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Neurotrophic Factor Control of Adult SVZ Neurogenesis

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Abstract

Neurogenesis is the process by which cells divide, migrate, and subsequently differentiate into a neuronal phenotype. Significant rates of neurogenesis persist into adulthood in two brain regions, the subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) of the lateral ventricles. Cells of the SVZ divide and migrate via the rostral migratory stream (RMS) to the olfactory bulb (OB) where they differentiate into granule and periglomerular cells. With the discovery of large-scale neurogenesis in the adult brain, there have been significant efforts to identify the mechanisms that control this process as well as the role of these cells in neuronal functioning. Neurotrophic factors are a family of molecules that serve critical roles in the survival and differentiation of neurons during development, as well as contribute to continued plasticity throughout life. Several members of the neurotrophin family have been implicated in the control of adult postnatal SVZ neurogenesis. In this review we will address what is currently known regarding neurotrophic factor-dependent control of SVZ neurogenesis and place these findings in the context of what is known regarding other growth factors.

Keywords

neurotrophins; SVZ; neurogenesis; BDNF; TrkB; olfactory bulb

Introduction

Until recently, neurogenesis was largely understood to be restricted to prenatal and early postnatal development, with no neuronal regeneration in the adult brain. This notion was initially challenged by Altman and Das, who, using tritiated-thymidine labeling, identified newly dividing cells in the hippocampus and lateral ventricles of the adult rat (Altman, 1962, 1969; Altman and Das, 1965). Since that time, the advent of new and more accessible techniques to label and track newly born neurons has led to an explosion in the study of adult neurogenesis. Many recent studies have been focused on understanding the basic mechanisms controlling this process, the role of these cells for adult neuronal functioning, and the potential therapeutic benefits that these cells may provide. Despite intensive study, still many basic questions remain.

The two brain regions that contain the majority of neural stem cells are the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. These stem cell populations divide to form neuroblasts, which eventually differentiate into neuronal or glial phenotypes and are integrated into the existing network. Neuroblasts of the SGZ primarily replace granule cells of the dentate gyrus (DG). Neuroblasts that originate in the SVZ migrate long distances along a rostral migratory stream (RMS) (Luskin, 1993; Lois

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and Alvarez-Buylla, 1994) to the OB where the majority differentiate into granule cells (~95%) and a small population become periglomerular cells (~5%). Within the SVZ, as many as 50,000 cells are born each day (Winner et al., 2002). The majority of neuroblasts that reach the OB die, with about 40% of newly born cells surviving throughout the life of the animal (Petreanu and Alvarez-Buylla, 2002; Winner et al., 2002). Approximately 95% of the newly born cells differentiate into a neuronal phenotype and functionally integrate into the existing circuitry. Nearly all of these cells become GABA or Calretinin positive inhibitory interneurons (Winner et al., 2002; Batista-Brito et al., 2008). However, a small percentage of these cells become tyrosin-hydroxylase (TH) positive dopaminergic neurons (Baker et al., 2001; Saino-Saito et al., 2004). This "turnover" of cells, represents an ~6–10% replacement of the existing cellular population within the OB granule cell layer.

SVZ Neurogenesis and Olfactory Functioning

The incorporation of new cells into the OB occurs in an odor-specific, learning-dependent manner (Alonso et al., 2006; Mandairon et al., 2006a,b), suggesting that the influence of granule cell activity on odor representations is in turn regulated by the selective survival and differentiation of these migrating neuroblasts. The signaling molecules that modulate cell migration and eventual survival are not yet well understood. However, studies of OB neurogenesis, though correlational, have provided some of the clearest evidence for the functional importance of granule cells in olfactory performance. Computational models of the activity-dependent survival of newborn granule cells suggest that these interneurons modulate the tuning of bulbar activity to enhance olfactory discrimination performance and potentially regulate the categorization of novel odorants (Cecchi et al., 2001). Indeed, low rates of neurogenesis have been linked to impairments in olfactory discrimination, and the increased survival of newly born neurons has been associated with enhanced olfactory short-term memory (Gheusi et al., 2000; Mandairon et al., 2003, 2006a,b; Saghatelyan et al., 2005). In this context, the olfactory system provides a potential model system for examining the functional importance of adult neurogenesis.

Role for Neurotrophins in SVZ Neurogenesis

BDNF and SVZ Neurogenesis—A number of mechanisms involving diffusible signaling molecules, such as neurotransmitters, neuropeptides, and growth factors, have been proposed to regulate SVZ neurogenesis and its effects on olfactory tuning and plasticity. One growth factor implicated in the control of adult SVZ neurogenesis is brain-derived neurotrophic factor (BDNF). BDNF exists in two forms (proBDNF and mature BDNF) that may play divergent roles during neuronal development and throughout the life of the animal. BDNF mediates its diverse actions by binding to two structurally distinct receptors; a member of the Trk family of receptor tyrosine kinases (TrkB) and the p75 ^{NTR} receptor, a member of the tumor necrosis factor (TNF) receptor superfamily. BDNF signaling via these two pathways has typically been dichotomized, with positive effects, such as neuronal differentiation, dendritic branching, cell survival, and synaptic long-term potentiation (LTP) being attributed to mature BDNF signaling via TrkB, and processes such as cell death and synaptic long-term depression (LTD) being attributed to proBDNF signaling through p75^{NTR} (Chao, 2003; Gentry et al., 2004; Lu et al., 2005). Thus far, the majority of studies that have focused on the role of BDNF in regulating postnatal SVZ neurogenesis have attributed their effects to the mature form of BDNF. However, future studies will be needed to disentangle effects attributable to pro relative to mature BDNF in regulating such processes.

As mature BDNF has been shown to promote the survival and differentiation of a variety of neuronal populations, it was an excellent candidate molecule to regulate the survival and/or differentiation of neural stem cells and neuroblasts in the adult brain. Goldman and

coworkers demonstrated that BDNF administered to rat SVZ derived neuroblasts *in vitro*, promoted the long-term survival of these cells (Kirschenbaum and Goldman, 1995). In related studies, Luskin and coworkers demonstrated that following infusion of BDNF into the lateral ventricles of adult rats there was a near doubling of newly born neurons in the OB (Zigova et al., 1998). Furthermore, following intraventricular infusion of BDNF other groups also observed increases in the number of newly born neurons in adjacent structures, such as the striatum and septum (Pencea et al., 2001). These initial findings have been replicated by a number of labs using either BDNF infusion or viral overexpression of BDNF to attempt to augment SVZ neurogenesis (Benraiss et al., 2001; Chmielnicki et al., 2004; Henry et al., 2007). In addition, the viral overexpression of BDNF in typically nonneurogenic regions, such as the striatum, can support the survival of grafted progenitor cells, further supporting a role for BDNF as a trophic factor capable of promoting neurogenesis (Chen et al., 2007). It should also be noted here that some recent studies in mouse have failed to replicate the neurogenic properties of infusion of BDNF into the lateral ventricles (Galvao et al., 2008). This same group has also found in rats that the administration of BDNF into the lateral ventricles led to a decrease in SVZ neurogenesis (Galvao et al., 2008). Further studies may be required to clarify how these results fit with previous studies. Furthermore, alternative forms of BDNF exist (pro and mature) which may regulate opposing phenotypic outcomes. In the context of these studies demonstrating that exogenous BDNF can alter (either positively or negatively) SVZ neurogenesis, the role of endogenously produced BDNF and proBDNF remain to be determined.

Advances in transgenic mouse technologies have allowed for the development of a series of genetically altered mice in which the levels of BDNF expression *in vivo* can be altered and then alterations in basal rates of neurogenesis can be assessed. In mice in which a single copy of BDNF has been deleted, we have found a significant reduction in the number of newborn neurons in the OB (Bath et al., 2008). Interestingly, in these BDNF haploinsufficient mice, we found no effect of reduced BDNF levels on cell proliferation in the SVZ. From these data, we hypothesized that endogenous BDNF plays a significant role in the migration or survival of neuroblasts following cell division. It should be noted, that in these mice 50% of BDNF has been missing throughout the development of the animal, and these effects on postnatal neurogenesis may be the result of an earlier disruption in the organization of the neurogenic niche. Indeed, previous reports from Miller and coworkers have shown that disruptions in BDNF signaling lead to impairments in cortical development and subsequently a thinning of the subventricular zone (Bartkowska et al., 2007). However, in relation to OB development, others have shown that the complete loss of BDNF or any of its receptors, leads to no impairments in the embryonic development of the OB (Nef et al., 2001). Furthermore, in BDNF null mice, defects in SVZ neurogenesis are not detectable until at least 2 weeks after birth (Linnarsson et al., 2000). Using realtime quantitative PCR, we tested for changes in BDNF expression within the OB across development and found BDNF levels to significantly increase with age [Fig. 1(a)]. This increase in BDNF expression was mirrored by a decrease in $p75^{NTR}$ expression and no significant changes in total TrkB expression [Fig. 1(b,c)]. These findings taken together could indicate that SVZ derived stem cells destined for the OB cells may not depend upon BDNF signaling during embryonic and early postnatal development. Instead, during the first several weeks of life there may be a shift in the sensitivity of these cells to extrinsic factors such as BDNF. Such findings may explain why grafted cells derived from postnatal day 1 mice that lack the BDNF receptor TrkB, might not show impairment in migration or survival (Galvao et al., 2008). However, similar studies to those described in Galvao et al. would need to be performed using TrkB null neural stem cells derived from adults to support such a hypothesis.

A major question that remains to be addressed is the localization of the source of BDNF regulating SVZ neurogenesis. Reports by Goldman and coworkers have suggested that endothelial cells are a primary source of BDNF (Leventhal et al., 1999). Much of this data comes from studies of SVZ explants cocultured with endothelial cells. They demonstrated that endothelial cells produce significant amounts of BDNF, and when cocultured, lead to increased survival of SVZ-derived cells that can be blocked by TrkB-Fc, a fusion complex that can sequester free BDNF. A role for endothelial cells as a significant source of BDNF has been supported by recent studies from Saghatelyan and coworkers (Snapyan et al., 2009). They demonstrated through the use of targeted knockout mice and biochemical means, that sequestering BDNF from the vasculature leads to significant impairments in neuroblast migration in the RMS. Recently, we generated a targeted knock-in mouse in which we replaced the wildtype BDNF with BDNF that contains a uniquely human single nucleotide polymorphism (SNP), a valine to methionine substitution in the prodomain (BDNF Val66Met) (Chen et al., 2006). This SNP leads to a significant reduction in regulated but not constitutive secretion of BDNF. In those same mice, we found a significant reduction in the survival of newly born OB granule cells (Bath et al., 2008). These findings are important as endothelial cells lack a regulated release mechanism, and thus do not explain the observed decrease in survival of newly born neurons in BDNF Val66Met mice. On the basis of these findings, we have hypothesized that a second source of BDNF exists, which is released in an activity-dependent manner, and can regulate the survival of newly born neurons in the OB. BDNF is released from neurons in an activity-dependent manner, a process known to support synaptic formation and neuronal excitability. BDNF Val66Met mutant mice, in which regulated BDNF secretion is impaired, may have defects in synaptic formation in the OB. Thus, newly born neurons, which may depend upon synaptic formation and activity to promote their integration into circuits and eventual survival, may fail to survive in Val66Met mice.

TrkB and SVZ Neurogenesis—Evidence for a role of BDNF in mediating neurogenesis has been quite compelling. However, BDNF can signal through either of two receptors (TrkB or $p75^{NTR}$). As such, significant questions remain regarding which of these receptors is responsible for mediating the observed effects of BDNF on neurogenesis *in vitro* and *in vivo*. We will first focus on reviewing what is known regarding the role of TrkB in SVZ neurogenesis.

TrkB exists in four distinct isoforms, two full-length form (TrkB.FL) which differ in a short amino acid insert on the extracellular domain, both of which contain an active kinase domain with multiple phosphorylation sites. In addition, two truncated forms of TrkB have been identified, TrkB.T1 and TrkB.T2 which all lack the intracellular kinase domain (Reichardt, 2006). Activation of TrkB.FL can lead to downstream signaling via PLC-gamma, ERK, and/or PI3Kinase. Given the absence of the kinase domain, the truncated forms of TrkB have been largely believed to function as endogenous dominant negatives that bind excess BDNF but do not signal. However, in recent reports, Mattson and coworkers have identified a potential novel signaling pathway for TrkB.T1, through the activation of a G-protein coupled receptor and protein kinase C (Rose et al., 2003; Cheng et al., 2007). They have shown that activation of this pathway can significantly impact the cell fate decision of neural stem cells during early postnatal development and possibly guide them toward a glial fate.

Given the presence of an active kinase domain, TrkB.FL has received the most attention as a potential regulator of SVZ neurogenesis. Using antibodies specific to the intracellular domain, TrkB protein has been found to be highly enriched within subpopulations of cells of the SVZ across species (Yan et al., 1997; Zigova et al., 1998; Tonchev et al., 2007). However, the specific subpopulation of cells within this region that express TrkB has been

somewhat controversial, with some groups identifying TrkB on migrating neuroblasts (Chiaramello et al., 2007; Bath et al., 2008) while others have shown TrkB to be restricted to astocytes (Galvao et al., 2008; Snapyan et al., 2009). Using an antibody specific to the phosphorylated form of TrkB (pTrkB), we found pTrkB to be selectively localized to migrating neuroblasts within the SVZ, RMS, and subependymal layer of the OB of mice (Bath et al., 2008). These findings are consistent with *in vitro* and *in vivo* studies where TrkB has been shown to be localized to PSA-NCAM positive migrating neuroblasts (Chiaramello et al., 2007). Consistent with these results, others have demonstrated a similar selective expression of TrkB on postmitotic immature neuroblasts within the SGZ of the hippocampus (Donovan et al., 2008; Li et al., 2008). This localization of TrkB to migrating neuroblasts is consistent with results from BDNF infusion and BDNF knockout animal studies, demonstrating a role for BDNF in the migration or survival but not proliferation of neuroblasts (Kirschenbaum and Goldman, 1995; Benraiss et al., 2001; Chiaramello et al., 2007; Bath et al., 2008; Snapyan et al., 2009). Through careful *in vitro* studies, TrkB signaling via PI3-K and ERK has shown to be critical for the appropriate migration of neuroblasts (Chiaramello et al., 2007). In further studies, BDNF stimulation of TrkB has been shown to be capable of rescuing inactivation or loss of the polysialated head (PSA) of PSA-NCAM, a molecule critical for cell adhesion during the migratory process (Vutskits et al., 2001). Consistent with these data, we found a significant reduction in the survival but not proliferation of newly born cells in the OB of TrkB heterozygous mice (Bath et al., 2008) an effect that is also observed in the hippocampus of these same mice (von Bohlen und Halbach et al., 2003; Bath et al., 2009). In recent reports, Alvarez-Buylla and coworkers show a similar trend toward a decrement in survival of newly born cells (14% fewer) in TrkB heterozygous mice compared to wildtype controls, through with a small *n* (three wild-type and four heterozygous mice), this difference approached but did not reach significance (Galvao et al., 2008).

Little data exists with regard to the role of the truncated forms of TrkB in the regulation of SVZ neurogenesis. Recent reports have shown that TrkB.T1 protein and message are enriched within the SVZ (Galvao et al., 2008) and in SVZ-derived cells in culture (Tervonen et al., 2006). Using cultures of SVZ-derived progenitor cells from mice in which the truncated TrkB.T1 was overexpressed, Tervonen and coworkers found a significant reduction in the number of neurosphere-forming progenitors compared with cells derived from wild-type mice. Interestingly, these same cells showed an increased rate of cell proliferation and differentiated into a neuronal phenotype at higher rates than wild-type-derived cells (Tervonen et al., 2006). These data suggest multiple roles for TrkB.T1 in regulating SVZ neurogenesis, proliferation, and differentiation. In addition, during early postnatal cortical development, TrkB.T1 has also been identified as playing a significant role in the regulation of gliogenesis (Cheng et al., 2007). Recently, a mouse has been generated in which the TrkB.T1 form of the TrkB receptor has been selectively knocked out (Carim-Todd et al., 2009). Future studies from this mouse will be important for understanding potential unique contributions of the truncated form of TrkB to the process of adult SVZ neurogenesis.

p75^{NTR} and SVZ Neurogenesis—p75^{NTR} is a member of the tumor necrosis receptor superfamily and is composed of an extracellular domain that includes four cysteine-rich motifs, a single transmembrane domain, and a cytoplasmic domain that includes a “death” domain (Liepinsh et al., 1997; He and Garcia, 2004). p75^{NTR} exerts its potent effects on nervous system development through a variety of mechanisms. p75^{NTR} is capable of inhibiting the activation of some forms of tropomysin-related kinase (Trk) receptors, the preferred receptor for neurotrophins (Benedetti et al., 1993; Bibel et al., 1999; Brennan et al., 1999). p75^{NTR} can also interact with multiple novel signaling partners such as Nogo, Lingo, and Par-3 (Mi et al., 2004; Chan et al., 2006) to enhance responsiveness to ligands

other than neurotrophins (e.g., oligodendrocyte myelin glycoprotein (OMgP), Nogo-66, and myelin-associated glycoprotein (MAG)) (reviewed in Bandtlow and Dechant, 2004; Barker, 2004; Gentry et al., 2004). $p75^{NTR}$ interaction in such signaling pathways occurs primarily during embryonic and early postnatal development to facilitate axonal outgrowth, axon targeting, synaptic stabilization, and myelination (Barker, 2004; Gentry et al., 2004). During postnatal brain development, $p75^{NTR}$ is significantly down-regulated in most neuronal populations including the OB [Fig. 1(c)]. This may in part be due to $p75^{NTR}$'s ability to induce cell death in response to high concentrations of neurotrophin or proneurotrophins which are upregulated postnatally. Such effects of $p75^{NTR}$ are most apparent following injury when $p75^{NTR}$ and proneurotrophins can be upregulated and induce death of cells in the injured area (Volosin et al., 2008).

In recent years $p75^{NTR}$ has also been implicated as a controller of adult SVZ neurogenesis. Using Western Blot analysis, Barde and coworkers have shown that stem cells that have been induced to differentiate into a neuronal phenotype, express high levels of $p75^{NTR}$ early postplating. $p75^{NTR}$ expression then decreases with a concomitant increase in TrkB expression (Bibel et al., 2004). These findings have been replicated in SVZ-derived neuroblasts *in vitro* (Gascon et al., 2005). Consistent with these findings, in initial immunohistochemical studies of the SVZ, a high degree of colocalization was found between $p75^{NTR}$ and nestin, a marker that labels proliferating cells within the SVZ and RMS (Giuliani et al., 2004). Others, including our lab, have found similar localization of $p75^{NTR}$ to nestin-positive cells using antibodies from different companies (Giuliani et al., 2004; Young et al., 2007; Bath et al., 2008), but the percent colocalization between $p75^{NTR}$-nestin positive cells was extremely low (5–10%). It should also be noted that in recent reports, others have identified $p75^{NTR}$ colocalization with PSA-NCAM (Galvao et al., 2008) or doublecortin (Snapyan et al., 2009), markers found on migrating neuroblasts. The disparities in the subpopulations of cells identified may be due to the use of different antibodies by different groups. However, this is difficult to disentangle as all groups report the use of different antibodies and some groups report the use of multiple antibodies (Galvao et al. lists five antibodies for $p75^{NTR}$). In an attempt to rectify the disparity between our and Young et al.'s findings, and those of Giuliani et al. regarding the percent of $p75^{NTR}$-positive cells that are also nestin-positive, we conducted a comparison of $p75^{NTR}$ labeling in the rostral migratory stream (RMS) using several of the commercially available $p75^{NTR}$ antibodies in wildtype and $p75^{NTR}$-null mice. As a control we included labeling in the basal forebrain, a $p75^{NTR}$-rich region. We found that in the basal forebrain, the c-terminal [Fig. 2(a)] but not n-terminal [Fig. 2(e)] antibodies from Santa Cruz detect $p75^{NTR}$-positive neurons and that staining is largely abolished in $p75^{NTR}$ null mice [Fig. 2(b,f)]. Both Santa Cruz antibodies showed a high degree of staining through the RMS of sections from a wild-type mouse [Fig. 2(c,g)]. However, much of the staining in the RMS remained in knockout tissue for both antibodies [Fig. 2(d,h)]. Antibodies from R&D showed greater specificity, detecting $p75^{NTR}$ in wild-type sections on basal forebrain neurons [Fig. 2(i)], staining that was abolished in tissue from $p75^{NTR}$-null sections [Fig. 2(j)]. In addition, using this antibody we detected a small population of $p75^{NTR}$-positive cells in the RMS [Fig. 2(k), arrows]. Labeling in the RMS was completely abolished in $p75^{NTR}$ null tissue [Fig. 2(l)].

To assess the *in vivo* and *in vitro* consequence of disruptions in $p75^{NTR}$ signaling on adult SVZ neurogenesis, we and others have taken advantage of $p75^{NTR}$ null mice. Using FACS sorting, Bartlett and coworkers have shown that only a small population of cells (~0.3%) within the SVZ are $p75^{NTR}$-positive (Young et al., 2007). Using *in vitro* assays they argue that this population of cells is responsible for the production of all neurospheres, and that $p75^{NTR}$-positive cells alone are neurogenic. These data are in part supported by their findings that $p75^{NTR}$-null mice show a 70% reduction in their neurogenic potential *in vitro*. For *in vivo* studies they conducted whole mount staining of PSA-NCAM from wild-type and

p75^{NTR}-null mice and found a significant reduction in pixel density in p75^{NTR}-null animals. However, no quantification of total cell density was conducted. Furthermore, they weighed OB's of p75^{NTR}-null and wild-type mice and found a significant reduction in OB weight in p75^{NTR}-null animals (Young et al., 2007). From these data they argue that p75^{NTR} significantly contributes to neurogenesis *in vivo*. We carried out similar studies in wild-type and p75^{NTR}-null mice and found no effect of the loss of p75^{NTR} on cell proliferation in the SVZ or neuron survival in the OB using BrdU labeling and stereological sampling (Bath et al., 2008). Similarly, we found no reduction in volume of the olfactory bulbs of p75^{NTR}-null mice compared to age matched wild-type controls using Cavaleri estimation or magnetic resonance microscopy. It should be noted, that Snapyan et al., also implicate p75^{NTR} as a potential regulating of neurogenesis through its control of neuroblast migration. Based upon these three disparate findings, the question of p75^{NTR}'s role as a regulator of neurogenesis remains to be clarified.

Other Neurotrophin Family Members—Thus far, few studies exist characterizing the role of other members of the neurotrophin family of genes on adult SVZ neurogenesis. One group has shown that the intraventricular administration of NGF can increase SVZ proliferation *in vivo* (Fiore et al., 2002). However, they also demonstrate that this same protocol leads to an increased BDNF expression in the SVZ (Tirassa et al., 2003), making the individual contribution of NGF to SVZ neurogenesis less clear. This same group has also shown that in EAE rats, that message for NGF and its cognate receptor TrkA can be detected within the SVZ (Triaca et al., 2005). In addition, *in vitro* application of NGF can augment the survival and dendritic outgrowth of cells derived from the SVZ of rats (Gascon et al., 2005), but likely through p75^{NTR} and not TrkA as this same group, as well as others, was unable to detect TrkA protein or mRNA in the SVZ (Giuliani et al., 2004; Gascon et al., 2005; Galvao et al., 2008).

Another neurotrophin family member, NT-3 has also been implicated in the proliferation of cells within the perinatal SVZ. However, instead of impacting neurogenesis, loss of NT-3 seems to selectively impact the survival and proliferation of SVZ-derived oligodendrocytes (Kahn et al., 1999). In subsequent studies using NT-3 null mice or mice lacking TrkC, the primary receptor to which NT-3 binds, no alterations were found in the development, organization, or size of the OB (Nef et al., 2001). To date, we are not aware of any studies that have assessed adult SVZ neurogenesis in NT-3 mutant mice or of studies assessing the expression of NT-3 or TrkC protein within the SVZ.

Other Growth Factors

Fibroblast Growth Factor (FGF-2)—In addition to neurotrophic factors, several other growth factors have been implicated in the control of SVZ neurogenesis. The first, fibroblast growth factor (FGF)-2, has also been shown to be capable of augmenting neurogenesis following intraventricular administration (Kuhn et al., 1997; Tropepe et al., 1999). In studies of rat brain, FGF-2 is expressed by GFAP-positive cells (Mudo et al., 2007), and the FGF receptors (FGFR-1 and FGFR-2) are present on the proliferating precursor and ependymal cells (Gonzalez et al., 1995). Use of FGF-2 in cultures promote both cell proliferation as well as increased survival and neurite outgrowth (Pincus et al., 1998). The primary action of FGF-2 seems to be in regulating cell cycle as mice lacking FGF-2 show significant impairments in SVZ cell proliferation (Raballo et al., 2000; Zheng et al., 2004). However, more work is required to specifically identify if FGF-2 regulates cell cycle length, cell cycle progression, or cell cycle reentry.

Epidermal Growth Factor (EGF)—A second growth factor shown to significantly influence adult SVZ neurogenesis is epidermal growth factor (EGF). Like FGF-2, EFG

administration into lateral ventricles leads to significant upregulation of cell proliferation within the SVZ (Seroogy et al., 1995; Craig et al., 1996; Okano et al., 1996; Morshead et al., 2003). However, despite serving as a significant modulator of cell proliferation within the SVZ and in culture, the role of EGF in regulating neurogenesis *per se*, is somewhat less clear due to questions regarding the levels of its endogenous expression in neural tissue. In recent studies, Alvarez-Buylla and coworkers have shown that intraventricular infusion of EGF leads to augmentation in cell proliferation and migration of newly born cells into structures adjacent to the lateral ventricles. However, instead of becoming neurons, the vast majority of these cells upon differentiation express an oligodendrocyte or glial-like phenotype (Gonzalez-Perez et al., 2009). These findings are supported by data showing that suppression of EGFR signaling following injury leads to a decrease in the migration of SVZ-derived cells to the site of the lesion and subsequent oligodendrogenesis (Aguirre and Gallo, 2007).

Transforming Growth Factor (TGF)—Like other growth factors studied, transforming growth factor (TGF) also plays a significant role in regulating proliferation of cells of the SVZ and act on the same receptors as EGF (the EGF receptor; EGFR). TGF has been shown to be highly expressed in the striatum, a region adjacent to the SVZ (Wilcox and Derynck, 1988; Seroogy et al., 1993). Intraventricular infusion of TGF-alpha leads to a dramatic increase in cell proliferation in the SVZ (Craig et al., 1996). Furthermore, mice that lack TGF-alpha have significantly decreased rates of cell proliferation within the SVZ and fewer newly born cells within the OB (Tropepe et al., 1997). Interestingly, the intranasal administration of TGF-beta1 to mice after stroke leads to an increased SVZ neurogenesis and can abrogate some of the deleterious effects of stroke (Ma et al., 2008).

Vascular Endothelial Growth Factor (VEGF)—One of the most well studied growth factors capable of regulating adult SVZ neurogenesis is vascular endothelial growth factor (VEGF). Again, like other growth factors, intraventricular infusion of VEGF leads to increased cell proliferation in the SVZ (Jin et al., 2002; Sun et al., 2006). Mice lacking VEGF-B also show significant impairments in SVZ neurogenesis, with fewer cells reaching the OB (Sun et al., 2006). Using targeted KO mice, release of VEGF-A from GFAP positive cells stimulates VEGFR1 and VEGFR2 to regulate proliferation and migration of SVZ neuroblasts, and ultimately alters rates of surviving cells *in vivo* (Wittko et al., 2009). Finally, the overexpression of VEGF can increase rates of SVZ cell proliferation and also leads to increased migration of newly dividing cells to sites of ischemic injury in mouse models (Wang et al., 2007a,b).

Ciliary Neurotrophic Factor (CNTF)—Cilliary neurotrophic factor (CNTF) is a growth factor that is exclusively expressed within the CNS (Ip et al., 1993; Ip and Yancopoulos, 1996) and predominantly localized to astrocytes (Sendtner et al., 1994; Dallner et al., 2002). The CNTF receptor, CNTFR-alpha, is expressed in the adult SVZ (Ip et al., 1993) and may reflect a potential role in regulating adult SVZ neurogenesis. In recent reports, Emsley and Heff localized CNTFR-alpha to a subset of GFAP positive cells within the SVZ (Emsley and Hagg, 2003). They found that forebrain administration of CNTF increased the incorporation of BrdU into cells of the adult SVZ and increased the percentage of CNTFR-alpha BrdU double-positive cells. Furthermore, anti-CNTF antibody administration abrogated these effects, and led to a reduction in BrdU labeling in the SVZ (Emsley and Hagg, 2003). Mice in which CNTF has been genetically ablated have an ~20% reduction in cell proliferation within the SVZ (Yang et al., 2008). This same group identified dopaminergic activation of CNTF-positive astrocytes as one potential mechanism by which CNTF may regulate adult neurogenesis (Yang et al., 2008). CNTF is also a potent regulator of adult neurogenesis in brain regions other than the SVZ, including the dentate gyrus

(Emsley and Hagg, 2003; Muller et al., 2009), the hypothalamus (Kokoeva et al., 2005, 2007).

Discussion

Uncovering the molecular mechanisms that guide adult neurogenesis will pave the way to answering questions that have to this point remained elusive. Specifically, what is the functional relevance of adult neurogenesis and can these cells be recruited to aid in the treatment of neurodegenerative diseases or injury? Recently, several groups have begun to apply what has been learned regarding neurotrophic control of neurogenesis to such ends. Using adenoviral over-expression of BDNF following quinolinic acid lesioning of the striatum, one group was able to recruit SVZ-derived cells to the site of injury (Henry et al., 2007). Similarly, another group has shown that following the induction of stroke in rats, BDNF infusions leads to an augmentation in SVZ neurogenesis and newly born cells migrating to the striatum of the affected hemisphere (Schabitz et al., 2007). In yet another series of studies, infusions of BDNF in combination with VEGF increased SVZ neurogenesis and resulted in significant functional improvements in mice following stroke (Chen et al., 2005). Despite these early successes, much more work will be required to truly discover the potential and harness the power of these cells for such purposes.

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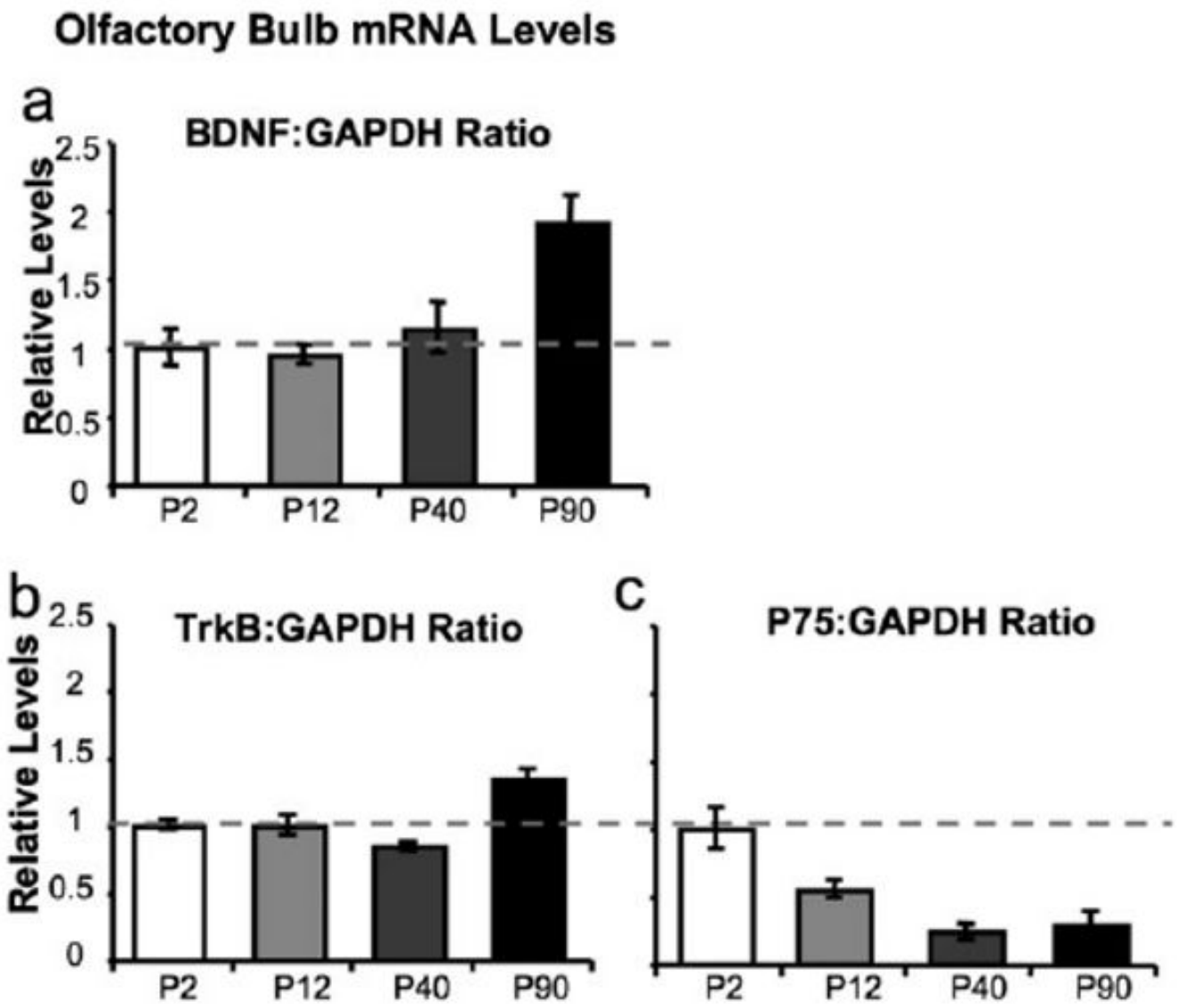

Figure 1.

Developmental expression of BDNF, TrkB, and $p75^{NTR}$ in mouse OB. Histograms depict relative levels of (a) BDNF, (b) TrkB, and (c) p75NTR mRNA in the olfactory bulb of mice at different developmental time points (n = 3 per group). All samples were run in triplicate and normalize to GAPDH.

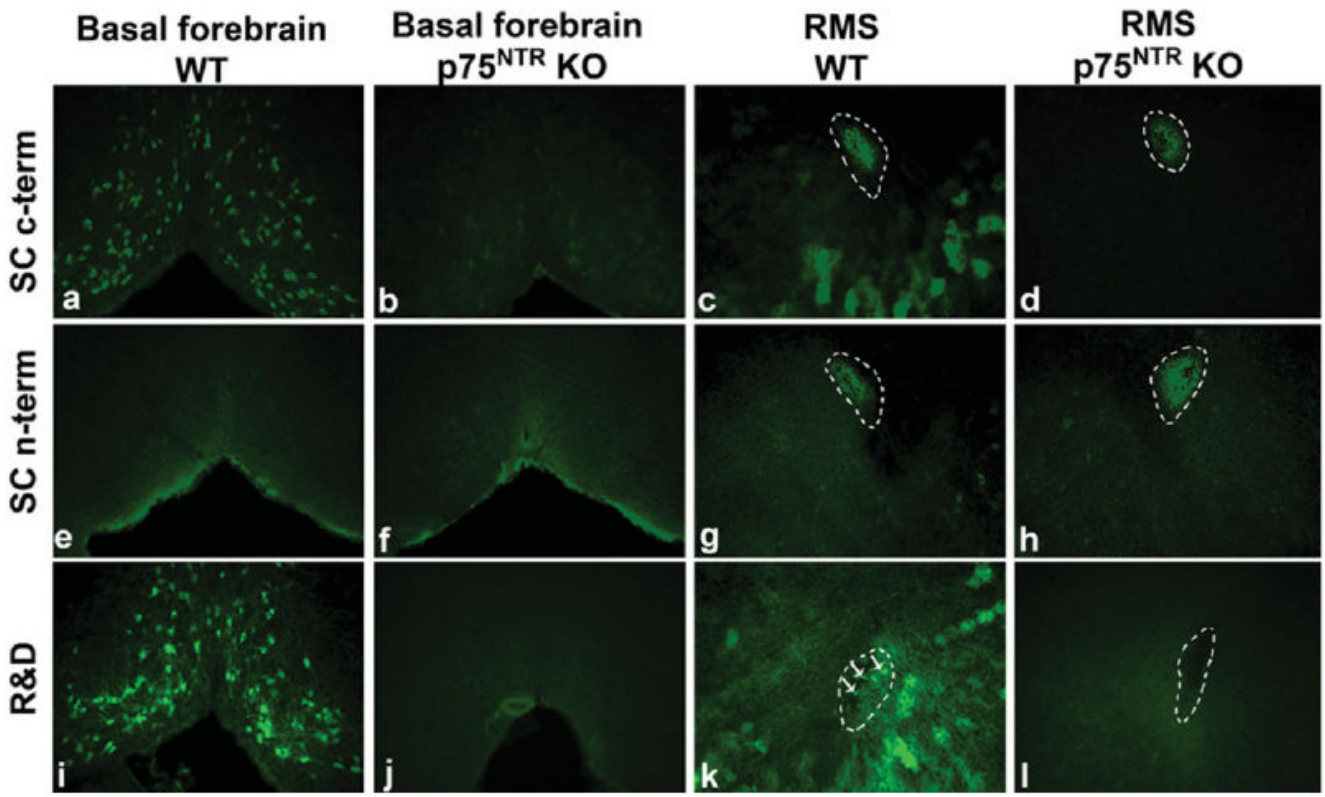

Figure 2.

Comparison of commercially available $p75^{NTR}$ antibodies. Photomicrographs of $p75^{NTR}$ immunoreactivity in brains of wild-type (WT) and $p75^{NTR}$-null ($p75^{NTR}$ KO) mice. Comparisons were made between the c-terminal (c-term) and n-terminal (n-term) antibodies from Santa Cruz Biotechnology, (SC- Cat#'s sc6188 and sc6189 respectively) and a c-terminal antibody from R&D Systems (R&D- Cat# AF1157). Immunolabeling was carried out in adjacent sections from a single wild-type and a single $p75^{NTR}$ null mouse. Immunoreactivity was compared in the basal forebrain (a, b, e, f, i, and j) and rostral migratory stream (RMS) (c, d, h, k, and l).