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Environmental Enrichment and Voluntary Exercise Massively Increase Neurogenesis in the Adult Hippocampus via Dissociable Pathways

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ABSTRACT: Environmental enrichment (EE) and voluntary exercise (VEx) have consistently been shown to increase adult hippocampal neurogenesis and improve spatial learning ability. Although it appears that these two manipulations are equivalent in this regard, evidence exists that EE and VEx affect different phases of the neurogenic process in distinct ways. We review the data suggesting that EE increases the likelihood of survival of new cells, whereas VEx increases the level of proliferation of progenitor cells. We then outline the factors that may mediate these relationships. Finally, we provide a model showing that VEx leads to the convergence of key somatic and cerebral factors in the dentate gyrus (DG) to induce cell proliferation. Although insufficient evidence exists to provide a similar model for EE, we suggest that EE-induced cell survival in the DG involves cortical restructuring as a means of promoting survival. We conclude that EE and VEx lead to an increase in overall hippocampal neurogenesis via dissociable pathways, and should therefore, be considered distinct interventions with regard to hippocampal plasticity and associated behaviors. © 2006 Wiley-Liss, Inc.

KEY WORDS: neurogenesis; environmental enrichment; exercise

INTRODUCTION

The hippocampus is a dynamic brain structure critical to the process of memory consolidation (Scoville and Milner, 1957; Frankland and Bontempi, 2005). One of its unusual features is that the dentate gyrus (DG) subfield is known to constitutively engage in the process of neurogenesis throughout adulthood. Ultimately these new cells appear to be functionally integrated into the existing neuronal network (van Praag et al., 2002; Overstreet et al., 2004; Schmidt-Hieber et al., 2004). Interestingly, this process is not static, and behavioral manipulations such as housing an animal in an enriched environment (EE), or allowing them to engage in voluntary exercise (VEx) on a running wheel, can increase the rate of hippocampal neurogenesis.

Early studies noted that animals raised in an EE performed better on hippocampal dependent tasks than age-matched cohorts that were raised in standard caging conditions (Hebb, 1949; Paylor et al., 1992). Subsequently, it was shown that EE produced an overall increase in the amount of neurogenesis, which could be observed in both rats and mice (Paylor et al., 1992; Kempermann et al., 1997; Pham et al., 1999; van Praag et al., 1999a,b; Auvergne et al., 2002; Frick and Fernandez, 2003; Cao et al., 2004; Bruel-Jungerman et al., 2005). In a series of experiments, van Praag and colleagues (1999a) found that when the individual components of EE were separated, only one component, the exercise wheel, continued to be associated with enhanced neurogenesis. Animals that were housed in cages that also contained a running wheel were observed to engage in prodigious amounts of VEx, running upwards of 4 km a night. These animals also showed almost a 3-fold increase in neurogenesis, as well as increased performance in the Morris watermaze (van Praag et al., 1999b). During these studies it became evident that EE and VEx appeared to increase neurogenesis differently. VEx increased both cell proliferation and neurogenesis, while EE only appeared to increase neurogenesis without affecting cell proliferation (Fig. 1). In this review we will explore how EE and VEx might differentially affect mechanisms that are involved in distinct phases in the overall process of neurogenesis, and these changes are summarized in Figure 2.

CORTICAL REORGANIZATION WITH VEx AND EE

Both VEx and EE produce a number of changes in the cortex. Rearing mice in an EE expedites the development of the visual cortex (Cancedda et al., 2004; Sale et al., 2004), as well as the auditory (Dinse, 2004; Engineer et al., 2004), olfactory (Hennessy et al., 1977), and even tactile systems (Xerri et al., 1996; Coq and Xerri, 1998). EE can also enhance the performance of animals on several different learning and memory tasks that involve hippocampal functioning (Krech et al., 1962; Pacteau et al., 1989; Wainwright et al., 1993; Rosenzweig and Bennett, 1996; Kempermann et al., 1998; Schrijver et al., 2004). In addition to this cognitive enhancement, EE is correlated with the restructuring of a number of nonsensory regions of the brain, including the association cortices and the hippocampus (Diamond et al., 1972, 1976; Berman et al., 1996; Faherty et al., 2003; Turner et al., 2003). It seems plausible, then, that EE might promote cell survival by way of these mechanisms that are already engaged in this cortical reorganization. In other words, increased cell survival might

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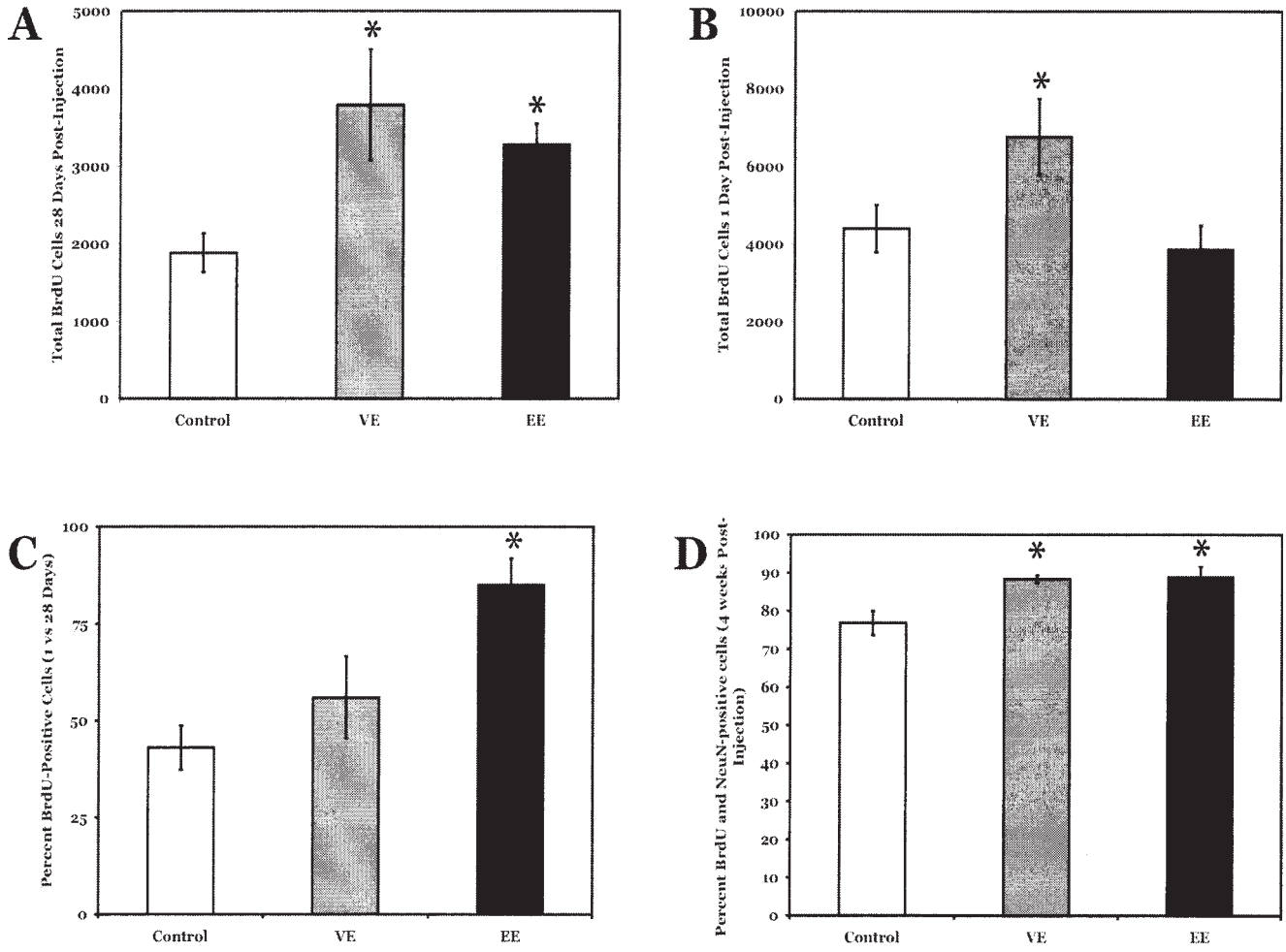

FIGURE 1. Voluntary exercise leads to an increase in overall neurogenesis by increasing cellular proliferation, whereas environmental enrichment does so by decreasing the normal loss of cells between 24 h and 4 weeks in cellular development. (A) Both manipulations lead to a massive increase in the number of BrdU-positive cells at 28 days post-BrdU injection. (B) Voluntary exercise leads to increase in the number of BrdU-positive cells 24 h post-BrdU injection and environmental enrichment (EE) leads to no change at this time point. (C) The percentage of BrdU-positive cells remaining at 4 weeks. (D) Both manipulations lead to a comparable increase in neuronal differentiation.

be a by-product of these intrinsic changes ongoing in already established neurons.

Few studies have directly investigated the relationship between cortical reorganization and VEx. VEx has been shown to increase the thickness of specific subregions in the motor cortex (Anderson et al., 2002), indicating that some cortical restructuring does occur following exercise. Additionally, access to a running wheel increased the metabolic capacity within the motor cortex (McCloskey et al., 2001). These studies indicate that VEx might induce some cortical restructuring; however, this area needs to be further investigated to draw any specific conclusions.

EE has been shown to increase both the density of dendritic spines and basal synaptic strength (Green and Greenough, 1986; Berman et al., 1996; Foster et al., 1996). It is therefore not surprising that this manipulation also increases the expression of two proteins found at a mature synapse: synaptophysin and Postsynptic-Density-95 (PSD-95; also known as SAP-90). Synaptophysin is a synaptic vesicle glycoprotein that has been used by several groups to mark presynaptic growth. In a recent study, young female C57Bl/6 mice exposed to an EE for 3 h/day for 6 weeks had significantly higher levels of synaptophysin in the hippocampus (Lambert et al., 2005); others have also reported similar findings (Frick and Fernandez, 2003; Nithianantharajah et al., 2004). PSD-95 is a major component of mature dendritic spines that is involved in the clustering of synaptic proteins and channels involved in synaptic plasticity, (i.e., N-methyl-D-aspartate (NMDA) receptors), and shows increased expression in the hippocampus following EE (Nithianantharajah et al., 2004). This increase in the levels of synaptophysin and PSD-95 in response to enrichment may reflect alterations in existing dendritic spines that may also contribute to the beneficial effects of enrichment on synaptic plasticity and learning and memory.

VEx has also been recently shown to increase spine density (Eadie et al., 2005), which suggests that key synaptic molecules

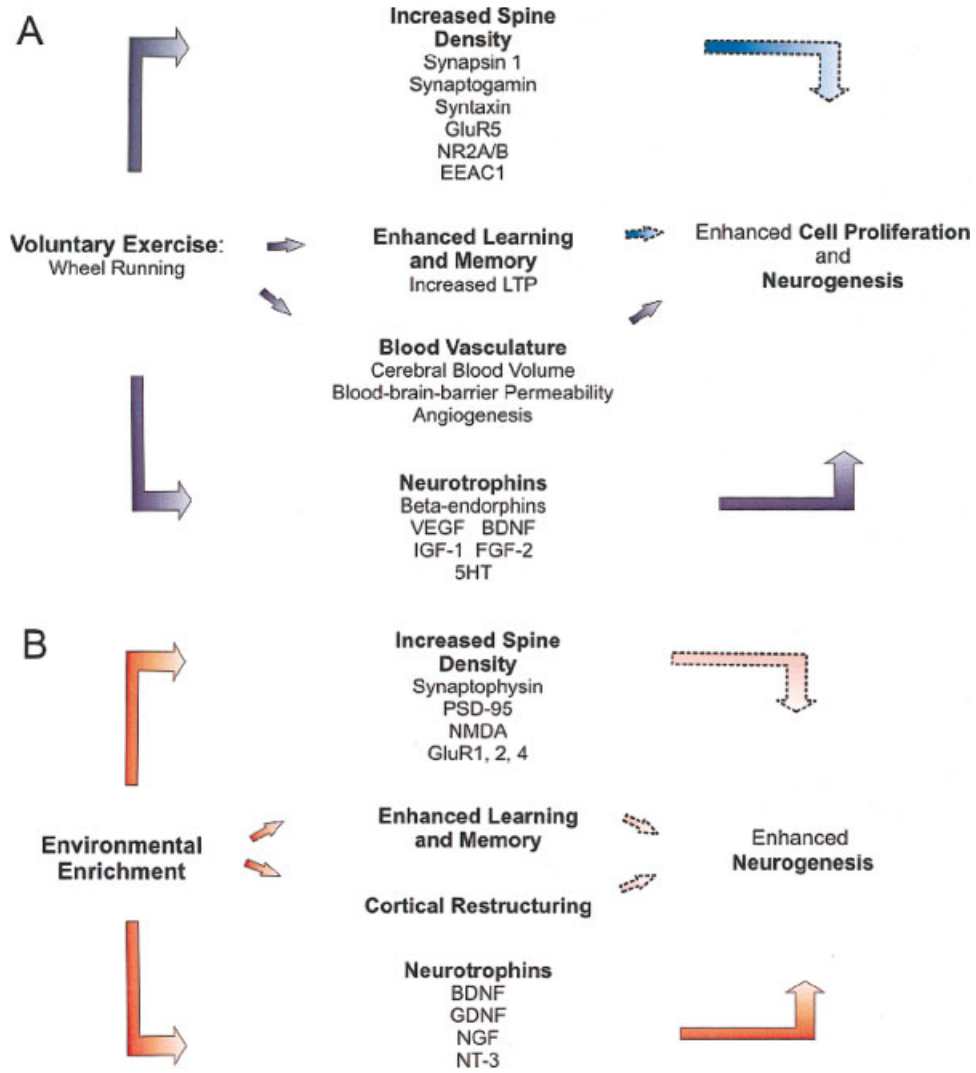

FIGURE 2. Summary of changes induced by voluntary exercise and environmental enrichment. A. Voluntary exercise (VEx) affects dendritic spine density, the expression of synaptic proteins, receptors, and neurotrophins, induces vascular changes, and alters learning and memory. The changes, in turn, have either been shown to increase cell proliferation and neurogenesis or it is proposed that a relationship might exist. B. Environmental enrichment (EE) affects dendritic spine density, synaptic proteins, receptors, cortical reorganization, learning and memory, and the expression of neurotrophins. These EE-induced changes have either been shown to increase neurogenesis or it is proposed that a relationship exists. Solid arrows indicate a direct relationship while dashed and lighter arrows indicate hypothesized relationships. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

are altered following this behavioral manipulation. Indeed several genes important for synaptic plasticity have been found to be altered following both acute and chronic VEx (Molteni et al., 2002). A number of presynaptic vesicle trafficking proteins were increased, including synapsin 1, synaptotagmin, and syntaxin. Despite these changes, alterations in presynaptic transmitter release have not been reported following VEx (van Praag et al., 1999b, Farmer et al., 2004). Postsynaptic modifications clearly exist that could affect synaptic communication as well. For example, the mRNA for GluR5, NR2A, NR2B, and excitatory amino acid carrier 1 (EAAC1) have all been shown to be increased following VEx, whereas mRNAs associated with synaptic inhibition, such as GABAA and GAD65, have been shown to be downregulated (Farmer et al., 2004; Molteni et al., 2002). Although these structural changes might enhance synaptic plasticity by upregulating the proteins important for long-term potentiation (LTP), the effects on neurogenesis might be related to an overall increase in excitability that could result from such changes. Indeed, there is evidence for changes in both synaptic plasticity and electrical activity with exercise.

CHANGES IN SYNAPTIC PLASTICITY

Long lasting changes in the ability of the cells to communicate with one another were first shown in the DG (Bliss and Gardner-Medwin, 1971, 1973). LTP is an increase in the communication between cells following electrical stimulation, while long-

term depression (LTD) is a decrease in communication between cells. Both LTP and LTD appear to be dependent upon the activity of NMDA receptors in the DG (Christie and Abraham, 1992), and it has been suggested that NR2A subunits may be necessary for LTP whereas NR2B subunits may be necessary for LTD (Christie and Abraham, 1992; Liu et al., 2004). VEx is associated with increased LTP in the DG, as well as enhanced performance on a hippocampal-dependent learning and memory tasks (van Praag et al., 1999a); these findings have also been replicated since the initial report (Brown et al., 2003; Fabel et al., 2003; Kitamura et al., 2003; Rhodes et al., 2003; Crews et al., 2004; Farmer et al., 2004; Holmes et al., 2004; Bjornebekk et al., 2005; Naylor et al., 2005). VEx can also lead to an increase in NMDA NR2B subunit mRNA in the DG (Farmer et al., 2004). Interestingly, transgenic mice that overexpress NR2B subunits also show enhanced LTP and increased performance on learning and memory tasks (Tang et al., 2001). These studies are seemingly incongruent with the notion that NR2B subunits preferentially contribute to LTD, but synaptic alterations to and changes in dendritic structures that result from VEx might account for the enhanced LTP and learning following Vex, despite an increase in the number of NR2B subunits.

It also appears that VEx can also act as a therapeutic intervention for some of the deficits associated with disorders such as fetal alcohol syndrome and alcohol withdrawal (Crews et al., 2004; Christie et al., 2005). Normally, prenatal ethanol exposure induces neuronal loss, decreased LTP and impaired learning on hippocampal dependent tasks. These deficits can be largely ameliorated in the hippocampus if these animals are allowed exposure to a running wheel early in life (Christie et al., 2005). Interestingly, VEx can even ameliorate the detrimental effects of ethanol consumption on cell proliferation (Nixon and Crews, 2002). Although ethanol can act as an NMDA antagonist (Yang et al., 1996; Steffensen et al., 2000; Ariwodola et al., 2003), other reports have also indicated that NMDA antagonists can increase cell proliferation and neurogenesis (Cameron et al., 1995). One possible explanation for these opposing results might be that transient NMDA receptor blockade leads to a subsequent increase in excitatory activity (Krystal et al., 2003), while chronic ethanol consumption leads to a general increase in inhibition. It remains to be determined whether EE, following prenatal ethanol exposure, can provide these same benefits in animals.

In contrast to Vex, EE is not associated with increased LTP in the DG; rather EE exposure actually reverses already established LTP (Abraham et al., 2002). The reason for this reversal is not clear, as an increase in the expression of number of molecules that are associated with LTP has been reported following EE (Tang et al., 2001). Among these changes are increases in particular AMPA receptor subunits, including the number of GluR1, GluR2, and GluR4 subunits (Tang et al., 2001; Naka et al., 2005) and the sensitivity of these subunits (Gagne et al., 1998). Interestingly, mice that overexpress the NR2B subunit of the NMDA receptor show an increase in the expression of NR2A and NR2B subunits following EE, similar to that seen in control animals (Tang et al., 2001). Therefore, the relationship between EE and LTP still needs to be further elucidated.

ELECTRICAL ACTIVITY

There is some evidence that different forms of electrical activity might play a role in neurogenesis, and this may serve as a common ground for both Vex- and EE-induced changes in neurogenesis. When animals engage in voluntary movements or sensory exploration, the hippocampal EEG is predominantly composed of rhythmic oscillatory activity in the form of theta wave activity (2 and 12 Hz) (Bland and Oddie, 1998). On the other hand, sensory information reaches the hippocampus via the thalamocortical system in the form of alpha wave activity (8–15 Hz) (Schurmann et al., 2000). It is likely that the relative strength or nature of this input signal to the hippocampus is enhanced in response to EE, a view which has been supported by studies showing an increase in basal synaptic strength in the molecular layer of the DG following EE (Green and Greenough, 1986; Foster et al., 1996).

Although few studies have systematically studied the effect of electrical activity on adult hippocampal neurogenesis, it has become clear that this relationship is important. The induction of LTP at mossy fibers, a condition that would antidromically activate the DG, enhances neurogenesis in the DG (Derrick et al., 2000). Recently, hippocampal neuroprogenitor cells were also shown to proliferate following excitatory activity (Deisseroth et al., 2004). Indeed, acute increases in excitatory input induced by ischemia or seizure activity can also induce proliferation in the DG in vivo (Liu et al., 1998; Parent et al., 1997, 1998; Gould et al., 2000; Arvidsson et al., 2001) while disrupting excitatory input to the hippocampus decreases cell survival (Van der Borght et al., 2005). Again the finding that the NMDA receptor also induces proliferation in the DG (Cameron et al., 1995) seems to contradict this notion and it needs to be clarified if the application of NMDA antagonists in vivo can lead to increased excitatory activity by disinhibiting local circuits (Krystal et al., 2003). Any alterations in excitability might also be indirect. NMDA antagonists reduce the power of theta activity in the hippocampus directly (Leung and Shen, 2004); however, this may be followed by some sort of rebound excitation when the effects of the antagonists wear off. Excitotoxic lesions of the entorhinal cortex (EC) induce proliferation in the hippocampus (Cameron et al., 1995); however, this likely reflects the effects of the seizure activity induced by the lesion. In a similar study, deafferentation of the EC to the hippocampus was shown to increase mRNA for vascular endothelial growth factor (VEGF), a potent neurotrophic factor (Wang et al., 2005). Thus the effects of electrical activity on hippocampal neurogenesis may be either direct (activation of glutamate receptors) or indirect (increases in neurotrophic factors).

CHANGES IN THE VASCULATURE

One of the more obvious differences between VEx and EE is that the activity level of animals in the VEx condition is much higher than that in the EE condition. While animals may

engage in some exploratory behavior whenever new objects are introduced to the EE, animals in cages with wheels spend an incredible amount of time running and, on average, can run approximately 4.8 km/day (Farmer et al., 2004). Because of this vigorous physical activity, one might expect that VEx (rather than EE) would be more likely to increase blood flow through the vasculature of the brain. This is indeed the case. Motor activity is associated with an increase in cerebral blood volume (Swain et al., 2003), cerebral blood flow (Yancey and Overton, 1993), blood-brain-barrier (BBB) permeability (Sharma et al., 1991), angiogenesis (Black et al., 1989, 1990; Isaacs et al., 1992; Kleim et al., 2002; Swain et al., 2003), and glucose utilization (Vissing et al., 1996). Motor activity is also accompanied by substantial increases in circulating hormone and growth factor levels. Because of increased circulation, factors that may promote mitotic activity and cell survival might more readily be delivered to the hippocampus, which may account for why VEx has such a robust effect on cell proliferation in the DG.

To our knowledge, not a single study exists that demonstrates EE-induced alterations to the cerebrovascular system (blood flow, angiogenesis or BBB permeability). In fact, one study has actually reported that EE does not affect the reductions in cerebral blood flow that normally occur with age (Goldman et al., 1987). Therefore, no specific conclusions can be drawn as to the contribution of EE to changes in vascular activity, leaving this an interesting area for future studies.

MOLECULAR EFFECTS OF VEx AND EE

Perhaps most pertinent to our discussion of neurogenesis are alterations in the expression of trophic factors, which are powerful promoters of neuronal survival and differentiation during development (Barde, 1994). EE increases the expression of several different neurotrophic factors that have been implicated in cell proliferation and neuronal differentiation and survival. The levels of brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), neuronal growth factor (NGF), neurotrophin-3 (NT-3) and many of their corresponding receptors increase in the hippocampus following EE (Torasdotter et al., 1996, 1998; Pham et al., 1999; Young et al., 1999; Ickes et al., 2000; Gobbo and O'Mara, 2004). Like EE, VEx can increase levels of BDNF, (Adlard et al., 2004; Farmer et al., 2004; Vaynman et al., 2004a) and the amount of BDNF expression is directly related to the amount of VEx in which an animal engages in (Adlard et al., 2004). Additionally, the observed increase in cerebral blood flow, angiogenesis and BBB permeability may be important in shuttling key circulating factors to neuronal circuits, which Palmer has called "somatic regulators" (Fabel et al., 2003). These factors include VEGF, insulin-like growth factor 1 (IGF-1) and fibroblast growth factor 2 (FGF-2). Importantly, all of these somatic regulators have been reported to be increased in circulation following exercise (Schwarz et al., 1996; Asano et al., 1998; Schobersberger et al., 2000; Trejo et al., 2001; Campuzano et al., 2002) and stimulate hippocampal neurogenesis in the absence of VEx (Aberg et al., 2000; Jin et al., 2002). The following is a review of the contribution of each trophic factor to cell proliferation and or cell survival.

β-ENDORPHINS

Exercise has long been known to increase β-endorphins in humans, and in fact β-endorphins are a candidate mechanism to explain why people become "addicted" to running (Appenzeller, 1981; Colt et al., 1981; Gambert et al., 1981; Farrell et al., 1982). β-endorphins are created when the pre-pro-hormone proopiomelanocortin (POMC) undergoes cleavage to give way to a number of hormones including the melanocortins and the opiate peptides (Hadley and Haskell-Luevano, 1999). When β-endorphins bind to their receptors in neural membranes, cAMP levels in the neurons are reduced, and the conductance of voltage-gated Ca^{2+} channels is decreased (Hadley and Haskell-Luevano, 1999). Recent studies have shown that an increase in cell proliferation can be produced by the direct infusion of opiates, and that opiate receptor antagonists decrease cell proliferation in the DG (Persson et al., 2003a,b). Furthermore, when the transcriptional control of enhanced green fluorescent protein (eGFP) is linked to POMC genomic sequences, eGFP is expressed in only new cells in the DG (Overstreet et al., 2004). Additionally, VEx was shown to increase the number of EGFP-labeled cells in this particular study (Overstreet et al., 2004). Together these results implicate POMC, and possibly β-endorphins, in the genesis of new neurons in the DG of adult animals.

VASCULAR ENDOTHELIAL GROWTH FACTOR

VEGF is an angiogenic protein with both neurotrophic and neuroprotective effects and has been shown to increase when humans exercise (Schobersberger et al., 2000). Normally VEGF promotes the proliferation of vascular endothelial cells, but it has also been shown to stimulate neuronal precursors in murine cerebral cortical cultures and in vivo in the adult rat brain (Jin et al., 2002). The effects were primarily to increase cell proliferation, and no alterations in cell survival were observed (Jin et al., 2002). Additionally, when VEGF is secreted from the blood, it can stimulate the formation of new blood vessels (Senger et al., 1983; Leung et al., 1989; Holmes and Zachary, 2005). Therefore, VEGF seems like an ideal trophic factor to induce the changes in angiogenesis and cellular proliferation that occur with VEx.

BRAIN-DERIVED NEUROTROPHIC FACTOR

BDNF is a member of the neurotrophin family—the same family that includes nerve growth factor and neurotrophins 3 and 4 (Barde, 1989). BDNF plays a critical role in the brain

throughout development and adulthood by promoting neuronal survival and regeneration (Thoenen, 1991; Wozniak, 1993; Vanhoutte and Bading, 2003; Horch, 2004).

Many studies have demonstrated that exercise leads to increased levels of BDNF mRNA or protein (Neeper et al., 1996; Russo-Neustadt et al., 1999; Widenfalk et al., 1999; Berchtold et al., 2001, 2002; Cotman and Berchtold, 2002). Interestingly, VEx increases BDNF expression in the CNS (Gomez-Pinilla et al., 2002; Farmer et al., 2004; Vaynman et al., 2004b), but not in skeletal muscle (Widegren et al., 2000), indicating that BDNF may play a significant role specifically in the brain. Indeed, injecting BDNF directly into the hippocampus of rats can enhance proliferation and neurogenesis in the subgranular zone of the DG (Scharfman et al., 2005). A recent study of mice genetically engineered to exhibit decreased levels of BDNF suggest that BDNF is necessary for the long term survival of new neurons in the DG, as these mice had fewer BrdU labeled cells 3 weeks after the initial BrdU injection (Sairanen et al., 2005). Lowenstein and Arsenault (1996) have shown that application of BDNF (and FGF-2—discussed later) onto microdissected dentate granule cells increases their survival and neuronal differentiation by 30–80% (Lowenstein and Arsenault, 1996). Application of BDNF and NGF to cultured hippocampal neurons has also shown to be protective against hypoglycemic damage (Kokaia et al., 1994; Mitchell et al., 1999), ischemia (Ferrer et al., 1998; Mitchell et al., 1999), and ethanol (Mitchell et al., 1999). Further, BDNF knockout mice show an increase in apoptosis specifically in the DG and subventricular zone (Linnarsson et al., 2000)—the two regions that have consistently been shown to exhibit adult neurogenic activity. Taken together, these data suggest that VEx might be an effective method for increasing BDNF, which, in turn, can enhance the survival of newborn cells in the hippocampus.

INSULIN-LIKE GROWTH FACTOR 1 AND FIBROBLAST GROWTH FACTOR 2

Trejo et al. (2001) have shown that IGF-1 is critical to exercise-induced increases in adult hippocampal neurogenesis by blocking the entrance of circulating IGF-1 into the brain and, in turn, completely inhibiting exercise-induced neurogenesis. Similarly, Fabel et al. (2003) have shown that VEGF is also critical for this effect. Using an adenoviral vector system to produce high levels of circulating VEGF antagonist, which does not cross the BBB, these authors also blocked exercise-induced increase in adult hippocampal neurogenesis. A similar study has not yet been conducted for FGF-2. However, FGF-2 can affect proliferation as it has been found that maximal cell proliferation is produced with coapplication of IGF-1 and FGF-2 (Aberg et al., 2003). Additionally, FGF-2 mRNA is upregulated in the hippocampus following exercise (Gomez-Pinilla et al., 1997). Therefore, circulating IGF-1 and VEGF need to cross the BBB so as to affect neurogenesis, and appear to be necessary for exercise-induced neurogenesis while exercise-induced upregulation of FGF-2 mRNA might complement the effect of IGF-1 on cell proliferation.

GLIAL-DERIVED NEUROTROPHIC FACTOR, NERVE GROWTH FACTOR, AND NEUROTROPHIN-3

EE increases the expression of GDNF, NGF, and neurotrophin-3 (NT-3) (Torasdotter et al., 1998; Young et al., 1999; Ickes et al., 2000). In relation to neurogenesis, GDNF appears to increase proliferation and differentiation (Chen et al., 2005), while NT-3 enhances neurite outgrowth and branching (Morfini et al., 1994), and promotes cell survival (Bertollini et al., 1997; Vicario-Abejon et al., 1995).VEx, however, has been shown to actually decrease the expression of NT-3 (Johnson and Mitchell, 2003) while it has been shown to increase the expression of NGF (Neeper et al., 1996). The relationship between GDNF and exercise, however, needs to be further elucidated. Taken together, these studies suggest that GDNF and NT-3 might account for enhanced neurogenesis following EE as these trophic factors appear to be more instrumental with survival instead of proliferation.

SEROTONIN (5HT)

Although not generally considered a neurotrophic factor, 5HT also appears to act like a trophic factor in some instances. Alterations in the levels of 5HT seem to have a direct relationship with neurogenesis, with increasing levels of 5HT associated with enhanced neurogenesis, and decreased 5HT levels with reduced neurogenesis (Brezun and Daszuta, 2000). The manner in which these alterations might occur as a result of VEx is quite interesting. VEx can elevate the levels of tryptophan hydroxylase (the enzyme involved in the rate limiting step for the synthesis of 5HT) in the raphe nucleus (Davis and Bailey, 1997; Lim et al., 2001; Min et al., 2003). Projections to the hippocampus from the raphe nucleus, which is densely populated with serotonergic cells (Jacobs and Azmitia, 1992; Vertes and Crane, 1997), can influence hippocampal activity (Nitz and McNaughton, 1999; Viana Di Prisco et al., 2002). VEx does not specifically increase the levels of 5HT in the hippocampus, although there was an increase in tryptophan (Chaouloff et al., 1989), which is an obligatory molecule for 5HT synthesis. Although there was not a specific increase in 5HT following exercise, the altered expression of tryptophan creates an atmosphere in which 5HT might be more readily synthesized because of higher levels of this precursor. This therefore raises the possibility that exercise-induced alterations to the serotonergic system might augment neurogenesis.

Few studies have been conducted on the manner in which EE alters the expression of 5HT, although EE has been shown to increase the expression of a specific serotonin receptors in the hippocampus (Rasmuson et al., 1998). It has also recently

been found that serotonin depletion in the hippocampus does not affect the survival of new neurons in the hippocampus following EE, but that the initial number of newborn cells created is decreased (Ueda et al., 2005). These studies therefore suggest that 5HT in the hippocampus is more instrumental in cell proliferation than in cell survival, and as the 5HT system is affected by exercise, this might account for the differences in proliferation and survival observed between VEx and EE. However, the role of 5HT in both VEx and EE still needs to be explored more exhaustively before its role in the process of neurogenesis can be better defined.

INTRACELLULAR PATHWAYS

It is interesting to consider that only exercise increases cell proliferation in the hippocampus but both VEx and EE increase cell survival (van Praag et al., 1999b), despite the observation that both behavioral manipulations increase the expression of certain neurotrophic factors such as BDNF and NGF. Perhaps exercise induces cell proliferation due to the actions of IGF-1 and FGF-2, the expression of which is not altered following EE. Aberg et al. (2003) found increases in the total number of new cells, thymidine incorporation, and number of cells that were entering mitosis in response to the application of IGF-1 to adult rat hippocampal stem/progenitor cells; exposure to both IGF-1 and FGF-2 induced maximal cell proliferation (Aberg et al., 2003). Additionally, peripheral infusion of IGF-1 selectively induced cellular proliferation of progenitor cells in the hippocampus (Aberg et al., 2000). Therefore, exercise-induced increases in the expression of IGF-1 and FGF-2 might account for the increased cell proliferation not seen with EE.

In terms of cell survival, both VEx and EE may activate the intracellular pathways that were thought to play a role in cell survival. BDNF, IGF-1, and NGF activate the IP3 and MAPK pathways (Culmsee et al., 2002; Aberg et al., 2003; Zheng and Quirion, 2004), and the former pathway appears to be essential for cell survival (Zheng and Quirion, 2004). A common downstream effector of the IP3 pathways is a serine-threonine kinase, AkT, which has been shown to be activated by exercise (Chen and Russo-Neustadt, 2005) and is instrumental in BDNF and IGF-1-induced cell survival (Zheng and Quirion, 2004). Therefore, both VEx and EE might augment the activity of AkT to promote cell survival through increases in BDNF and NGF via EE, and BDNF, IGF-1, and NGF via VEx. Additionally, both behavioral manipulations increase the expression of BDNF and the immunoreactivity of CREB (Shen et al., 2001; Williams et al., 2001), which has been shown to augment neurogenesis in the hippocampus (Nakagawa et al., 2002).

In summary, certain trophic factors regulated by VEx (IGF-1 and FGF-2) might be more instrumental in the induction of cell proliferation, especially because blocking IGF-1 disrupts exercise-induced neurogenesis (Trejo et al., 2001). On the other hand, enhanced neurogenesis following VEx and EE might result from the activation of intracellular pathways thought to play a role in cell survival.

CONCLUSIONS AND FUTURE DIRECTIONS

The initial evidence is that EE and VEx can increase neurogenesis in two distinctly different methods (van Praag et al., 1999a). VEx increases cellular proliferation, and thus more cells are created that can become neurons. In contrast, EE produces an increase in neurogenesis without altering cell proliferation. Both VEx and EE increase the expression of similar trophic factors, produce alterations in dendritic structure, utilize similar intracellular signaling pathways, and improve learning and memory on hippocampal-dependent tasks. It is therefore surprising that VEx and EE have such distinct effects on neurogenesis. However, vascular changes, such as increased blood flow and enhanced BBB permeability, might more readily deliver trophic factors that are specifically increased following VEx (e.g., FGF-2 and IGF-1) and that are more instrumental in stimulating cell proliferation. This might account for some of the differences in neurogenesis following VEx and EE. However, the electrical activity induced by VEx and EE might also account for the differences in neurogenesis, which needs to be further elucidated, especially because LTP is enhanced by VEx and reversed by EE.

One important goal of research on adult mammalian neurogenesis is to understand the underlying mechanisms and, eventually, use this knowledge to induce proliferation or sustain cell survival in regions in need of new neurons in various human neurological and psychiatric diseases (Gage, 2002). The indications are that VEx and EE differentially affect cellular proliferation and cell survival via dissociable pathways.

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