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Mechanisms underlying the effect of voluntary running on adult hippocampal neurogenesis

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Abstract

Adult hippocampal neurogenesis is important for preserving learning and memory-related cognitive functions. Physical exercise, especially voluntary running, is one of the strongest stimuli to promote neurogenesis and has beneficial effects on cognitive functions. Voluntary running promotes exit of neural stem cells (NSCs) from the quiescent stage, proliferation of NSCs and progenitors, survival of newborn cells, morphological development of immature neuron, and integration of new neurons into the hippocampal circuitry. However, the detailed mechanisms driving these changes remain unclear. In this review, we will summarize current knowledge on molecular mechanisms underlying voluntary running-induced neurogenesis, highlighting recent genome-wide gene expression analyses. In addition, we will discuss new approaches and future directions for dissecting the complex cellular mechanisms driving change in adult-born new neurons in response to physical exercise.

1. Introduction

The assumption that the generation of new neurons ceases after birth in mammals has dominated the field of neuroscience for over 100 years (Gross, 2000; Kempermann, 2015b; Kuhn et al., 2018; Toda and Gage, 2018) In 1965, a historical study (Altman and Das, 1965) demonstrates the presence of a germinal matrix of mitotic, “undifferentiated” cells near the granular cell layer of the dentate gyrus (DG) in the hippocampi of young rats. They show that the number of these “undifferentiated” cells exhibits a rapid rise followed by a sharp decline during postnatal development. Interestingly, the decline of these “undifferentiated” cells is accompanied by a rise in the number of differentiated granule cells (Altman and Das, 1965). This is the first observation of adult hippocampal neurogenesis in mammals, which has been substantiated by subsequent studies illustrating the existence of this phenomenon (Christian et al., 2020; Goldman and Nottebohm, 1983; Kaplan and Hinds, 1977; Kempermann et al., 2018; Kornack and Rakic, 1999; Kuhn et al., 1996).

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To date, extensive studies have illustrated that adult neurogenesis is limited to specific regions within the adult brain and this process is characterized by stepwise cell genesis In mammals, the subgranular zone (SGZ) in the DG of the hippocampus is one of a few brain regions capable of generating new neurons throughout life. In the adult DG, most neural stem cells (NSCs) residing in the SGZ remain in a quiescent state and divide infrequently. Once activated, dividing NSCs either self-renew or differentiate into intermediate progenitor cells (IPCs). IPCs further differentiate into neuroblasts and then immature neurons. These immature neurons undergo a characteristic maturation process, including morphological and physiological changes, and finally become mature excitatory neurons that integrate into existing circuitry (Christian et al., 2020; Li and Guo, 2021; Toda and Gage, 2018)..

The hippocampus is critical for neuroplasticity and learning, and is involved in memory processing and consolidation (Bekinschtein et al., 2010). Many neurodevelopmental and neurodegenerative diseases have been linked to hippocampal dysfunction (Armstrong and Cairns, 2015; Li et al., 2019). The contribution of adult hippocampal neurogenesis to hippocampal functions has been extensively investigated in animal models. To date, ample experimental evidence supports the role of adult hippocampal neurogenesis in neuroplasticity, brain homeostasis, and cognitive function(Christian et al., 2020; Kempermann, 2022; Toda and Gage, 2018).

Adult hippocampal neurogenesis is tightly regulated by both intrinsic mechanisms and extrinsic stem cell niche and is modulated by external stimuli (Figure 1). Some of the stimuli that promote neurogenesis include enriched environment (Kempermann et al., 2002; Kempermann et al., 1997; Kobilo et al., 2011; Leiter et al., 2016; Mustroph et al., 2012), voluntary running (Clark et al., 2009; Garrett et al., 2012; Schoenfeld and Swanson, 2021; Speisman et al., 2013; van Praag et al., 1999), and learning (Gould et al., 1999). Some of the stimuli that inhibit adult hippocampal neurogenesis include aging (Altman and Das, 1965; Foster, 2006; Olariu et al., 2007; Rai et al., 2007), stress (Gould et al., 1997; Heine et al., 2005; Mirescu and Gould, 2006; Surget and Belzung, 2022; Veena et al., 2011), addiction (Castilla-Ortega and Santin, 2020; Zhang et al., 2016), neurodegenerative disorders (Babcock et al., 2021; Kim et al., 2022; Regensburger et al., 2014), and genetic mutations (Ceccarelli et al., 2020; Li and Zhao, 2014; Patzlaff et al., 2018). In addition, depending on the context of exposure, the same stimulus can either promote or inhibit neurogenesis. For example, ischemic injuries inhibit adult neurogenesis; however, transient focal or global ischemia enhances hippocampal neurogenesis (Takagi et al., 1999; Tan et al., 2010; Tureyen et al., 2004; Yagita et al., 2001). Traumatic brain injury can induce the death of immature neurons in the DG (Perry et al., 2016; Salmond and Sahakian, 2005; Zhou et al., 2012), but increase NSC proliferation in the adult hippocampus of both rodents and humans (Marzano et al., 2022; Ramaswamy et al., 2005; Sun et al., 2005). Acute seizures abnormally increase the amount of hippocampal neurogenesis (Bengzon et al., 1997; Jessberger et al., 2005; Kralic et al., 2005; Parent et al., 1997). In contrast, recurrent spontaneous seizures lead to dramatically reduced neurogenesis (Chen et al., 2020; Hattiangady et al., 2004; Kralic et al., 2005). High-fat and high-sugar diets inhibit neurogenesis, but diets enriched with polyphenols and polyunsaturated fatty acids increase neurogenesis (Guzzetta et al., 2022; Poulose et al., 2017; Stangl and Thuret, 2009).

Since modulating adult hippocampal neurogenesis may lead to functional changes in disease conditions, numerous studies have attempted to identify the factors that can promote adult hippocampal neurogenesis. Van Praag et al published the first evidence to show mice that have access to running wheels have increased cell proliferation in the DG (van Praag et al., 1999). Since then, voluntary running has been shown to be one of the most effective ways to promote adult neurogenesis without significant negative effects(Cooper et al., 2018; Schoenfeld and Swanson, 2021). However, the mechanism underlying physical exercise-induced neurogenesis is not fully clear. In this review, we will summarize our current understanding of the mechanisms underlying physical exercise, mainly voluntary running, that promote adult hippocampal neurogenesis.

2. Physical exercise

Physical exercise includes aerobic exercise such as running, walking, cycling, and anaerobic exercise such as strength training and resistance training. A large amount of data have demonstrated that in both humans and rodent models, aerobic exercise leads to increased cardiovascular functions and cognitive abilities (Falkai et al., 2017; Hamilton and Rhodes, 2015). Although anaerobic exercise does not increase cardiovascular function as much as aerobic exercise, anaerobic exercise has also been shown to have beneficial effects on brain functions (Hamilton and Rhodes, 2015). Until recently, most studies using rodent models have focused on aerobic exercise with voluntary wheel running as the experimental paradigm. Therefore, literatures we discuss in this review primarily employ voluntary wheel running models.

2.1 Physical exercise and peripheral factors that mediate brain changes

Physical exercise leads to the release of many peripheral factors, including myokines from muscle, hepatokines from liver, and adipokines from adipose tissue (Cooper et al., 2018; Madhu et al., 2022). Studies using parabiosis have demonstrated that peripheral factors in the blood have significant regulatory roles on brain functions and behaviors(Bieri et al., 2023). As described below, among all the neurotrophic factors, brain-derived neurotrophic factor (BDNF) exhibits the most substantial increase in the brain during voluntary running and BDNF is a well-established positive regulator of adult neurogenesis (Farmer et al., 2004; Liu and Nusslock, 2018; Reichardt, 2006). Voluntary running leads to increased expression of FDNC5 in muscle (Handschin and Spiegelman, 2008). FDNC5 is a membrane protein that is cleaved and secreted as a 112 amino acid peptide hormone, irisin which can pass the BBB to activate adult neurogenesis and cognitive functions through upregulation of BDNF (Wrann et al., 2013). Interestingly, FDNC5 expression is also upregulated in the hippocampus but not other brain regions in mice subjected to voluntary running (Wrann et al., 2013), however it is not clear whether the FDBC5/irisin expressed by the hippocampus contribute to voluntary running-induced neurogenesis. Irisin has been proposed to be a promising therapeutic for aging and Alzheimer's Disease (Madhu et al., 2022). Voluntary running also leads to increased expression of cathepsin B from peripheral muscles that can diffuse through the BBB to enhance BDNF expression in the hippocampus leading to enhanced adult neurogenesis and learning and hippocampus-dependent memory (Moon et al., 2016; Moon et al., 2019). Furthermore, metabolite lactate released by the muscles during

exercise can also cross the BBB to induce BDNF expression and TrkB signaling in the hippocampus (El Hayek et al., 2019) Interestingly, BDNF itself is also expressed in muscle progenitor cells(Mousavi and Jasmin, 2006) and peripheral BDNF can pass the blood brain barrier (BBB)(Pan et al., 1998). Therefore, BDNF may be a convergent target in the brain for physical exercise-induced peripheral factors.

Physical exercise also leads to upregulation of several other neurotrophins known to be important for neuronal development, including nerve growth factor (NGF), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), and hormone adiponectin (Chae and Kim, 2009; Molteni et al., 2002; Neeper et al., 1996; Qi et al., 2022; Tong et al., 2001; Zaben and Gray, 2013). In addition, a number of other neurotrophins, growth factors, and cellular signaling molecules are also upregulated by physical exercise, including leptin, angiotensin II, glucocorticoids, adrenaline, reactive oxygen species, AMP-kinase, peroxisome proliferator-activated receptor (PPAR), PPAR γ co-activator 1α (PGC-1α), ciliary neurotrophic factor (CNTF), and proinflammatory cytokines (Bolijn, 2015; Eisinger and Zhao, 2018) (Lippi et al., 2020; Pahlavani, 2022). However, whether these neurotrophins and growth factors are the causes or the consequences of physical exercise-induced neurogenesis, and how they mediate physical exercise-induced neurogenesis remain unclear.

Voluntary running leads to increased levels of other peripheral factors in the blood, including platelet factor 4 mediating platelet activation in the blood (Leiter et al., 2019), liver-derived glycosylphosphatidylinositol (GPI)–specific phospholipase D1 (Gpld1) that modulates coagulation and complement pathways (Horowitz et al., 2020), the antioxidant selenium transport protein selenoprotein P (SEPP1) in the plasma which increases neurogenesis and cognitive functions in aged mice (Leiter et al., 2022), although the source of the SEPP1 has yet to be identified.

2.2. Physical exercise and aging

Adult neurogenesis declines with age and this aging-dependent decline includes decreased generation of new neurons, reduced neuroplasticity, and increased neuronal death(Babcock et al., 2021; Zocher and Toda, 2023). This aging-dependent neurogenic decline is likely a result of a complex interplay of multiple factors(Katsimpardi and Lledo, 2018; Zocher and Toda, 2023), including reduced expression levels of neurotrophic factors such as FGF-2 (Shetty et al., 2005), BDNF (Calabrese et al., 2013; Rex et al., 2006), VEGF (Bernal and Peterson, 2011; Shetty et al., 2005), and NGF (Larkfors et al., 1987), reduction in hippocampal volume (Pruessner et al., 2001), reduced blood flow in hippocampus (Small et al., 2004) degeneration of hippocampal vessels (Zhang et al., 2012), reduced activation of NSCs from quiescence (Hattiangady and Shetty, 2008), and increased activation of microglia (Griffin et al., 2006; Ogura et al., 1994). In addition to the aforementioned pro-neurogenic effects on young adult animals, physical exercise has been shown to prevent age-related decline of neurogenesis as well. There are several potential mechanisms through which physical exercise may help the mammalian brain to resist aging, including increasing expression levels of neurotrophic factors such as BDNF (Fang et al., 2013; Ferris et al., 2007; Gibbons et al., 2014; Johnson and Mitchell, 2003; Johnson et al., 2003), NGF (Chae

and Kim, 2009; Molteni et al., 2002; Neeper et al., 1996; Tong et al., 2001; Zaben and Gray, 2013), FGF-2 (Gomez-Pinilla et al., 1997; Molteni et al., 2002), IGF-1 (Schwarz et al., 1996), and VEGF (Cheng et al., 2013; Lou et al., 2008; Schobersberger et al., 2000; Waters et al., 2004), increasing the volume of the hippocampus and the volume of the CA1 and DG subregions in the hippocampus (Chen et al., 2017; Erickson et al., 2011), expanding capillary volume (Chen et al., 2017), blood flow (Nishijima et al., 2012; Nishijima et al., 2016; Osborne, 1997), and vascular density in the hippocampus or the DG (Clark et al., 2009; Smith et al., 2018), promoting NSCs to exit quiescence (Dong et al., 2019; Li and Guo, 2021; Lugert et al., 2010; Wang et al., 2011), and reducing the number of microglia (Ehninger and Kempermann, 2003; Gebara et al., 2013; Marchetti et al., 2020). While some of the physical exercise-induced changes may not directly impact adult hippocampal neurogenesis, other changes, especially those affecting blood flow, may directly impact adult-born new neurons (Kim et al., 2021).

3. Impact of physical exercise on adult hippocampal neurogenesis

3.1. NSC Quiescence and Activation

New neurons are generated from NSCs in the adult DG and a portion of NSCs can switch between mitotically active or quiescent states (Li and Guo, 2021; Urban and Guillemot, 2014; Zhao and Moore, 2018). Voluntary running activates the quiescent NSC populations (Dong et al., 2019; Lugert et al., 2010; Wang et al., 2011). Dong et al injects thymidine analog 5-ethynyl-20-deoxyuridine (EdU) into *Nestin*-GFP transgenic mice that express GFP in NESTIN-expressing NSCs and IPCs. They have found that 7-day voluntary running enhances activation of GFP-positive NSCs (Dong et al., 2019). On the other hand, an earlier study using the same *Nestin*-GFP mouse line shows that 24-hour voluntary running has no effect on NSC activation (Steiner et al., 2008). The differences between these two studies suggest that sustained periods of running may be required for activating quiescent NSCs (Figure 2). In fact, although voluntary running experiments using free running wheels seem to be simple to perform, differences in experimental design, particularly in the duration of running can result in differences among data collected(Cooper et al., 2018).

3.2. NSC and IPC Proliferation

Running has been shown to increase cell proliferation in the DG of adult hippocampus (Cooper et al., 2018; van Praag et al., 1999) (Figure 2). In this classical study (van Praag et al., 1999), van Praag et al has assigned the mice to 5 different treatment conditions: enriched environment, hidden-platform water-maze learning, forced exercise (yoked-swim controls), voluntary exercise (running wheel), or standard living (control). They have found that water-maze learning, forced-exercise, and enriched-environment do not have a significant effect on cell proliferation. On the other hand, voluntary running has a profound impact on cell proliferation (van Praag et al., 1999). This observation has been confirmed by many other independent studies (Brandt et al., 2010; Cooper et al., 2018; Koehl et al., 2008; Kronenberg et al., 2006; Lou et al., 2008; Snyder et al., 2009; Steiner et al., 2008). These studies have uncovered three intriguing features of voluntary running-induced cell proliferation in the DG. Firstly, it is a transient phenomenon. Increased cell proliferation in the DG can be detected as early as 24 hours after running (Korol et al., 2013), but cell proliferation goes

back to the baseline level after 14 days of running (Snyder et al., 2009; Trejo et al., 2001). Secondly, running-induced change is more prominent in young adult animals (3 month old) compared to old mice (19 month old) (Kronenberg et al., 2006; van Praag et al., 2005). Thirdly, running-induced neurogenesis is not sex-biased. Although male and female mice are reported to show different levels of stress in response to running, with female mice showing a slightly higher stress response, both male and female exhibit a similar neurogenic response to running (Lightfoot, 2008; Ransome and Hannan, 2013; Westenbroek et al., 2004).

3.3. Differentiation and survival of new DG neurons

In addition to increased NSC and IPC proliferation, voluntary running has also been shown to enhance neuronal differentiation and survival (Figure 2). van Praag et al have assessed neuronal differentiation of newborn DG cells using BrdU pulse labeling in both young and old mice housed with or without running wheels, followed by analysis using mature neuron marker NeuN at about 5 weeks after BrdU injection (van Praag et al., 2005). Although old mice had a significantly reduced proportion of new neurons (BrdU and NeuN double positive among total BrdU-labeled newborn cells) compared to those in young mice, both young and old running mice exhibit significantly higher proportion of new neurons compared to sedentary mice of their own ages. Another study has analyzed rats at 6 days after BrdU injection and demonstrated that running rats have elevated proportion of BrdU-labeled cells expressing Doublecortin (DCX), a marker for immature neurons (Yau et al., 2011). However, the increased proportion of NeuN or DCX positive cells among BrdU labeled cells may be a result of increased neuronal differentiation, increased survival of new neurons, or both. Hodge et al (Hodge et al., 2008) has shown that running significantly increases the number of cells expressing T-box brain protein 2 (TBR2 or EMOES), a protein transiently expressed by immature neurons within the first two days of NSC differentiation into the neuronal lineage. All these studies suggest that running may increase neuronal differentiation of newborn cells; however, variations in study designs and methodology impact the interpretation of their results. Therefore, more direct methods of monitoring the fate of newborn cells, such as live cell imaging, would be helpful.

Indirect assessment of the effect of voluntary running on NSC differentiation has been carried out *in vitro*. Moon et al (Moon et al., 2019) aims to study how exercise-induced changes in skeletal muscle may regulate adult hippocampal neurogenesis. To do so, they culture adult DG-isolated neural progenitor cells (aNPCs) with fractionated conditioned media (CM) derived from rat L6 skeletal muscle cells treated with 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), an activator of AMP-kinase known to be elevated in skeletal muscle during exercise (Moon et al., 2016). They show that treatment of aNPCs with AICAR-CM results in upregulation of immature neuronal markers TUJ1 and DCX. Proteomic analysis of the AICAR-CM identifies Cathepsin B, which has previously been shown to increase the number of DCX-expressing immature neurons in the adult hippocampus (Moon et al., 2016). Together, their data illustrate that exercise-induced skeletal muscle secretory proteins promote neuronal differentiation. Although *in vitro* analysis has limitations, it may serve as an effective experimental platform for mechanistic analysis of exercise-induced neurogenic responses.

Voluntary running prevents neuronal death of the hippocampal neurons resulting from inflammatory response (Ko and Ko, 2020). In healthy rodents, a significant proportion of newborn DG cells undergoes apoptotic cell death and fails to become mature neurons (Kuhn, 2015). The effects of voluntary running on survival of new neurons are well documented [reviewed by (Bolijn and Lucassen, 2015)]. Vivar et al exposes BrdU-injected adult mice to running wheels for one month and demonstrates that running mice have increased BrdU-positive cells in the dorsal but not ventral DG of the hippocampus (Vivar et al., 2016). Since the BrdU-positive cells were analyzed at 4-weeks post BrdU injection, this increase in BrdU-labeled cells is likely a result of both increased NSC/IPC proliferation and new neuron survival in the DG. The molecular mechanisms underlying enhanced differentiation and survival of adult-born new neurons by exercise, especially among different subregions of DG, are among the hottest topics in adult neurogenesis.

3.4 Maturation of new neurons

In addition to increasing the number of newborn neurons, voluntary running impacts morphological development in new neurons as well (Figure 2). It has been shown that voluntary exercise promotes dendritic arborization (Eadie et al., 2005; Sah et al., 2017). In another study, adult mice injected with a retrovirus expressing fluorescent proteins to label dividing neural stem/progenitor cells were housed in cages either with or without running wheels. The mice were then perfused after either 16 or 28 days post-viral injection (dpi) to assess neuronal morphology (Steib et al., 2014). New neurons in running and non-running mice at 16 dpi show dramatic morphological differences, with new neurons in running mice having longer and more elaborate dendrites compared to those in non-running mice. In contrast, both running and non-running mice exhibit similar dendritic complexity at 28 dpi, indicating that the retrovirally labeled new neurons have eventually reached a morphological plateau in both running and non-running mice (Steib et al., 2014). The running-induced increase in dendritic length and complexity has also been observed by other studies using similar retroviral labeling method (Gao et al., 2020; Vivar et al., 2016). Therefore, voluntary running likely accelerates morphological maturation of new neurons.

Dendritic spines are another morphological feature of neurons that voluntary running has been shown to affect (von Bohlen Und Halbach and von Bohlen Und Halbach, 2018). Dendritic spines of new adult DG neurons begin to develop at around 16 dpi and spine density increases rapidly until around 56 dpi (Steib et al., 2014). Among four tested timepoints (21, 28, 42, and 56 dpi), the period between 21 and 28 dpi is associated with the greatest increase in spine density. Spines have various shapes. While filopodia are more abundant in immature neurons, mushroom spines are present in mature neurons (Jones and Powell, 1969; Nimchinsky et al., 2002; Peters and Kaiserman-Abramof, 1970; Sala, 2002). It has been shown that mushroom spines are much more abundant in new neurons at 56 dpi in mice with unlimited access to running wheels compared to mice housed without running wheels (Zhao et al., 2006). Voluntary running also increases spine motility at 21 dpi, which is the peak of spine development (Zhao et al., 2006). The stimulation of spine development has also been demonstrated by other independent studies (Eadie et al., 2005; Gradari et al., 2021; Lin et al., 2012; Stranahan et al., 2009; Zhao et al., 2014). Interestingly, adult-born new neurons display regional differences in maturation and responses to voluntary running.

The maturation rate of new neurons in the temporal DG is slower than those in the septal DG, with the newborn neurons in the temporal already show increased dendritic spine density at 21 dpi in response to running, but those new neurons in the septal DG of running mice do not (Piatti et al., 2011). The functional significance of these spatial differences remains to be investigated.

3.5 Integration of new neurons into the hippocampal circuitry

Newborn neurons must integrate into existing hippocampal circuit to exert functional impact. Assessing the synaptic connectivity of adult-born hippocampal neurons is therefore essential for understanding the roles of adult born neurons. Using a pseudotyped rabies virus-mediated monosynaptic retrograde tracing method (Wickersham et al., 2007), studies have demonstrated that adult-born new DG neurons form first local and then long-range presynaptic connections (Deshpande et al., 2013; Sah et al., 2017; Sun et al., 2019; Vivar et al., 2012). One-week-old DG neurons have already formed presynaptic connections, mostly with local neurons within the hippocampal region, including mature DG granule neurons, the pyramidal cell layer of the Cornu Ammonis (CA) area, and mossy cells. Although voluntary running does not significantly change the number of presynaptic neurons innervating new neurons, it does change the properties of excitatory presynaptic input, likely modifying the functional integration of mature new neurons (Sah et al., 2017). Voluntary running increases total presynaptic input onto newly matured adult-born neurons (Deshpande et al., 2013; Vivar et al., 2016). Vivar et al (Vivar et al., 2016) performed comprehensive analysis of presynaptic input onto adult new neurons. They illustrate that voluntary running specifically reduces innervation from local hippocampal inhibitory neurons, but increases input from long-range neural circuits, such as the entorhinal cortex. Therefore, voluntary running significantly modifies integration of adult new neurons into the brain circuitry (Figure 2).

3.6 Adult neurogenesis-dependent behavior

Alterations at cellular and circuit levels ultimate modify behavior. Indeed, physical exercise has been shown to enhance hippocampal neurogenesis-dependent behaviors in rodents (reviewed by (Eisinger and Zhao, 2018; Kempermann, 2022; Vivar et al., 2013; Voss et al., 2019)). It has been shown that voluntary running leads to better performance in several behavioral tests that reflect hippocampal neurogenesis-dependent spatial learning and memory, including radial arm maze (RAM) test (Gregoire et al., 2018), Morris water maze test (Cassilhas et al., 2012; Fordyce and Farrar, 1991; Yook et al., 2019), Y-maze test (Juliandi et al., 2015), spatial pattern separation test (Creer et al., 2010), context-conditioned fear conditioning test (Gao et al., 2020; Lin et al., 2012; Shevtsova et al., 2017), Novel location test (NLT) (Gao et al., 2020; Snigdha et al., 2014), and Novel object recognition (NOR) test (McGreevy et al., 2019) in rodents. Adult hippocampal neurogenesis has been shown to have an anxiolytic effect (Anacker and Hen, 2017; Cameron and Schoenfeld, 2018), with voluntary running correlating with improved elevated plus maze test (EPM) performance (Gao et al., 2020; Schoenfeld et al., 2016).

4. Molecular mechanisms underlying enhanced adult hippocampal neurogenesis induced by physical exercise

4.1 Growth factors and trophic molecules.

Using both candidate gene approaches and genome-wide gene expression analysis, a large number of studies have reported upregulation of growth factors in physically active animals and among them, BDNF stands out (von Bohlen Und Halbach and von Bohlen Und Halbach, 2018). BDNF functions by binding to its receptor tropomyosin receptor kinase B (TrkB). The BDNF-TrkB complex is then internalized and transported via retrograde axonal transport to the neuronal soma, where it serves as a docking site for different signaling pathways, such as PLC/PKC, PI3K/Akt, Ras/ERK, AMPK/ACC, and NFB pathways (Phillips et al., 2014). BDNF is a key molecule involved in neuroplasticity (Fang et al., 2013; Ferris et al., 2007; Gibbons et al., 2014; Johnson and Mitchell, 2003; Johnson et al., 2003). Therefore BDNF may serve as a convergent point for many physical exercise-induced neurogenic regulators to enhance maturation and survival of adult new neurons.

Several other growth factors are also induced by physical exercise, including nerve growth factor (NGF) that regulates cell proliferation, growth, and survival (Chae and Kim, 2009; Molteni et al., 2002; Neeper et al., 1996; Tong et al., 2001; Zaben and Gray, 2013); FGF-2 that modulates NF-κB expression (Gomez-Pinilla et al., 1997; Molteni et al., 2002), insulin-like growth factor 1 (IGF-1) that may inhibit apoptosis (Schwarz et al., 1996), and vascular endothelial growth factor (VEGF) that stimulate angiogenesis in the brain (Cheng et al., 2013; Lou et al., 2008; Schobersberger et al., 2000; Waters et al., 2004). In addition, several hormones and peripheral factors have also been shown to act as mediators of physical exercise-induced neurogenic responses such as adiponectin, leptin, angiotensin II, glucocorticoids, adrenaline, reactive oxygen species, AMP-kinase, peroxisome proliferator-activated receptor (PPAR), PPARγ co-activator 1α (PGC-1 α), ciliary neurotrophic factor (CNTF), and proinflammatory cytokine [reviewed by (Bolijn, 2015; Eisinger and Zhao, 2018)]. Since many tissue and cell types produce these growth and trophic factors, the in vivo sources of these factors are not fully clear. The functions of these factors can also vary depending on the timing and cellular context. Therefore, their effective application for enhancing adult hippocampal neurogenesis as potential therapies for nervous system disorders remain challenging.

4.2 Genetic and epigenetic factors mediating the impact of physical exercise on NSCs and new neurons

To uncover molecular mechanisms that mediate physical-exercise-induced neurogenesis, extensive efforts have been made towards identifying genes regulating neurogenesis and rodent models especially transgenic mouse models are instrumental in these studies (Hsieh and Zhao, 2016). Here we present a few examples. Several transcriptional regulators have been found to influence adult NSCs and play important roles in controlling intrinsic gene expression within adult NSCs and new neurons in response to physical exercise. For example, using Orphan nuclear receptor TLX (Nr2e1) knockout (TLX-null) mice, Shi et al has demonstrated that TLX is expressed in neurogenic regions in the brain and is essential for maintaining the pool of adult NSCs in the hippocampus (Shi et al., 2004).

Deletion of TLX from adult NSCs leads to reduced NSC proliferation and hippocampal neurogenesis-dependent behavioral deficits (Zhang et al., 2008). Voluntary running fails to increase neurogenesis in TLX-null adolescent mice and these mice exhibit reduced neuronal survival compared to wild type mice, suggesting that TLX maintenance of adult NSCs is needed for voluntary-running-induced increase in adult neurogenesis (Kozareva et al., 2018). Gradari et al (Gradari et al., 2021) has assessed differential DNA methylation of neurogenesis and stem cell-related transcription factors induced by mildly forced exercise (treadmill) using candidate gene methylation array and identified demethylation of the *Smd2* gene, encoding the SMAD2 protein, in the hippocampal tissue of the exercise group. Although this study illustrates importance of SMAD2 in regulating adult neurogenesis through their retrovirus-mediated gain and loss of functions assays, the necessity of SMAD2 for exercise-induced neurogenesis is unverified. Ten-eleven translocation methylcytosine dioxygenase 1 and 2 (TET1 and TET2) catalyze the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). Both TET1 and TET2 levels are reduced in aged mice, but can be partially restored by voluntary running (Jessop and Toledo-Rodriguez, 2018). Since running partially restores age-related hippocampus-dependent memories, TET1 and TET2 may contribute to improved memory (Jessop and Toledo-Rodriguez, 2018).

In addition to transcription factors, Bouchard-Cannon et al has shown that Dexras1, a small GTPase, is required for running-induced proliferation of NPCs in the DG (Bouchard-Cannon et al., 2018). Dexras1 knockout mice fail to exhibit increased NSC proliferation in the DG. They also show that Dexras1 is essential for voluntary running-induced activation of ERK/MAPK signaling pathway and activation of transcription factor CREB, as well as the upregulation of BDNF, VEGF, and NMDA receptor subunit NR2A (Bouchard-Cannon et al., 2018). Cyclin-dependent kinase inhibitor p16Ink4a, has higher levels of expression in neural progenitors of aged mice compared to young mice (Molofsky et al., 2006), suggesting that p16Ink4a may play a role in maintaining NSC quiescence in the adult DG. Running is known to activate NSCs from a quiescent to proliferative state. Indeed, the IPC cell population is larger in $p16^{Ink4a}$ knockout running mice compared to wild-type running mice (Micheli et al., 2019). Therefore, $p16^{Ink4a}$ may help NSCs to maintain their capacity for self-renewal during aging when the mice are subject to running (Micheli et al., 2019).

Noncoding microRNAs are major regulators of adult neurogenesis (Esteves et al., 2020; Jobe et al., 2012; Oliver and Mandyam, 2018). One study (Pons-Espinal et al., 2019) has discovered that voluntary running leads to reduced levels of microRNA 135a-5p (miR-135a) in NESTIN-expressing NSCs or NPCs isolated through fluorescence activated cell sorting (FACS) from Nestin-CFPnuc transgenic mice that express nuclear fluorescent protein in NESTIN-expressing NSCs/NPCs. They show that miR-135a-5p inhibits NSC proliferation and voluntary running-induced hippocampal neurogenesis. On the other hand, inhibiting miR-135a in aged mice enhances NPC proliferation. The observed effect of physical exercise may be mediated by miR-135a-mediated regulation of its targeted mRNAs including inositol 1,4,5-trisphosphate (IP3) receptor 1 and inositol polyphosphate-4-phosphatase type I, both of which are involved PI3 kinase signaling pathway.

4.3 Identifying novel mechanisms using genome-wide analysis

4.3.1 genome-wide analysis of hippocampal or DG tissues—To discover novel molecular mechanisms driving enhanced hippocampal neurogenesis resulting from physical exercise, unbiased gene expression profiling is necessary (Table 1). While early studies have used microarray analyses of dissected tissues to investigate voluntary-running-induced gene expression changes in the hippocampus or the DG, Tong et al uses advanced high-density oligonucleotide microarrays containing probes representing 5139 genes to determine levels of transcripts in hippocampi of rats that have undergone a 3-week running regimen. They find that 88 genes exhibit more than 1.5-fold changes in running rats, with 44 genes upregulated and 44 down regulated, compared to sedentary rats. Many of the differentially expressed genes are associated with neuronal activity, synaptic structure, and neuroplasticity (Tong et al., 2001). Molteni et al (Molteni et al., 2002) used a microarray with 1176 cDNAs expressed primarily in the brain to examine gene expressions in the hippocampi of rats that have run for 3, 7, and 28 days to determine both acute and chronic effects of voluntary running on hippocampal gene expression. They show that many upregulated genes are associated with synaptic trafficking, signal transduction pathways, and transcription regulators. Interestingly, while genes related to the glutamatergic system are upregulated, genes linked to the GABAergic (gamma-aminobutyric acid) system are downregulated. In addition, the gene encoding BDNF is upregulated at all time points. Furthermore, many of the other upregulated genes have functional interactions with BDNF, suggesting a central role of BDNF in mediating running's effect on the hippocampus. Moreover, differential changes in several molecular pathways have been observed between acute and chronic running. While activation of Calcium/calmodulin-dependent kinase (CaMK) signaling is found during both acute and chronic periods of exercise, the MAPK/ERK pathways exhibit higher activity only after chronic exercise (Molteni et al., 2002).

Voluntary running counteracts the negative effects of aging on adult hippocampal neurogenesis (Babcock et al., 2021). To elucidate the mechanisms behind the effects of running on aged brains, Stranahan et al have analyzed expression levels across 24,000 genes in the hippocampus of lifelong (16 months) running and sedentary mice using a highly sensitive Illumina bead microarray. They have found that the upregulated genes are associated with synaptic plasticity and mitochondrial function, whereas the downregulated genes are associated with oxidative stress and lipid metabolism (Stranahan et al., 2010). Kohman et al (Kohman et al., 2011) have conducted a similar experiment examining the short-term effects of running on the hippocampi of both young adult (3.5-month-old) and aged (18-month-old) mice. Instead of giving lifelong access to running wheels for each experimental group, both young adult mice and aged mice are provided running wheels for only 8 weeks before analysis to better compare the difference between the two ages. They have discovered that genes with altered expression levels in aging mice are associated with chromatin remodeling, cell growth, immune activity, and synapse organization. Interestingly, the 8-week running period is sufficient to improve age-related gene expression changes. These findings indicate that late-onset voluntary running may counteract age-related changes of gene expression in the aged hippocampus and improve memory and cognition (Kohman et al., 2011).

Several studies have examined how the intensity of physical exercise affects gene expression profiles in the hippocampus. Lee et al (Lee et al., 2014) have compared resistance-wheel-running rats and free-wheel-running rats after a 4-week running period. There are more upregulated (169 vs 128) and downregulated genes (468 vs 97) identified in the hippocampi of resistance-wheel-running rats than in the hippocampi of free wheel running rats. The differentially expressed genes in both groups are related to nervous system disorders, molecular functions, and physiological system development and function. Genes specifically changed in resistance-wheel-running rats include genes encoding known neurogenic mediators BDNF and CREB, as well as new genes that were previously unknown to mediate physical exercise, such as NFATc1, AVPR1A, and FGFR4. Interestingly, many downregulated genes in resistance-wheel-running are associated with hippocampal neuroplasticity (Lee et al., 2014). Thus, it is plausible that physical exercise of too high an intensity may have negative effects on adult neurogenesis. Another group shows that the intensity of exercise can be defined based on lactate threshold (LT), which serves as a reference point. At any intensities above LT, exercise causes a rise in the levels of adrenocorticotropic hormone and corticosterone in the blood, both of which are stress responses (Saito and Soya, 2004; Soya et al., 2007). Although exercise has a positive effect on the function of the hippocampus, forced exercise with intensity above LT does not improve cognitive function, whereas mild exercise with intensity below LT does has beneficial effects on cognition (Inoue et al., 2015a). They show that rats subjected to mild exercise exhibit augmented adult hippocampal neurogenesis compared to intense-exercise rats, as characterized by the survival and maturation of newborn neurons (Inoue et al., 2015b). To unravel the molecular mechanisms behind this exercise intensity-dependent cognitive change, Inoue et al have performed transcriptomic profiling using a whole-genome DNA microarray of the hippocampi of both mild-exercise and intense-exercise rats (Inoue et al., 2015b). Their results have identified more differentially expressed genes in the mild-exercise rats than the intense-exercise rats (604 genes vs 415 genes), Curiously, only a small number of genes (41 genes) are differentially expressed in both conditions. Among all the differentially expressed genes, the mild-exercise-influenced genes are associated with lipid metabolism, protein synthesis and inflammatory response, which are related to hippocampal neurogenesis. On the contrary, the differentially expressed genes following intense exercise are associated with excessive inflammatory immune response, which leads to inhibition of hippocampal neurogenesis. Unexpectedly, the most well-known mediator of exercise-induced neurogenesis, BDNF is among the differentially expressed genes (Inoue et al., 2015b).

Most gene expression profiling studies on voluntary running have been conducted using rodent models. Recently, one exciting study has investigated the effects of exercise on the human hippocampus using genome-wide gene expression analysis (Berchtold et al., 2019). In this study, the authors have performed microarray-based transcriptomic profiling of the postmortem hippocampal tissues of aged and neurotypical individuals who have been physically active before death. By comparing their data with published microarray data on hippocampal tissue from young, aged, and age-matched Alzheimer's disease (AD) cases, they have identified potential anti-aging and anti-AD genes. Astonishingly, a majority of the genes (95% of the 2210 probe sets) showing significant changes among all three groups

exhibits opposite transcriptional patterns in physically active, aged, and age-matched AD groups. Over 70% of known anti-aging/AD genes are downregulated in the aged and age-matched AD groups but are upregulated in the physically active group. The anti-aging/AD genes that are upregulated in physically active group are associated with mitochondrial energy production and synaptic function, as well as axonal function and myelin integrity. In contrast, anti-aging/AD genes that are downregulated in physically active group are related to negative regulation of transcription. These data reveal a potential role for physical exercise on delaying aging and counteracting AD, and provide a framework for a gene-targeted approach to counteract the cognitive repercussions of aging (Berchtold et al., 2019).

Overall, these microarray studies have uncovered changes in many exercise-promoted genes and pathways. However, microarray-based studies are limited by the selection of genes and specificity of the probes used to create microarrays, thereby contributing to discrepancies in results among studies.

Next-generation RNA sequencing (RNA-seq) has expanded the capability of transcriptomic analyses in both sensitivity and gene coverage. Both environmental enrichment (EE) and running are powerful stimuli for adult hippocampal neurogenesis. In rodent experiments, EE includes running wheels, social interaction, and novel complexes. Yet, adult hippocampal neurogenesis responds differently to EE and running (Gregoire et al., 2014; Gregoire et al., 2018). To understand the basis for these distinct responses, Grégoire et al have utilized RNA-seq to profile the DG of mice that have been exposed to 3 different environmental conditions: locked running wheels, free running wheels, and EE. The results have revealed distinct patterns of gene expression changes between running and EE mice. Running specifically regulates synapse and growth-related pathways. In contrast, EE preferentially modulates extracellular-matrix-associated functions (Gregoire et al., 2018). These differential gene expression profiles suggest that EE and exercise may have separate impacts on neurogenesis and subsequent behavioral phenotypes(Kempermann, 2015a).

Several studies have utilized RNA-seq to interrogate excise-induced gene expression changes in disease models. Zhang et al (Zhang et al., 2022), have assessed gene expression changes in an Alzheimer's disease model, APP/PS1 double transgenic mice that express a chimeric mouse/human amyloid precursor protein and a mutant human presenilin 1. They subject APP/PS1 mice and wild type controls to running wheels for 3 months and performed RNA-seq of the hippocampal tissues. They have found that found "starch and sucrose metabolism", "pyruvate metabolism", "glycolysis/gluconeogenesis", "pentose phosphate pathway", and "fructose and mannose metabolism" are upregulated in APP/PS1 mice subjected to wheel running compared with those without wheels. Therefore, the hippocampus of APP/PS1 mice may have hypometabolism may that can be rescued by running exercise. B-Cell Translocation Gene 1 (*Btg1)* is important for adult NSC maintenance and Btg1 gene knockout mice exhibit NSC deletion during aging (Micheli et al., 2021). Micheli et al use *Btg1 knockout mice to assess* how exercise may affect gene expression of the DG during aging. They have found that 12-day exposure to running wheels leads to significant changes in gene expression in the DG. They have identified 42 voluntary running induced genes that counter act the absence of BTG1 and these genes include those known to be involved in Alzheimer's Diseases, such as alpha-synuclein (Micheli et al.,

2021). In another study, Li et al demonstrates that mice subjected to treadmill running have reduced addiction to Methamphetamine. Using RNA-seq, they show that the a number of genes are differentially regulated between running and sedentary mice subjected to Methamphetamine (Li et al., 2022).

McGreevy et al have investigated the heritability of the impact of physical exercise from father to offspring. They show that increased adult neurogenesis, greater mitochondrial citrate synthase activity, and paternal cognitive improvements of the runner-fathers can be inherited by their offspring. They have performed RNA-seq to compare gene expression s patterns in the adult hippocampus and shown that the gene expression patterns of the runner-fathers can also be inherited by their offspring. These data suggest that paternal physical exercise significantly influences its offspring's hippocampal functions (McGreevy et al., 2019).

To understand the mechanism underlying physical exercise-induced adult neurogenesis, it is necessary to determine whether and how each cell type in the adult neurogenic zone responds to exercise. Chatzi et al (Chatzi et al., 2019) have utilized Fos-TRAP mice to identify genes that are differentially expressed only in activated neurons because these neurons express the immediately early gene cFOS. They have crossed inducible Fos-CreER^{T2} mice with tdTomato reporter line to create FOS-TRAP mice in which FOS-expressing (activated) neurons are permanently expressing tdTomato. They have collected tdTomato-positive neurons using laser capture microdissection and performed RNA-seq. They have found that Mtss1L, known to affect membrane curvature and dendritic spine formation, to be among the most upregulated transcripts in voluntary running mice. Their data indicate that Mtss1L serves as a mediator of activity-dependent synaptic rearrangement in neurons activated by exercise (Chatzi et al., 2019). However, their study does not distinguish the adult-born new neurons from existing DG granule neurons, highlighting the necessity for cell-type specific transcriptomic analysis of the DG.

4.3.2 Genome-wide analysis of intrinsic changes in NSCs and new-born cells in response to physical exercise—

Given that newborn neurons in the adult brain undergo many more changes towards maturation in physically active animals than in sedentary animals (Steib et al., 2014), spatial and temporal molecular mechanisms are likely present in adult NSCs and new neurons to promote neurogenesis and neuronal maturation in physically active animals. However, the DG tissue contains mostly mature neurons and glia as well as many other cell types and adult new neurons constitute an extremely small portion of cells in the DG (Gao and Zhao, 2021; Hochgerner et al., 2018). Therefore, the differentially expressed genes identified in the hippocampal or the DG tissues (Table 1) may not represent those differentially expressed genes in adult NSCs and new neurons. Genome-wide gene expression analysis of only the newborn neurons would allow for comprehensive investigation into the intrinsic molecular mechanisms that regulate new neurons. In our recent study, we have used adult new neuron-specific RiboTag-seq to identify translational changes in the adult-born hippocampal neurons of voluntary running mice compared to those of sedentary mice. We have crossed inducible Nestin-CreERT2 driver mice with conditional RiboTag (Rpl22HA) mice (Sanz et al., 2009) to generate a mouse line allowing for inducible adult new neuron-specific tagging of ribosomes (*Nes-*

CreERT2;RiboTag) (Gao et al., 2020; Gao and Zhao, 2021). Upon tamoxifen injection, ribosomes in NESTIN-expressing NSCs and their differentiated progenies are tagged with hemagglutinin (HA). The mice were then exposed to running wheels for 11, 18, and 28 days representing early, middle, and late stages of developmental maturation of adult new neurons. The results have revealed that adult-born neurons exhibit dynamic translational changes in response to voluntary running, and the changes in gene expression are more dramatic in new neurons compared to the DG tissue, supporting the notion that new neurons are more responsive to physical exercise than mature cells. Many differentially expressed genes in new neurons are important for neuronal maturation and human diseases. We have shown that G protein signaling 6 (RGS6) is a key mediator of running-induced neurogenesis. Manipulating expression of *RGS6* in adult new neurons affects both their morphological and electrophysiological maturation. We demonstrate that overexpression of *RGS6* in new neurons, mimicking running condition, reduces their sensitivity to the inhibitory effect of GABA-B receptor activation on neuronal maturation (Gao et al., 2020). Our study demonstrates the importance in analyzing adult NSC and new neuron-specific gene expression profiles in response to voluntary running.

4.4. New technology applicable to adult neurogenesis research

Single cell analysis: To gain insight into the effect of voluntary running on newborn neurons in particular, cell stage-specific genome-wide gene expression analysis of newborn neurons in the voluntary-running animals is essential. Our RiboTag-seq has taken a one step towards this goal by illustrating changes in adult-new-neuron-specific gene expression profile in response to physical activity. However, our results do not have single-cell resolution and therefore may have overlooked significant individual cell diversities. Single-cell transcriptomic analyses have been used to identified transcriptome in hippocampal NSCs and newborn neurons at different stages of differentiation (Gao et al., 2017; Habib et al., 2016; Shin et al., 2015). Recently, single cell RNA-seq of the hippocampus of the adult mouse, non-human primate, and humans have demonstrated the presence of immature NSCs and neurons (Franjic et al., 2022; Zhou et al., 2022). However, no study has assessed gene expression changes in single hippocampal cells in response to exercise. Since adult NSCs and new neurons are rare, a number of approaches can be used to enrich their numbers for single cell analysis. One approach is FACS sorting followed by single-cell RNA -seq (Sakai et al., 2018). However, both tissue dissociation and FACS sorting cause extensive cellular stress, especially to neurons. In addition, tissue dissociation may not recover mRNA localized in dendrites. Furthermore, the read coverage of single-cell analysis remains limited, prohibiting the identification of low-expressing genes, including transcription factors. To overcome the negative impact of cell dissociation, single-nucleus RNA sequencing (snRNA-seq) techniques, such as DIV-seq (Habib et al., 2016) can be an alternative. Additionally, snRNA-seq may have unique advantages in quantifying bona fide transposable element RNA expression in mouse hippocampus (Linker et al., 2020). However, the nucleus contains less RNA than the cytosol, which further complicates the read coverage of single-cell analysis. Thus, these technologies must be further improved for optimal implementation in studies of adult neurogenesis.

Spatial genomics: Despite the similarity in cell population and composition in dorsal and ventral hippocampus, distinct connectivity and functional roles have been observed in these regions (Besnard et al., 2020; Fanselow and Dong, 2010; Wu et al., 2015). Voluntary running differentially impacts dorsal and ventral hippocampal regions and is therefore likely to differentially modulate the transcriptome of newborn neurons in these regions. In addition, the adult-born neurons are located in a unique neurogenic niche surrounded by numerous cell types, including other newborn immature neurons, NSCs, IPCs, astrocytes, microglia, etc. A study has reported that the NSCs also contribute to neuronal maturation through the neurogenic niche (Tang et al., 2019). Thus, spatial genomic profiling of each of these cell types in their native neurogenic niche of voluntary-running animals will further delineate how voluntary running regulates neurogenesis.

Epigenetic changes: DNA methylation is among the primary epigenetic markers that distinguish the transcriptome in different cell types to tightly control their functional and developmental potential. DNA methylation varies with neuronal activity and is induced by certain stimuli in the neurons of the dentate gyrus (Guo et al., 2011). Additionally, differential DNA methylation and transcript-level gene expression have been reported in dorsal and ventral hippocampus of mice that underwent an enriched environment treatment (Zhang et al., 2018). Although single cell DNA methylation analysis has been used to profile brain cells (Luo et al., 2022), single cell DNA methylation analysis of adult new neurons has not been done, largely due to the limited cell number. On the other hand, chromatin accessibility analysis has significantly higher sensitivity and has been applied to adult new neurons. Continuous fluctuations in the physical availability of DNA for transcription is a key feature of chromatin that serves to establish and maintain a cell's identity. In the genome, the organization of accessible chromatin (euchromatin) reflects permissible physical interactions in a network. This permits strict regulation of gene expression by chromatin-binding factors, promoters, enhancers, and insulators in a cooperative way. These changes in chromatin accessibility can be dynamically triggered by both external stimuli and intrinsic, developmental cues. Thus, patterns of chromatin accessibility may represent more "real-time" shifts in gene expression following some stimulus. Alterations in chromatin accessibility occur earlier than alterations of gene expression. Therefore, analysis of chromatin accessibility in newborn neurons in response to voluntary running may provide profound insights into the initial repercussions of voluntary running in newborn neurons, as changes in chromatin state embody the immediate intrinsic changes of cells in response to voluntary running. Only the nucleus is required for chromatin accessibility analysis and therefore can be readily applied to isolated nuclei. The recently developed Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-seq), utilizing the hyperactive transposase Tn5 to sequence transposable regions of euchromatin, is among the best options for studying chromatin accessibility of adult new neurons because it requires very fewer cells and can even be performed at the single-cell level (Buenrostro et al., 2015). Although the gene coverage and resolution of this methodology is not as good as that of transcriptomic analysis, ATAC-seq provides information on chromatin changes that cannot be revealed by RNA-seq. Recently, simultaneous snRNA-seq and snATAC-seq of the same nucleus (snMultiome) (Trevino et al., 2021) has been developed for cells that can be

easily isolated using single-nucleus capture. However, this method has yet to be optimized for adult neurogenesis analysis.

Proteomics: With advancement of proteomics in terms of both sensitivity and specificity, proteomic profiling of adult newborn neurons will offer valuable information for studying intrinsic effects of the interplay of voluntary running and neurogenesis.

5. Summary and perspectives

Studies in the past 30 years have contributed to our understanding in physical exercise-induced neurogenesis (Overall et al., 2016; Voss et al., 2019). Because adult hippocampal neurogenesis occurs in a spatially and temporally specific manner, specific and sensitive methods must be applied to further probe the effects of voluntary running on neurogenesis. In addition to new cell type-specific -omics technology, in vivo live cell imaging methods (Pilz et al., 2018) will allow for real time monitoring of cell genesis in animals undergoing physical exercise. Furthermore, development of adult NSC or new neuron-specific tracers for non-invasive brain imaging may finally allow us to observe adult neurogenesis in humans, to assess the prevalence and variability of adult neurogenesis across human population, and to evaluate the effect of physical exercise and other factors on human adult neurogenesis.

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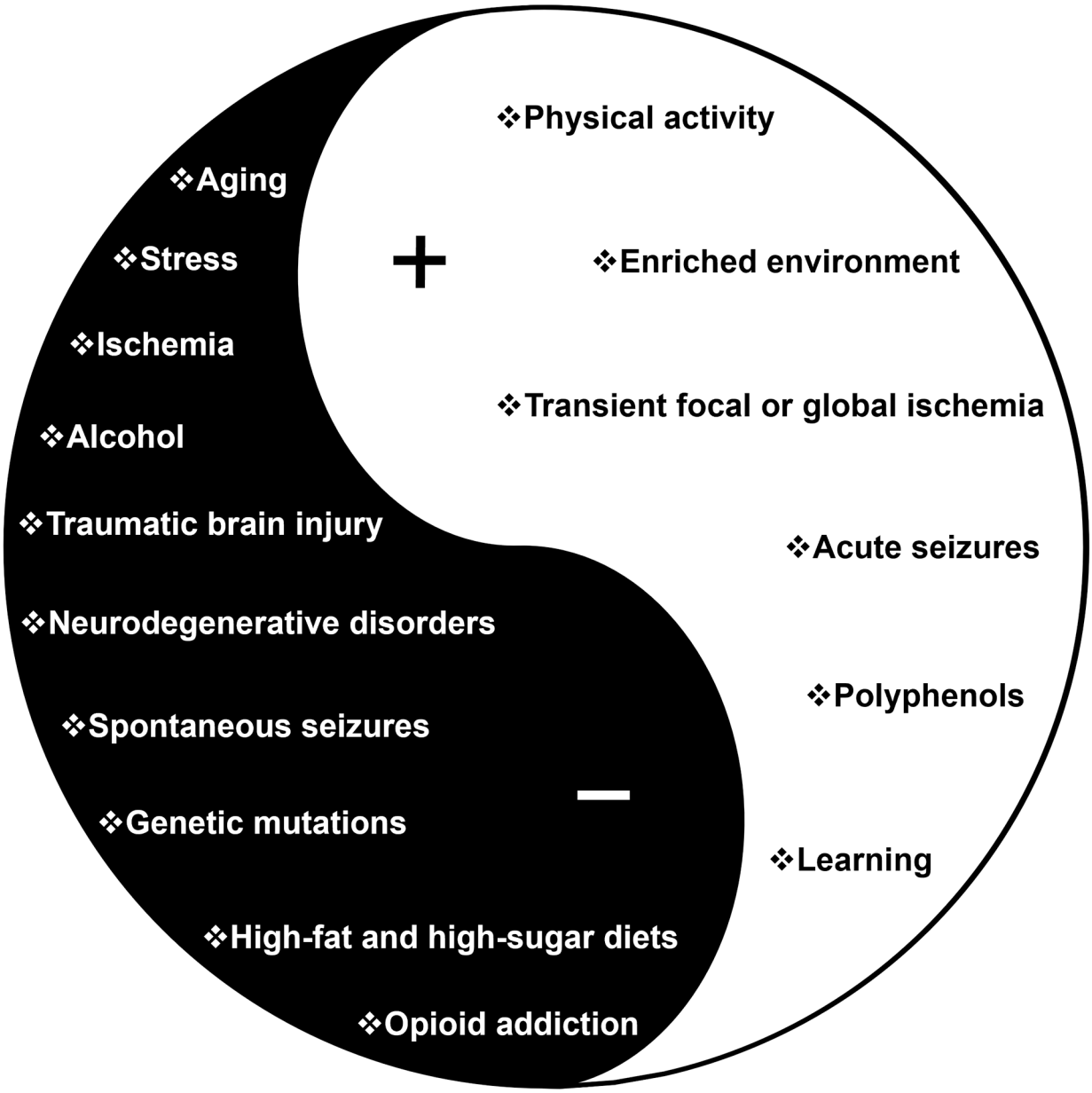

Figure 1. Factors that promote and inhibit adult hippocampal neurogenesis

The summary of negative factors that inhibit adult hippocampal neurogenesis (black) and positive factors that promote adult hippocampal neurogenesis (white) is based on extensive literature [see relevant reviews: (Bieri et al., 2023; Cooper et al., 2018; Kempermann, 2022; Kempermann et al., 2015; Zocher and Toda, 2023)

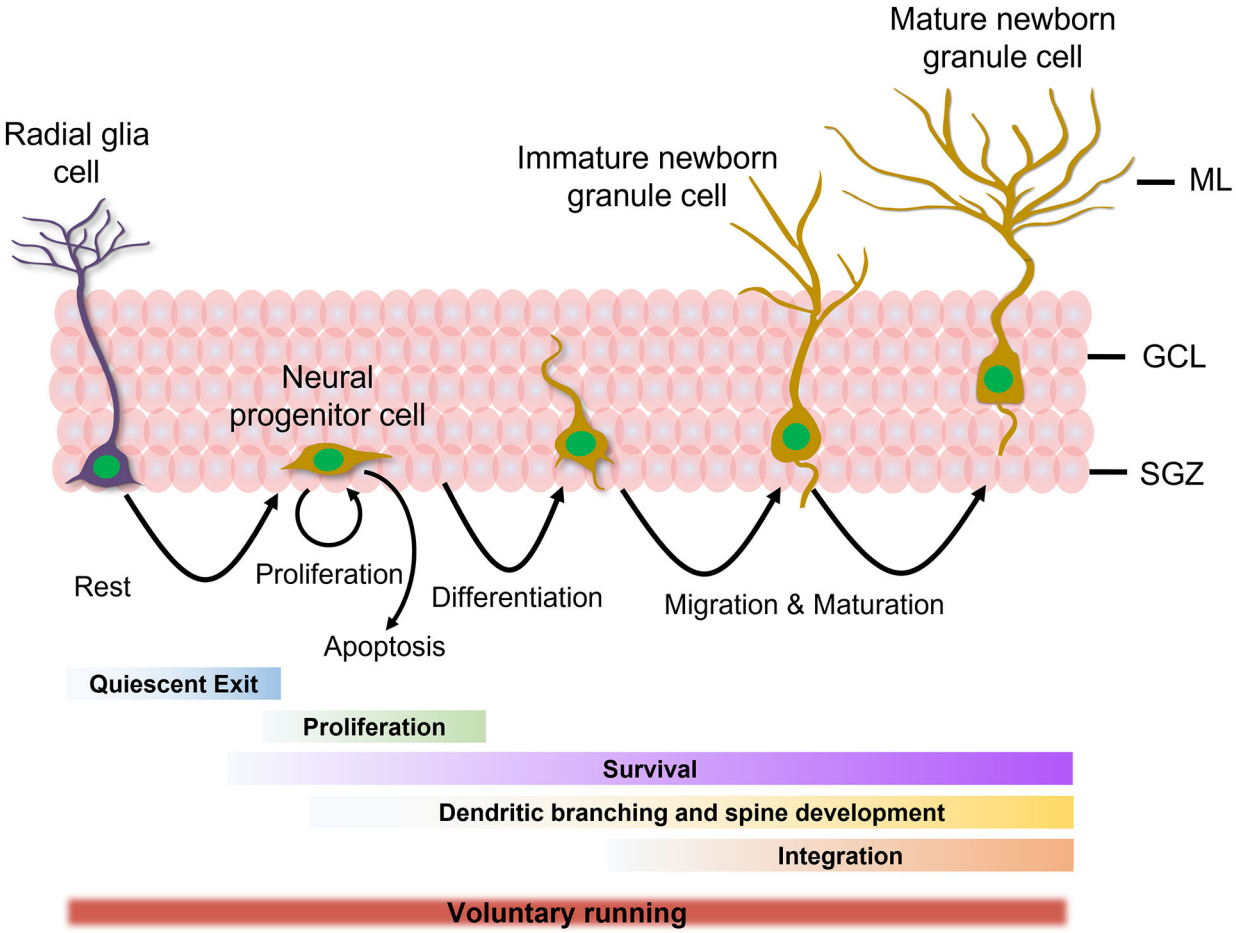

Figure. 2. Voluntary running has positive impact on all developmental stages of new neurons during adult hippocampal neurogenesis:

Voluntary running activates quiescent NSCs (Dong et al., 2019; Lugert et al., 2010; Wang et al., 2011), leads to increased NSC and IPC proliferation: (Farioli-Vecchioli et al., 2014; Overall et al., 2016; van Praag et al., 1999), enhances differentiation, survival of newborn immature neurons (van Praag et al., 2005; Vivar et al., 2016), promotes migration and maturation of new neurons (Gao et al., 2020; Piatti et al., 2011; Steib et al., 2014; Zhao et al., 2006), improves dendritic spine formation (Zhao et al., 2014), circuit integration (Vivar et al., 2016), and synaptic plasticity (Schmidt-Hieber et al., 2004) of new neurons.

Table 1.

Genome-wide studies to investigate physical exercise-induced gene expression changes in the hippocampus or the DG

Year	Species	Type of study	Treatment	Duration	Tissue	Reference
2001	Rat	Microarray	Running wheel	3 weeks	Hippocampus	(Tong et al., 2001)
2002	Rat	Microarray	Resistance running wheel	3 days, 1 week, 4 weeks	Hippocampus	(Molteni et al., 2002)
2010	Mouse	Microarray	Running wheel	16 months	Hippocampus	(Stranahan et al., 2010)
2011	Rat	Microarray	Running wheel	2 weeks	Hippocampus	(Funk et al., 2011)
2011	Mouse	Microarray	Running wheel	8 weeks	Hippocampus	(Kohman et al., 2011)
2013	Mouse	Microarray	Running wheel	3 days per week; 6 months	Hippocampus	(Alvarez-Lopez et al., 2013)
2013	Mouse	Microarray	Running wheel	4, 30 days	Granular zones of dentate gyrus	(Miller et al., 2013)
2014	Rat	Microarray	Resistance running wheel	4 weeks	Hippocampus	(Lee et al., 2014)
			Running wheel (no resistance			
2015	Rat	Microarray	Treadmill (mild exercise)	1 hour per day; 6 weeks	Hippocampus	(Inoue et al., 2015b)
			Treadmill (intense exercise)			
2015	Mouse	Microarray	Running wheel	3 days,1 week,2 weeks	Dentate gyrus	(Guerrieri and van Praag, 2015)
2018	mouse	RNA-seq	Running wheel	4 weeks	Dentate gyrus	(Gregoire et al., 2018)
2019	mouse	Microarray	Treadmill	30 min/day and 5 times/week, 4 weeks	Hippocampus	(Yook et al., 2019)
2019	Human	Microarray; Nano string	Human exercise	Late-life physical exercise	Hippocampus	(Berchtold et al., 2019)
2019	mouse	RNA-seq	Treadmill	6 weeks	Hippocampus	(McGreevy et al., 2019)
2019	mouse	RNA-seq	Running wheel	3 days	Dentate gyrus, Fos positive cells	(Chatzi et al., 2019)
2020	mouse	RNA-seq	Running wheel	11, 18 and 27 days	New neurons	(Gao et al., 2020)
2021	mouse	RNA-seq	Running wheel	12 days	Dentate gyrus	(Micheli et al., 2021)
2022	mouse	RNA-seq	Treadmill	7 days	Hippocampus	(Li et al., 2022)
2022	mouse	RNA-seq	Running wheel	3 months	Hippocampus	(Zhang et al., 2022)