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REVIEW PAPER

# Neurogenesis and Exercise: Past and Future Directions

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**Abstract** Research in humans and animals has shown that exercise improves mood and cognition. Physical activity also causes a robust increase in neurogenesis in the dentate gyrus of the hippocampus, a brain area important for learning and memory. The positive correlation between running and neurogenesis has raised the hypothesis that the new hippocampal neurons may mediate, in part, improved learning associated with exercise. The present review gives an overview of research pertaining to exercise-induced cell genesis, its possible relevance to memory function and the cellular mechanisms that may be involved in this process.

**Keywords** Neurogenesis · Exercise · Hippocampus · Learning and memory · Growth factors · Angiogenesis

## Introduction: Exercise and Cognitive Function

A sedentary lifestyle is accompanied by increased risk for cardiovascular, metabolic, and metastatic diseases (Powell and Blair 1994; Allison et al. 1999). It is well-known that the incidence of cancer, diabetes, and heart disease can be reduced by physical activity (Steinmetz and Potter 1996; Booth et al. 2002). More recently, evidence has accumulated that the beneficial effects of exercise extend beyond the periphery to the central nervous system. In humans and rodents physical activity enhances cognition (Suominen-Troyer et al.1986; Rogers et al. 1990; Winter et al. 2007; van Praag et al. 1999b), counteracts age-related memory decline (Kramer et al. 1999; Laurin et al. 2001; van Praag et al. 2005), delays onset of neurodegenerative diseases (Friedland et al. 2001; Tillerson et al. 2003; Adlard et al. 2005; Kaspar et al. 2005), enhances recovery from brain injury (Bohannon 1993; Grealy et al. 1999; Gobbo and O'Mara 2005) and depression (Babyak et al. 2000; Lawlor and Hopker 2001). Research pertaining to mechanisms underlying the effects of exercise on brain function has focused on changes in neurotransmitters, neurotrophins, and vasculature (Black et al. 1990; Neeper et al. 1995). Unique to the hippocampus, a brain area important for learning and memory, is the robust increase in new neurons associated with exercise (van Praag et al. 1999a, b). It has been hypothesized that the beneficial effects of running on mood and cognition may be mediated at least in part by enhanced hippocampal neurogenesis.

### Neurogenesis and Exercise

Although the initial description of adult neurogenesis in the early 1960s (Altman 1962) was met with skepticism, it has become well-established that the adult mammalian brain can produce new neurons. The existence of newborn neurons in the olfactory bulb and dentate gyrus has been confirmed using bromodeoxyuridine (BrdU) and retroviral labeling in conjunction with specific neuronal markers (Kuhn et al. 1996; van Praag et al. 2002; Carleton et al. 2003; Ming and Song 2005). In addition, the developmental time course and physiology of newborn neurons has been described (Zhao et al. 2006; Ge et al. 2006). Furthermore, research over the past decade has shown that adult neurogenesis is highly regulatable. Joseph Altman, investigated as early as 1964 whether environmental enrichment could affect the production of new neurons—at that time with no result (Altman and Das 1964). More

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recent studies showed that adult neurogenesis can be modified by a variety of factors, including stress (Gould et al. 1990), aging (Kuhn et al. 1996), environmental enrichment (Kempermann et al. 1997, 1998), and physical activity (van Praag et al. 1999a, b).

The first study that showed a positive effect of environmental enrichment on neurogenesis was carried out by Kempermann and colleagues (Kempermann et al. 1997). Specifically, mice were housed in either enriched or control conditions for 40 days and then injected with BrdU over 12 days. A subset of mice was killed 24 h after the last injection, to study cell proliferation. The remaining mice survived for another 4 weeks, to allow for maturation and differentiation of the BrdU-labeled newborn cells. As the number of BrdU-positive cells declines with time after labeling (since not all dividing cells become mature neural cells (Tashiro et al. 2006)) this is called the 'survival' timepoint. It was found that there was no change in cell division as a result of enrichment. However, an increased number of new neurons survived in enriched as compared to control mice. These mice were also tested in a spatial memory task, the Morris water maze (Morris et al. 1982), in which mice are trained to find a platform hidden under the surface of a pool in which the water is colored with paint. Over time mice learn to find the hidden platform based on cues on the testing room walls. The enriched mice learned faster than controls raising the possibility that the new neurons contribute to enhanced cognition (Kempermann et al. 1997). Recently, however, it was shown that water maze performance was still improved by enrichment when neurogenesis was ablated by radiation (Meshi et al. 2006). Even so, this does not preclude that neurogenesis is important for cognition. It should be taken into account that the learning task used is not selective for the function of the dentate gyrus (Kesner 2007; McHugh et al. 2007) and probably even less suited to dissect out the role of newly born neurons in learning and memory. Thus, the positive correlation between enhanced neurogenesis and improved learning following enrichment remains a valid basis for the suggestion that newly generated cells may be important for memory function (Kempermann et al. 1997).

Environmental enrichment has many aspects, including increased opportunity for learning, socialization, and physical activity. It was not known which of these variables may mediate the beneficial effect of enrichment on new born neuron number. Based on avian research indicating that food storing experience enhanced neurogenesis (Patel et al. 1997) an initial hypothesis was that learning may be the essential component of enrichment. However, since the mouse-enriched environment contained running wheels, I included mice that only exercised in the attempt to elucidate the neurogenic factor. Specifically, mice were assigned to groups with a learning task, wheel running, enrichment, or standard housing. Mice were injected with BrdU for the first 10 days of the experiment. A subset of mice was killed after the last BrdU injection to study cell proliferation, whereas the remaining mice were allowed to survive an additional 4 weeks. Similar to environmental enrichment, voluntary exercise in a running wheel enhanced the survival of newborn neurons in the dentate gyrus, whereas none of the other conditions had any effect on cell genesis (van Praag et al. 1999a). In addition, wheel running increased cell division as compared to all the other groups. In this initial study, the total number of surviving cells was similar between the enriched and running condition. A possible confounding variable in this regard could have been that the enriched environment also contained a running wheel. Indeed, in experiments in which running and enrichment without a wheel were compared there were more BrdU positive cells in the running than in the enriched condition (Ehninger and Kempermann 2003).

In a subsequent study we investigated whether there is an association between the amount of running and the number of new cells produced. In the studies with individually housed C57Bl/6 mice where there was little variation in distance run between animals (van Praag et al. 1999b), there was no obvious correlation. A different strain, 129SvEv, does show a wide range of wheel revolutions between individuals. In these mice we found a significant positive correlation between cell proliferation/survival and distance run (Allen et al. 2001). The correlation between wheel running and neurogenesis was also studied in mice bred for high levels of voluntary exercise over 26 generations (Rhodes et al. 2003). Hyperactive mice run about 12 km/day whereas controls run an average of 5 km/day. In this study mice were housed with or without running wheels, injected with BrdU daily for the first 10 days of the study and then allowed to survive for an additional 4 weeks. There was no difference between sedentary control and sedentary hyperactive animals in the number of BrdU-positive cells. However, there was a 5-fold increase in cell genesis in the hyperactive runners versus a 4-fold increase relative to sedentary conditions in running controls. Interestingly, there was a strong positive correlation between cell genesis and running in the control mice, whereas there was no relationship between neurogenesis and distance run in the hyperactive mice. In addition, exercise enhanced spatial learning in the water maze in control but not hyperactive runners. It appears that selective breeding for hyperactivity is associated with neurological deficits that affect brain function and behavior (Rhodes et al. 2001). Thus, a lack of association between running distance and the amount of cells produced may be indicative of impairment, whereas a positive correlation between the amount of running and the number of new cells produced may represent normal brain function.

A number of studies have investigated the kinetics of the effects of exercise on cell proliferation and neurogenesis. Research has shown that 10 days of wheel running increased cell genesis in individually housed rodents (Allen et al. 2001; Persson et al. 2004; van der Borght et al. 2006; see however Stranahan et al. 2006). The onset of the effect of running on cell genesis, however, occurs sooner. In mice that were housed with a running wheel for 5 days and received a daily injection of BrdU a 30% increase in cell proliferation was observed (B. Jacobs, H. van Praag and F. Gage, unpublished data). Furthermore, Kronenberg et al. (2006) using a BrdU labeling paradigm in which group housed mice were injected once after the onset of running, one day before killing, reported that cell proliferation peaks after 3 days of running, and is still significantly enhanced at 10 days. After 32 days of running the pro-proliferative effect has returned to baseline. Interestingly, the number of immature neurons continues to increase at this time-point (Kronenberg et al. 2006). Furthermore, circadian rhythm studies in which single-housed mice were allowed to run 1 or 3 h per day for 7 days, and injected with BrdU at different times during the day–night cycle, have indicated that the greatest amount of cell genesis is the middle of the dark cycle (Holmes et al. 2004). Another study, however, using Ki67 labeling suggests that the onset of the active cycle is optimal for the effect of physical activity on cell genesis (van der Borght et al. 2006).

Enhancement of hippocampal neurogenesis by running is a robust phenomenon (Trejo et al. 2001; Fabel et al. 2003; Kitamura et al. 2003; Overstreet et al. 2004; van der Borght et al. 2007; van Praag et al. 2007). In several studies it was investigated whether exercise influences the production of new neurons or glia in other brain regions. It was found that there was no effect of physical activity on neurogenesis in the subventricular zone / olfactory bulb (Brown et al. 2003). This is not due to a lack of plasticity in olfactory neurogenesis. Indeed, it was shown that the production of new olfactory neurons can be enhanced by exposure to an odor-enriched environment (Rochefort et al. 2002). In brain regions other than the hippocampus and olfactory bulb evidence for neurogenesis has been controversial (Gould et al. 1999; Dayer et al. 2005; Kornack and Rakic 2001; Magavi et al. 2000). In a recent investigation a few cells that double-labeled for BrdU and the neuronal marker Neun were observed in frontal cortex. The number of cortical BrdU/Neun cells was not influenced by physical, though interestingly a trend toward an exercise-induced increase was observed (Mandyam et al. 2007) toward an exercise-induced increase (Mandyam et al. 2007). Physical activity has been found to enhance proliferation of microglia in superficial cortical layers and of astrocytes in motor cortex without a change in oligodendrocyte number (Ehninger and Kempermann 2003). In this study, frontal cortex was not examined. Other researchers, however, showed that running elevates both astrocyte and oligodendrocyte number in rat prefrontal cortex (Mandyam et al. 2007). The functional significance of this increase in gliogenesis remains to be determined.

Exercise does not only increase the number of new neurons, it also influences the morphology of individual newly born cells, suggesting that that the benefits of exercise for new neurons are qualitative as well as quantitative. Using a retroviral labeling strategy it was shown that newborn neurons develop over several months in the adult brain (van Praag et al. 2002; Zhao et al. 2006). Exercise enhances the maturation of newborn neurons. Specifically, the density of mushroom spines is enhanced and spine motility is decreased during development of new neurons in the adult brain, even though the total number of dendritic protrusions does not change (Zhao et al. 2006). These findings are consistent with research in existing neurons, where it was shown that exercise influences dentate gyrus dendritic morphology (Redila and Christie 2006) as well as spine density in the dentate gyrus, area CA1, and entorhinal cortex layer III (Stranahan et al. 2007).

## New Neurons and Synaptic Plasticity

The exercise-induced increase in cell genesis is associated with enhanced hippocampal synaptic plasticity. In particular, long-term potentiation (LTP) a physiological model of certain forms of learning and memory (Bliss and Collingridge 1993) is influenced by physical activity. In our initial study, field excitatory post-synaptic potential (fEPSP) amplitudes as well as LTP, were compared in hippocampal slices from running and control mice. fEPSPs were unchanged in both groups. However, LTP amplitude was enhanced in the dentate gyrus in slices from running mice as compared to controls. Recordings from another hippocampal subfield, area CA1, showed no change in LTP in response to running (van Praag et al. 1999b). In subsequent studies, dentate gyrus LTP was studied in vivo in urethane anesthetized rats that have been housed with a running wheel (Farmer et al. 2004) or given forced treadmill exercise (O'Callaghan et al. 2007). In both the voluntary and forced exercise condition LTP in the dentate gyus was increased.

Changes in synaptic plasticity associated with exercise occurred in the same region where neurogenesis was stimulated by running, suggesting that newborn cells have a functional role in this process. Although the new cells are a small percentage of the granule cell layer several studies have indicated that they have greater plasticity than do mature cells. Indeed, in immature rats, dentate gyrus LTP lasts longer than in adults (Bronzino et al. 1994). In

another study properties of granule cells from the inner and outer layer of the dentate gyrus were compared. Inner layer cells were considered to be "young" cells and the outer layer "old" cells. It was found that putative young cells had a lower threshold for LTP and were unaffected by GABAA inhibition, indicating enhanced plasticity in the young cells (Wang et al. 2000). In a subsequent investigation, recordings were made from young neurons identified by electrophysiological criteria established during early postnatal development of dentate gyrus neurons, immunoreactivity for immature neuronal markers, and developing dendritic morphology. It was shown that LTP can be induced more easily in young neurons than in mature neurons under identical conditions. (Schmidt-Hieber et al. 2004). Recently, using retroviral labeling, it was reported that individual new neurons have increased LTP amplitude and a decreased induction threshold between 1 and 1.5 months of newborn neuron age. A proposed mechanism is increased dependence of LTP on NMDA NR2B receptors during this critical developmental period (Ge et al. 2007).

## Running, Neurogenesis and Cognition

### *Young Mice*

The enhanced synaptic plasticity of individual newborn neurons and the exercise associated increase in new dentate granule cell number may mediate some of the beneficial effects of exercise on learning and memory in humans and animals. Indeed, exercise has been shown to improve learning in young human subjects (Pereira et al. 2007; Winter et al. 2007). In rodents, both voluntary wheel running and forced treadmill training have been shown to enhance spatial learning using different types of mazes (such as water, y-, radial maze) and training paradigms (Fordyce and Farrar 1991; Fordyce and Wehner 1993; van Praag et al. 1999b; Anderson et al. 2000; Vaynman et al. 2004; van Praag et al. 2005; Ang et al. 2006; van der Borght et al. 2007). Running also improved performance in other hippocampus-dependent tasks, such as contextual fear conditioning (Baruch et al. 2004; Burghardt et al. 2006) and novel object recognition (O'Callaghan et al. 2007).

### *Normal Aging*

The correlation between exercise, neurogenesis, and memory function has been explored during normal aging. Physical activity has been shown to protect against age-related cognitive decline (Kramer et al. 1999; Yaffe et al. 2001) and brain atrophy (Colcombe et al. 2003) in aging adults. Neurogenesis declines to low levels with aging in rodents (Seki and Arai 1995; Kuhn et al. 1996) as well as non-human primates (Leuner et al. 2007) and has been associated with cognitive deficits (Drapeau et al. 2003; see however Bizon and Gallagher 2003; Merrill et al. 2003). The age-dependent reduction in cell genesis can be partially prevented when animals are housed with a running wheel over a 6-month period (Kronenberg et al. 2006). In addition, the decline in neurogenesis and cognition associated with normal aging can also be reversed in part by the onset of wheel running late in life. In a recent study, we placed normal-aged mice that had been sedentary until they were 18 months of age in a running wheel for 1 month, and tested spatial memory in the Morris water maze. We found that exercise significantly improved acquisition and retention of the water maze task in aged runners. In addition, newborn cell survival was increased in the aged mice housed with a running wheel to the level of young sedentary controls. Phenotype analysis of the BrdU-labeled cells showed that in aged runners more of the BrdU-positive cells co-labeled with the neuronal marker Neun ($\sim$25%) than in aged sedentary mice ($\sim$10%), though still less than in young sedentary animals ($\sim$50%). Morphological analysis of individual newborn neurons in young and aged runners showed that there was no difference in dendritic morphology between the groups (van Praag et al. 2005; Fig. 1).

### *Alzheimer's Disease*

The benefits of exercise on neurogenesis and learning were apparent in young and normal aging mice. However, this observation has not been quite as clear when mouse models of degenerative disease were evaluated. With regard to AD there is some controversy as to whether neurogenesis is altered under basal conditions. In human post-mortem tissue an increase in immature neuronal markers in the dentate gyrus was found (Jin et al. 2004a). However, in a subsequent study of presenile patients it was found that an observed change in cell proliferation could be attributed to an increase in glial and vascular cells (Boekhoorn et al. 2006). A similar degree of confusion exists when considering neurogenesis in amyloid precursor protein (APP) and/or presenilin-1 (PS1) transgenic mouse models of AD. In PS-1 over-expressing transgenic mice a decrease (Wen et al. 2004; Wang et al. 2004) and an increase in cell genesis (Chevallier et al. 2005) have been reported. In APP mutants also a reduction (Haughey et al. 2002; Dong et al. 2004; Verret et al. 2007) and an increase (Jin et al. 2004b; Donovan et al. 2006) in neurogenesis have been observed (for review see Verret et al. 2007). A confounding factor is that BrdU labeling and post-injection survival times vary, adding to the difficulty in interpretation of the various studies. Another part of the confusion is likely due to the

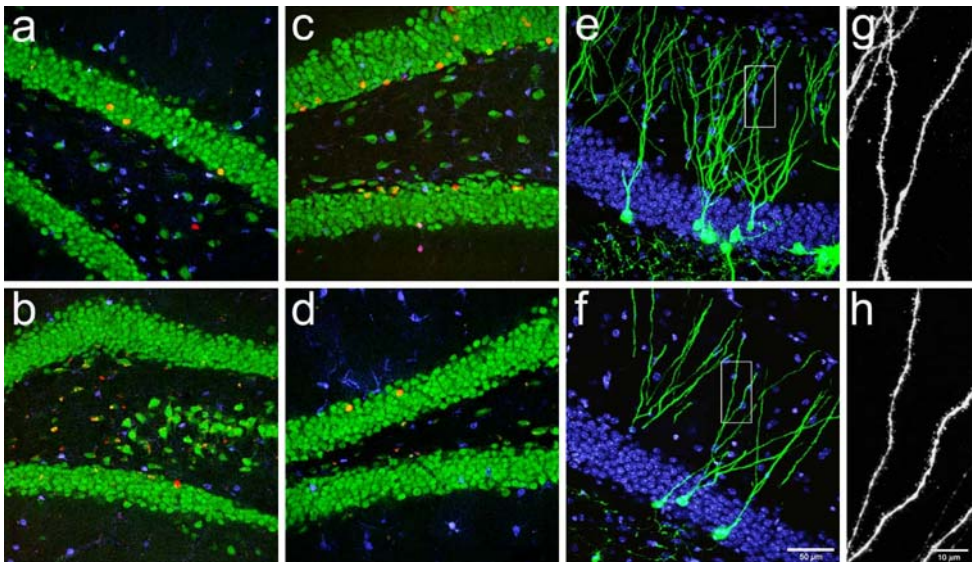


**Fig. 1** Neurogenesis in the young and aged dentate gyrus. Young (3 months) and aged (19 months) male C57Bl/6 mice were injected with BrdU (50 mg/kg) daily for 1 week and perfused 4 weeks later (**a**–**d**). Confocal images of immunofluorescent triple-labeled sections for BrdU (red), the neuronal marker NeuN (green), and the glial marker S100$\beta$ (blue), [BrdU-labeled neurons are orange (red plus green)]. Exercise enhanced neurogenesis in young (**c**) and aged (**d**) runners as compared to sedentary young (**a**) and aged (**b**) controls. In another set of experiments, retrovirus expressing green fluorescent protein (GFP) was injected into the dentate gyrus of young and aged runners. Photomicrographs show GFP+ new neurons in young (**e**) and aged (**f**) running mice at 4 weeks after virus injection. The boxed areas in e and f correspond to the enlarged images of spines in young (**g**) and aged (**h**) mice (DAPI, blue), (van Praag et al. 2005). Copyright 2005 by the Society for Neuroscience

use of different lines of transgenic mice, their background strain, gender, age, and degree of amyloid pathology. Therefore, it may be of interest to examine neurogenesis in the recently generated triple mutant mouse model of AD, in which the mice express FAD, APP, and PS1 mutations together with a tau mutation (Oddo et al. 2003). These mice show age-dependent A$\beta$ deposition and tau pathology in the hippocampus and cerebral cortex, associated with impaired synaptic plasticity and spatial learning (Halagappa et al. 2007).

Similar to the disparate results under basal conditions, there is a lack of concordance with regard to the effects of exercise in mouse models of AD. Studies have found beneficial effects of exercise on cognition and amyloid deposits (Adlard et al. 2005), even after the onset of pathology (Nichol et al. 2007), whereas other researchers report no benefit of wheel running (Wolf et al. 2006; Cracchiolo et al. 2007) on learning in APP mutant mice. Environmental enrichment has been reported by several labs to improve cognition in mouse models of Alzheimer's disease (Jankowsky et al. 2005; Lazarov et al. 2005; Wolf et al. 2006; Costa et al. 2007; Cracchiolo et al. 2007). Indeed, Lazarov and colleagues (2005) showed that enrichment results in decreased A$\beta$ levels and amyloid deposits, as well as in increased activity of the A$\beta$-degrading protease neprilysin.

In the studies where environmental enrichment and exercise were compared directly in AD transgenic mouse models, enrichment seems to be more beneficial for cognition than exercise (Wolf et al. 2006; Cracchiolo et al. 2007). Long-term exercise (8 months duration) did not change the survival of new neurons in APP23 mice and did not improve spatial performance in the water maze (Wolf et al. 2006). However, in both studies where physical activity was shown to not to be beneficial (Wolf et al. 2006; Cracchiolo et al. 2007), mice were group housed. Therefore, it is not clear how much each mouse ran and if mice were still running after 8 months of housing with the wheel (Wolf et al. 2006). In addition, in the study by Cracchiolo and colleagues it appears that in the physical activity condition the mice are housed with a rotating dish and that only the enriched environment contains at least two running wheels (Cracchiolo et al. 2007).

### *Huntington's Disease*

Neurogenesis has also been studied in the context of HD. Similar to AD where cell genesis was reportedly increased the DG (Jin et al. 2004a), a post-mortem study of human brains showed that neurogenesis may be enhanced in the SVZ (Curtis et al. 2003). In addition, in excitotoxic models of HD cell genesis was found to be increased in the rodent

striatum (Tattersfield et al. 2004; Collin et al. 2005), likely due to a compensatory response to neural injury. In transgenic mouse models of HD, however, there is no change in SVZ cell genesis, though in the DG of transgenic R6/1 and R6/2 mice there is a significant decrease in neurogenesis (Lazic et al. 2004; Grote et al. 2005; Gil et al. 2005). Both environmental enrichment (van Dellen et al. 2000; Lazic et al. 2006) and voluntary exercise (Pang et al. 2006) have been found to delay the onset of disease symptoms and improve spatial memory function in R6/1 transgenic mice. Exercise did not reverse the observed decrease in neurogenesis in R6/2 mice (Kohl et al. 2007). It is possible that this is due to a lack of exercise-induced upregulation of proteins which may mediate newborn cell survival, such as brain-derived neurotrophic factor (BDNF), with running (Pang et al. 2006; Kitamura et al. 2003). However, hippocampal BDNF levels were not measured and it is not clear how much the mice ran (Kohl et al. 2007). Moreover, R6/2 mice are mainly a model for the juvenile-onset form of HD (Mangiarini et al. 1996). They exhibit motor deficits as early as 5–6 weeks of age, display overt behavioral abnormalities at 8–9 weeks, and typically die between 11 and 13 weeks (Menalled and Chesselet 2002). In other mouse models for HD disease onset (Pang et al. 2006; Duan et al. 2003), such as neurodegenerative changes in the striatum and progressive motor dysfunction occurs at about 3 months of age, leaving more time for intervention with physical activity in adulthood.

## Mechanisms Underlying Effects of Exercise on Neurogenesis

### *Neurotransmitters in Running and Neurogenesis*

Physical activity can change the function of neurotransmitter systems in the brain. Microarray analysis has shown that both acute and chronic voluntary exercise affect the expression of hippocampal genes related to synaptic plasticity (Tong et al. 2001). In particular, genes related to the glutamatergic system are up-regulated, whereas those related to the GABA system are down-regulated (Molteni et al. 2002). Glutamatergic function in the dentate gyrus may regulate neurogenesis (for review see Schlett 2006). In sedentary animals NR2B has been found to mediate enhanced synaptic plasticity in newborn neurons (Ge et al. 2007). Under exercise conditions, using whole hippocampus it was found that after 3 days of running both NR2A and NR2B subtypes of the NMDA receptor were elevated, and that after 7 days of running only NR2A gene expression remained elevated (Molteni et al. 2002). It is of interest that in mice lacking the NMDA receptor ε1 subunit (NR2A) the increase in neurogenesis and BDNF protein levels did not change with exercise in these mice (Kitamura et al. 2003). In another study in rats, it was found that after 1 month of running mRNA levels for NR2B, the glutamate receptor 5 and BDNF gene expression were increased by exercise. In this study, however, the hippocampal subfields were separated in the dissection. The observed changes were specific for the dentate gyrus and did not occur in other, non-neurogenic hippocampal subfields (Farmer et al. 2004). Exercise induced changes in glutamatergic function may influence the production and function of new neurons in the adult brain. It is unlikely that this enhanced activation will result in glutamate-related excitotoxicity, in particular since exercise also elevates the production of neuroprotective factors such as BDNF (Neeper et al. 1995).

Exercise also enhances endogenous opioid systems (Sforzo et al. 1986). However, exogenous opiate agonists such as morphine and heroin have been shown to suppress neurogenesis in vivo, and knockout of the mu opioid receptor increases neurogenesis (Eisch et al. 2000; Harburg et al. 2007). Interestingly, endorphins and enkephalins stimulate cell genesis in vitro (Persson et al. 2003; Narita et al. 2006). Moreover, administration of the mu receptor antagonist naltrexone decreased running-induced cell proliferation (Persson et al. 2004). The complex effects of opiates on the production of new neurons remain to be resolved (Koehl et al. 2008).

Physical activity also activates monoamines (Chaouloff 1989) and enhances recovery from depression (Lawlor and Hopker 2001). In this context it is of interest that serotonergic agonists, including antidepressants such as fluoxetine (Malberg et al. 2000; Encinas et al. 2006), can enhance cell genesis, whereas administration of the serotonin 5-HT (1A) receptor antagonists, decreases cell proliferation in the DG (Radley and Jacobs 2002). Indeed, the antidepressant effect of exercise in humans (for review see Ernst et al. 2006) has been shown to be just as potent as that of serotonergic medications (Babyak et al. 2000), raising the possibility that enhanced neurogenesis may be a common underlying treatment mechanism. Indeed, mutant 5HT-1A receptor knockout mice show an increased anxiety and a reduced neurogenic response when treated with fluoxetine (Santarelli et al. 2003). However, it remains to be determined whether neurogenesis is relevant to the etiology of depression (Jacobs et al. 2000; Vollmayr et al. 2007). Beneficial effects of environmental enrichment on anxiety-like behavior can occur when cell genesis is ablated (Meshi et al. 2006). In BALB/c mice the antidepressant effect of chronic fluoxetine is not blocked by radiation-induced reduction of neurogenesis (Holick et al. 2008). Moreover, although the time course of maturation of new neurons (Zhao et al. 2006) is consistent with the delayed onset of therapeutic action of classical antidepressants, newer compounds with a rapid onset of action are under investigation (Lucas et al. 2007). Thus, influencing neurogenesis

may be important but not critical for treatment of depression.

### *Growth Factors and Running Induced Cell Genesis*

Growth factors provide important extracellular signals regulating proliferation and differentiation of stem and progenitor cells in the brain and spinal cord during development (Calof 1995). These factors continue to play an important role in the adult brain in synaptic plasticity (Kang and Schuman 1995), learning (Fischer et al. 1994), exercise, and neurogenesis. Trophic factors that influence adult neurogenesis, include basic fibroblast growth factor (bFGF-2), epidermal growth factor (EGF), BDNF, insulin like growth factor I (IGF-I), and vascular endothelial growth factor (VEGF). Intra-cerebro-ventricular (i.c.v.) infusion of FGF-2 and EGF results in increased neurogenesis in SVZ (Craig et al. 1996; Kuhn et al. 1997; Wagner et al. 1999), and in the DG of the hippocampus (Rai et al. 2007). I.c.v. administration of BDNF increased the number of new neurons in adult olfactory bulb (Zigova et al. 1998) and induced neurogenesis in the striatum (Pencea et al. 2001). In addition, in BDNF knockout mice enhancement of hippocampal neurogenesis following environmental enrichment did not occur (Rossi et al. 2006). Furthermore, exercise has been shown to elevate gene expression of FGF (Gomez-Pinilla et al. 1997, 1998), NGF, and BDNF (Neeper et al. 1995; Widenfalk et al. 1999) in the hippocampus.

### *Vascular Trophic Factors*

In recent years there has been a growing interest in the relationship between angiogenic factors and neurogenesis. In the dentate gyrus new cells are clustered close to blood vessels (Palmer et al. 2000) and proliferate in response to vascular growth factors (Jin et al. 2002; Cao et al. 2004). This had lead to the hypothesis that neural progenitors cells are associated with a vascular niche and that neurogenesis and angiogenesis are closely correlated (Palmer et al. 2000; Shen et al. 2004; Pereira et al. 2007; Thored et al. 2007). In particular, hippocampal gene transfer of VEGF in adult rats resulted in approximately double the number of new neurons in the DG and improved cognition (Cao et al. 2004). Peripheral infusion of IGF-1 also increased adult neurogenesis (Aberg et al. 2000), and reversed the aging-related reduction in new neuron production (Lichtenwalner et al. 2001).

Vasculature changes associated with exercise have been shown to occur in the brain and may be mediated by IGF and VEGF. Physical activity increases the proliferation of brain endothelial cells (Lopez-Lopez et al. 2004) and angiogenesis (Black et al. 1990; Kleim et al. 2002; Swain et al. 2003; Anderson et al. 2002) throughout the brain. Running enhances IGF gene expression (Ding et al. 2006a, b) and protein levels in the hippocampus (Carro et al. 2000). In addition, physical activity increases serum levels of both IGF (Carro et al. 2000) and VEGF (Fabel et al. 2003) and blockade of peripheral VEGF and IGF-1 inhibited the increase in neurogenesis observed with running (Trejo et al. 2001; Fabel et al. 2003).

In the dentate gyrus, unlimited voluntary exercise enhanced the perimeter and surface area of blood vessels in the dentate gyrus of young, but not aged mice (van Praag et al. 2005). Recently, using MRI imaging in mice and humans a correlation between blood flow in the dentate gyrus and neurogenesis was reported, suggesting that changes in blood flow in humans may be an indirect measure for levels of neurogenesis in humans (Pereira et al. 2007). Interestingly, in a study in which we aimed to determine whether the plant derived flavanol (-)epicatechin could enhance neurogenesis, we found that this compound caused a robust expansion of the vasculature but did not enhance cell genesis (van Praag et al. 2007). In addition, it was observed that 2 h of daily running increases the survival of newly generated cells but does not change vascularization. This indicates that enhanced angiogenesis is not necessarily predictive of increased neurogenesis and vice versa (van Praag et al. 2007). Indeed, development of new methods, such as proton nuclear magnetic resonance spectroscopy (Jansen et al. 2006; Manganas et al. 2007), may lead to a better way to study the regulation of cell genesis by exercise in the human brain.

## Functional Significance of Neurogenesis in the Adult Brain

Despite the avid research and continued strong interest in adult neurogenesis, the functional significance of this phenomenon remains elusive. To determine whether neurogenesis is important for learning it is of interest to selectively ablate the newly generated cells and subsequently test memory function. Research has been carried out in this regard using radiation (Santarelli et al. 2003) and transgenic mouse models (Garcia et al. 2004). However, the behavioral tasks that are used should be re-evaluated. It would be important to design learning and memory tasks that preferentially test the function of the dentate gyrus subfield of the hippocampus (McHugh et al. 2007; Kesner 2007; Hernández-Rabaza et al. 2007). In the context of exercise it will be important to study memory in runners in the absence of exercise-induced neurogenesis. In addition, a side by side functional comparison of pharmacological methods that increase neurogenesis and physical activity would provide insight into this unique population of dentate granule cells.

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