CHAPTER SIXTEEN

Exercise Regulation of Cognitive Function and Neuroplasticity in the Healthy and Diseased Brain

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Abstract

Regular exercise broadly enhances physical and mental health throughout the lifespan. Animal models have provided us with the tools to gain a better understanding of the underlying biochemical, physiological, and morphological mechanisms through which exercise exerts its beneficial cognitive effects. One brain region in particular, the hippocampus, is especially responsive to exercise. It is critically involved in learning and memory and is one of two regions in the mammalian brain that continues to generate new neurons throughout life. Exercise prevents the decline of the hippocampus from aging and ameliorates many neurodegenerative diseases, in part by increasing adult

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hippocampal neurogenesis but also by activating a multitude of molecular mechanisms that promote brain health. In this chapter, we first describe some rodent models used to study effects of exercise on the brain. Then we review the rodent work focusing on the mechanisms behind which exercise improves cognition and brain health in both the normal and the diseased brain, with emphasis on the hippocampus.

1. INTRODUCTION

As compared to many other animals, humans have a sustained long-distance running capability.[1–3] This high running ability has evolved in concert with cellular and molecular mechanisms that aid in the proper functioning of the human body.[2,3] This chapter will explore some of these health-enhancing effects of exercise in the brain.

Keeping physically active as you age maintains the speed of central nervous system processing. One of the earliest mentions of this beneficial effect was in a study by Spirduso and Clifford.[4] In their study, older active men (60–70 years old) with an established pattern of playing racket sports or running at least 3 miles four times a week moved and reacted faster to simple stimuli when compared to their sedentary aged-matched counterparts.[4] Since then, positive correlations between physical activity, brain health, and cognitive performance consistently have been demonstrated in humans.[5] Moreover, consistent exercising maintains cardiovascular, immune, and mental health and also delays aging.[6,7] In order to examine how exercise achieves its dramatic influence over body and mind, researchers have developed many different animal models in order to uncover the mechanisms. They can typically be divided into two categories: aerobic or anaerobic. Each model of exercise may uniquely impact the brain and the body. Section 2 will discuss the functionality and use of animal models of exercise.

2. ANIMAL MODELS OF EXERCISE

In humans, aerobic exercise consistently has been associated with improved cognition and increased volume of certain regions of the brain. Aerobic exercise involves low- to high-intensity activities that increase the efficiency and endurance of the cardiovascular system. This includes activities such as walking, jogging, swimming, and cycling. As such, aerobic exercise has been shown to increase both frontal cortex and hippocampal blood flow and oxygen delivery. This increase in blood flow appears to

aid in earlier recall for complex spatial objects.[8,9] Further, in elderly subjects, 6 months of aerobic training has been shown to mitigate age-related decline in both verbal and spatial memory,[10] while a low activity, 8-week yoga intervention significantly improved performance on task switching, working memory, and the n-back task.[11] In young males, high-intensity cycling has been associated with better acquisition and retention 7 days later on the visuomotor tracking task.[12] Further, in aging human adults, those that participated in leisure time physical activity at midlife had 60% lower odds of developing Alzheimer's disease compared to their sedentary counterparts.[13] Moreover, a 16-week exercise intervention (treadmill, 30 min, twice a week and moderate intensity of 60% VO_2 max) aids in cognitive functioning of elderly adults suffering from mild dementia.[14] Thus, exercising a few times a week for approximately 30–45 min at a moderate level of intensity improves mental health in humans.

Therefore, the question becomes, can we see the same beneficial effects of aerobic exercise in rodents, given their use in the laboratory setting. Doing so would allow us to identify and study the mechanisms through which exercise exerts its influence. The most commonly used model of aerobic activity in rodents is free access to a running wheel (Fig. 1). Mice enjoy running and they will take advantage of the access to the running wheel, some more than others. In fact, mice have been recorded as running as much as 2–10 km/day.[15] Thus, using the voluntary wheel-running model,

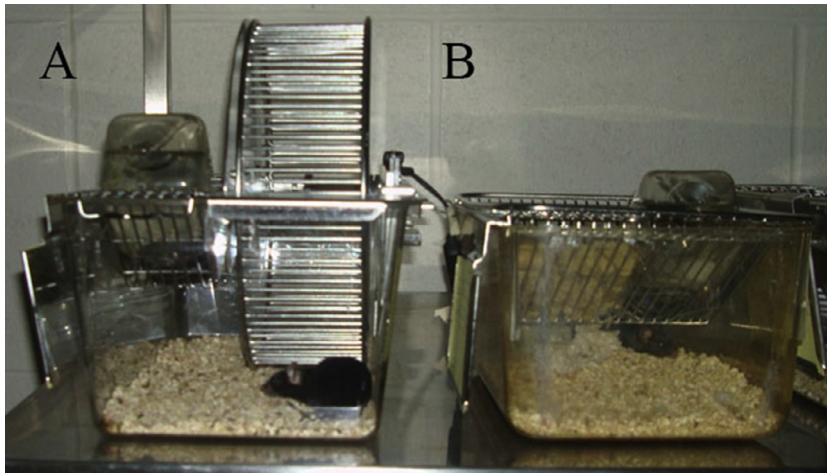

Figure 1 Wheel-running paradigm. (A) A standard laboratory cage where a mouse has 24-h access to a running wheel. (B) Standard laboratory cage without a running wheel.

researchers do not have control over how much the animal will run, but the researcher can precisely record wheel-running activity, and then use individual variation in running as a the predictor or dependent variable influencing the neurological outcomes.

Similar to the effects in humans, voluntary wheel running produces a plethora of positive consequences including enhanced cognitive performance and regional changes in brain volume. For example, male and female C57BL/6J mice that were given 40 days voluntary access to running wheels exhibited significantly enhanced performance on the Morris Water Maze when compared to their nonrunning peers.[16] The Morris Water Maze is a standard behavioral test in the laboratory setting that tests whether an animal can remember where a location is based on the surrounding environment (Fig. 2). Further, similar to its influence in humans, voluntary aerobic exercise alters the volume of certain brain regions that are linked to spatial memory performance. In fact, voluntary access to a running wheel in rodents has also been shown to increase hippocampal volume.[17] Therefore, voluntary wheel running produces similar benefits in rodents as aerobic exercise does in humans.

A second model of aerobic activity that is known to be beneficial is forced running. This model is exactly what it sounds: an animal is placed on a treadmill and forced to run (either via mild shocks or via foam pads that

Figure 2 Morris Water Maze. A photo of a mouse in the middle of a trial. For this task, the animal is placed in one of the four cardinal starting points, and then using landmarks around the room, it must navigate the water as quickly as possible to find the platform that is submerged under the water (note the black dot in the bottom left-hand corner).

restrict the animal's placement to only the treadmill) for a period of time. Similar to both the human aerobic and rodent voluntary wheel-running literature, forced treadmill running improves cognitive performance and brain health in rodents. For example, rats that are forced to run on a treadmill for 6 weeks (30 min at 8 m/min 5 days/weeks[18]) or 12 weeks (50 min 30 m/min[19]) exhibit improved performance on the Morris Water Maze. Additionally, forced exercise has been shown to improve cognitive impairments that result from amphetamine withdrawal in rats.[20] The benefits of forced exercise are not restricted to cognitive performance. About 16 weeks of forced exercise (60 min $\sim 10.9 \pm 1.6$ m/min 5 days/week) increased the hippocampal volume of mice when compared to their sedentary counterparts.[17] However, rats exposed to forced exercise exhibit signs of stress such as increased anxiety levels.[18] Further, research shows that voluntary exercise produces more prominent plastic changes in the hippocampus when compared to the impact of forced exercise on the hippocampus.[21] This suggests that forced exercise may not be the best way to model aerobic activity in rodents as it unintentionally produces stress-inducing side effects that make it more difficult to tease apart the influence of exercise from psychological stress effects on the brain. Despite this, forced exercise still improves learning and memory along with overall brain health in rodents.

Much less research has explored the influence of anaerobic exercise, such as strength training, on cognitive performance and behavior as compared to aerobic exercise in rodents and humans. The limited evidence suggests cognitive performance is enhanced with strength training. In humans, strength training refers to sets of repetitions of certain exercises (i.e., leg presses, leg or arm-extensions, chest presses, lat-pulldowns, etc.) performed multiple times per week with a gradual increase in weights. Strength training uses resistance to induce muscular contractions and thus increases muscle strength and endurance. Unlike aerobic exercise, however, it does not necessarily enhance cardiovascular endurance. In humans, strength training has been shown to increase gray and white matter volume in multiple brain regions of aging adults, including the hippocampus.[22] Further, in aged adults, a resistance-type exercise program of two sessions per week improved attention and working memory on a variety of tasks.[23] Further, a 24-week strength training intervention significantly reduced scores of the Geriatric Depression Scale in elderly females. It is interesting that strength training failed to impact cognitive function in this study.[24] Finally, in late-middle-age adults, a single bout of resistance exercise (two sets of 10 repetitions of 70% of 10-repetition maximum of seven exercises) led to better

performance on the Tower of London task,[25] suggesting that acute strength training has a positive effect on cognition. Together, these data suggest that strength training improves brain function in humans, but more research in this area is needed.

Until recently, most of the rodent literature has focused on aerobic exercise given their natural desire to run, thus leaving a gap in the field for effects of anerobic exercise on cognitive performance in rodent models. However, more recently, the field has begun to develop rodent models of strength training. Strength training in rodents can be achieved through resistance-based training such as a squat-training apparatus,[26] weight pulling on a treadmill,[27] and ladder climbing with weights attached to their tails.[28] Studies examining the beneficial effects of strength training in rodents are not as plentiful as the aerobic exercise studies. However, it has been found that adult male Wistar rats that underwent 8 weeks of resistance training on a vertical ladder showed improved learning and spatial memory on the Morris Water Maze that mirrored their treadmill-running peers, when compared to control animals.[29] Additionally, the resistance training group exhibited enhanced performance on a step-through passive avoidance task, when compared to both a sedentary and a sham-treated group that were left at the top of the vertical ladder for 15 min while resistance training animals exercised on the same apparatus.[30] Still, similar to forced exercise, these models of strength training are riddled with confounding stress variables, as the animals are many times motivated to lift the weights or to move through food deprivation or mild shocks (for review, see Ref. 31). Still, strength training does appear to be a viable new avenue to examine the beneficial role of exercise on brain function.

While we have so far focused on chronic exposures to exercise (i.e., consistent running over a long period of time), it is important to recognize the influence of acute exercise exposure on brain function in both rodents and humans. Acute refers to a single exercise bout. In humans, a single 12-min aerobic exercise exposure (jogging in place while maintaining target heart rate range) improved the selective visual attention performance in adolescents, a benefit that lasted 45 min.[32] Children exposed to an aerobic fitness assessment (PACER task), demonstrated significantly better learning of the word lists and significantly better recall of the words after a brief delay.[33] Further, rodent work demonstrates that a single 3-h bout of wheel running significantly enhanced the acquisition, extinction, and reconsolidation of context-conditioned fear.[34] It is clear that both acute and chronic exercise paradigms influence learning and memory. However, the influence of acute

exercise is ephemeral. Benefits from acute exercise are no longer apparent after 24 h.[33] Therefore, the remainder of this chapter will focus on the influence of chronic exercise exposure. Specifically, in section 3, we will examine the mechanisms through which chronic exercise exposure exerts it influence on cognitive function.

3. HOW EXERCISE IMPACTS THE PHYSIOLOGY OF THE BRAIN

Overall, the message of this chapter is clear: exercise is good for the brain. High levels of exercise lead to larger regional brain volumes and better brain functioning. For example, older adults who participated in light aerobic activity for 6 months (walked for 40 min a day once a week) exhibited a 2% increase in hippocampal volume compared to adults that did not.[35] Thus, exercise effectively reversed the natural age-related decline of hippocampal volume. Not only does aerobic fitness appear to prevent cortical decay, but it also improves cognitive performance. In humans, exercise has been shown to enhance spatial learning, pattern separation, executive function, working memory, and processing speed, among others.[5,36] For example, 6 months of aerobic training mitigated age-related decline in both verbal and spatial memory[10] and a low activity, 8-week yoga intervention significantly improved performance on working memory.[11]

Still, how does exercise produce these changes in brain function? To produce both acute and chronic neurological effects on many brain regions and systems, exercise triggers a variety of neurobiological mechanisms. These neurobiological mechanisms produce long-term neurological changes. For example, chronic exposure to exercise increases the total number of granule neurons in the dentate gyrus of the hippocampus.[37,38] It is theorized that the increased production of these neurons may play a substantial role in the improved hippocampal-dependent spatial learning and memory that is seen following chronic exercise. Still, the influence of exercise on the hippocampus is immense, and it will be described in more detail later in Section 5. First, we must focus on the neurobiological mechanisms through which exercise produces such drastic changes both morphologically and functionally in the brain.

3.1 Exercise and Neurotransmitters

Exercise modulates chemicals that communicate information in the brain known as neurotransmitters. This influence over neurotransmitters may play

a role in how exercise exerts its neurological effects. Physical activity directly influences the central dopaminergic, noradrenergic, and serotonergic systems (for review, see Ref. 39). Alterations in these systems can cause disorders (i.e., depression). Therefore, it is possible that activation of these systems through exercise could repair brain function. In fact, both administration of a 6-month low-dosage dopamine agonist (ropinirole—Adartrel®, GlaxoSmithKline, UK) and a 6-month exercise training intervention (cycling in a recumbent position at an intensity of 60–65% of the patient's maximal exercise intensity three times per week) in patients suffering from restless legs syndrome were effective in treating symptoms, such as depression.[40] Further, 16 weeks of aerobic training (45 min, 6 km/h, 3 days/week) has been shown to produce transient elevations in plasma tryptophan (a serotonin precursor) availability to the brain.[41] Together, these data illustrate that exercise increases neurotransmitter levels and suggest that in doing so exercise may restore proper brain function.

Still, in order to determine the functional role of neurotransmitters, researchers have utilized rodent models wherein they can directly manipulate and measure levels of neurotransmitters in the brain. Rodent models also demonstrate the link between exercise, neurotransmitters, and improved brain function. For example, exercise has been shown to alter levels of monoamines as a mechanism for alleviating symptoms in rodent models of Parkinson's disease,[42] ADHD,[43] and Huntington's disease.[44] Together, these data illustrate the overt influence exercise has on the neurotransmitter systems in order to promote healthy brain plasticity.

3.2 Exercise and Hormones

An interaction between exercise and hormones may be vital to a properly functioning brain. In regularly menstruating women (24–37 years old), physical activity levels are strongly associated with salivary levels of estradiol. Low levels of physical activity produced high levels of estradiol, while high levels of physical activity produced low levels of estradiol.[45] Alterations in hormonal levels can lead to health problems (i.e., high levels of estradiol are associated with a higher risk of cancer).

Approximately 50% of the world's population will suffer a significant loss in sex steroid hormones due to menopause. Female menopause occurs due to a cessation of estradiol and progesterone production by the ovaries. This causes a variety of symptoms that include short-term memory loss and difficulty concentrating. The most commonly utilized treatment for

postmenopausal cognitive decline in women is hormone therapy. However, it has been shown that a combination of exercise and hormone therapy is much more efficient. In fact, higher fitness levels can augment the effects of shorter durations of hormone treatment, which can offset the associated risks of a longer hormone replacement therapy.[46] Through the use of rodent models, researchers have further validated the role of exercise in rescuing behavioral deficits caused by low levels of hormones. For example, Garcia-Mesa and colleagues[47] examined the neuroprotective effect of voluntary running exercise in a mouse model of Alzheimer's disease (3× Tg-AD female mice). Mice were either ovariectomized or sham operated at 4 months of age and then 2 months later received either voluntary wheel running or remained in standard housing for 3 months. Ovariectomized mice without access to a running wheel exhibited major cognitive impairments on the Morris Water Maze, which was rescued by exposure to a running wheel. Therefore, exercise and estrogen levels may interact in order to maintain proper brain function.

3.3 Exercise and Neurotrophic Factors

Growing support implicates the role of neurotrophic factors in exercise-induced neurological changes. Voluntary wheel running increases the concentration of several different growth and trophic factors that likely support the morphological changes in the brain discussed above including fibroblast growth factor-2 (FGF-2),[48] insulin-like growth factor-1 (IGF-1),[49] brain-derived neurotrophic factor (BDNF),[50] and vascular endothelial growth factor (VEGF)[18] among others. BDNF in particular appears to be especially susceptible to regulation by exercise.[50,51] Physical activity increases levels of BDNF in the lumbar spinal cord, cerebellum, cortex, and hippocampus.[51,52] BDNF promotes the differentiation, neurite extension, and survival of a variety of neuronal populations, and it potentiates synaptic transmission, participates in gene transcription, modifies synaptic morphology, and enhances neuronal resilience,[53] implicating BDNF as a prime candidate behind exercise-induced neuronal plasticity and learning enhancement. Adult humans participating in intense rowing exercise and treadmill exercise exhibit increased levels of plasma BDNF.[54] Further, forced treadmill exercise, voluntary exercise, and strength training paradigms have all proven to increase serum levels of BDNF in rodents.[55–57] However, in the human studies, the source of the BDNF in the plasma is not clear as it could come from many different tissues including brain or muscle.

The activity-dependent enhancement of BDNF in the brain may provide a mechanism through which exercise improves learning and memory. About 1 week of forced treadmill exercise significantly enhanced BDNF levels throughout the hippocampus and resulted in both spatial and non-spatial learning improvements in rodents.[56] Further, Vaynman, Ying, and Gomez-Pinilla[51] showed that in rats, 1 week of voluntary exercise enhanced spatial memory performance on the Morris Water Maze along with increased hippocampal BDNF levels. Interestingly, blockade of hippocampal TrkB receptors during the pretesting exercise period eliminated the behavioral performance enhancement from exercise, suggesting the necessity of BDNF for the exercise-induced memory enhancements.

3.4 Exercise, Blood Flow, and Microvasculature

Physical activity may produce neurological changes by altering cerebral blood flow, microvasculature, and VEGF expression. In humans, aerobic exercise has been shown to increase frontal cortex blood flow and oxygen delivery with more intense exercise creating a greater enhancement.[9] Additionally, Sato and colleagues[58] reported increased blood flow through the carotid and vertebral arteries in an intensity-graded manner in adults involved in graded cycling exercise.

In animal models, angiogenesis has been shown to be a prerequisite for many forms of neural and behavioral plasticity.[59] More recently, the beneficial effects of exercise-enhanced microvasculature have been shown in macaque monkeys given 1 h a day of treadmill exercise for 5 months. This exercise paradigm increased vascular density in the motor cortex and resulted in the monkeys needing fewer trials to reach criterion on a spatial learning task.[60] Interestingly, when the monkeys were left sedentary for 3 months, their performance diminished. This suggests exercise must remain continuous in order to gain benefit. This is further evidenced in mice given access to a running wheel for either 1, 3 or 10 days. Although both blood vessel density increased after only 3 days and levels of hippocampal neurogenesis increased after 10 days, both measures returned to baseline following 24 h removal of the running wheel.[61] Thus, it appears that the continuous exercise exposure is essential to produce substantial changes in microvasculature and blood flow.

3.5 Exercise and Oxidative Stress

Physical activity may produce neurological changes in the brain, in part, through a reduction in oxidative stress levels. Oxidative stress occurs when

an organism cannot eliminate chemically reactive molecules (produced from metabolism) fast enough before they start attacking and degrading important molecules for biological functions. In rodents, exercise reduces levels of reactive oxygen species[62,63] and oxidative protein damage[64] and increases levels of some endogenous antioxidants.[62] For example, voluntary access to a running wheel reduced levels of reactive oxygen species and increased endogenous antioxidants in the hippocampus of 12-month-old female rats.[65] Further, in 12-month-old male and female mice, moderate treadmill exercise significantly extended lifespan and behavioral performance on spatial and nonspatial tasks. This was associated with decreased oxidative stress markers in the brain, heart liver, and kidney.[66] These data illustrate the beneficial influence of exercise on reducing oxidative stress.

3.6 Exercise and Apoptosis

Exercise has consistently proven to alter levels of apoptosis in the brain. For example, during the first week of voluntary wheel running, there is a rapid increase of apoptosis that is evident in the hippocampus[67]; however, this effect is transient and signs of apoptosis are no longer present following 2[68] or 8 weeks[69] of voluntary exercise. This temporary increase in apoptosis at the onset of exercise may trigger a cascade of events that promotes the birth of new cells and enhanced functioning in the hippocampus. One example of this can be found in a study that utilized aged animals. Approximately 24-month-old aged rats were given 30 min of forced treadmill running once a day for 6 weeks. This exercise exposure significantly reduced the number of hippocampal apoptotic cells, while it significantly increased the number of newly born hippocampal cells. Moreover, the treadmill exercise exposure prevented age-related impairments on a short-term memory task.[70] Still, it is important to note that alongside these aged animals, Kim and colleagues[70] also tested a cohort of young 5-month-old animals and although they saw an increase in the number of newly born hippocampal cells, there was no impact on apoptosis levels. Therefore, it appears that the influence of exercise on apoptosis is more apparent in the aged brain. Exercise appears to cause a transient increase in apoptosis that triggers neuroprotective mechanisms (e.g., the birth of new cells).

4. EXERCISE-INDUCED SIGNALING PATHWAYS IN THE BRAIN

It is through the modulation of many different signaling pathways that exercise ultimately influences behavior and cognition (Fig. 3). In fact, the

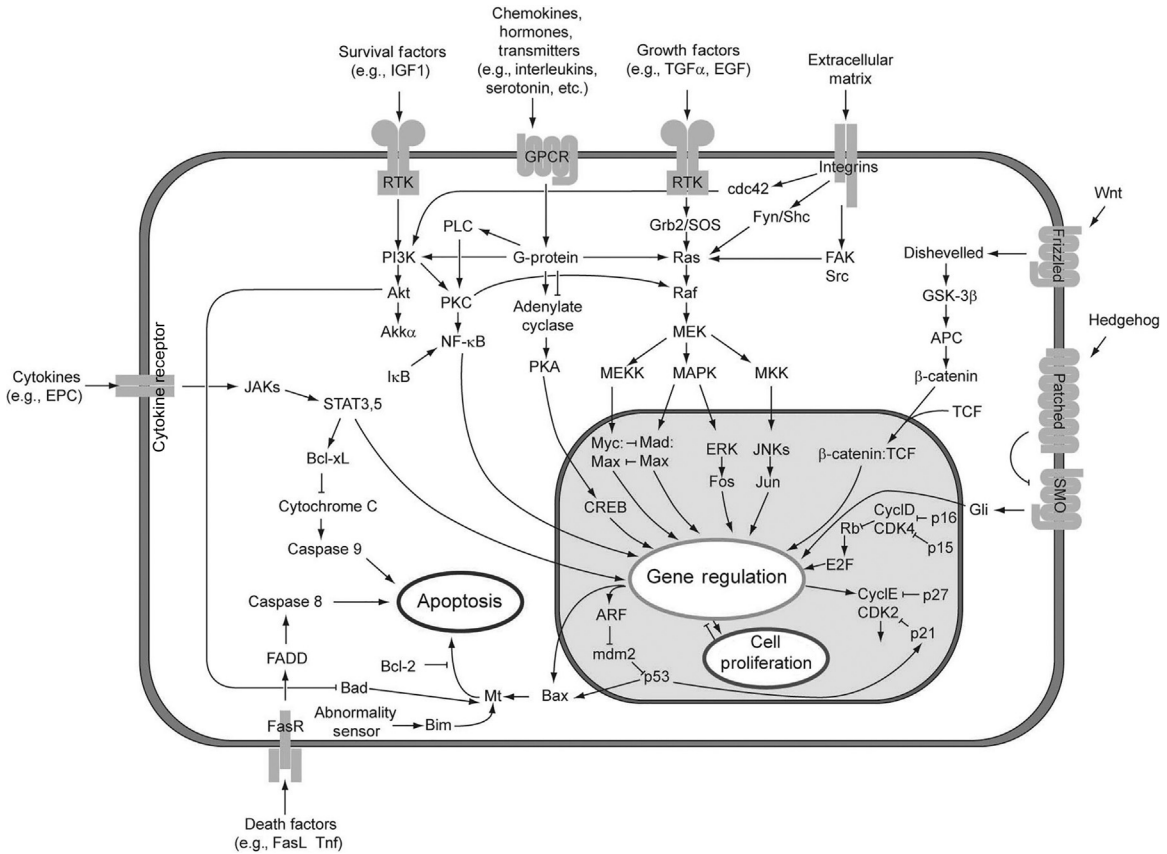

Figure 3 An overview of the major signal transduction pathways modulated by exercise in mammals. Please note that this still does not include all of the pathways.

response to exercise is so massive that the ability to pinpoint a single signaling pathway through which exercise exerts its effect is next to impossible. Rather, exercise appears to activate various components of different signaling pathways that promote cellular growth and brain plasticity concurrently. Cassilhas and colleagues[29] alluded to this vast influence by exposing 90-day-old male rats to either an aerobic treadmill intervention (week 1: 15 m/min for 25 min and increased to week 8: 20 m/min for 30 min) or an anaerobic strength training intervention (vertical ladder training: eight climbing series with a progressively heavier load). The results demonstrated that not only did both forms of exercise enhance spatial learning and memory but, interestingly, they activated divergent intracellular signal transduction pathways. For example, aerobic exercise increased levels of IGF-1, BDNF, TrkB, and calcium/calmodulin-dependent kinase II (β-CaMKII) in the hippocampus, while strength training acted on the central nervous system through induced IGF-1 with concomitant activation of receptor for IGF-1 (IGF-1R) and AKT in the hippocampus. Still, the end result was the same: increased synapsin 1 and synaptophysin protein expression, which are important for synaptic transmission and neurotransmitter release (i.e., greater neuronal function). This study illustrates that depending on the form of exercise; different signaling pathways may be activated in order to enhance cellular plasticity and, resultantly, improve spatial learning and memory. There are many different intracellular signaling pathways that influence cellular plasticity and proliferation, and through its ability to modulate them, exercise may produce both neurobiological and behavioral improvements.

Exercise also exerts its influence by causing stable long-term change of gene expression (in which genes are turned on or off), i.e., epigenetic changes. For example, adolescent male mice exposed to 1 week of wheel running exhibited increased global acetylation of histone 3 in the hippocampus that was correlated with increased hippocampal BDNF.[71] Further, in 3-month-old male Sprague–Dawley rats, 1 week of voluntary exercise increased DNA demethylation, specifically in the **BDNF** promotor IV, which is known to be highly responsive to neuronal activity. Further, exercise increased levels of chromatin remodeling through elevated levels of phosphorylated *CAMKII* and *cAMP response element-binding protein*.[72] Exercise exerts a similar influence on *Wnt* signaling, proteins known to play an important role in adult hippocampal neurogenesis. About 5-week-old Sprague–Dawley rats exposed to 4–5 days of forced treadmill exercise (start speed of 4.2 m/min, increased progressively by 1 m/min every 30 s to a

speed of 12 m/min) for 36 weeks exhibited significantly lower levels of *Dkk-1*, a *Wnt* antagonist that has been associated with neuronal death in Alzheimer's disease and Parkinson's disease, when compared to levels exhibited by sedentary animals. In comparison to their sedentary counterparts, exercising animals also expressed higher protein levels of the anti-apoptotic protein *Bcl-2*.[73] Exercise may activate the **Wnt** pathway in order to prevent neuronal degeneration in both the aging and the diseased brain. These studies illustrate that changes in gene expression are occurring alongside long-term continued activation of the signaling pathways, which produce the neurobiological changes. Overall, the impact of exercise on molecular mechanisms is complex and vast (Fig. 3; for review, see Ref. 5). Perhaps, the reason exercise is such a powerful therapeutic tool is that it can modulate a variety of pathways in order to promote enhanced brain health and function.

5. THE HIPPOCAMPUS IS THE BRAIN REGION MOST INFLUENCED BY EXERCISE

The hippocampus is located in the medial temporal lobe (Fig. 4), and it plays an integral role in learning and memory. This was notably exemplified by H.M., one of the most well-known case studies in the neuroscience field. In order to cure his epilepsy, H.M. underwent a bilateral medial temporal lobectomy, which resulted in severe anterograde amnesia, and he was unable to commit new events to his explicit memory. Still, over the years, H.M. retained his short-term working memory and intellect, and he was left with residual learning capabilities.[74] For example, he could still perform many

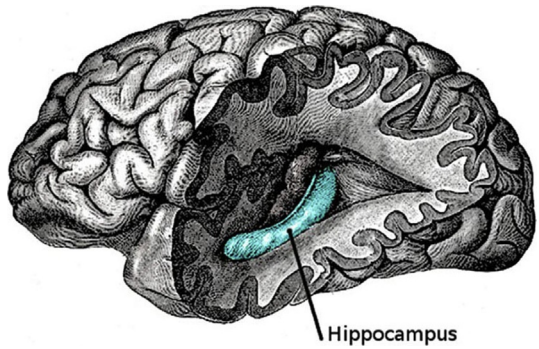

Figure 4 Gross anatomy of the hippocampus. The hippocampus is located in the medial temporal lobe of the brain.

types of motor learning tasks, though he could not remember learning them. The case of H.M. was pivotal in demonstrating the important role of the hippocampus in long-term memory formation, given that he was unable to create new memories following the removal of his hippocampus.

5.1 The Influence of Exercise on Hippocampal Adult Neurogenesis

One important region of the hippocampus is the dentate gyrus. The dentate gyrus is the first region where all sensory modalities merge together to form unique representations and memories that bind stimuli together, and thus, it plays a critical role in learning and memory. Furthermore, the dentate gyrus is one of two known regions in which adult neurogenesis—the continuous birth of new neurons throughout adult hood—occurs.[75] The process of hippocampal adult neurogenesis begins with the proliferation of a precursor progenitor cell and ends with the integration of a functional cell into the preexisting hippocampal network. Exercise not only increases levels of hippocampal adult neurogenesis, the continuous birth of new neurons in adulthood[37,38,76] but it also increases the dendritic length and complexity of dentate granule cells.[76] Thus, exercise appears to modulate both the structure and function of the hippocampal dentate gyrus.

Adult neurogenesis can be modulated by many different extrinsic and intrinsic factors, but none is greater than the influence of exercise over adult neurogenesis. In fact, many of the intrinsic factors governed by exercise (i.e., hormones, neurotrophic factors) are known to regulate levels of adult neurogenesis. Thus, as a result, when it comes to modulation of adult neurogenesis, exercise is a powerful source. Exercise triggers a multitude of intrinsic factors and in doing so, it substantially increases levels of adult-born neurons, more so than a single intrinsic factor alone.

In 1999, van Praag hypothesized that exercise increased levels of adult neurogenesis by increasing the survival of proliferating cells in the dentate gyrus. This effect has been countlessly replicated.[15,16,37] In fact, the distance an animal runs strongly predicts the level of neurogenesis. This is evident in a study by Clark and colleagues[15] in which running activity was studied in 12 different strains of mice that varied greatly with respect to voluntary running levels. For example, 129S1/SvlmJ mice ran approximately 2 km/day, whereas B6129SF1/J mice ran approximately 10 km/day. As a result, B6129SF1/J mice had a four- to fivefold increase, while 129S1/SvlmJ mice exhibited a modest two- to threefold increase in levels of adult neurogenesis. Additionally, in genetically identical mice, levels of adult neurogenesis were

positively correlated with the level of their physical activity in an environmental enrichment cage.[77] Thus, physical activity modulates levels of adult neurogenesis, and this effect is dependent on the amount of physical activity an animal undertakes.

Not only does exercise consistently increase levels of hippocampal adult neurogenesis, but it also enhances cognitive performance. In particular, it improves spatial memory: the ability to remember the location of an object relative to other objects in the environment.[15,37] For example, allowing mice access to a running wheel for either 1 or 6 months improves performance on the Morris Water Maze and increased levels of adult neurogenesis when compared to aged-matched controls.[78]

More recently, adult-born neurons have been implicated in pattern separation. Pattern separation is the ability to recognize and encode a subtle difference between two very similar stimuli (e.g., objects, textures, patterns, etc.). Creer and colleagues[79] examined the relationship between levels of adult neurogenesis and pattern separation. In their study, 3- and 22-month-old male mice were given either housed with a running wheel or in standard cages and then tested on a spatial discrimination task. In the young mice, exercise significantly increased levels of adult neurogenesis, and these levels were tightly correlated with their improved performance on the spatial pattern separation task. In contrast, the aged mice were impaired on the spatial discrimination task regardless of exercise condition coincident with greatly reduced cell genesis that was refractory to running. Together, these data imply a causal link between exercise-induced levels of adult neurogenesis and spatial learning and memory. In fact, when levels of adult neurogenesis are ablated through focal irradiation, the procognitive effects of exercise are no longer present on Morris Water Maze performance in C57BL/6J mice.[16] Recently, Groves and colleagues[80] performed a meta-analysis that explored the relationship between newly generated neurons and performance on spatial tasks. The results showed that the new neurons were not required for baseline performance. Although this meta-analysis did not take into account the role of exercise, the results are still important, as they indicate a possible limitation of the neurogenesis lesion method. It is possible that the brain is able to compensate from the loss of neurons. Therefore, one hypothesis may be that new neurons are preferentially recruited when an animal is learning a task; however, if they are not present, then there are redundant mechanisms in the brain to compensate for their loss.

Exercise-enhanced levels of adult neurogenesis also are correlated with improved performance on a multitude of nonspatial tasks. For example,

Wojtowicz and colleagues (2008) found that a 68% reduction in neurogenesis produced a striking 68% reduction in freezing in the contextual fear conditioning task. Moreover, performance on the motor performance task, the rotarod, is consistently enhanced from wheel running and hence associated with increased levels of adult neurogenesis.[16,78] Therefore, although exercise-enhanced levels of adult neurogenesis correlate with improved performance on spatial memory tasks, a causal role remains unclear.

6. THERAPEUTIC ROLE OF EXERCISE

The beneficial influence of exercise appears to be even greater in the damaged brain. The hippocampus is a brain region severely impacted by fetal alcohol spectrum disorders (FASD),[81–83] Alzheimer's disease,[84–86] and aging.[6,35,86] If we can understand how to grow new neurons in this region, perhaps through exercise, we may be able to treat these diseases and others. Researchers have therefore begun to explore the therapeutic role of exercise on the diseased brain. In this section, we will examine how exercise protects against some brain-related diseases.

6.1 Exercise as an Intervention for FASD

Despite growing awareness of the dangers of prenatal alcohol exposure, between 2.4% and 4.8% of children have some form of FASD. Furthermore, this number is not decreasing and is a conservative estimate.[87] From an economic standpoint, annual cost estimates for the United States were 75 million dollars in 1984. However, as of 1998, this cost had blossomed to be as high as 4 billion dollars.[88] Therefore, the need for interventions is overdue. Thus, research has focused on the therapeutic role of exercise.

Developmental alcohol exposure can disrupt proper functioning of the cerebellum. For example, postnatal day (PD) 4–9 alcohol exposure (4.5 g/kg/day), in rats, reduced cerebellar Purkinje and granule cell number, and also impaired performance on a complex motor task. However, a 10-day exposure to a rehabilitative motor skill training paradigm, but not pure running alone, enhanced cerebellar plasticity along with motor skill performance.[89] Further, pure running alone was sufficient to reverse increased levels of oxidative stress in the cerebellum of rats exposed to alcohol during all three trimester equivalents.[90] These studies suggest that exercise may protect against some alcohol damage in the cerebellum.

In addition, postnatal alcohol exposure impairs hippocampal-associated learning and memory, an effect that is mitigated by exercise. Christie and

colleagues[81] administered a liquid diet of ethanol (35.5% ethanol) to pregnant rat dams, provided a running wheel intervention to half the pups beginning on PD28 and then tested the pups at PD60 on the Morris Water Maze. Alcohol exposure produced pronounced deficits in both reference and working memory; however, this was attenuated by exercise. Further, exercise also rescued deficits on Morris Water Maze performance along with open field performance that resulted from a third trimester equivalent (PD4–9; 5.25 g/kg/day) alcohol exposure.[83] In addition, exercise can enhance long-term potentiation in the perforant pathway in prenatally exposed animals,[81] and it can also increase hippocampal expression of immediate early gene c-Fos, which is a marker of neuronal activation,[91] suggesting that anatomical changes may be correlated with behavioral changes.

In fact, exercise has been found to increase levels of adult neurogenesis in rodent models of FASD. Sprague–Dawley rats exposed to alcohol throughout gestation that were provided access to a running wheel from PD35–50 exhibited enhanced levels of cell proliferation and cell survival.[92] While, in Long–Evan rats administered alcohol on PD4–9 (5.25 g/kg/day), a 12-day exposure to a running wheel was sufficient to increase cell proliferation but not cell survival.[82] In contrast, Sprague–Dawley rats administered alcohol through all three trimesters equivalents receiving 12 days of voluntary exercise exhibited a robust benefit in both cell proliferation and cell survival.[93] Reasons for these conflicting results could be the sex or strain of the animals used, as well as differing developmental time points for wheel-running access (early vs. late adolescence), timing of BrdU administration and tissue analysis. Together, these data suggest that exercise is a potential behavioral therapy for individuals with FASD.

6.2 Exercise as an Intervention for Alzheimer's Disease

Physical activity is a strong candidate for treatment against Alzheimer's disease (for review, see Ref. 84), a disease from which approximately 5.2 million Americans suffer.[94] In aging human adults, those that participated in leisure time physical activity at midlife had 60% lower odds of Alzheimer's disease compared to their sedentary counterparts.[13] Further, elderly adults suffering from mild dementia presented with significant improvement on the Cambridge Cognitive Examination following a 16-week exercise intervention (treadmill, 30 min, twice a week and moderate intensity of 60% VO_2 max[14]).

Rodent work has attempted to understand the mechanisms through which exercise inhibits the progression of Alzheimer's disease. Through the use of a transgenic mouse model of AD (APP/PS1), Liu and colleagues[85] investigated the long-term influence of treadmill exercise. Results showed that a 5-month exposure to exercise significantly reduced hippocampal β-amyloid (Aβ) deposition and tau phosphorylation along with APP phosphorylation and PS1 expression. Further, inhibition of the GSK3-dependent signaling pathway was observed, suggesting this may be a potential target to attenuate Alzheimer's disease-like neuropathology. In addition, transgenic Alzheimer's disease mice given 4 months of voluntary exercise exhibited improved spatial learning in the Barnes maze along with lowered soluble Aβ1–42 levels in the cortex and hippocampus.[86] It is possible that the neuroprotective effect of physical activity is achieved through BDNF mechanisms[47] or through lowered levels of apoptosis.[95] Overall, it appears that in patients with dementia or Alzheimer's disease, simply being more active may stimulate brain plasticity, and provide neuroprotection.

6.3 Exercise as an Intervention for Aging

Aerobic fitness appears effective as an intervention to prevent age-related cortical decay and cognitive impairments. In older adults (58–77 years old), there is a positive association between cardiovascular fitness and executive functioning[36] and cognition.[96] Further, continued exercise performance in older adults is associated with larger left and right hippocampi,[6,10] increased prefrontal cortical volume,[53] and increased prefrontal and cingulated gray matter.[97] A 3-month aerobic exercise intervention produced changes in hippocampal perfusion of older adults along earlier recall for complex spatial objects.[8] Further, 6 months of exercise mitigated age-related decline in both verbal and spatial memory.[98] Finally, in older adults, a low activity, 8-week yoga intervention significantly improved performance on task switching, running memory, and the n-back task.[11] Again, these data illustrate that simply being physically active will promote brain plasticity and serve to protect against aging.

6.4 Exercise as an Intervention for Stroke

Exercise has proven to be an effective treatment in stroke recovery. Rand and colleagues[99] investigated the effectiveness of a 6-month program of exercise for 2 h and recreation for 1 h weekly in aged adults suffering from chronic stroke. The exercise intervention improved performance on the

dual task (walking while talking), response inhibition (Stroop test), and memory (Rey Auditory Verbal Learning Test-long delay). In rodent models, mice subjected to focal cerebral ischemia have impaired performance on the Morris Water Maze; however, voluntary exercise mitigated these effects, increased levels of adult neurogenesis, and upregulated phosphorylation of cAMP response element-binding protein.[100] Similarly, in rats, exercise rescued stroke-induced deficits on the Morris Water Maze; however, this was accompanied by a reduction in oxidative stress[101] along with increased hippocampal dendritic complexity, levels of BDNF and PSD-95.[102] In fact, exercise-induced levels of BDNF appear to play a key role in stroke recovery.[103–105] Thus, physical activity induces neuroplasticity, which aids in the recovery from stroke.

7. CONCLUSION

This chapter illustrates that exercise is critical for physical and mental health throughout the lifespan. Despite the many different forms of exercise, the overall result appears to be that any type of activity be it acute or chronic, forced or voluntary improves cognitive functions and enhances brain plasticity. In fact, through the use of a variety of animal models of exercise in both humans and rodents, research has demonstrated that exercise increases longevity and improves cognitive and spatial memory performance in both the healthy and the damaged brain. Further, given its role in learning and memory, this chapter focused on the influence of exercise on the hippocampus. The hippocampus is a highly plastic brain region, due, in part, to the continuous birth of adult neurons that occur in the dentate gyrus. As such, it is highly susceptible to beneficial factors such as exercise and detrimental factors such as disease and decay. The ability of exercise to not only improve hippocampal learning and memory but also increase levels of hippocampal neurogenesis is remarkable. Further, exercise activates a multitude of signaling pathways that promote neuroplasticity and that are associated with enhanced learning and memory, which indicates the therapeutic role of exercise in both a healthy and a diseased brain. Exercise also produces beneficial long-term epigenetic changes that have the potential to be passed on to future generations. The evidence justifies serious consideration of a role for exercise in therapeutics. Overall, the data presented in this chapter provide evidence in support of exercise as a means to promote enhanced cognitive function and brain plasticity, both in the healthy and in the diseased brain.

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