receptors has been shown to be associated with decreased NMDAR-mediated currents in pyramidal neurons of the prefrontal cortex, which in turn destabilises $NMDA_{2B}$ receptors; in contrast, activation of 5-$HT_{2A/2C}$ receptors increases NMDA receptor-mediated currents by activating intracellular signalling cascades [284–286]. These observations are of relevance when considering the role of NMDA-mediated signalling in LTP and synaptic plasticity. Indeed, exercise-enhanced learning has been associated with the downregulation of 5-HT_{1A} receptors and, conversely, upregulation of 5-HT_{2A} receptors in the hippocampus [287–289]. The inhibition of 5-HT_{1A} (a G_i protein–coupled receptor) and activation of 5-HT_{2A} (a G_s protein–coupled recep-

tor) results in elevated levels of cAMP, which in turn is involved in intracellular kinases and transcriptional factors supporting learning and memory [290]. Moreover, different 5-HT receptor subtypes have been demonstrated to play acute and opposing roles during various stages of neuronal development *in vitro*: where 5-HT_{1A} receptors promote self-renewal of precursor cells, 5-$HT_{2A/C}$ receptors effect both proliferation and promote neuronal differentiation [291].

Recent studies demonstrate 5-HT to be required for activity-induced neurogenesis in both young and aged mice [292, 293]. Mice deficient in tryptophan hydroxylase 2 (*Tph2-/-*), the enzyme mediating *de novo* 5-HT production in the raphe nucleus, exhibit selective depletion of brain-derived 5-HT. While *Tph2-/-* mice show normal baseline hippocampal neurogenesis, the proproliferative effect of voluntary running (6 days) was shown to required the release of central 5-HT [292]. Similarly, running-stimulated neurogenesis was reported to be impaired in mice deficient in Ang-converting enzyme 2 (ACE2), an enzyme which converts Ang II to Ang-(1–7); this modification transforms Ang signalling from a vasoconstrictive and pro-inflammatory signal to one that is vasodilatory and anti-inflammatory. ACE2 is also involved in the intestinal absorption of tryptophan, the precursor to serontonin, with ACE2-/- mice showing significant reductions in both blood and brain 5-HT levels [293]. Worth noting is that there is great variation in the literature pertaining to the tissue content of 5-HT following periods of physical activity, signifying that the duration and intensity of both acute sessions and chronic training impacts the synthesis of 5-HT, and the expression of its receptors and transporters, likely in a region-specific manner.

Glutamate

Glutamatergic neurotransmission, altered in normal aging and disease, is critically involved in facilitating neuronal plasticity and modulating both LTP and long-term depression (LTD) [294–297]. Aging has been associated with a decline of glutamate content in the prefrontal cortex and hippocampus, a reduction in high–affinity glutamate transporters and glutamatergic receptors, and reduced glutamate uptake capacity [298–300]. Expression of the NMDA receptor class is particularly influenced by advanced age [200, 298, 301, 302]. As neuronal plasticity is in large part dependent on synaptic NMDAR activation, a decrease in synaptic NMDAR expression may functionally contribute to the age-related in memory and cognition [295, 303–305].

In rodents, short-term periods of voluntary running have been shown to modulate expression of glutamate receptors, upregulating NR2A and NR2B NMDA subunits within 3 and 7 days (respectively) [85, 236, 303] and glutamate receptor 5 (GlutR5), within 10 days [186]. Glutamatergic signalling has been shown to promote transcription of several genes involved in synaptic transmission as well as neuronal survival, via CREB activation. In this way, NMDA-mediated transmission has also been shown to contribute to the upregulation of BDNF and TrkB following exercise, further facilitating its effects [4]. Site-specific blockade of hippocampal NMDARs with MK-801 prevented increases in the transcription of *Bdnf*, *TrkB*, *CREB*, and *synapsin I* mRNA observed in control animals following 3 days of wheel running (against 100 g resistance) [4, 5]. In addition, rats given unrestricted access to a running wheel for 10 days had a significantly lower threshold for the induction of LTP in the dentate gyrus *in vivo*, as well as a potentiated LTP response to tetanic stimulation [186]. Similar results were demonstrated *in vitro* using hippocampal slices from running and non-running mice, showing that following 7–10 days, changes in NR2A and [to a lesser] extent NR2B were responsible for the augmentation of LTP and LTD [236]. More recent research shows that, together with GABA, exercise-mediated increases in glutamatergic transmission also influences the integration of young adult-born neurons into neural networks, which may underlie improvements to specific cognitive tasks [296].

Notably, activation of extracellular NMDARs induces excitatory neurotoxicity that has been implicated in neurodegeneration, including that in AD. Studies have suggested that an inverse relationship exists between excessive glutamate levels in the brain and neurogenesis and/or cell survival, possibly due to extrasynaptic calcium influx. Activation of extracellular NMDARs has recently been linked to accelerated transcription of tau, concomitant with a suppression of the mitogen-activated protein kinases/extracellular signal-regulated kinases pathway (MAP/ERK) signalling pathway [306]. Rodent studies suggest that increased physical activity may ameliorate excessive glutamatergic activity, in part by regulating glutamate release and oxidation, as well as through the BDNF-mediated activation of the ERK pathway [163, 164, 307–309]. In the latter respect, it shares mechanistic similarities to treatment with low doses of antidepressants such as ketamine,

an NMDAR antagonist that dampens spontaneous glutamate signalling [163]. Mice given free access to a running wheel for 6–8 weeks show a decrease hippocampal glutamate levels that correlated with increased hippocampal volume on magnetic resonance (MR) imaging [307]. These studies reveal that exercise-induced alterations to glutamatergic transmission play an important role in promoting the transcription of genes involved in synaptic plasticity, as well as in promoting cell survival.

EXERCISE AND BDNF-MEDIATED PATHWAYS: NEUROPROTECTION AND SYNAPTIC PLASTICITY

Neurogenic and pro-survival pathways

Exercise promotes neuronal differentiation, survival and plasticity through the phosphorylation of CREB by BDNF [310], with likely contributions by excitatory noradrenergic and glutamatergic signalling pathways. Foundational experiments demonstrated BDNF to be neuroprotective using hippocampal slices and cortical neurons *in vitro*: under apoptotic conditions, BDNF activates the phosphatidylinositol-3 kinase/protein kinase B pathway (PI-3k/AKT) as well as MAPS/ERK to stimulate the transcription of survival-promoting genes via CREB (Fig. 4A and B, respectively) [171, 287, 310–313]. The phospholipase Cγ/Ca2 + /calmodulin-dependent protein kinase II (PLCγ/CaMKII) pathway is also activated by BDNF-TrkB signalling, again resulting in gene transcription of pro-survival genes [314]. *In vivo* studies have revealed notable mechanistic similarities between antidepressant treatments and exercise in rodents, with both activating excitatory pro-survival pathways. These studies offer insight into how exercise may mediate proliferative and/or neurogenic processes in the dentate gyrus via a combination of neuronal activation (i.e. synaptic transmission) and BDNF/TrkB signalling [184, 188, 189, 191, 315].

Recently, Ma et al. (2017) showed that BDNF/TrkB signalling is responsible for the persistent adult neurogenesis in the dentate gyrus stimulated by chronic treatment with antidepressants, such as low-dose ketamine [163]. Ketamine treatment produced a rapid increase in BDNF levels in the dentate gyrus that coincided with accelerated differentiation of doublecortin positive (DCX+) progenitor cells into functionally mature neurons. Ablation of TrkB in progenitor cells or disruption of TrkB-dependent ERK signalling blocked the generation of newborn neurons as well as the anti-depressant behavioural effects of the drug [163]. In addition, both antidepressants and voluntary exercise are known to activate the PI-3k/AKT pathway in the hippocampus, which promotes neuronal survival and inhibit apoptosis [287, 316, 317]. Chen et al. (2005) showed that 2 weeks of voluntary running in rats produced a robust increase in the phosphorylation of the full-length TrkB receptor, a result that was potentiated when animals were concurrently treated with an antidepressant [188–190, 287]. The study reported that levels of active (i.e. phosphorylated) forms of PI-3k, protein-dependent kinase-1 (PDK-1) and Akt were increased in the hippocampus, as were levels of phosphorylated glycogen synthase kinase-3β (GSK3β, inactive form), which ultimately led to a significant enhancement of CREB [287]. Chen and colleagues further showed that phosphorylation of CREB was augmented when antidepressant treatment was combined with voluntary running (beyond either treatment alone) suggesting they work synergistically to modulate the PI-3k/AKT neuroprotective pathway, possibly a result of the transactivation of TrkB or a consequence of increased NA and/or 5-HT–mediated neuronal stimulation [287].

Another mechanism by which BDNF may faciliate neuroprotection is through the initiation of a synaptic NMDAR-associated intracellular cascade that attenuates the excitotoxicity that results from extrasynaptic NMDAR-mediated calcium influx [164, 303, 318]. Lau et al. (2015) found that BDNF/TrkB signalling induces protective adaptations, termed "adaptogenomics", by enhancing the nuclear calcium-inhibin β-A pathway [164]. In turn, inhibin β-A (or 'activin A', as a heterodimer) was shown to reduce extrasynaptic calcium influx and mitochondrial dysfunction, both of which contribute to excitotoxicity. Physical activity may therefore contribute to the neuroprotective adaptogenomic pathway by upregulating BDNF by enhancing synaptic NMDA activity while reducing extrasynaptic NMDA activity [164].

Exercise, signal transduction and synaptic plasticity

BDNF is known to alter gene transcription both pre– and post–synaptically [81, 160, 165, 319]. Quantitative analyses have revealed that elevated BDNF/TrkB signalling, resulting from short-term

increases in physical activity, positively correlates with mRNA expression of several proteins involved in vesicular trafficking and neurotransmitter release. For instance, in freely running rats, *syntaxin* and *synaptotagmin* mRNA levels were shown to be upregulated by 3 days (continuing for at least 28 days), while *synapsin I* was elevated at 3 and 7 days [4, 5, 85, 86]. Site-specific blockade of hippocampal TrkB was sufficient to abolish the exercise-induced increases in *Bdnf*, *TrkB*, *CREB*, *synapsin I* and *synaptophysin* reported after 3 days of voluntary running [4, 86]. Blocking CaMKII had similar effects as TrkB inhibition, demonstrating its downstream involvement in upregulating both signalling molecules and *Bdnf* and *TrkB* expression in response to physical activity [4]. Together, these results demonstrate that short-term exercise has the capacity to regulate synaptic transmission under the direction of BDNF [4, 5, 86, 320–322]. The effects of extended-periods of running are equally dependent on BDNF/TrkB signalling. After having undergone chronic treadmill running for a total of 4 weeks, mice showed increased hippocampal protein levels of BDNF, total and phosphorylated TrkB, and synaptotagmin. These molecular changes were associated with behavioural outcomes, as exercised mice showed improved performance on the passive avoidance test as compared to sedentary controls [81]. Again, TrkB inhibition abolished the exercise-induced increases in BDNF and synaptotagmin levels, and impaired performance on the same test of aversion memory [81].

In vitro studies suggest that alterations in protein synthesis in response to BDNF can occur on the order of hours and are regionally localised to dendrites and axons, with protein synthesis machinery residing in pre– and post–synaptic terminals [158, 171, 319, 323]. The rapidly increased production of signal transduction molecules may be in part responsible for the relatively quick effects of exercise on mood and cognitive performance. By modulating the transcription of synaptic proteins such as synapsin I, synaptophysin, and synaptotagmin, exercise puts in place pre-synaptic structures to support enhanced neurotransmission. A complimentary increase in the expression of neurotransmitter receptor proteins, such as subunit-specific increases in NMDARs, further facilitates the enhancement of neurotransmission. As selective blockade of NMDARs and BDNF both abolished exercise-facilitated gene transcription, both neuronal activity and BDNF/TrkB signalling seem to be an essential part of both the pro-survival and plastic response.

BDNF has been shown to be involved in several forms of LTP. Using site-specific gene deletion, Zakharenko and colleagues dissociated the effects of BDNF released from pre-synaptic neurons in the C1 and C3 regions from that released post-synaptically at C1, finding that presynaptic release of BDNF from C3 was required to modulate a pre-synaptic component of LTP [319]. In particular, BDNF was shown to be required for a pre-synaptic component of theta burst LTP, which is thought to be of relevance for behavioural activity, as well as for the full expression of 200 Hz LTP. Exercise may then influence LTP by way of BDNF but also through its governance of neurotransmitter release, such as ACh, which is found to be elevated in the hippocampus and cortex with increased physical activity [226, 227, 237]. An increased concentration of ACh in the hippocampus supports the generation of theta oscillations, which in turn, serves to facilitate synaptic plasticity, learning and memory [240, 324, 325]. Acute physical activity has also been reported to produce immediate and robust neuronal activation of the hippocampal formation, as measured by c-fos positive cells [315]. On-going movements (i.e. wheel running, walking, swimming, etc.) generate theta oscillations that are positively correlated to the force or intensity of these movements and remain elevated the duration of activity. These theta oscillations have been associated with glutamatergic inputs originating from the medial septal nucleus and/or the entorhinal cortex, as lesioning experiments have eliminated movement-related theta [315]. Recalling that physical activity is known to modulate the expression of NMDAR, it is interesting to note that changes in the levels of BDNF, ACh, and NMDA-mediated signalling likely work synergistically to mediated enhancement of synaptic plasticity.

CLOSING REMARKS

In this review, we highlighted the many contributions of an active lifestyle to continued brain health. First, as discussed, the BDNF/TrkB pathways initiated by physical activity are involved in neuroprotection, synaptic plasticity, and neurogenesis. Knockout mice have demonstrated that BDNF is required for the enhancement of hippocampal neurogenesis following housing in enriched environments [326]. Moreover, intracerebroventricular injections of BDNF have mimicked the effects of 1 week of treadmill running on spatial and non-spatial learning

[187], and chronic intrahippocampal administration of BDNF has been shown to rescue cognitive deficits following a ventricular injection of Aβ in rats [327]. Of note, only enriched environments that include a running wheel were shown to increase BDNF levels, showing it may have a unique role in neuroprotection [74, 75, 328]. Indeed, much past literature has focused on the link between physical activity and neurogenesis, showing that physical activity alone is sufficient for increasing cell proliferation and promoting cell survival [54, 56, 57]. However some studies suggest that cognitive stimulation is an essential part of differentiating proliferating cells into neurons and integrating them into networks [41, 329]. Considerable efforts are now being made to better understand the complexities of adult neural stem cells and the dynamic range of states in which they can exist (for excellent review, see [63]). Moreover, though a greater proportion of adult neural stem cells have entered quiescence, current research centres on how certain stimuli may transition these cells from quiescence to a proliferative state. Nonetheless, mitigating the age-related decline in neurogenesis is only one way by which an active lifestyle can keep the brain 'young' [330]. Several decades of literature demonstrate its benefit to the neurons, glia and cerebrovaculature of the brain. In animal models of aging, disease and toxicity, physical exercise has been shown to upregulate TJs of the BBB and to protect the neurovascular unit. Exercise has also been shown to reduce markers of microglia activation in the brain of aged mice, further mitigating damage to the neurovascular unit [90, 95, 331–333]. Finally, exercise may also aid in the protection of an aging brain by increasing glymphatic clearance, and promoting the clearance and degradation of Aβ [76, 94, 96–99].

Both animal and human literature suggest that many of the protective benefits of exercise are orchestrated by elevations in central and peripheral neurotrophic factors. Increases in neurotrophic levels have been reported to be associated with both acute sessions of high-intensity exercise and chronic aerobic exercise. In healthy, young human adults, BDNF levels in the serum were shown to increase during acute sessions of high-intensity anaerobic cycling (correlating with lactate levels), but not at workloads below the ventilatory threshold [7]. However, BDNF in plasma were shown to be elevate during moderate-intensity endurance exercise, such as a 4-hour row at a workload 10-15% below the lactate threshold [9]. Other studies still show that both acute high-intensity exercise and regular, moderate aerobic exercise increases serum levels of BDNF and IGF-1, and improves some measures of memory and cognition in young participants [8, 13, 334, 335]. Notably, a recent meta-analysis of 29 studies showed that aerobic exercise, but not resistance training, increased resting concentrations of peripheral BDNF [183]. As circulating BDNF receives contributions from both the brain and other sources, including contracting muscle, this discrepancy may reflect a difference in the relative contribution of these sources during aerobic and anaerobic exercise.

Many studies demonstrate a correlation between BDNF and/or work levels and improved performance in various tests of memory and cognition (with the support of many meta-analyses). Still, the degree to which exercise specifically affects memory and cognition in young participants, independent of mood or acute effects on attention, lacks firm consensus [16, 183, 335–338]. To-date, clinic research has been somewhat limited by study size and is not often sex-balance; it also shows great variability in experimental and sampling protocols. It is possible that performance on certain memory testing may be more malleable to acute exercise sessions than others and augmented via different mechanisms, such as rapid changes in blood flow or the release of neurotransmitters that modulate attention. In this way, it is possible that acute cognitive changes may be independent of elevated BDNF and more reliant on other rapid physiological processes. In contrast, improvements to memory, cognition or executive function that correlate with regular exercise may be a result of long-term neuronal adaptations. Cognitive improvements associated with exercise are most striking in aged participants, and possibly even more so in the eldest of participants due to an age-dependent decline in baseline BDNF levels relative to young individuals [18, 23]. In cognitively-unimpaired aging participants as well as those with mild cognitive impairment, aerobic activity correlates with a reduced risk of developing deficits in executive functions and a reduced incidence of dementia [18, 21, 22]. In these prospective studies, the intensity, duration and frequency of exercise correlate with improved scores on tests of memory and cognition, though it is worth noting that sex differences may emerge. Moreover, while these parameters correlate to performance, it is important to recognise the feasibility of intense exercise, even with supervision, in some elderly populations, particularly following an event such as a stroke. To this end,

even light and moderate exercise, with regularity, has been shown to be beneficial.

Together, human and preclinical studies shape a powerful story demonstrating that physical activity can counteract many aspects of decline in the brain's environment associated with aging. Because 'exercise regimens' of various work-levels and durations seem to produce similar effects in animals and humans, we are able to gain valuable insight into the downstream mechanisms by which physical activity might contribute to continued brain health. It is important to recognise that the topic addressed in this review cover only a fraction of the potential benefits of exercise — particularly regular, aerobic exercise — to adaptive changes in the hippocampus. The objective of this review was to highlight the protective effects of neurotropic factors to the brain and how, in addition to the well-established enhancement of synaptic plasticity, adaptive effects may include changes in support for the BBB, clearance of toxic species and reduced neuroinflammation. These rest heavily on brain-derived alterations driving gene transcription. The relative contributions that centrally vs peripherally-derived trophic factors have to a single cognitive test score is likely dependent on whether testing follows an acute, isolated session or a history of regular exercise. Still, recent literature provides evidence to support a strong (and, perhaps underappreciated) contribution from peripheral neurotrophins and hormones to hippocampus adaptations, such as those that are muscle- or liver-derived [1, 2, 89, 192, 339–344]. In addition, it is possible that acute changes in cortical activity during exercise may contribute to long-term adaptations (for an excellent recent review, see [315]). Therefore, the lasting impression should be one that emphasizes that different durations, intensities, and forms of exercise may contribute unique benefits to the brain, though long-term exercise provides the greatest and longest-lasting benefits. Individual persons may have individual limitations to the types of exercise they do, possibly restricted by age or mobility. It is also possible that sex and polymorphics differences may influence the degree to which exercise influences the different systems discussed here. Indeed, a limitation of animal and human research alike is the lack of well-powered, sex-balanced studies. Nonetheless, there is a great body of evidence that demonstrates that an active lifestyle bestows a diverse set of benefits that mitigate the age-related changes in the brain that contribute to cognitive decline.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

ACKNOWLEDGMENTS

We thank our medical illustrator, Hang Yu Lin, for her wonderful contributions to this paper.

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