All About Running: Synaptic Plasticity, Growth Factors and Adult Hippocampal Neurogenesis

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Abstract

Accumulating evidence from animal and human research shows exercise benefits learning and memory, which may reduce the risk of neurodegenerative diseases, and could delay age-related cognitive decline. Exercise-induced improvements in learning and memory are correlated with enhanced adult hippocampal neurogenesis and increased activity-dependent synaptic plasticity. In this present chapter we will highlight the effects of physical activity on cognition in rodents, as well as on dentate gyrus (DG) neurogenesis, synaptic plasticity, spine density, neurotransmission and growth factors, in particular brain-derived nerve growth factor (BDNF).

1 Exercise and Cognition

Cognition studies in adult rodents have shown that both voluntary and forced exercise enhance spatial memory in the Morris water maze, Y-maze, T-maze and radial arm maze tests (Fordyce and Farrar 1991; van Praag 2008). Running also improves performance on tasks that require minimal spatial navigation. For example, contextual fear conditioning, passive avoidance learning and novel object recognition are enhanced by running (Baruch et al. 2004; Falls et al. 2010; Liu et al. 2008; Mello et al. 2009; O'Callaghan et al. O'Callaghan et al. 2007; Hopkins and Bucci 2010; Fahey et al. 2008; Griffin et al. 2009). It remains to be determined whether the beneficial effects of exercise for performance on these tasks is mediated by the hippocampus and/or whether other brain areas are involved to a similar extent. For example, contextual fear conditioning depends on both the hippocampus and amygdala (Phillips and LeDoux 1992; Myers and Gluck 1994; Wiltgen et al. 2006; Maren 2001, 2008). The hippocampus is critical for memory of context; whereas the amygdala stores the context–shock association (Huff and Ruddy 2004). However, the effects of physical activity on the amygdala are still unclear. Greenwood et al. (2009) showed that 6 weeks of running before conditioning improves hippocampus dependent memory for context, but not extinction (amygdala-dependent), suggesting that voluntary physical activity

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selectively increased hippocampus-dependent memory. Subsequent studies showed that physical activity improved learning and consolidation of cued conditioned fear, an amygdala-dependent process, but not the retrieval or performance of conditioned fear (Falls et al. 2010; Lin et al. 2012). Interestingly, exercise increases BDNF mRNA, and synaptic proteins such as TrkB and SNAP-25 levels in both the dentate gyrus (DG) and amygdala (Greenwood et al. 2009; Lin et al. 2012), albeit more so in the DG (Greenwood et al. 2009). Thus, physical activity may differentially affect amygdala and hippocampus-dependent plasticity.

Within the hippocampal subfields (area CA1, area CA3, DG), physical activity likely has differential functional effects. Indeed, it has become increasingly well-established that the subfields of the hippocampus may mediate different aspects of memory formation. Area CA1 is deemed important for encoding, area CA3 for pattern completion and the DG is considered to mediate pattern separation (McHugh et al. 2007; Leutgeb et al. 2007; Leutgeb and Leutgeb 2007; Gilbert et al. 2001; Bakker et al. 2008; Gold and Kesner 2005; Kesner 2007; Schmidt et al. 2012). The DG is one of the brain regions with substantial addition of new neurons throughout the lifetime of mammals, (Altman and Das 1965) and it has been suggested that these new neurons contribute significantly to pattern separation. Ablation of adult neurogenesis results in deficits in fine pattern discrimination in the touchscreen (Clelland et al. 2009) and the ability to distinguish between two similar contexts in fear conditioning (Tronel et al. 2010). Spatial pattern separation was evaluated recently in running versus sedentary mice (Creer et al. 2010). Specifically, mice were tested on a spatial discrimination task, where stimuli were presented in close or distal proximity using a touchscreen method that requires minimal motor activity (Morton et al. 2006). There was no difference between the groups when the separation between stimuli was large, however, runners outperformed sedentary mice when the difference between stimuli was small (Creer et al. 2010). The observed improvement in making fine spatial distinctions may be due at least in part to the increase in adult neurogenesis that is observed in the hippocampus with exercise (van Praag et al. 1999a). Indeed, in a transgenic mouse with increased adult hippocampal neurogenesis there is improved differentiation between overlapping contextual representations, indicative of enhanced pattern separation (Sahay et al. 2011).

2 Neurogenesis and Exercise

Many different extrinsic and intrinsic factors can regulate the production of new neurons. Housing mice in an enriched environment (EE) resulted in the first evidence that adult neurogenesis could be enhanced (Kempermann et al. 1997, 1998). Increased neurogenesis was correlated with improved performance in a hippocampus-dependent spatial learning task, the Morris water maze (Kempermann et al. 1997). However, an enriched environment is a complex combination of inanimate and social stimulation, learning and physical activity. Separation of the different elements of the EE showed that running per se increases cell proliferation, neurogenesis, and synaptic plasticity, as well as spatial memory function in the mouse DG (van Praag et al. 1999a, b; Kronenberg et al. 2003; van der Borght et al. 2007). A potential confound in the initial study was that the positive control, the EE also contained a running wheel (van Praag et al. 1999a). However, at that time the finding that running increased neurogenesis was completely unexpected and so an EE group without a wheel was

not included. Subsequent research suggested that running enhanced the number of bromodeoxyuridine (BrdU) positive cells more so than EE without running wheels, but that EE still differed from standard housing conditions (Ehninger and Kempermann 2003), even though only marginally so (Fabel et al. 2009). However, in these studies the control mouse cages were typically smaller than those of the EE group, allowing less activity.

In a recent study, we aimed to dissociate the effects of physical activity and enrichment in young female C57Bl/6 mice housed in identically sized cages under control, running, and EE with or without running wheels. Cell proliferation, neuron survival, and neurotrophin levels were enhanced only when running wheels were accessible, suggesting that exercise is the critical factor mediating increased BDNF levels and adult hippocampal neurogenesis (Kobilo et al. 2011a); Fig. 1). This study has been replicated and extended in individually housed male C57Bl/6 mice. Specifically, the authors added more enrichment in the form of dietary treats and continuous addition of novel objects. Even so, only running and running plus enrichment increased neurogenesis. The greatest amount of physical activity was observed in the running only condition and these mice exhibited improved spatial learning in the Morris water maze (Mustroph et al. 2012). Altogether, these findings do not preclude the effects of EE only on behavior. Indeed, EE only has effects on synaptic plasticity, such as increased dendritic complexity of young granule neurons (Beauquis et al. 2010), enhanced arborization of cortical neurons (Ip et al. 2002), and elevated synaptophysin levels in hippocampus and cortex (Lambert et al. 2005). Moreover, EE only has been shown to have profound effects on dendritic spines and synapses in cortex and cerebellum (Greenough et al. 1978, 1985, 1986). Therefore, these findings suggest that EE and physical activity share common features pertaining to synaptic plasticity (van Praag et al. 2000), but that the increment in adult neurogenesis and BDNF levels in the hippocampus is specific to physical activity.

Reduced neurogenesis occurs naturally with aging and is observed in certain mouse models of neurodegenerative disease. Exercise may ameliorate or reverse this change in some but likely not all conditions. Indeed, it has been shown that neurogenesis declines as early as middle-age (Kuhn et al. 1996), and may contribute to age-related reductions in cognitive function (Erickson and Barnes 2003). However, the robust effect of exercise on neurogenesis is maintained throughout life in rodents. It has been shown that exercise from 3 to 9 months of age significantly reduced the age-dependent decline in cell proliferation and led to a consecutive increase in the number of more mature cells (Kronenberg et al. 2006). Moreover, in mice that started wheel running in middle age (Wu et al. 2008; Marlatt et al. 2012) or old age (van Praag et al. 2005), new neuron number was elevated. Furthermore, recent studies have shown that physical activity can reverse radiation-treatment-related decline in hippocampal neurogenesis (Naylor et al. 2008; Wong-Goodrich et al. 2010). In addition, running can ameliorate the genetically reduced generation of proliferating hippocampal cells and enhance the dendritic arborization of newly generated neurons in synRas mice (Lafenetre et al. 2010).

The effects of exercise have also been evaluated in mouse models of neurodegenerative disease. In certain mouse models of Alzheimer's disease (AD), exercise is able to reduce pathology and enhance cognition and adult neurogenesis. In TgCRND8 mice (which express

APP695swe, Ind), running improved spatial memory and reduced extracellular Aβ plaque load (Adlard et al. 2005). Exercise was also found to be beneficial in Tg2576 mice (which express APP695swe), even after the onset of pathology (Nichol et al. 2007). Similarly, APOE4 mice have been shown to benefit from regular physical activity (Nichol et al. 2009). Furthermore, in the 3xTG model of the disease, physical activity reduced disease symptoms and improved synaptic plasticity in a recent study (Garcia-Mesa et al. 2011). Reduced neurogenesis in this model (Rodriguez et al. 2008) was improved by running (Rodriguez et al. 2011). Altogether, the effects of exercise appears to be promising in mouse models of AD and is consistent with positive data emerging from studies in humans (Buchman et al. 2012; Lautenschlager et al. 2012).

A notable exception to the beneficial effects of exercise on brain and behavior appears to be in mouse models of Huntington's disease (HD). While initial research showed that EE delays symptom onset in R6/1 transgenic mice (van Dellen et al. 2000), physical activity had equivocal results. In R6/1 mice, running normalized rearing behavior and delayed the onset of deficits in rear-paw clasping, motor coordination and spatial working memory. However, rotarod performance, ubiquitinated protein aggregates, hippocampal BDNF protein levels (Pang et al. 2006; van Dellen et al. 2008), and hippocampal neurogenesis in R6/2 mice (Kohl et al. 2007) were unchanged by exercise. In a recent study, running started in presymptomatic 6-week-old male HD (N171-82Q) mice did not improve function and appeared to accelerate disease onset (shaking, hunched back and poor grooming), reduced striatal volume, and impaired motor behavior compared to sedentary controls. Furthermore, weight loss, reduced lifespan, hyperglycemia, Morris water maze learning deficits, diminished hippocampal neurogenesis, deficits in immature neuronal morphology, intranuclear inclusions, and decreased DG volume were refractory to physical activity (Potter et al. 2010; Fig. 2). It remains to be determined whether similar observations will be made in other mouse models of the disease. Interestingly, a case study in humans also has indicated that physical exercise may not prevent or delay disease onset or progression. In humans, the number of polyglutamine repeats can predict disease onset to some extent (Langbehn et al. 2004). A marathon runner presented with myopathy 20 years before the predicted disease onset for 41 CAG repeats (Altschuler 2006; Kosinski et al. 2007). Thus, the neurogenic and cognitive effects of physical activity should be evaluated carefully across the spectrum of neurological diseases.

3 Synaptic Plasticity: Effects of Exercise On Long-Term Potentiation/ Depression, Dendritic/Spine Size and Morphology

Running can influence neural plasticity on many levels, including modifications in synaptic function. Induction of long-term potentiation (LTP), a physiological model of certain forms of learning and memory (Bliss and Collingridge 1993), was measured in hippocampal slices from running and control mice. Field recordings showed a significantly greater LTP in the DG of running mice as compared to controls (van Praag et al. 1999b; Vasuta et al. 2007). Recordings from CA1 region in the same mice showed no differences between groups, suggesting that the changes observed in the DG were the direct result of increased neurogenesis (van Praag et al. 1999b). Subsequent studies have shown similarly enhanced

LTP in vivo in anesthetized rats subject to voluntary (Farmer et al. 2004) and forced running (O'Callaghan et al. 2007). Field recordings in vivo showed a significantly enhanced LTP in the DG induced with a weak theta patterned stimulation which did not produce LTP in control subjects, as well as more short-term potentiation in running rats as compared to controls (Farmer et al. 2004).

Thus exercise modifies the synaptic plasticity of the DG likely as a result of the enhanced neurogenesis. Indeed, recordings of individual newborn dentate granule cells in hippocampal slices have shown that they display a low threshold for LTP induction and enhanced LTP compared to mature granule cells (Wang et al. 2000; Schmidt-Hieber et al. 2004; Ge et al. 2007). This enhanced plasticity was observed in a specific time window (1–1.5 months old) of their maturation process and was dependent on transiently increased synaptic expression of NR2B containing N-methyl-D-asparate (NMDA) receptors (Ge et al. 2007). Together, these results support the hypothesis that newborn granule cells have a unique role in synaptic plasticity of the hippocampus and that their contribution can be enhanced with exercise. Indeed, protective effects induced by exercise on hippocampal plasticity have been observed in middle age to old age rodents. The age-related impairment in expression of LTP was reversed in middle age rodents exposed to regular exercise (O'Callaghan et al. 2009), which correlates with improved memory, enhanced hippocampal neurogenesis and increments of BDNF levels in middle-age rodents exposed to long periods of running (O'Callaghan et al. 2009; Marlatt et al. 2012). It should also be noted that in contrast to the enhanced LTP observed in running rodents, long-term depression (LTD), another type of synaptic plasticity (Bear and Abraham 1996), induced by low frequency stimulation was relatively unaffected by exercise. However, the involvement of NR2A containing NMDA receptors was increased by exercise compared to non-runner mice (Vasuta et al. 2007) suggesting that exercise can alter the contribution of NMDA subunits to LTD.

Modifications in synaptic plasticity have also been associated with morphological changes in response to neural activity (Nägerl et al. 2004). In particular, morphological changes in DG have been observed with exercise (Eadie et al. 2005; Redila and Christie 2006; Zhao et al. 2006; Stranahan et al. 2007). Analysis of individual granule cells revealed that exercise significantly increased the total length, complexity, and spine density of granule cell dendrites (Eadie et al. 2005). Upon classification of individual DG cells by their position in the layer, it was shown that exercise enhances dendritic complexity in all the zones of the granule cell layer (subgranular, inner and outer granule cell zones) (Redila and Christie 2006). Moreover, long-term exercise (2 months) induced morphological changes not only in the DG, but also in the entorhinal cortex and CA1 pyramidal cells (Stranahan et al. 2007).

Use of retrovirus-mediated labeling of newborn neurons has made it possible to examine and characterize morphological details of these cells throughout their lifetime (van Praag et al. 2002). Retroviral labeling showed that exercise does not modify spine density of newborn granule cells in young compared to aged runner mice (van Praag et al. 2005). A subsequent detailed study in young mice showed that running increased the motility of the dendritic spines of newborn neurons (21 days postvirus-injection) and accelerated their maturation, as quantified by the presence of mushroom spines (28–52 days postvirus-injection), without

modifying dendritic complexity (Zhao et al. 2006). Thus, exercise modifies the morphology of dentate granule cells and other parameters related to memory function, and may also influence the rate of integration of newborn granule cells into the hippocampal circuitry.

4 Exercise and Neurotrophic Factors (BDNF, FGF-2, NGF, VEGF and IGF)

Several cellular and molecular systems important for maintaining neuronal function and plasticity, such as neurotrophins may be instrumental for positive effects of exercise on the brain. In particular, brain-derived neurotrophic factor (BDNF) is well known to play an important role in the adult brain in synaptic plasticity (Kuipers and Bramham 2006), learning (Yamada and Nabeshima 2003), and neurogenesis (van Praag 2008; Bekinschtein et al. 2011) and is considered to be the most important factor upregulated by physical activity (Cotman et al. 2007). The first study showing exercise-induced increases in neurotrophins in the hippocampus was by Neeper and colleagues (Neeper et al. 1995). Specifically, they described that 2–7 days of running increases the level of BDNF mRNA in specific brain areas, including the hippocampus. Indeed, BDNF gene and protein expression in the hippocampus were elevated as long as the animals were housed with the running wheels (Berchtold et al. 2005). Furthermore BDNF levels remained upregulated for 2 weeks after running wheels were no longer accessible (Berchtold et al. 2010). Many studies have now demonstrated exercise-dependent changes in BDNF expression (see Cotman and Berchtold 2002, Cotman et al. 2007; Vaynman and Gomez-Pinilla 2005).

A detailed analysis of the hippocampal subfields showed that exercise increases BDNF mRNA levels in the DG but not in CA1 (Farmer et al. 2004). Moreover, exercise induced an increment in the DG of synapsin I, a vesicle-associated phosphoprotein that modulates transmitter release as well as the formation and maintenance of presynaptic structures, suggesting that exercise may induce plasticity in a specific hippocampal subfield, the DG (Vaynman et al. 2004a, b). Changes in the levels of BDNF mRNA and protein, NMDA receptor subunit NR2B mRNA, GluR5 and synapsin I, (Farmer et al. 2004; Vaynman et al. 2004a, b; O'Callaghan et al. 2007) may be associated with the enhanced LTP and neurogenesis observed in the DG of running mice (van Praag et al. 1999b; Farmer et al. 2004; O'Callaghan et al. 2007). Indeed, BDNF is proposed to regulate the synaptic transmission and activity-dependent synaptic plasticity by pre- and postsynaptic mechanisms (Poo 2001; Binder and Scharfman 2004; Kuipers and Bramham 2006). Genetic deletion of BDNF in mice showed disruption of normal induction of LTP (Korte et al. 1995), a defect that was rescued with BDNF replacement, either through the BDNF-expressing adenovirus (Korte et al. 1996) or by supplying exogenous BDNF (Patterson et al. 1996). Moreover, blockade of tyrosine receptor kinase B (TrkB), the high-affinity receptor for BDNF, with a specific immune-adhesin chimera (TrkB-IgG; Vaynman et al. 2004b) or a TrkB inhibitor (K252a; Liu et al. 2008) was sufficient to inhibit BDNF actions and its beneficial effects on learning and memory.

Over the past years, the effects of exercise on adult neurogenesis and BDNF levels have been extensively studied (for review see van Praag 2008, 2009). Selective ablation of the gene encoding TrkB in hippocampal neural progenitor cells has been shown to prevent the exercise-induced increase in neurogenesis (Li et al. 2008) and the neurogenesis-dependent

LTP (Bergami et al. 2008). Using BDNF knockdown by RNA interference using lentiviral vectors injected into the DG has also resulted in reduced neurogenesis (Taliaz et al. 2010). Furthermore, intracerebral infusion of BDNF increases neurogenesis in the DG (Scharfman et al. 2005) and mimics exercise-induced changes in learning (Griffin et al. 2009). The effects of exercise on hippocampal neurogenesis, and BDNF levels have been suggested to be mediated by activation of NMDA receptor containing ε1 subunit (Kitamura et al. 2003). BDNF's neurogenic effects are area-specific, since BDNF infusion does not induce neurogenic changes in the subventricular zone (Galvão et al. 2008), consistent with data showing that the neurogenic effect of exercise is limited to the hippocampus (Brown et al. 2003).

The beneficial effects of exercise be may to some extent age-dependent. In a recent study, Titterness and colleagues (Titterness et al. 2011) have shown that 13 days of exercise did not increase BDNF protein levels in the DG of adolescent female and male mice (postnatal 22), which correlated with no differences in LTP induction between sedentary and runner female mice. Interestingly, enhanced LTP was observed in male runner mice suggesting a differential sensitivity to exercise in adolescent female and male mice, possibly due to differences in development. However, in male and female adult and aged mice the effects are generally positive. Five weeks (Wu et al. 2008) and 8 months of forced exercise on a treadmill (O'Callaghan et al. 2009) as well as voluntary exercise (Marlatt et al. 2012) restored reduced BDNF and TrkB levels in the DG of middle-aged mice (Hattiangady et al. 2005; Wu et al. 2008; O'Callaghan et al. 2009). This effect correlates with enhanced neurogenesis and improvement of cognitive function (Wu et al. 2008; O'Callaghan et al. 2009; Marlatt et al. 2012). Effects of exercise on proBDNF levels, important for synaptic plasticity (Ding et al. 2006) remain to be determined.

In addition to BDNF, other neurotrophins, such as fibroblast growth factor 2 (FGF-2) (Gomez-Pinilla et al. 1997) and nerve growth factor (NGF) (Neeper et al. 1996) show a marked upregulation of mRNA in the hippocampus as a result of exercise. However, the increase in these factors is transient and less pronounced than exercise-induced increases in BDNF. In particular, upregulation of FGF-2 mRNA level was found after four nights of running and only observed in the hippocampus (Gomez-Pinilla et al. 1997). Similarly, NGF mRNA increased after the second night of running, mainly in the DG and hilus (Neeper et al. 1996). Furthermore, 8 weeks of treadmill exercise restored NGF mRNA levels in the hippocampus of aged rats (Chae and Kim 2009), as well as long-term forced exercise (8 months) in the DG of middle-aged mice (O'Callaghan et al. 2009). Both FGF-2 and NGF, have been implicated in adult neurogenesis. Using mice genetically deficient in FGF-2 (FGF-2$^{-/-}$ mice), intraventricular application of FGF-2 by viral gene transfer showed increased proliferation of progenitor cells in the DG (Yoshimura et al. 2001). Similarly, intracerebroventricular infusion of FGF-2 has been found enhance the neurogenesis and the dendritic complexity of the newborn granule cells (Rai et al. 2007). In a recent study, it was shown that FGF-2 deficiency in mice (FGF-2$^{-/-}$ mice) does not produce alterations in cell proliferation, but causes defects in neural differentiation in the adult DG. This defect was not rescued by exogenous FGF-2. Neutralization of FGF-2 with an antibody to FGF-2 did not interfere with neurogenesis, suggesting that FGF-2 may operate synergistically in

combination with other mechanisms/growth factors to mediate the maturation of new neurons in the adult DG (Werner et al. 2011).

Other trophic factors that have been shown to be regulated by exercise and influence adult neurogenesis include vascular endothelial growth factor (VEGF) and insulin like growth factor I (IGF-I). Recent evidence indicates that VEGF can act as a neurotrophic factor (Ogunshola et al. 2002) and produces neurogenic effects on progenitor cells (Jin et al. 2002; Cao et al. 2004). Interestingly, it has been shown adult hippocampal neurogenesis occurs near the local microvasculature of hippocampus (Palmer et al. 2000; Fabel et al. 2003). Angiogenic changes associated with exercise have been shown to occur in the hippocampus (Fabel et al. 2003; van Praag et al. 2005; Clark et al. 2009; Van der Borght et al. 2009) that may be mediated by VEGF. Indeed, VEGF is a hypoxia-inducible protein that promotes angiogenesis through receptor tyrosine kinases on endothelial cells (Krum et al. 2002). Fabel and colleagues (Fabel et al. 2003) have shown that blockade of peripheral VEGF inhibits the increase in neurogenesis observed with running. Moreover, it has been shown that 50 days of exercise increases neurogenesis, density of blood vessels in the DG, but not other hippocampal subfields, and enhances performance in the water maze (Clark et al. 2009). Changes in neurogenesis and angiogenesis can be observed as early as 3 days of running (Van der Borght et al. 2009). Changes in cerebral blood volume measured using MRI imaging have been shown to be correlated with enhanced neurogenesis in exercising mice; these changes were specific to the DG. As in mice, exercise increased cerebral blood volume in humans and correlated with cognitive function, suggesting that this measurement may be an indirect measure for levels of neuro-genesis in humans (Pereira et al. 2007). However, it should also be noted that an increase in angiogenesis is not necessarily linked to increased neurogenesis (van Praag et al. 2007).

Vasculature changes associated with exercise in the adult brain are also mediated by IGF-1 (Lopez–Lopez et al. 2004). Exercise enhances IGF-1 levels in the periphery (Trejo et al. 2001) and brain (Carro et al. 2000). At least part of the increase in the brain reflects elevated transport from the periphery across the blood–brain barrier (Reinhardt and Bondy 1994). It has been shown that systemic injection of IGF-1 in sedentary rats mimics the effects of exercise, including enhanced neurogenesis, patterns of neuronal accumulation of IGF-1, c-Fos and BDNF expression in the hippocampus, while subcutaneous infusion of a blocking IGF-1 antibody produces the opposite effects (Carro et al. 2000; Trejo et al. 2001). 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). Because IGF-1 induced-modifications correlated with BDNF levels, it has been suggested that BDNF may be a potential downstream target that mediates some of the protective effects of IGF-1 (Ding et al. 2006). In addition, IGF-1 is able to increase the spontaneous firing in neurons accumulating IGF-1; therefore, peripheral IGF-1 may initiate growth factor cascades in the brain that can alter synaptic plasticity.

5 Exercise and Neurotransmitters

Physical activity influences many neurotransmitter systems in the brain including the glutamatergic (Farmer et al. 2004; Kitamura et al. 2003; Lou et al. 2008; Vasuta et al. 2007),

GABAergic (Molteni et al. 2002), endocannabinoid (Hill et al. 2010), opioidergic (Sforzo et al. 1986), and monoaminergic systems (Chaouloff 1989). One of the main components of the glutamatergic system that has been linked to neurogenesis and synaptic plasticity is the NMDA receptor. The expression of the NR2A and NR2B subunits of this receptor were found to be significantly increased after physical activity (Farmer et al. 2004; Kitamura et al. 2003; Lou et al. 2008; Vasuta et al. 2007). However, genes related to the gamma-aminobutyric acid (GABA) (GABA$_A$ receptor, glutamate decarboxylase GAD65) system were downregulated after physical activity (Molteni et al. 2002). Knowledge of the role of the AMPA receptor in exercise induced plasticity is limited, though a recent study revealed exercise-induced changes to the AMPA receptor subunits, GluR1 and GluR2/3 (Real et al. 2010).

The psychological changes associated with prolonged physical activity are often described as a `runner's high'. Exercise induced changes in psychological functions are frequently reported to being as a direct consequence of alterations in the endogenous opioid system (Schwarz and Kindermann 1992). More recently, an alternative hypothesis to explain this phenomenon was proposed, showing that exercise increases blood concentrations of endogenous endocannabinoids (Heyman et al. 2012). Voluntary wheel running increased the agonist binding site density of the cannabinoid CB(1) receptor, CB(1) receptor-mediated GTPgammaS binding, and the levels of anandamide in the hippocampus (Hill et al. 2010). These alterations were required for the exercise-induced increase in progenitor cell proliferation in the hippocampus (Hill et al. 2010), and may play a role in the well-documented antidepressant effects of exercise (for review see Ota and Duman 2012). Indeed, the changes in monoamines with exercise are of particular interest as physical activity has been shown to lead to recovery from depression (Lawlor and Hopker 2001). The antidepressant effect of exercise for mild depression in humans (Ernst et al. 2006) has been shown to be just as potent as that of serotonergic medications (Babyak et al. 2000). Therefore, it is of interest that serotonergic agonists, including antidepressants such as fluoxetine (Encinas et al. 2006; Malberg et al. 2000), have been suggested to enhance cell genesis, whereas administration of the serotonin 5-HT (1A) receptor antagonists, decreases cell proliferation in the DG (Radley and Jacobs 2002).

In a recent study, we aimed to evaluate to what extent the effects of antidepressants on neurogenesis are comparable to those of voluntary wheel running. Specifically, neurogenesis was evaluated in 2-month-old female C57Bl/6 mice after 28 days of treatment with either fluoxetine, a selective serotonin reuptake inhibitor which has been shown to enhance neurogenesis (Santarelli et al. 2003), duloxetine, a dual serotoninergic-noradrenergic reuptake inhibitor, or exercise. Interestingly, only exercise enhanced (by 200 %) the BrdU positive cell survival. In addition, only fluoxetine and exercise resulted in a phenotype shift with a greater percentage of BrdU-positive cells becoming new neurons (Fig. 3). Thus, the neurogenic response to exercise is much stronger than to antidepressants, and it is not very likely that anxiolytic effects of these drugs are mediated by adult neurogenesis (Marlatt et al. 2010). Recent research by others supports our findings in this regard (Hanson et al. 2011).

6 Endurance Factors

Another logical approach toward identifying pharmacological ways to enhance neurogenesis is the investigation into whether skeletal muscle activation as a result of exercise or pharmacological agents underlies neurogenic and cognitive effects of aerobic activity. Indeed, much research pertaining to the effects of exercise on brain function has focused on cellular, structural, and biochemical changes in the brain without much consideration for the peripheral factors that may elicit changes in synaptic plasticity, angiogenesis, neurogenesis, and cognition (Cotman et al. 2007; Gomez-Pinilla et al. 2008; Hillman et al. 2008; van Praag 2008). Physical activity has also shown effects on neurotropic factors in mammalian skeletal muscle (for review see Sakuma and Yamaguchi 2011), an abundant source of neurotrophins (Chevrel et al. 2006). Increased BDNF levels and BDNF mRNA expression in the peripheral system have been described following exercise (Gomez-Pinilla et al. 2002; Allard et al. 2004; Ferris et al. 2007). These increments may play a role in enhancing glucose metabolism and may act as a myokine, producing neurotrophic effects in the brain (Sakuma and Yamaguchi 2011). Indeed, the possibility that skeletal muscle activation as a result of exercise or pharmacological agents underlies cognitive effects of aerobic activity has just begun to be explored.

Recently, transcriptional factors regulating muscle fiber contractile and metabolic genes have been identified (Wang et al. 2004) and led to the identification of compounds that can increase the ability of cells to burn fat and enhance exercise endurance (Narkar et al. 2008). The peroxisome proliferator activated receptor delta (PPARδ) is a transcription factor that regulates fast-twitch muscle fiber contraction and metabolism. Overexpression of this factor increased oxidative muscle fiber number. In addition, administration of the selective agonist GW501516 increased exercise stamina when combined with training (Narkar et al. 2008). PPARδ is controlled by AMP-activated protein kinase (AMPK), a master metabolic regulator important for glucose homeostasis, appetite, and exercise physiology (Hardie 2004). Treatment with AMPK agonist AICAR enhanced running endurance by 45 % in sedentary mice (Narkar et al. 2008).

We investigated the effects of endurance factors, PPARδ agonist GW501516 and AICAR, activator of AMPK on memory and neurogenesis. Specifically, mice were injected with GW or AICAR for 7 days and concurrently with BrdU to label dividing cells. Both AICAR and GW improved retention of spatial memory in the Morris water maze. Moreover, AICAR significantly and GW modestly elevated DG neurogenesis. Thus, pharmacological activation of skeletal muscle may mediate cognitive effects of aerobic exercise (Kobilo et al. 2011b) and provide a possible therapeutic approach for conditions in which exercise is limited. Interestingly, although these compounds mimic some of the results of exercise their effects are not identical to physical activity itself. Prolonged administration of AICAR (14 days) no longer enhances spatial memory function or neurogenesis (Kobilo et al. 2011b). Similarly, short-term AICAR treatment promoted sirtuin 1 protein expression in skeletal muscle whereas 14 days of treatment did not (Suwa et al. 2011).

7 Conclusions

While previous studies suggested that both EE and exercise increase adult neurogenesis, recent research has shown only exercise enhances the production of new DG neurons. The positive effects of exercise are likely the result of a combination of factors including, but not limited to enhanced neurogenesis, modifications in synaptic plasticity, spine density, neurotrophins, and angiogenesis that may mediate the beneficial effects on learning and memory, reduction of the risk of neurodegenerative diseases and delay age-related cognitive decline. Within the hippocampus, the most pronounced changes with physical activity are in the DG subfield, with an increased production of new neurons and BDNF levels, which are associated with improved performance on tasks presumably mediated by the DG. Furthermore, running, but not antidepressants that block serotonergic or noradrenergic reuptake, triggers the production of new neurons in the DG. However, we also suggest that caution should be used when applying exercise to conditions of brain injury and neurodegenerative disease as the consequences could be detrimental as found in a mouse model of Huntington's disease. While further research is needed to understand the cellular mechanisms underlying effects of aerobic activity on the brain, exercise is a powerful lifestyle intervention that could be used to augment and maintain cognitive function throughout the lifespan.

Acknowledgments

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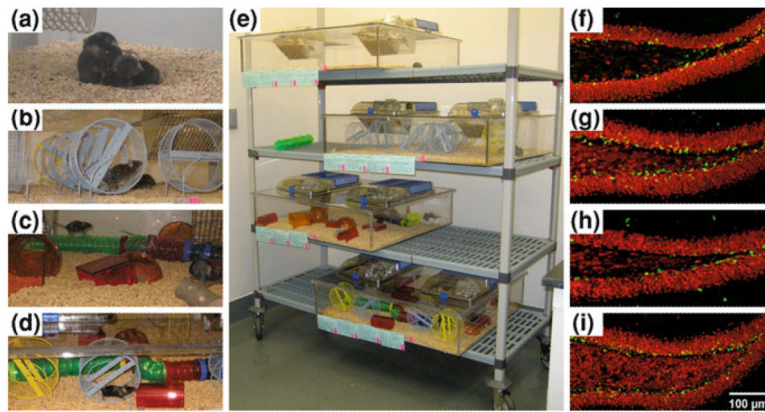
Fig. 1.

Exercise but not enrichment increases DG neurogenesis. Female C57Bl/6 mice ($n = 10$ per group) were housed in large cages (30"×33"×8") as follows: **a** Control (CON). **b** Running (RUN). **c** Enriched environment only (EEO). **d** Enrichment and running (EER), this cage contained enrichment objects similar to (**c**), as well as 10 running wheels. **e** Overview of the experimental cages. (**f**–**g**) Confocal images of BrdU-positive cells in the dentate gyrus in sections derived from mice housed in (**f**) CON, (**g**) RUN, (**h**) EEO, or (**i**) EER conditions. Sections were immunofluorescent double-labeled for BrdU (*green*) and NeuN (*red*) indicating neuronal phenotype (Kobilo et al. 2011a)
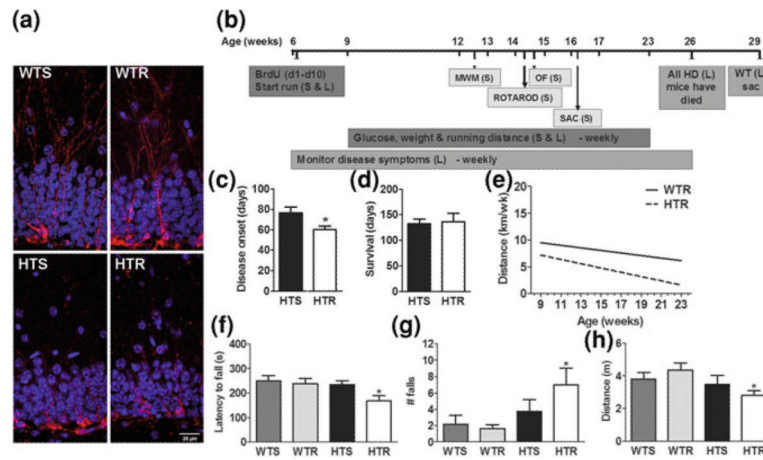
Fig. 2.
Exercise is not beneficial in a mouse model of Huntington's disease (HD) N171-82Q. a
Morphology of Doublecortin (DCX) expressing immature neurons in the DG of WT and HD
mice. Dendritic branching complexity of DCX-labeled (*red*) immature neurons was reduced
in the transgenic mice, HD sedentary (HTS) and HD runner (HTR) compared to Wildtype
sedentary (WTS) and Wildtype runner (WTR). Granular cell layer neurons were labeled
with DAPI (*blue*). **b** Timeline of experiment in weeks of age for the subset of mice tested for
behavior (S) and mice evaluated over their lifespan (L) mice. BrdU was injected over the
first 10 days of the study. Behavioral testing was carried out from week 12 to 15 and mice
(S) were sacrificed (SAC) at approximately 16 weeks of age. Survival analysis indicated that
HD mice died between 11 and 26 weeks of age. **c** Onset of disease symptoms such as
hunched back, poor grooming and involuntary shaking occurred earlier in HD runners; *
$p<0.03$. **d** Lifespan did not change as a result of exercise. **e** There was no significant
difference between the groups in running distance over the duration of the experiment. (**f**–**g**)
Exercise may exacerbate locomotor deficits in HD mice. (**f**) The latency to fall off an
accelerating rotarod was shorter in HTR mice than in all other groups; * $p<0.03$. **g** The total
number of falls from the rotarod over 5 min was increased in HD runners compared to WT
mice; * $p<0.02$, HTR versus WTS and WTR. **h** The total distance traveled over 30 min in an
open field was reduced in HD mice compared to WT mice, specifically in HTR mice
compared to WTR mice; * $p<0.03$. Abbreviations: *MWM* Morris water maze; *OF* Open
field; *S* Subset tested for behavior; *L* Lifespan group; *SAC* sacrificed (Potter et al. 2010)

Fig. 3.
Running but not antidepressants enhances neurogenesis. Photomicrographs of the dentate gyrus in sections derived from mice injected with saline, duloxetine 6 mg/kg, fluoxetine 18 mg/kg, or housed with a running wheel for 28 days. BrdU labeled cells (*green*) and cells labeled with the neuronal marker NeuN (*red*). Co-labeling analysis indicated that running mice had more than 2-fold increase in the number of new neurons compared to all the other groups (Marlatt et al. 2010)