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Compensatory Neurogenesis in the Injured Adult Brain

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1. Introduction

The occurrence of neurogenesis, defined as the generation of new neurons, has become well established in the adult mammalian brain, including the human brain over the last two decades. Neurogenesis in the adult brain can be divided into four phases: (a) progenitor cell proliferation; (b) migration of progenitor cells towards a target area; (c) terminal differentiation into a specific phenotype, and; (d) integration into established networks. Neural stem/progenitor cells generate neurons throughout life in the mammalian forebrain subventricular zone (SVZ)–olfactory bulb (OB) pathway and the hippocampal dentate gyrus [for review see (Whitman, *et al.*, 2009)]. Neural progenitor cells can be isolated from these two regions and cultured *in vitro* as self-renewable neurospheres in epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF2) containing media (Reynolds, *et al.*, 1992, Reynolds, *et al.*, 1996). Upon withdrawal of growth factors, they differentiate into the three main neural lineages; neurons, astrocytes and oligodendrocytes (Reynolds & Weiss, 1996).
There are four major cell types within the adult SVZ-OB pathway; ependymal cells, Type B, Type C and Type A cells (Doetsch, *et al.*, 1997). The true neural stem cells in this region are the Type B cells which have the characteristics of radial glial cells, including the expression of GFAP (Doetsch, *et al.*, 1997, Doetsch, *et al.*, 1999). Type B cells proliferate slowly to generate Type C cells, which are the most rapidly proliferating cell type in the SVZ. The bipotent Type C cells are able to divide either symmetrically or asymmetrically to generate glial or neural precursor cells. The SVZ-OB pathway is organized as an extensive network of chains of migrating neural precursor cells (neuroblasts; Type A cells) that travel through glial tubes formed by GFAP positive radial glial-like cells (Lois, *et al.*, 1994, Doetsch, *et al.*, 1996, Lois, *et al.*, 1996, Doetsch, *et al.*, 1997). SVZ- derived neuroblasts migrate long distances via a restricted forebrain pathway known as the rostral migratory stream (RMS) to their final destination in the olfactory bulb. This is achieved through a unique form of tangential chain migration. Migrating neuroblasts (Type A cells) in the SVZ – OB pathway can be identified by their expression of characteristic markers such as the polysialylated form of neural cell adhesion molecule (PSA-NCAM), neuron-specific βIII-tubulin and doublecortin (Dcx). Once the neuroblasts reach the subependymal region of the olfactory bulb, they disperse radially and differentiate into granule and periglomerular neurons (Luskin, 1993, Lois&Alvarez-Buylla, 1994, Lois, *et al.*, 1996, Thomas, *et al.*, 1996, Curtis, *et al.*,

2007). Studies have shown that olfactory granule and periglomerular cells are continuously added to the olfactory bulb to both increase total cell number over time in these layers as well as replace pre-existing cells (Lagace, *et al.*, 2007, Imayoshi, *et al.*, 2008). The function of persistent olfactory bulb neurogenesis is largely unknown, but increasing evidence supports a role for the new neurons in olfactory memory and odour discrimination (Gheusi, *et al.*, 2000, Petreanu, *et al.*, 2002, Rochefort, *et al.*, 2002).

In contrast to the extensive migration undertaken by neurons destined for the olfactory bulb, dentate gyrus granule neurons are born locally in the subgranular zone (SGZ), a germinal layer between the dentate gyrus and the hilus (Altman, *et al.*, 1965, Kaplan, *et al.*, 1977, Eriksson, *et al.*, 1998, Kornack, *et al.*, 1999, Gould, *et al.*, 2001). Within the SGZ, GFAP positive cells (Type B cells) divide to give rise to immature Type D cells, which then generate granule neurons (Palmer, *et al.*, 2000, Seri, *et al.*, 2001). Interestingly, Type D cells divide less frequently and are more differentiated than the transit amplifying Type C cells in the SVZ. SGZ-derived neural progenitor cells generate new neurons that make and receive functional synapses (Palmer, *et al.*, 2000, Song, *et al.*, 2002, Van Praag, *et al.*, 2002). Ongoing hippocampus neurogenesis is known to facilitate long-term potentiation and stimulate learning and memory (Van Praag, *et al.*, 1999, Wang, *et al.*, 2005, Imayoshi, *et al.*, 2008) with ablation of adult-born dentate granule cells impairing certain forms of hippocampal-dependent learning (Dupret, *et al.*, 2008, Imayoshi, *et al.*, 2008, Clelland, *et al.*, 2009).

Adult neurogenesis is not static, but its rate may fluctuate in response to environmental change. Evidence from *in vitro* and *in vivo* studies have demonstrated that neurogenesis can be regulated by a range of growth and neurotrophic factors, neurotransmitters and hormones [for review see (Parent, 2003, Lie, *et al.*, 2004)]. Neurogenesis has also been shown to be altered by the presence of cell death induced by brain injury or disease [for review see (Peterson, 2002, Parent, 2003, Lie, *et al.*, 2004, Goldman, 2005)]. A critical issue of neurogenesis, both during development and in adulthood, is the appropriate integration of different cell types to form mature neural cells. This means that progenitor cells need to migrate from their places of birth to their final positions. Such a highly regulated process is mediated by a number of environmental cues like substrates, chemoattractive/ chemorepulsive factors, and detachment/stop signals. Although some of these factors have been identified, many remain to be discovered [for review see (Cayre, *et al.*, 2009)]. Progenitor cell migration is most extensive in the developing and immature brain. In the adult brain, neural cell migration still continues, although in a more limited capacity with the most extensive region of migration observed in the SVZ-OB pathway. It is not yet clear why new neurons are not born in the place they need to reside. While the maintenance of stem cell niches in the adult brain may provide a potential source of cells for brain repair and cell replacement, these regions may be costly for the organism and may also require specific features that restrict the structures where they can persist. As a result, in both normal and pathological conditions cells need to be able to migrate from these discrete niches to their final destination. During pathological processes, such as brain injury, the brain demonstrates spontaneous attempts at repair and regeneration. These processes result in a distinct profile of cell proliferation and migration not observed in the normal adult brain, which appear to be mediated by an independent set of environmental cues. This chapter will discuss what is known about the response of endogenous adult neural progenitor cells to brain injury including stroke, traumatic brain injury, epilepsy and excitotoxic injury, the mechanisms by which this response may occur, and how this knowledge may be translated to effective therapeutic strategies.

2. The response of progenitor cells to the injured brain

2.1 Temporal lobe epilepsy

Epilepsy, characterized by periodic and unpredictable occurrence of seizure activity, affects ~50 million people worldwide and temporal lobe epilepsy (TLE) is among the most frequent types of intractable epilepsy. Abnormal hippocampal neurogenesis has emerged as an important pathophysiology of TLE over the past decade [for review see (Kuruba, *et al.*, 2009)]. Initial studies on neurogenesis in animal models of TLE by Parent and colleagues (Parent, *et al.*, 1997, Parent, *et al.*, 1998) and Bengzon and colleagues (Bengzon, *et al.*, 1997) provided the first evidence for increased hippocampal neurogenesis following acute seizures. In these studies, an increase in the production of new cells was observed in the SGZ of the dentate gyrus following pilocarpine-induced status epilepticus (SE) (Parent, *et al.*, 1997, Gray, *et al.*, 1998) or kindling stimulations (Bengzon, *et al.*, 1997, Parent, *et al.*, 1998). However, by 3-4 weeks after seizure induction, neurogenesis returned to baseline levels. In normal animals, proliferating cells labeled with the mitotic marker bromodeoxyuridine (BrdU) are restricted to the SGZ of the hippocampus. In contrast, following seizure activity BrdU+ cells were found extensively in the dentate hilus and/or dentate molecular layer of the hippocampus, indicating aberrant migration of dividing cells in response to seizure-induced cell loss (Parent, *et al.*, 1997, Scharfman, *et al.*, 2000, Scharfman, *et al.*, 2002, Scharfman, *et al.*, 2003, Parent, *et al.*, 2006). Similarly, displaced granule cells have been observed in hippocampal tissues obtained from patients with TLE (Houser, 1990, Thom, *et al.*, 2002, Liu, *et al.*, 2008). This suggests that acute seizure-induced dentate gyrus neurogenesis promotes aberrant circuitry development, which likely contributes to the evolution of initial seizure-induced hippocampal injury into chronic epilepsy (Kuruba, *et al.*, 2009).

In addition to the neurogenic response observed in the hippocampus, progenitor cells in the SVZ also respond to seizure activity in the adult rodent brain. Within 1-2 weeks following pilocarpine-induced seizure activity, Parent and colleagues (Parent, *et al.*, 2002) observed an increase in BrdU labeling and Nissl staining in the RMS. These changes were associated with an increase in expression of the Type A neuroblast marker Dcx 2 – 3 weeks following prolonged seizures. At these same time points the RMS expanded and contained more proliferating cells and immature neurons. BrdU labeling and retroviral tracing showed that prolonged seizures also increased neuroblast migration to the olfactory bulb. Importantly, a large number of labeled cells were found adjacent to the RMS instead of within its realms (most prominent at 14 days following seizure induction), indicating that seizure activity induces aberrant migration of SVZ-derived progenitor cells into surrounding regions of the brain (Parent, *et al.*, 2002).

Increased neurogenesis observed following acute seizure activity returns to baseline by about 2 months after the initial seizure episode in rats. The extent of neurogenesis has then been shown to decline significantly in the chronic phase of epilepsy when significant numbers of spontaneous seizures manifest [for review see (Hattiangady, *et al.*, 2008)]. A 64-81% decrease in neurogenesis was reported at 5 months post-SE with an inverse relationship evident between the frequency of spontaneous seizures and the extent of neurogenesis (Hattiangady, *et al.*, 2004). The severe reduction in hippocampal neurogenesis observed in chronic TLE is not however associated with either decreased production of new cells or reduced survival of newly born cells in the dentate gyrus. Rather, it is due to a decline in the neuronal fate-choice decision of newly generated cells with the majority of newly born

cells differentiating to a glial rather than a neuronal lineage in response to chronic TLE (Hattiangady, *et al.*, 2010). Thus, diminished hippocampal neurogenesis might contribute to the persistence of spontaneous seizures, learning and memory deficits, and depression prevalent in chronic TLE.

2.2 Traumatic brain injury

Traumatic brain injury (TBI) is characterized by both neuronal and white matter loss, with resultant brain atrophy and functional neurological impairment. Injury may be in the form of focal damage, or it may be diffuse with widespread delayed neuronal loss. In addition to local neuronal loss resulting from the mechanical primary insult, TBI also induces a cascade of delayed secondary events that contribute to neuronal death, including ischemia, Wallerian degeneration secondary to diffuse axonal injury, excitotoxicity, dysregulation of calcium homeostasis, mitochondrial dysfunction and free radical-mediated damage. Among the diffuse injury sites, the hippocampus is known to be especially vulnerable in humans and shows the earliest evidence of TBI-induced degeneration in experimental models. The most frequently used experimental models of TBI include the controlled cortical impact (CCI) and lateral fluid percussion (FPI) models (Wang, *et al.*, 2010). The lateral FPI model can reproduce multiple types of human TBI, including focal contusion, intraparenchymal and subarachnoid hemorrhage, tissue tears and axonal damage, and has been widely adopted as a combined model of focal and diffuse brain injury. The CCI model generally has been found to produce a more focused injury compared to lateral FPI; the severity of injury is also significantly greater in the gray matter relative to the underlying white matter. In both injury models there is an acute neurogenic response with an increase in hippocampal progenitor cell proliferation observed from 24hr to 1-2 weeks following TBI (Dash, *et al.*, 2001, Chirumamilla, *et al.*, 2002, Emery, *et al.*, 2005). Newly generated neurons in the dentate gyrus integrate into the existing hippocampal circuitry following TBI, potentially resulting in cognitive recovery (Sun, *et al.*, 2005). Transgenic approaches have demonstrated that following TBI, the nestin-expressing progenitor cells are first activated by injury, whereas the later Dcx-expressing committed neuroblasts appear to be eliminated (Miles, *et al.*, 2008, Yu, *et al.*, 2008). Later, the Dcx-expressing cells within the dentate gyrus reemerge and are likely contributors to stable neurogenesis (Yu, *et al.*, 2008).

Adult SVZ neurogenesis has also been investigated in the CCI model of TBI (Goings, *et al.*, 2002, Ramaswamy, *et al.*, 2005). In these studies, SVZ progenitor cell proliferation was observed either to be reduced (Goings, *et al.*, 2002), or to exhibit a delayed increase in proliferation (Ramaswamy, *et al.*, 2005) following TBI. In the lateral FPI model, an increase in SVZ progenitor cell incorporation of BrdU was observed between 2 – 8 days post injury (Chirumamilla, *et al.*, 2002). Interestingly, in the CCI model progenitor cell migration within the SVZ - OB pathway, as demonstrated by PSA-NCAM expression, was not enhanced until 25-35 days post TBI (Goings, *et al.*, 2002). Retroviral labeling of SVZ progenitor cells and examination of the location of labeled cells at 4 days and 3 weeks post injury in adult mice determined that very few cells migrated into the cerebral cortex in the normal brain, whereas a large number of labeled cells migrated into the lesioned area following cortical impact (Goings, *et al.*, 2004). Migration of progenitor cells into the lesioned cortex appeared to be at the expense of migration to the olfactory bulb; in control animals approximately half of the labeled SVZ cells were found in the olfactory bulb, whereas only a quarter of labeled cells migrated there following cortical injury (Goings, *et al.*, 2004). However, the majority of adult-born cells located in the lesioned area appear to be newly generated glial cells, with

limited to no neuronal differentiation observed (Chirumamilla, *et al.*, 2002, Goings, *et al.*, 2004). Finally, an increase in proliferative markers and the number of proliferative neural progenitor cells was recently observed to be increased in the perilesion cortex of the human brain following TBI (Zheng, *et al.*, 2011), indicating that TBI may also induce compensatory neurogenesis in the human brain. Thus, it appears that TBI results in compensatory neurogenesis in response to both hippocampal and cortical damage, with progenitor cell migration focused on recruitment to areas of neural injury. Further studies however are required to determine the fate and survival of adult-born cells in areas of TBI-induced injury.

2.3 Focal ischemia

Ischemic stroke involves an interruption in blood supply to the brain and results in the death of neural cells and corresponding loss of brain function. Focal ischemia is generated through the blockage of blood vessels which supply specific regions of the brain, and is commonly modeled by the occurrence of transient middle cerebral artery occlusion (tMCAo) which results in damage to the cortex and striatum. Studies of experimental stroke in rodents over the past decade indicate that focal ischemia potently stimulates SVZ cell proliferation and neurogenesis (Jin, *et al.*, 2001, Zhang, *et al.*, 2001, Arvidsson, *et al.*, 2002, Parent, *et al.*, 2002, Ohab, *et al.*, 2006). Although initial studies suggested that the increase in SVZ neurogenesis after stroke is transient (Arvidsson, *et al.*, 2002, Parent, *et al.*, 2002), more recent work indicates that it persists for at least 4 months after ischemia (Thored, *et al.*, 2006). SVZ progenitor cells have also been observed to migrate in chains into the ischemic striatum and cortex (Arvidsson, *et al.*, 2002, Parent, *et al.*, 2002, Jin, *et al.*, 2003, Ohab, *et al.*, 2006, Yamashita, *et al.*, 2006, Zhang, *et al.*, 2009). As with TBI, this appears to be at the expense of olfactory bulb migration. Recent evidence suggests that a similar long-distance migration of neuroblasts may occur in peri-infarct tissue in human stroke (Jin, *et al.*, 2006). Although a large number of neuroblasts reach regions of striatal damage after stroke, few of them differentiate into mature neurons. Most adult-born neurons appear to die (Arvidsson, *et al.*, 2002, Parent, *et al.*, 2002), perhaps from a failure to integrate or due to inflammatory milieu. However, the persistence of SVZ neuroblast migration to the injured striatum for up to a year after ischemia (Thored, *et al.*, 2006) suggests that the SVZ may serve as a constant reservoir of new neurons that offers an extended window for therapeutic manipulation. In most stroke models, many of the surviving cells differentiate into neurons, but the precise nature of the neurons that persist long term in the striatum is controversial. The generation of neurons expressing markers of the striatal medium spiny neurons including DARPP-32 and calbindin after tMCAo in adult rats has been reported by two groups (Arvidsson, *et al.*, 2002, Parent, *et al.*, 2002). More recently however, Liu and colleagues (Liu, *et al.*, 2009) used retroviral reporters to label SVZ progenitor cells prior to inducing stroke in adult rats and found that adult-born neurons exclusively differentiated into calretinin-expressing interneurons. This may be due to differences in the location and extent of focal ischemic injury, selectivity of ischemic-induced neural cell loss, or alternatively the response of the specific population of neural progenitor cells investigated (Lledo, *et al.*, 2008). Further research is also required to determine the potential for adult-born neurons to integrate into the surrounding parenchyma following focal ischemic injury.

2.4 Excitotoxic brain injury

Striatal injection of the neurotoxin quinolinic acid (QA) generates the selective loss of the GABAergic medium spiny neurons in the striatum. This model has been used to investigate

the effect of excitotoxic striatal injury on SVZ-derived neurogenesis. QA lesioning results in a significant increase in progenitor cell proliferation at days 1 – 14 following injury (Tattersfield, *et al.*, 2004, Collin, *et al.*, 2005). In addition, both expansion of the RMS and aberrant migration of SVZ-derived Dcx-expressing progenitor cells into the lesioned striatum has been demonstrated following QA-induced striatum cell loss (Tattersfield, *et al.*, 2004, Collin, *et al.*, 2005, Gordon, *et al.*, 2007). In order to elucidate the temporal profile of progenitor cell migration in response to QA-induced striatal cell loss, Gordon and colleagues (Gordon, *et al.*, 2007) used retroviral tracing to label SVZ-derived progenitor cells and track their migratory profile. This study demonstrated that SVZ-derived progenitor cell migration was significantly enhanced in the RMS of QA lesioned animals immediately following, and up to 30 days following QA-induced striatal cell loss. This was in contrast to the migratory response observed in both TBI and ischemic stroke, and demonstrated that recruitment of SVZ-derived progenitor cells into the QA lesioned striatum was not at the expense of olfactory bulb migration. In addition, Gordon and colleagues (Gordon, *et al.*, 2007) identified that aberrant migration of SVZ-derived progenitor cells into the QA lesioned striatum is transient, with progenitor cell recruitment predominantly observed by cells labeled either 2 days prior or up to 3 days following QA lesioning. Interestingly, a change in the morphology of the recruited SVZ-derived progenitor cells was observed over time. SVZ-derived progenitor cells labeled either 2 days prior, or on the day of QA lesioning predominantly exhibited a bipolar morphology and expressed Dcx. In contrast, the majority of progenitor cells labeled from the day of QA lesioning up to 3 days following lesioning displayed a multipolar morphology and did not express Dcx (Gordon, *et al.*, 2007). This indicates that striatal cell loss induces an expansion of the SVZ progenitor cell population, in which a sub-population of SVZ-derived progenitor cells are responsive to recruitment into the lesioned area. In addition, the novel observation of a temporal change in the morphological profile of progenitor cells recruited into the QA lesioned striatum is of great interest, and warrants further investigation. This alteration in progenitor cell morphology may be in response to changes in environmental cues present in the lesioned striatum. Following recruitment into the QA-lesioned striatum, about 80% of adult-born neurons survive up to 6 weeks, when they express the mature neuronal marker NeuN and phenotypic markers of striatal medium spiny neurons (DARPP-32) and interneurons (parvalbumin or neuropeptide Y) (Tattersfield, *et al.*, 2004, Collin, *et al.*, 2005). However, similar to the observations made in models of ischemic stroke, relatively few adult-born neurons survive long term. The low level of adult-born cell survival in models of both focal ischemia and excitotoxic striatal cell loss indicates that further investigation is required in both injury models to determine the effect of the environment of cell fate, integration and long-term survival.

3. Factors modulating compensatory neurogenesis

The precise mechanisms underlying injury-induced compensatory neurogenesis in the adult brain are unclear. However, several potential mechanisms have been proposed. First it is believed that the release of mitogenic factors from dying neurons and reactive glia probably increases the proliferation of neural progenitor cells and the survival of newly generated neurons. Expression of mitogenic factors can also alter transcriptional signaling pathways in neural progenitor cells, redirecting neurogenic processes from a normal physiological role (Bath, *et al.*, 2010, Hodge, *et al.*, 2011, Jones, *et al.*, 2011). Increased expression of cytokines

and chemokines from reactive microglia and blood vessels are also involved in directing the migration of neural progenitor cells to areas of neuronal loss and injury, as well as controlling adult-born neuron survival (Gonzalez-Perez, *et al.*, 2010). Angiogenesis and the expression of pro-angiogenic factors appear to play an important role both in progenitor cell proliferation and survival as well as migration (Xiong, *et al.*, 2010, Yang, *et al.*, 2011). In addition, alteration in neurochemical signaling, such as GABAergic and glutamtergic transmission, and neuronal activity have been shown to modulate neurogenesis following brain injury (Deisseroth, *et al.*, 2004, Ge, *et al.*, 2007). Thus, it appears multiple mechanisms underlie the regulation of compensatory neurogenesis following brain injury; these will be summarized in the following section.

3.1 Potential mechanisms of increased hippocampal neurogenesis after seizure activity

Multiple studies have demonstrated that several factors known to promote neural progenitor cell proliferation and neuron survival such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF2), vascular endothelial growth factor (VEGF) and sonic hedgehog (Shh) are all up-regulated in the hippocampus after acute seizures (Lowenstein, *et al.*, 1993, Gall, *et al.*, 1994, Riva, *et al.*, 1994, Gómez-Pinilla, *et al.*, 1995, Shetty, *et al.*, 2003, Croll, *et al.*, 2004, Shetty, *et al.*, 2004, Banerjee, *et al.*, 2005). Increased levels of GABA in the dentate gyrus during the early post-seizure period may also positively regulate hippocampal neurogenesis, as studies show that GABA has crucial roles in regulating various steps of adult neurogenesis, including progenitor cell proliferation, migration and differentiation of neuroblasts, and synaptic integration of adult-born neurons (Ge, *et al.*, 2007). Further, increased levels of neuropeptide Y (NPY) found typically after acute seizures may enhance the proliferation of neural progenitor cells in the dentate gyrus, as studies have shown that neural progenitor cells increase neurogenesis in the presence of NPY (Howell, *et al.*, 2003, Howell, *et al.*, 2005, Howell, *et al.*, 2007, Rodrigo, *et al.*, 2010).

3.2 Abnormal migration of adult-born cells after acute seizure activity

As discussed in Section 2.1, aberrant migration of progenitor cells is observed in response to seizure-induced cell loss. The precise reason for aberrant migration of adult-born granule cells is still being examined. However, it has been shown that acute seizures do not significantly influence the proliferation of nestin-expressing neural stem cells but rather stimulate the division of Dcx-expressing transient amplifying cells and immature neurons (Jessberger, *et al.*, 2005). Based on this, it has been proposed that delayed proliferation during the process of neurogenesis interferes with migration, leading to a significant dispersion of Dcx-positive cells away from the granule cell layer into the dentate hilus and the molecular layer. In addition, recent evidence suggests that a loss of the migration guidance cue Reelin due to seizure activity may lead to aberrant chain migration of newly born dentate granule cells (Gong, *et al.*, 2007). Interneuron subsets typically lost in human and experimental TLE express Reelin, and dentate granule progenitor cells express the downstream Reelin signaling molecule Disabled 1 (Dab1). Prolonged seizure activity has been shown to decrease Reelin expression in the adult rat dentate gyrus and increase Dab1 expression in hilar ectopic neuroblasts. Further, exogenous Reelin increased detachment of chain-migrating neuroblasts in dentate gyrus explants, and blockade of Reelin signaling

increased chain migration (Gong, *et al.*, 2007). These observations suggest that Reelin modulates dentate gyrus progenitor cell migration and loss of Reelin expression in the epileptic adult hippocampus may contribute to ectopic chain migration and aberrant integration of newborn granule cells.

3.3 Potential mechanisms underlying decreased neurogenesis in chronic TLE

The precise mechanisms underlying decreased neurogenesis in chronic TLE are unknown, however several explanations have been proposed [for review see (Kuruba, *et al.*, 2009)]. While a role for chronic inflammation is an attractive hypothesis, this has been ruled out as only minimal density of activated microglia have been observed in the hippocampus during chronic epilepsy (Hattiangady, *et al.*, 2004). One potential mechanism may be a reduction in mitogenic factors such as FGF-2, BDNF and insulin-like growth factor 1 (IGF-1) in the epileptic hippocampus resulting in an unfavourable neurogenic environment (Hattiangady, *et al.*, 2004, Shetty, *et al.*, 2004). As neuronal differentiation rather than progenitor cell number and proliferation is predominantly affected in chronic TLE, the presence of an unfavourable hippocampal milieu due to reduction of mitogenic factors currently remains the most plausible mechanism (Altar, *et al.*, 2004, Chan, *et al.*, 2008).

3.4 Potential mechanisms of increased neurogenesis after TBI

Several studies have shown that neurotrophic factor expression is significantly altered after TBI. Some neurotrophic factors such as NGF and BDNF are up-regulated, while others such as neurotrophic factor-3 (NT-3) have been shown to be down-regulated (Yang, *et al.*, 1996, Hicks, *et al.*, 1997, Oyesiku, *et al.*, 1999, Truettner, *et al.*, 1999). Interestingly, BDNF levels after TBI have been reported to be increased to a greater extent in older rather than younger animals (Shah, *et al.*, 2006), despite the well known fact that older age is correlated with a worse outcome after TBI. Results from the CCI model also suggest that FGF-2 is up-regulated, potentially stimulating post-traumatic neurogenesis (Yoshimura, *et al.*, 2003). In addition, up-regulation of VEGF has been observed following both CCI (Sköld, *et al.*, 2005, Lu, *et al.*, 2011) and lateral FPI (Lee, *et al.*, 2010), and may be involved in enhancing neurogenesis and promoting migration following TBI as observed in rodent models of focal ischemia.

3.5 Potential mechanisms of increased neurogenesis after stroke

Potential mediators of stroke-induced cell proliferation and neurogenesis are beginning to be identified (Yan, *et al.*, 2006, Zhang, *et al.*, 2008, Leker, *et al.*, 2009, Luo, 2011). Through infusion studies, a range of growth factors have been identified to play a role in regulating SVZ neurogenesis following focal ischemia. Factors such as GDNF, VEGF, EGF, transforming growth factor-α (TGF-α) and IGF-1 have all been shown to increase progenitor cell proliferation in the ipsilateral SVZ following ischemic damage (Jin, *et al.*, 2002, Sun, *et al.*, 2003, Schänzer, *et al.*, 2004, Kobayashi, *et al.*, 2006, Ninomiya, *et al.*, 2006, Yan, *et al.*, 2006, Leker, *et al.*, 2009, Guerra-Crespo, *et al.*, 2010). VEGF was shown not only to increase progenitor cell proliferation, but to also increase the survival of adult-born neurons and induce neurite outgrowth in newborn cells (Wang, *et al.*, 2009, Zheng, *et al.*, 2010). Another study (Ninomiya, *et al.*, 2006) demonstrated that EGF infusion into the ischemic brain caused the number of Type C transient amplifying cells to increase and the number of neuroblasts to decrease. However, 6 weeks after the discontinuation of EGF infusion, a significant

increase in the number of neuroblasts was found, both in the ischemic striatum and SVZ. Co-administration of EGF and FGF2 into the lateral ventricle for 5 days in a rodent model of global cerebral ischemia has been shown to increase the proliferative rate and differentiation of newly generated hippocampal neurons (Nakatomi, *et al.*, 2002). The newborn neurons exhibited histological markers of young and maturing neurons, appropriate connectivity and synapse formation as well as electrophysiological characteristics of young neurons. Further, memory deficits were resolved in EGF and FGF2 treated rats within 90 days. Erythropoietin (EPO) also plays a role in regulating compensatory SVZ neurogenesis following ischemic injury. EPO stimulates the maturation, differentiation and survival of hematopoietic progenitor cells and promotes angiogenesis. While EPO and its receptor are only weakly expressed in normal adult brain, expression of EPO and its receptor is greatly increased in neurons, neural progenitor cells, glia and cerebrovascular endothelial cells in response to brain injury. Infusion of EPO into the adult lateral ventricles results in a decrease in the number of neural progenitor cells in the SVZ, an increase in neural precursor cells migrating to the olfactory bulb and an increase in the generation of new olfactory bulb neurons (Shingo, *et al.*, 2001). Further, delivery of EPO for 7 days following 7 days of EGF treatment has been shown to enhance SVZ neurogenesis and direct progenitor cell migration to the ischemic cortex, resulting in cortical regeneration and functional recovery (Kolb, *et al.*, 2006). It is thought that EPO might affect the number of daughter cells that stay in cell cycle and promote cell cycle exit and terminal differentiation with preference towards neuronal differentiation (Shingo, *et al.*, 2001). Systemic administration of BDNF has also been shown to induce neurogenesis and improve sensorimotor function in a rodent model of ischemic injury (Schabitz, *et al.*, 2007). In addition, a range of signaling pathways appear to be important in regulating compensatory neurogenesis following ischemic injury. These include notch, retinoid, bone morphogenic protein, tumor necrosis factor-alpha (TNF-α) and Shh pathways (Androutsellis-Theotokis, *et al.*, 2006, Chou, *et al.*, 2006, Iosif, *et al.*, 2008, Plane, *et al.*, 2008, Zhang, *et al.*, 2008, Sims, *et al.*, 2009, Wang, *et al.*, 2009).

3.6 The role of chemoattractants in regulating neural progenitor cell migration following brain injury

A fundamental issue concerning progenitor cell migration in the adult brain is to understand the extracellular cues and mechanisms that allow the persistence of normal migratory pathways, as well as the recruitment of progenitor cells into the areas of neural damage. Increasing evidence indicates the involvement of developmental signals that are maintained in restricted regions of the adult brain, including factors such as extracellular matrix molecules, Eph-Ephrin interactions, neuregulins, and a range of chemoattractant and chemorepulsive molecules [for review see (Cayre, *et al.*, 2009)]. In addition, several mechanisms and migratory tracks have been proposed for the guidance of migrating progenitor cells towards regions of neural damage. These include migration along: 1) myelinated fiber tracks; 2) radial processes; and 3) blood vessels [for review see (Cayre, *et al.*, 2009)]. Besides these mechanisms, inflammation-induced chemoattraction plays a major role in progenitor cell migration following neural cell loss. Upon insult or infection, the brain exhibits a profound innate response, characterised predominantly by robust activation of microglia (resident macrophages of the CNS). Activated microglia play a dual role, scavenging the damaged and dying neurons as well as initiating a prompt local inflammatory reaction. The inflammatory response involves production of pro-inflammatory cytokines and chemokines, as well as various reactive nitrogen and oxygen

species. Cytokines released by microglia subsequently activate resident astrocytes, which again release cytokines. Peripheral macrophages are recruited into the brain by chemotaxis in response to a superfamily of cytokines called chemokines. Chemokines are small, secreted proteins that play crucial roles in leukocyte migration under normal conditions as well as during neuroinflammatory responses. Following injury to the adult brain, a range of cytokines and chemokines have been shown to be up-regulated in the region of neural cell death, including GRO-α, IL-8, IP-10, MCP-1, MCP-2, MIP-1α , RANTES , SDF-1α , and TNF-α (Mcmanus, *et al.*, 1998, Das, *et al.*, 2008, Gordon, *et al.*, 2009, Whitney, *et al.*, 2009). In addition, chemokine receptors, including CXCR1, CXCR2, CXCR4, CXCR7, CCR1, CCR2, CCR3 and CCR5, are widely expressed on neural progenitor cells (Ji, *et al.*, 2004, Tran, *et al.*, 2004, Gordon, *et al.*, 2009). The expression of chemokine receptors on neural progenitor cells signifies the crucial roles played by chemokines in guiding progenitor cell migration and the influence these factors have in the recovery process in the injured CNS.

While a number of cytokines and chemokines involved in the inflammatory process have been demonstrated to play a role in directing progenitor cell migration, MCP-1 and SDF-1α and their receptors have been the most widely examined and clearly regulate the directed migration of endogenous neural progenitor cells from the SVZ to the injured brain following either ischemic or excitotoxic neural cell loss (Imitola, *et al.*, 2004, Belmadani, *et al.*, 2006, Robin, *et al.*, 2006, Yan, *et al.*, 2006, Gordon, *et al.*, 2009). The SDF-1α receptors CXCR4 and CXCR7 are highly expressed on neural progenitor cells. SDF-1α expression is highly up-regulated in reactive astrocytes, microglia and endothelial cells in the ischemic striatum during several weeks after focal ischemic injury (Thored, *et al.*, 2006) and has been shown to induce the migration of progenitor cells *in vitro* (Peng, *et al.*, 2004) and *in vivo* to areas of hypoxic-ischemic-induced inflammation via CXCR4 signalling pathways (Imitola, *et al.*, 2004, Robin, *et al.*, 2006). The chemokine MCP-1 is also up-regulated in response to inflammation and induces the migration of neural progenitor cells. The MCP-1 receptor CCR2 is expressed by neural progenitor cells and MCP-1 recruits progenitor cells to the site of brain inflammation by binding to CCR2 and inducing their migration (Widera, *et al.*, 2004, Belmadani, *et al.*, 2006, Gordon, *et al.*, 2009). These studies clearly indicate that neuroinflammation and the resulting expression of cytokines and chemokines play a major role in directing the migration of progenitor cells in the injured brain. However, inflammatory cues involved in directing the migration of progenitor cells can also contribute to decreased survival of these migrating cells, creating juxtaposition between regeneration and ongoing cell loss and highlighting the complexity of the neuroinflammatory environment: on one hand it is useful for attracting progenitor cells to the appropriate region for neural replacement, but on the other hand it prevents efficient cell replacement by affecting the survival abilities of the migrating precursor cells (Whitney, *et al.*, 2009). The opposing properties of neuroinflammation therefore complicates the development of therapeutic strategies involving the use of cytokines or chemokines.

4. Therapeutic strategies

4.1 Chronic TLE

The major issue associated with chronic TLE is the observed reduction in hippocampal neurogenesis and potential contribution this plays to the persistence of spontaneous seizures, learning and memory deficits, and depression prevalent in chronic TLE. Based on studies in animal models of brain disease and injury, the following strategies may provide

mechanisms by which to increase hippocampal neurogenesis in chronic epilepsy; administration of neurotrophic factors, physical exercise, exposure to an enriched environment and antidepressant therapy [for review see (Kuruba, *et al.*, 2009)]. Administration of neurotrophic factors is relevant as many factors that promote neurogenesis (e.g: BDNF, FGF-2, IGF-1) are reduced in chronic epilepsy (Hattiangady, *et al.*, 2004, Shetty, *et al.*, 2004). Supporting this, a range of studies have demonstrated that administration of neurotrophic factors to both the normal and injured adult rodent brain can enhance hippocampal neurogenesis (Lichtenwalner, *et al.*, 2001, Yoshimura, *et al.*, 2001, Jin, *et al.*, 2003, Scharfman, *et al.*, 2005, Rai, *et al.*, 2007, Paradiso, *et al.*, 2009, Paradiso, *et al.*, 2011). Performing physical exercise and environmental enrichment have also been shown to enhance hippocampal neurogenesis, potentially through increased expression of a range of mitogenic factors such as BDNF, FGF2, NGF, IGF-1 and VEGF as well as phosphorylation of cAMP-response binding protein (CREB) (Nithianantharajah, *et al.*, 2006, Van Praag, 2008, Llorens-Martín, *et al.*, 2009, 2010, Lafenetre, *et al.*, 2011) and may provide an appealing non-invasive therapeutic approach for the treatment of chronic TLE (Dhanushkodi, *et al.*, 2008, Arida, *et al.*, 2009). Antidepressant therapy in chronic TLE is another interesting approach for increasing neurogenesis and reducing cognitive impairments, as antidepressant therapy enhances hippocampal neurogenesis probably via increases in levels of serotonin, noradrenaline, BDNF, CREB and a range of other mitogenic factors (Sahay, *et al.*, 2007, Thomas, *et al.*, 2008, Lanni, *et al.*, 2009). In particular, a recent study demonstrated that repeated administration of the antidepressant agent citalopram counteracted kainic acid-induced neuronal loss and dispersion of PSA-NCAM-positive cells within the granule cell layer of the hippocampus (Jaako, *et al.*, 2011). Citalopram also counteracted the downregulation of Reelin on both mRNA and protein levels. As decreased neurogenesis, cognitive impairment and depression coexist in chronic epilepsy, prolonged antidepressant treatment may provide an effective strategy for easing these problems.

4.2 Traumatic brain injury

For TBI, it remains unclear whether compensatory neurogenesis contributes at all to functional recovery. However, several studies have examined the effect of administering neurogenic agents to rodent models of TBI to assess the effect on neuronal replacement and functional recovery. Administration of EGF or FGF-2 into the lateral ventricles following FPI has been shown to increase the rate of memory recovery in the Morris Water Maze, and produce a concomitant increase in the number of new hippocampal neurons co-labeled with BrdU and NeuN (Sun, *et al.*, 2009, Sun, *et al.*, 2010). Interestingly, intraventricular administration of the calcium-binding protein S100β following TBI has also been shown to increase the percentage of newly generated hippocampal neurons expressing NeuN and improve cognitive recovery in the Morris water Maze [for review see (Kleindienst, *et al.*, 2007)]. This is in conflict with clinical data in which an increase in CSF levels of S100β is correlated with poor prognosis in patients with TBI. Delivery of VEGF to the lateral FPI model has been shown to significantly increase the number of BrdU labeled adult-born neurons in the adult hippocampus, but does not change the number of BrdU labeled newborn cells per se (Lee&Agoston, 2010) suggesting that in the hippocampus VEGF predominantly mediates survival of adult-born neurons rather than progenitor cell proliferation. In contrast, Thau-Zuchman and colleagues (Thau-Zuchman, *et al.*, 2010) observed an increase in the number of proliferating cells in the SVZ and the perilesion cortex following infusion of VEGF into the lateral ventricles of mice after TBI. Further, while

functional outcome was significantly improved in mice treated with VEGF compared to vehicle treated animals following TBI, fate analysis demonstrated that most newborn cells differentiated into astrocytes and oligodendroglia, and only a few cells differentiated into neurons (Thau-Zuchman, *et al.*, 2010).

The effect of mitogen support on hippocampal neurogenesis following TBI has also been examined using transgenic models. FGF-2(-/-) mice subjected to CCI injury exhibit a reduction in the number of both BrdU-positive cells and BrdU-positive neurons when compared to FGF-2(+/+) mice. In contrast, over-expression of FGF-2 by intracerebral injection of herpes simplex virus-1 amplicon vectors encoding for this factor increased both the number of dividing cells and BrdU-positive neurons (Yoshimura, *et al.*, 2003). This suggests that FGF-2 up-regulates neurogenesis and protects the survival of adult-born neurons in the adult hippocampus after TBI. BDNF has also been shown to play a role in regulating the survival of adult-born immature neurons in the hippocampus following TBI, with the level of adult-born immature neuron death in the dentate gyrus significantly increased in BDNF conditional knockout mice following TBI.

A number of studies have demonstrated that the injured brain can be stimulated to promote angiogenesis and neurogenesis, which are coupled restorative processes that contribute to functional recovery in both TBI and stroke [for review see (Xiong, *et al.*, 2010)]. Studies have demonstrated that intraperitoneal administration of EPO post-TBI significantly increases BDNF expression and enhances hippocampal neurogenesis with subsequent improvement in sensorimotor and spatial learning functions (Meng, *et al.*, Lu, *et al.*, 2005, Xiong, *et al.*, 2008, Xiong, *et al.*, 2010). Statins also show neurorestorative effects in animal models of TBI through the induction of angiogenesis and neurogenesis. Simvastatin treatment provides long-lasting (3 month) functional improvement after TBI in rats. This was coupled with increased expression of VEGF and BDNF and enhanced in the dentate gyrus of rats following TBI (Lu, *et al.*, 2007, Wu, *et al.*, 2008). Clinical trials investigating the use of either EPO or CEPO, or the use of statins for the treatment of TBI are currently being undertaken [for review see (Xiong, *et al.*, 2010)].

4.3 Stroke

A range of therapeutic strategies promoting regeneration in stroke are being investigated. However, some of the most interesting approaches are based around the use of statins and the phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil (Xiong, *et al.*, 2010). Statins have been shown to induce angiogenesis, neurogenesis and synaptogenesis, and to enhance functional recovery after stroke in rats (Chen, *et al.*, 2003). It is thought that expression of BDNF, VEGF and VEGFR2, and regulation of Notch signaling activity contribute to these regenerative processes (Chen, *et al.*, 2005, Chen, *et al.*, 2008). Clinical trials for both lovastatin and simvastatin in stroke patients are currently being undertaken [for review see (Xiong, *et al.*, 2010)]. Given the wide use of statins, their favourable safety profile, rare serious adverse effects and the extensive preclinical data showing neuroprotection and neurorestoration in rodent models of stroke, further clinical studies investigating the potential use of statins to promote neuroregeneration following stroke are warranted. The PDE5 inhibitor sildenafil has also been shown to promote neurogenesis and reduce functional deficits when administered to rats either 2 or 24 hours after ischemic injury (Zhang, *et al.*, 2002), or for 7 consecutive days starting 7 days following focal ischemia (Zhang, *et al.*, 2006). Further, treatment of ischemic stroke with a long-acting PDE5 inhibitor tadalafil improves functional recovery, which is associated with increases in brain cGMP levels and enhanced

angiogenesis and neurogenesis (Zhang, *et al*., 2006). Treatment of ischemic stroke with EPO is also under investigation, with additional studies examining the use of nonhematopoietic EPO analogues such as CEPO. As discussed in Section 4.2, EPO has been shown to promote both neurogenesis and angiogenesis, resulting in functional recovery in rodent models of focal ischemic injury. Clinical trials investigating the therapeutic application of EPO or CEPO for the treatment of stroke are currently being undertaken [for review see (Xiong, *et al*., 2010)].

5. Conclusions

The presence of both neural and glial progenitor cells in the adult central nervous system (CNS), and the capacity of these cells to migrate through this mature structure to areas of pathological damage and injury raises hope for the development of new therapeutic strategies to treat brain injury. Although at present time the compensatory neurogenesis described after various types of brain injuries appears to be modest, the development of a strategy promoting the proliferation, directed mobilization and phenotypic induction of endogenous progenitor cells to areas of neural cell loss remains of high interest. However, the development of novel neuroregenerative strategies focusing on the promotion of compensatory adult neurogenesis will only be achieved once we fully understand the mechanisms promoting the response of endogenous progenitor cells to neural injury and cell loss. An important factor that needs to be addressed when investigating therapeutic strategies by which to enhance compensatory neurogenesis following brain injury is whether adult-born cells become functional and integrate appropriately into existing circuitry and contribute to the recovery process, or whether they just enhance or restore the functionality and survival of existing dysfunctional cells. While striving to identify potential factors or the redirected use of current pharmaceuticals to promote compensatory neurogenesis for the treatment of brain injury, caution must also be taken. Post-traumatic epilepsy is a fairly common morbidity associated with both stroke and TBI and one postulated mechanism for this is that aberrant neurogenesis serves as the epileptic focus (Parent, *et al*., 2008). Therefore, any strategy aimed at enhancing neurogenesis may inadvertently result in this and other unwanted side effects. In addition, since many strategies aimed towards enhancing neurogenesis promote cell growth, it remains a possibility that increasing proliferation may result in potentially unwanted tumour growth. Thus, while enhancing compensatory neurogenesis for the treatment of brain injury remains an exciting and potentially revolutionary therapeutic strategy, many issues regarding specificity, mechanism and potential toxicity need to be thoroughly investigated before meaningful clinical intervention can occur.

6. References

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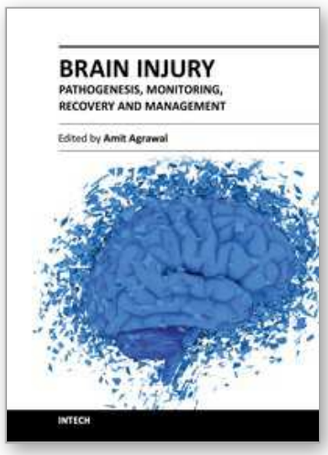

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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