Review

Plasticity following Injury to the Adult Central Nervous System: Is Recapitulation of a Developmental State Worth Promoting?

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ABSTRACT

The adult central nervous system (CNS) appears to initiate a transient increase in plasticity following injury, including increases in growth-related proteins and generation of new cells. Recent evidence is reviewed that the injured adult CNS exhibits events and patterns of gene expression that are also observed during development and during regeneration following damage to the mature peripheral nervous system (PNS). The growth of neurons during development or regeneration is correlated, in part, with a coordinated expression of growth-related proteins, such as growth-associated-protein-43 (GAP-43), microtubule-associated-protein-1B (MAP1B), and polysialylated-neural-cell-adhesion-molecule (PSA-NCAM). For each of these proteins, evidence is discussed regarding its specific role in neuronal development, signals that modify its expression, and reappearance following injury. The rate of adult hippocampal neurogenesis is also affected by numerous endogenous and exogenous factors including injury. The continuing study of developmental neurobiology will likely provide further gene and protein targets for increasing plasticity and regeneration in the mature adult CNS.

Key words: GAP-43; growth associated protein; MAP1B; PSA-NCAM; regeneration; traumatic brain injury

INTRODUCTION

CENTRAL NERVOUS SYSTEM (CNS) neurons in adult mammals have been traditionally associated with a reduced or limited regenerative response to injury, in comparison to CNS neurons of embryonic or neonatal animals. During development, the CNS can exhibit dramatic regenerative responses including the growth of fibers through and beyond lesions and reconnection to targets (Woodward et al., 1993; Nicholls et al., 1994; Saunders et al., 1995).

Reviewed below is recent evidence that following in-

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jury, the mature CNS exhibits events and patterns of gene expression that are normally observed during developmental stages. Experimentally induced CNS injuries including lesions, seizures, ischemic insults, and brain trauma result in increased rates of neurogenesis and expression of growth-related proteins. It is now established that neurogenic regions within the sub-ventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus of the adult mammalian brain can generate new neurons, astrocytes and oligodendrocytes (Johansson et al., 1999; Gage, 2000). The molecular mechanisms underlying the differentiation, migration and integration of these new cells to the brain has begun to be very intensively investigated. As direct remnants of the embryonic neurectoderm, these cells are likely to respond to the patterning signals that promote neurogenesis in the embryo. Is neurogenesis mechanistically similar in the adult and the embryo? Understanding the developmental process may provide insight into the regenerative capacity of the adult brain and accelerate the development of strategies to manipulate this neurogenic potential.

Although increased neuronal expression of growth-related proteins and neurogenesis after CNS injury may lead to desired connections, as seen during neuronal development or peripheral nervous system (PNS) regeneration, they may also contribute to formation of aberrant networks following injury to the adult CNS. Therefore, caution must be exercised when promoting post-injury recapitulation of a developmental state. A crucial event for functional neuronal regeneration is the ability to rebuild appropriate circuitry, implicating proper growth and guidance of the newly forming axons and dendrites towards the target cells. This process is under the control of intrinsic molecules within the growth cones and extrinsic guidance molecules (either attractant or repellent), sometimes acting over long distances in the CNS. These molecules include netrins, semaphorins, ephrins, slits and cell adhesion molecules all of which are transcriptionally regulated, constituting a system able to generate diverse and sometimes opposed outcomes (Yu and Bargmann, 2001; Grunwald and Klein, 2002). Axonal growth in the adult CNS is inhibited by some of these molecules via binding to the Nogo-p75 receptor complex, including myelin-associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (Omgp) and, most notably, NogoA, a myelin-associated neurite outgrowth inhibitor expressed by oligodendrocytes but not by Schwann cells, perhaps contributing to the failure of regeneration observed in the adult CNS (Chen et al., 2000; Grandpre et al., 2000; Prinjha et al., 2000; Wang et al., 2002). Whether incomplete regeneration following CNS injury to the adult brain results from a lack of intrinsic growth capacity or the presence of an extrinsic growth

inhibitory environment remains to be established. Here, we will focus on three molecules involved in CNS development and repair, growth-associated protein-43 (GAP-43), microtubule-associated protein-1B (MAP1B), and polysialylated–neural cell adhesion molecule (PSA-NCAM), exploring the responses of theses factors to CNS injury. Endogenous neurogenesis and its potential utility for repair of the injured CNS will also be reviewed.

GROWTH-RELATED PROTEINS

GAP-43: Distribution and Function

The distribution of GAP-43 message and protein during nervous system development has been well described both in rat (Oestreicher and Gispen, 1986; Jacobson et al., 1986; de la Monte et al., 1989; Dani et al., 1991; Mahalik et al., 1992) and in human (Ng et al., 1988; Neve et al., 1988; Milosevic et al., 1995; Kanazir et al., 1996). GAP-43 message and protein distribution have also been characterized in the normal adult rat brain (Benowitz et al., 1988; de la Monte et al., 1989; Li et al., 1993; Kruger et al., 1993; Curtis et al., 1993a; Casoli et al., 1996), in the CNS of adult cat and monkey (Linda et al., 1992), and in adult human brain (Neve et al., 1987; Ng et al., 1988; Neve et al., 1988). In the adult rat, GAP-43 is expressed in neurons of the forebrain regions, and expression is still moderately high in the entorhinal cortex (de la Monte et al., 1989), and strikingly high in the mature hippocampus and olfactory bulb, brain regions that are associated with continuing structural plasticity. Dopaminergic neurons of the substantia nigra projecting to the striatum also maintain higher than the average levels of GAP-43 mRNA in the adult rat (Clayton et al., 1994).

GAP-43 is perhaps the most well-studied of all growth-related proteins. It is an acidic membrane protein, present at high levels in the growth cone during neurite outgrowth and synaptogenesis, and is down-regulated as neurites begin to interact with their target cell and synaptic rearrangement is completed (Skene et al., 1986). The rat protein is 226 amino acids in length and contains an N-terminus membrane-binding region, a calmodulin-binding domain that is Ca^{2+}-independent, and several phosphorylation sites, including serine 41 (Basi et al., 1987; Benowitz and Routtenberg, 1997). Phosphorylation at serine 41 by protein kinase C–beta (PKC-β) regulates calmodulin binding and modulates the ability of GAP-43 to facilitate neural growth (He et al., 1997). Dephosphorylation of GAP-43 is mediated by phosphatases including calcineurin (Liu and Storm, 1989). Inhibition of calcineurin by FK506 is concomitant with axonal outgrowth (Steiner et al., 1992; Lyons et al., 1994). Convergent evi-

dence from several laboratories indicates that GAP-43 plays a key role in the guidance of axons and modulating the formation of new connections between neurons (Oestreicher and Gispen, 1986; Fishman, 1996; Benowitz and Routtenberg, 1997; Irwin and Madsen, 1997). An inverse pattern of myelination and GAP-43 expression in the adult rat CNS has been reported, suggesting that myelin-associated neurite growth inhibitors are involved in regulating the stability of neural connections (Kapfhammer and Schwab, 1994). GAP-43 has also been suggested to affect synaptic plasticity as it has been shown to regulate presynaptic properties and to dramatically enhance long-term potentiation (LTP) and learning (Routtenberg et al., 2000; Hulo et al., 2002). Overexpression of GAP-43 in neurons of adult transgenic mice leads to spontaneous nerve sprouting and greatly potentiates induced sprouting in the terminal fields of hippocampus mossy fibers and at the neuromuscular junction with complementary and synergistic activities with cytoskeleton-associated-protein 23 (CAP-23) (Aigner et al., 1995; Caroni et al., 1997). However, mice lacking GAP-43 have a delayed but grossly normal CNS development before dying in the early postnatal period (Strittmatter et al., 1995). In this mutant strain, retinal axons remain trapped in the chiasm for 6 days, unable to navigate past this decision point, before entering the appropriate tracts over the subsequent weeks of life. Nonetheless, dorsal root ganglion (DRG) neuron culture explants from these animals extend neurites and form growth cones in the absence of GAP-43. These studies suggest that, during development, this protein is not essential for neurite outgrowth or growth cone formation per se, but rather is required to amplify pathfinding signals from the growth cone.

Factors That Modulate GAP-43 Expression

Factors that affect neuronal expression of GAP-43 are numerous and include a variety of growth factors, hormones, and receptor-specific agonists and antagonists. *In vitro*, GAP-43 mRNA and protein expression is increased by basic fibroblast growth factor (FGF-2), epidermal growth factor (EGF), insulin-like growth factor–1 (IGF-1) and -2 (IGF-2), ciliary neurotrophic factor (CNTF), neurotrophin-3 (NT-3), and nerve growth factor (NGF) (Federoff et al., 1988; Costello et al., 1990; Mohiuddin et al., 1995; McNamara and Routtenberg, 1995; Piehl et al., 1998). NGF stimulates phosphorylation (Meiri and Burdick, 1991) as well as translocation of GAP-43 protein to the plasma membrane (Van Hooff et al., 1989). Neuronal GAP-43 expression has also been shown to be increased *in vivo* by administration of brain-derived growth factor (BDNF), neurotrophin-4/5 (NT-4/5), FGF-2, and NGF (Kobayashi et al., 1997; Fournier et al., 1997;

Kawamata et al., 1997; Mearow, 1998; Schicho et al., 1999). The application of FGF-2, CNTF, or IGF-2 has also been demonstrated to attenuate decreases in GAP-43 seen at neuromuscular junctions during normal postnatal development (Piehl et al., 1998), effectively prolonging the developmental patterns of GAP-43 expression.

Expression of GAP-43 mRNA is also increased by a number of gonadal hormones. *In vivo* expression is increased by estrogen (Lustig et al., 1991), the estrogen receptor agonist diethylstilbestrol, testosterone, and the androgen receptor agonist dihydrotestosterone (Shughrue and Dorsa, 1994) and is decreased by estrogen (tamoxifen) or androgen (cyproterone acetate) receptor antagonists (Shughrue and Dorsa, 1994). A regulatory role for endogenous gonadal hormones on GAP-43 expression has been postulated, and may account for decreased levels of GAP-43 observed within CNS regions of aged animals. In female rats, an age-related decline in GAP-43 mRNA hybridization signal can be prevented with estrogen treatment (Singer et al., 1996).

Glutamate receptors and adrenal steroids may also regulate GAP-43 expression. Activation of non-NMDA receptors in hippocampal slice cultures after transection of the Schaffer collateral pathway appears necessary for GAP-43 expression, reactive sprouting and the recovery of synaptic transmission (McKinney et al., 1999). Congruent with this observation, studies of cultured cerebellar neurons indicate that exposure to non-NMDA glutamate receptor antagonists, NMDA receptor antagonists, or metabotropic receptor glutamate agonists each decrease levels of GAP-43 mRNA. Furthermore, exposure to the NMDA receptor antagonist MK-801 blocks induction of GAP-43 mRNA in hippocampal granule neurons following kainic acid administration (McNamara and Routtenberg, 1995; Console-Bram et al., 1998). Paradoxically, NMDA receptor antagonists have been shown to enhance neurogenesis (Cameron et al., 1995; Gould et al., 1997). Although treatment with MK-801 has provided neuroprotection following experimental spinal injury or traumatic brain injury (TBI) in adult animals (Gomez-Pinilla et al., 1989; Yum and Faden, 1990), GAP-43 mRNA expression is diminished *in vivo* following MK-801 administration during post-natal development (Cantallops and Routtenberg, 1999).

Likewise, although high dose glucocorticosteroid therapy has become the standard of care for hyperacute management of non-penetrating spinal cord injury, and its use in TBI continues into the present day (Segatore, 1999), adrenal steroids have a negative regulatory effect upon expression of GAP-43. GAP-43 mRNA expression is decreased following corticosteroid administration in vivo (Gonzalez Deniselle et al., 1999) and *in*

vitro (Federoff et al., 1988; Costello et al., 1990; Jap Tjoen et al., 1992), and is increased *in vivo* following adrenalectomy (Chao et al., 1998). These effects suggest that some neuroprotective therapies may concurrently and paradoxically affect plasticity by decreasing expression of GAP-43, and that relationships between neuroprotection and regeneration are complex and need to be further explored.

Alterations in GAP-43 Expression following Brain Injury

The expression of GAP-43 appears to be a common event following injuries to the adult nervous system. An upregulation and rapid transport of GAP-43 to distal axonal segments including growth cones has been observed within axotomized neurons and afferents that sprout in response to denervation (Hoffman, 1989). Post-injury increases in GAP-43 mRNA and protein expression may correlate with the ability of CNS neurons to extend processes into a permissive environment such as PNS grafts, and may identify neurons that are capable of undergoing axonal regeneration or sprouting.

The first report that GAP-43 expression is altered in injured neurons within the adult brain described increased GAP-43 mRNA in hippocampal granule cells in conjunction with mossy fiber sprouting after seizures (Meberg et al., 1993). Elevated GAP-43 mRNA and protein following induced seizure activity has subsequently been observed in granule neurons and in sprouting mossy fibers within the supragranular layer of kainic acid-lesioned rats (Bendotti et al., 1994b; Cantallops and Routtenberg, 1996), with GAP-43 protein within the inner molecular layer (iml) of the DG ultrastructurally localizing to mossy fiber boutons (Bendotti et al., 1994a). Increased GAP-43 has also been demonstrated within the iml of the DG following pilocarpine-induced status epilepticus (Naffah-Mazzacoratti et al., 1999). Kindling, an animal model of epilepsy in which repeated electrical stimulation produces sprouting of fibers, also results in increased GAP-43 expression. Electrical stimulation of the ventral hippocampus produces elevated GAP-43 mRNA and protein within DG granule cells and the amygdala-piriform cortex (Elmer et al., 1996), while perforant path kindling has been shown to lead to increased GAP-43 immunoreactivity within the CA1 stratum lacunosum moleculare and the DG inner and outer molecular layers (Dalby et al., 1995). These increases in GAP-43 expression have been suggested to underlie structural rearrangements within the hippocampus due to seizure-induced neuronal damage. In humans, temporal lobe epilepsy associated with hippocampal sclerosis was also shown to be accompanied with an increase in GAP-43 together with synaptophysin immunoreactivity in the supragranular layer of the DG, suggestive of mossy fiber sprouting (Proper et al., 2000). However, some studies suggest that, in mice, induction of GAP-43 is not a necessary component of the sprouting response since a lack of GAP-43 mRNA induction was observed following kainic acid-induced behavioral seizures (Schauwecker et al., 1995, 2000; McNamara and Routtenberg, 1995; McNamara et al., 1996; Kinney et al., 1996). These observations might reflect different transcriptional regulatory mechanism between mice and rats and are related to distinct behavior and pharmacological response in these species.

There is a plethora of reports documenting increases in GAP-43 within axotomized adult CNS neurons. Transection of the mature axons of CA3 pyramidal cells in hippocampal slice cultures leads to the formation of new axon collaterals by these cells that are GAP-43 immunopositive (McKinney et al., 1997). GAP-43 immunostaining is prominent within commissural afferent fibers by two weeks following fimbria/fornix or perforant pathway lesion (Patanow et al., 1997). Increased expression of GAP-43 mRNA and/or protein has also been reported in facial and rubrospinal neurons (Tetzlaff et al., 1989, 1991), in central processes of axotomized primary afferents in the adult spinal cord (Coggeshall et al., 1991), in central catecholaminergic and serotonergic axons (Alonso et al., 1995), and in motoneurons (Linda et al., 1992) following axotomy. After unilateral removal of the olfactory bulb, expression of GAP-43 in the olfactory axonal bundles has been shown to be elevated in the acute period (3 and 4 days) following injury (Yamashita et al., 1998). Following axotomy of olfactory bulb mitral cells, enhanced expression of GAP-43 mRNA is reported to persist for 10 days post-lesion, but declines to control levels by 4 weeks (Verhaagen et al., 1993). Axotomy of retinal ganglion cells induces an increase in GAP-43 mRNA (Fournier et al., 1997) and immunoreactivity (Doster et al., 1991), and regenerating axons in PNS grafts derive specifically from GAP-43 re-expressing retinal ganglion cells (Schaden et al., 1994). Overexpression of GAP-43 in the neurons of adult transgenic mice has been shown to induce partial regeneration in Purkinje cells in response to axotomy (Buffo et al., 1997). Common findings of post-injury increases in GAP-43 expression in axotomized CNS neurons may suggest that re-expression following injury reflects a transient increase in regenerative capacity. However, following unilateral entorhinal cortex lesion, no dramatic increase in GAP-43 mRNA expression was observed either in the dentate granule cells or in neurons giving rise to the reinnervating fibers (Stew-

ard, 1995). As GAP-43 expression alone does not appear to be sufficient for regeneration to occur, expression of other genes may be necessary to develop a full regenerative program (Strata et al., 1999).

Increased GAP-43 expression has also been observed during reactive synaptogenesis in response to deafferentation. GAP-43 mRNA increases in both ipsilateral and contralateral hilar and CA3 pyramidal neurons and the cell bodies of origin for the commissural/associational pathway following partial deafferentation of the hippocampus (Schauwecker et al., 1995, 2000). Following unilateral entorhinal cortex lesions, a two-fold increase has been reported in the transport of newly synthesized GAP-43 to the contralateral or "sprouting" hippocampus (Lin et al., 1992). The timing of this upregulation (between 6 and 15 days) suggests that changes in GAP-43 expression occur in response to the growth of presynaptic terminals during sprouting. At 14 days following deafferentation, increased numbers of GAP-43-positive terminals were observed in the molecular layer of the DG (Masliah et al., 1991). Between 2 and 4 days after lesions of the perforant pathway, levels of GAP-43 were found to increase markedly in the iml of the DG, coincident with the time at which commissural-associational fibers begin to sprout axon collaterals into regions denervated by the lesion (Benowitz et al., 1990). These results demonstrate that GAP-43 levels change during reactive synaptogenesis, and suggest that GAP-43 plays a role in the synaptic remodeling that occurs following experimental denervation of the hippocampus. However, it has been shown that, in mice overexpressing GAP-43, sciatic nerve axotomy induces prolonged sprouting and causes death of motorneurons and muscle weakness suggesting the need for a precise regulation of this protein in order to promote appropriate regeneration (Harding et al., 1999). Other studies suggest that GAP-43 is not sufficient to promote regeneration of cerebellar Purkinje cells and can increase their susceptibility to cell death (Wehrle et al., 2001) while the absence of GAP-43 can protect neurons from dying (Gagliardini et al., 2000).

Transient increases in GAP-43 expression have also been reported following experimental traumatic spinal cord injury. Supranormal levels of GAP-43 have been detected in cell bodies and sprouting axons around the lesion within four days of compression injury to the adult rat spinal cord (Curtis et al., 1993b), normalizing 9 days after the injury (Li et al., 1996). GAP-43 mRNA is also transiently upregulated in axotomized CNS neurons following spinal cord lesions, peaking at 7 days after injury (Schmitt et al., 1999). Furthermore, a neutralizing monoclonal antibody raised against the growth inhibitory protein Nogo-A (IN-1) has been shown to induce long-lasting sprouting associated

with upregulation of growth-related proteins, including GAP-43, actin, and myosin, together with the growth factors BDNF and vascular endothelial growth factor (VEGF) in rats after spinal cord injury (Bareyre et al., 2002). Recently, Bomze et al. (2001) used transgenic mice overexpressing either GAP-43 or CAP-23, or both, to show that co-expression of these growth-associated proteins elicits long axon extension by adult DRG neurons *in vitro* and is required to promote regeneration of DRG sensory neurons in adult mice after spinal cord injury. CAP-23, a protein that is bound by acylation to the intracellular surface of the membrane, is regulated by calmodulin, PKC and phosphoinositides. This protein interacts with actin filaments and represents, together with GAP-43 and myristoylated alanine-rich C kinase substrate (MARKCS), a class of functionally related proteins conferring plastic properties to the cortical cytoskeleton of cells (Wiederkehr et al., 1997).

Elevated GAP-43 protein has also been observed after cerebral ischemia within cell bodies of cortical neurons in the infarct penumbra at 4 days after transient focal cerebral ischemia (Furuya et al., 1997) and in axons of morphologically intact neurons in the boundary zone of the ischemic core at 2 days post-ischemia (Li et al., 1998), suggestive of a relationship between GAP-43 expression and compensatory and repair mechanisms. GAP-43 and synaptophysin expression are elevated in the cortex following permanent focal neocortical ischemia (Stroemer et al., 1993), supporting a hypothesis of a role for GAP-43 in the cortical sprouting and synaptogenesis following cerebral infarction that corresponds temporally with behavioral recovery (Stroemer et al., 1995). Following global cerebral ischemia in rats, a transient increase in GAP-43 mRNA and protein is observed within a subset of vulnerable neurons of the hippocampus (Schmidt-Kastner et al., 1997). In gerbils subjected to global cerebral ischemia, robust GAP-43 mRNA increases in hippocampal granule cells persist through 7 days and decline by 14 days (Tagaya et al., 1995). GAP-43 expression in the substantia nigra increases at 3 and 4 days following deafferentation by transient middle cerebral artery occlusion (Goto et al., 1994), providing further support for the involvement of GAP-43 in fiber sprouting and synaptic reorganization. Following ischemic injury, high levels of GAP-43 have additionally been documented in regions normally low in this protein in postmortem human tissue, suggesting a role for GAP-43 in remodeling and repair of mature CNS neurons (Ng et al., 1988). Blockade of the glutamate NMDA receptor has been shown to prevent the induction of GAP-43 following cerebral ischemia (Luque et al., 2001).

Finally, GAP-43 expression also increases in experimental models of TBI. Midline central fluid percussion (FP) brain injury of moderate severity in rats produces increased GAP-43 expression within cortical and hip-

pocampal regions, with increases in cortical regions correlating with recovery of motor function (Hulsebosch et al., 1998). Midline FP brain injury in cats also results in numerous GAP-43 positive, disconnected reactive axonal swellings in the brainstem up to 28 days post-injury, suggesting that diffusely injured axons can mount a sustained regenerative attempt (Christman et al., 1997). By 48 h following lateral FP brain injury in rats, GAP-43 protein has been shown to be elevated bilaterally within the iml of the DG, and the stratum lacunosum moleculare, stratum radiatum, and stratum oriens of the hippocampus, suggesting the existence of a posttraumatic state in which the CNS may have increased regenerative potential (Emery et al., 2000). At 7 days after a mechanical cortical injury in rats, GAP-43 immunoreactivity has also been observed in neurites adjacent to the lesion, and was accompanied by axonal sprouting (King et al., 2001).

Some of the same neurotrophic factors that increase expression of GAP-43 have been shown to produce improvements in cognitive and/or motor function following *in vivo* models of CNS injury, including NGF (Altar et al., 1992; Fernandez et al., 1993; Sinson et al., 1997; Dixon et al., 1997), FGF-2 (Kawamata et al., 1996; McDermott et al., 1997; Kawamata et al., 1997), and IGF-1 (Saatman et al., 1997; Fernandez et al., 1999). In view of a report that supplementation with NGF following TBI did not appear to enhance the capacity of damaged brain axons to express GAP-43 (Christman et al., 1997), it is possible that NGF infusion produces beneficial effects upon recovery through signaling cascades that do not involve GAP-43. However, beneficial effects of FGF-2 treatment following focal stroke can be blocked by intracisternal antisense oligonucleotides to GAP-43 (Kawamata et al., 1999), suggesting a link between increased GAP-43 expression and functional recovery following post-injury neurotrophin therapy in these CNS injury models.

Although experimental injury paradigms vary considerably with regard to regional characteristics of CNS damage, early and transient elevation of GAP-43 expression is a consequence of many different injury models, suggesting that the injured mature CNS can increase its expression of GAP-43. The elevated expression of GAP-43 during fiber outgrowth and synapse formation, following CNS lesions, and during sprouting of central terminals support the use of GAP-43 expression as a marker for synaptic plasticity in the adult CNS (Kapfhammer and Schwab, 1994; Benowitz and Routtenberg, 1997).

MAP1B Protein and Gene Structure

Although MAP1B has been cloned and sequenced from several species a decade ago (Noble et al., 1989; Lien et al., 1994), recent studies using molecular genetics approaches, paradigms of injury and plasticity, and *in vitro* neuronal cultures have provided a better insight into the relationship between the structure of the protein and its role in axonal growth and regeneration following injury (Gordon-Weeks and Fischer, 2000). These studies have also underscored the importance of MAP1B phosphorylation and interactions with other neuronal proteins in modulating MAP1B distribution, expression levels and function with respect to CNS plasticity.

MAP1B is a polyprotein composed of a heavy chain and two light chains, one of which, `LC1, is the product of a post-translational cleavage from the C-terminus (Hammarback et al., 1991). MAP1B contains a microtubule binding domain composed of repeat motifs of basic amino acids, shared with the structurally related MAP1A, but distinct from the binding domain of tau and MAP2, (Noble et al., 1989). It appears that binding of MAP1B increases microtubule stability, but unlike tau and MAP2, does not induce bundling (Takemura et al., 1992). Recent studies also suggest that the light chains of MAP1A and MAP1B have microtubule and actin filament binding domains and may therefore modulate the interaction between microtubules and microfilaments (Noiges et al., 2002). The transcription of MAP1B is under the control of the Engrailed homeoprotein (Montesinos et al., 2001) and is mediated by two alternative and overlapping promoters, one inducible and the other constitutive, which regulate the temporal and tissue-specific expression of the rat MAP1B gene (Liu and Fischer, 1996). Recent studies have identified two new exons (3A and 3U) that generate alternative transcripts and a protein product that is lacking the N-terminal domain, but retains the microtubule-binding regions (Kutschera et al., 1998).

The Role of MAP1B in Neuronal Differentiation and Axon Growth

During development of the nervous system the expression of MAP1B follows a time course that resembles neurogenesis—with high levels early during development and a marked down-regulation in the adult except for CNS regions that continue to generate new neurons such as the olfactory system (Riederer and Matus, 1985; Safaei and Fischer, 1989). Furthermore, numerous studies have shown that the expression of MAP1B in cultured neurons correlates with axonal growth and the protein is preferentially localized in growing axons (Fischer and Romano-Clarke, 1990; Black et al., 1994). These observations, together with the binding properties of the protein, suggest that MAP1B plays a role in neuronal differentiation and the growth of axons by modulating the dynamic properties of microtubules. Further evidence has been provided by antisense inhibition experiments with

cultured neuronal cells indicating that the inhibition of MAP1B expression resulted in the inhibition of neurite outgrowth (Brugg et al., 1993; DiTella et al., 1996). The most dramatic demonstration of the importance of MAP1B to neuronal development comes from the phenotypic analysis of knockout mice in which the MAP1B gene has been deleted (Edelmann et al., 1996; Takei et al., 1997; Gonzalez-Billault and Avila, 2000; Meixner et al., 2000). In most of the cases the homozygous animals either did not survive or had striking developmental and neurological abnormalities such as the absence of the corpus callosum, alteration in the structure of several brain regions and the presence of misguided cortical axons, while the heterozygous animals were less affected, and in some cases, normal. The phenotypic variations between the different knockout experiments are most likely the result of the specific targeting vectors used for the deletion of selective regions of the MAP1B gene and the low level expression of the alternative transcripts in some of the knockout mice. Neuronal cultures derived from the affected animals show inhibition of axon formation and microtubule organization particularly at growth cones (Gonzalez-Billault et al., 2002). Double knockouts of MAP1B and tau (Takei et al., 2000) or MAP1B and MAP2 (Teng et al., 2001) show more deficits that a single mutation and indicate that MAP1B acts synergistically with other neuronal MAPs in affecting microtubule organization, axonal and dendrite structure, and neuronal migration. Interestingly, mutation of the Drosophila MAP1B analogue, the Futch gene, disrupts dendritic and axonal growth, particularly synaptic microtubule organization (Roos et al., 2000; Hummel et al., 2000), and the Drosophila fragile X-related gene (a model of a mental retardation syndrome) represses the Futsch function through mRNA binding and thus disrupts synaptic structure and alters neurotransmission (Zhang et al., 2001b).

Although MAP1B has been traditionally viewed as a microtubule associated protein that modulates the dynamic properties of microtubules there is evidence that it can also bind and associate with GABA(C) receptors in the visual system, possibly linking these receptors with the cytoskeleton and allowing them to be differentially localized at inhibitory synapses (Pattnaik et al., 2000; Hanley et al., 2000). Other studies propose that some of MAP1B is a neuronal plasma membrane glycoprotein enriched in the axolemma fraction (Tanner et al., 2000) and that the phosphorylated form of MAP1B is a binding partner for MAG present on the myelin sheath (Franzen et al., 2001). The interaction of MAG with axons appears to induce a signal transduction cascade that regulates expression of several cytoskeletal proteins and their phosphorylation and may therefore affect the organization of the neuronal cytoskeleton. The interactions of neurons

with astroglial membranes has been shown to increase the length of axons and dendrites resulting in redistribution of MAP1B and GAP-43 toward the growth cones (Piontek et al., 2002), suggesting that the organization of the neuronal cytoskeleton can be modulated by cues transmitted through physical contact with glial cells.

MAP1B Phosphorylation

Like most cytoskeleton proteins in general and other microtubule-associated proteins in particular, the differential phosphorylation of MAP1B at multiple sites is an important mechanism in modifying the properties of the protein, and modulating its function. The phosphorylation of MAP1B is mediated by numerous kinases including casein kinase II (Diaz-Nido et al., 1988), cdk5 (Pigino et al., 1997) and glycogen synthase kinase 3β, GSK3β (Goold et al., 1999). The phosphorylation sites of MAP1B are recognized by a variety of monoclonal antibodies (reviewed in Gordon-Weeks and Fischer, 2000) and can be dephosphorylated by protein phosphatase-2A and -2B (Gong et al., 2000). The expression of phosphorylated MAP1B is strongly correlated with the period of brain development (Fischer and Romano-Clarke, 1990), neuronal differentiation in culture (Aletta et al., 1988; Goold and Gordon-Weeks, 2001) and acquisition of polarity (Mandell and Banker, 1996). Phosphorylated MAP1B is distributed in the distal region of growing neurites and at growth cones (Black et al., 1994), and may be requited for local stabilization of turning growth cones (Mack et al., 2000). Phosphorylated MAP1B is transported as a distinct fraction of slow axonal transport at rates that are significantly faster than most other cytoskeleton proteins of 7–9 mm/day and may account for the high concentration of this isoform in the distal end of growing axons (Ma et al., 2000). Inhibition of the GSK3β by lithium depletes the levels of phosphorylated MAP1B in the growth cone and dramatically increases the number of stable microtubules. This observation is consistent with the proposed role of phosphorylated MAP1B and has important implications for the development of drugs such as lithium used to treat bipolar disorders (Hall et al., 2002). The differential localization of phosphorylated MAP1B in growing axons and its role in axonal remodeling allows antibodies against the phosphorylated MAP1B isoforms to be used as sensitive markers, which identify growing and regenerating axons (Gordon-Weeks and Fischer, 2000).

Regulation of MAP1B Expression following Injury

The expression of developmentally regulated phosphorylated isoforms of MAP1B has been spatially and

temporally correlated with axonal regeneration in the lesioned adult PNS (Ma et al., 1999; Ramon-Cueto and Avila, 1999), suggesting that neuronal regeneration is accompanied by increases in cytoskeletal proteins that are characteristically expressed in the developing nervous system. Recent studies indicated that a peripheral nerve lesion can also induce sprouting of primary afferents from the DRG into the dorsal horn of the spinal cord. This response to injury is accompanied by an increase in MAP1B mRNA and expression of phosphorylated MAP1B in the new myelinating axons. In contrast, rhizotomy, a central injury that spares one root, induces unmyelinated CGRP-expressing fibers that do not express phosphorylated MAP1B (Soares et al., 2002). Phosphorylated MAP1B also increases in axons following axotomy of the trochlear nerve (Book et al., 1996) and following partial optic nerve crush in rats (Dieterich et al., 2002). Many of the crushed optic nerve axons that crossed the injury site have growth cones containing phosphorylated MAP1B. These studies support the idea that regeneration of axotomized neurons requires some recapulation of a growth program in which growth associated proteins such as MAP1B are upregulated, phosphorylated and correctly localized.

The failure of CNS neurons to regenerate reflects not only intrinsic limitation with respect to the regenerative program, but also the inhibitory signals of the CNS particularly at the injury site. What is often observed is a transient increase in gene expression associated with the early steps of the injury response, which includes both sprouting and proteolysis. Vigorous upregulation of MAP1B mRNA and protein has been reported in the border zone adjacent to a cortical infarct following focal cerebral ischemia in both young and aged rats (Popa-Wagner et al., 1999), and profiles reminiscent of axonal bulbs have been observed in MAP1B-stained sections within infarcted areas (Yam et al., 1998). Transient increases in expression of both MAP1B and phosphorylated MAP1B proteins within hippocampal, cortical, and thalamic regions begin by 24 h following TBI in adult rats, and may reflect limited proteolysis (leading to increased immunoreactivity) and/or increased MAP1B expression associated with conversion of the cytoskeleton from a stable to a dynamic structure (Emery et al., 2000). Interestingly, the well-documented regeneration of CNS neurons in low vertebrates is also associated with the expression of phosphorylated MAP1B as is the case for the regenerating optic nerve of the fish (Vecino and Avila, 2001).

Complex patterns of increased MAP1B mRNA and protein have also been observed following pentylenetetrazole-induced seizure activity. In cortical and hippocampal regions, elevated MAP1B mRNA is detectable at 15 h, and the level of MAP1B protein is increased as late as 35 h post-seizure (Popa-Wagner et al., 1997). These elevations in MAP1B may reflect structural reorganization in response to experimentally induced seizures. Kainic acid lesion-induced axonal remodeling in the adult rat CNS is also associated with an induction of MAP1B phosphorylation in a proximo-distal gradient originating from undamaged neurons located outside of the lesion (Soares et al., 1998). These studies led to a proposal that MAP1B, at a specific state of phosphorylation, is correlated with axonal remodeling in the adult CNS, and that the interaction of phosphorylated MAP1B with microtubules allows for the modulation of their dynamic properties during periods of increased axonal plasticity. Observations of acute, transient increases in MAP1B and its phosphorylated isoforms further support the concept that the initial molecular responses following injury to the CNS present some similarities with those observed during development.

PSA-NCAM: Distribution and Function

Polysialylated neural cell adhesion molecule (PSA-NCAM) is a dynamically regulated product of post-translational modification by polysialyl-transferase of NCAM (Hoffman and Edelman, 1983; Rutishauser et al., 1988). During development, PSA-NCAM is present along the cytoplasmic membranes and in growth cones of striatal neurons (Uryu et al., 1999) and in cortical and hippocampal regions (Seki and Arai, 1993a). In the adult brain, PSA-NCAM is localized to regions of continuing plasticity (Seki and Arai, 1993a; Theodosis et al., 1999), and has been found to be co-localized both with GAP-43 (Alonso et al., 1997) and with phosphorylated MAP1B (Le Gal et al., 1992; Nothias et al., 1996). In adults, PSA-NCAM reappears during regeneration of peripheral neurons (Martini and Schachner, 1988) or central neurons into peripheral nerve grafts (Anderson et al., 1998), or during sprouting within the hippocampus (Aubert et al., 1998). PSA-NCAM is also observed in newly generated neurons within the adult dentate granule cell layer (Seki and Arai, 1993b). Although it has been suggested that PSA-NCAM does not itself provide a specific signal for migration or target interaction, it appears to open a permissive "gate" with regard to cell–cell interactions that allows cells to respond to internal and external guidance cues at the appropriate time and place (Rutishauser and Landmesser, 1991). This large and abundant glycoprotein can exert steric effects at the cell surface that lead to the attenuation of cell–cell bonds mediated not only by NCAM but also a variety of other adhesion receptors. This global modulation of cell–cell attachment has been shown to facilitate cell migration, axon pathfinding and

targeting, and plastic changes in the embryonic and adult nervous system (Bruses and Rutishauser, 2001). Expression of "embryonic NCAM" or PSA-NCAM in the adult is suggestive of maintenance or reappearance of a developmental state (Edelman and Chuong, 1982).

Factors That Modulate PSA-NCAM Expression

Adrenal steroids, serotonin, and NMDA receptor ligands have each been reported to affect *in vivo* expression of PSA-NCAM protein. Similar to their effect upon GAP-43 expression, corticosteroids exert an inhibitory influence upon PSA-NCAM expression (Cremer et al., 2000), and adrenalectomy has been shown to increase expression of PSA-NCAM within the hippocampus (Rodriguez et al., 1998). Depletion of serotonin (5-HT) levels by denervation or by inhibition of 5-HT synthesis decreases hippocampal PSA-NCAM expression (Brezun and Daszuta, 1999; Brezun and Daszuta, 2000a). These decreases in PSA-NCAM can be reversed by serotonergic reinnervation (Brezun and Daszuta, 2000b). NMDA receptors also appear to affect PSA-NCAM expression in a manner reminiscent of their modulation of GAP-43 expression, since administration of MK-801 decreases PSA-NCAM expression during development (Butler et al., 1999).

Increases in PSA-NCAM Expression following Injury

Previous studies have shown that the expression of PSA-NCAM is associated with the induction of synaptic plasticity, neurite outgrowth, neuronal migration, and events requiring remodeling or repair of tissue. Increased expression of PSA-NCAM has been observed during the regeneration of CNS axons into peripheral nerve grafts, suggesting that this molecule may play a role in cellular interactions during successful regrowth of CNS axons (Zhang et al., 1995). Following aspiration lesions of the sensorimotor cortex in adult rats, increased PSA-NCAM immunoreactivity has been reported in the subventricular zone (SVZ) at the level of the striatum, in conjunction with a transient doubling of the number of cells in the SVZ without consistent increases in bromodeoxyuridine-labeled cells (Szele and Chesselet, 1996). The majority of cells in the SVZ express PSA-NCAM during development (Szele et al., 1994), suggesting that, following TBI, adult SVZ cells re-express developmental characteristics and may be capable of plasticity. Increased punctate PSA-NCAM immunoreactivity in the inner and outer molecular layers of the DG, in the CA1 subfield of the hippocampus, and in the entorhinal cortex has also been described in humans with temporal lobe epilepsy, suggestive of synaptic remodeling (Mikkonen et al., 1998). Increased numbers of PSA-NCAM-immunoreactive neurons within the granule layers of the DG are detected bilaterally following experimental TBI in rats (Emery et al., 2000). These increases in neuronal PSA-NCAM expression may be associated with increased plasticity, with regenerating neurons, or with newly generated neurons.

ENDOGENOUS PROGENITOR CELLS

Distribution and Roles

Neurogenesis in the mammalian CNS continues throughout adulthood within the SVZ (Corotto et al., 1993; Goldman, 1998) and the subgranular zone of the DG (Reznikov, 1991). Generation of new neurons within the adult DG has been documented across numerous species including non-human primates (Eckenhoff and Rakic, 1988; Gould et al., 1999a; Kornack and Rakic, 2001) and humans (Eriksson et al., 1998; Kukekov et al., 1999). The discovery of endogenous progenitor cells and continuing neurogenesis within the adult brain has engendered great enthusiasm for the expansion of these populations as a neuronal replacement therapy (Gage et al., 1995; Cameron and McKay, 1998). In adult rodents, cells arising in the anterior part of the SVZ migrate through the rostral migratory stream (RMS) to the olfactory bulb and become fully differentiated interneurons (Altman, 1969; Bayer, 1983) in order to, theoretically, replenish the olfactory neurons throughout life (Lois and Alvarez-Buylla, 1993). Newly generated granule cells have been shown to extend axonal projections to the CA3 region (Hastings and Gould, 1999; Markakis and Gage, 1999), and have been implicated in hippocampal-dependent learning and in spatial memory (Nilsson et al., 1999; Gould et al., 1999b), suggesting that new cells can establish appropriate connections. More recently, endogenous neural precursors have been induced *in situ* to differentiate into mature neurons in regions of adult mouse neocortex that do not normally undergo any neurogenesis (Magavi et al., 2000).

Factors That Affect Neurogenesis in the Adult Brain

The identification of the factors regulating adult neurogenesis has been intensively investigated during the past decade. The complete understanding of the mechanisms controlling the division, migration, differentiation and axon extension of endogenous precursors, will likely aid the development of efficient therapies for brain injury and disease. The birth and survival of new hippocampal dentate granule neurons in adults appears to be

under complex regulation. This dynamic state makes this brain region particularly sensitive to environmental stimuli. Studies have demonstrated that chronic stress elevates circulating adrenal steroids and stimulates glutamate release in the hippocampus. Subsequent activation of the NMDA receptors decreases DG granule cell proliferation, while administration of NMDA antagonists leads to an increase in production of new granule cells (Gould, 1994; Cameron et al., 1995; Gould et al., 1997; Nacher et al., 2001). Consistent with these findings, adrenalectomy increases the rate of neurogenesis in the subgranular zone (Cameron and Gould, 1994; Rodriguez et al., 1998; Montaron et al., 1999), while corticosterone administration appears to decrease the rate of neurogenesis (Cameron and Gould, 1994). In addition, studies demonstrating stress-induced suppression of LTP suggest that stress can potentially alter learning and memory (Mesches et al., 1999; Diamond et al., 1999).

Adult animals housed in an enriched environment exhibit increased dentate granule cell neurogenesis (Kempermann et al., 1997) and decreased apoptotic death of new granule neurons (Young et al., 1999) as well as improved spatial memory (Nilsson et al., 1999), while voluntary exercise is sufficient for enhanced neurogenesis in the adult mouse DG (van Praag et al., 1999). Age-related decreases in production of hippocampal neurons in laboratory animals can be attenuated or reversed by housing in an enriched environment (Kempermann et al., 1998) or by decreasing levels of corticosteroids (Cameron and McKay, 1999). Neurogenesis is also increased in female rats by estrogen (Tanapat et al., 1999), suggesting that further avenues for increasing endogenous hippocampal neurogenesis might include manipulating environmental stimuli inputs or circulating corticosteroid or gonadal steroid hormone levels.

Growth factors that affect neurogenesis *in vivo* have also been identified. Peripheral administration of IGF-1 has been shown to selectively induce neurogenesis in the adult rat hippocampus, increasing the fraction of new cells that differentiate into neurons, and the proportion of new cells that survive (Aberg et al., 2000)). A recent study also demonstrated that exercise-induced neurogenesis in the adult rat hippocampus is mediated by uptake of IGF-1 into the brain parenchyma (Trejo et al., 2001). Epidermal growth factor (EGF) and FGF-2 appear to have different effects on neural progenitors. While intracerebroventricular (icv) administration of both growth factors has been shown to expand the SVZ progenitor population, only FGF-2 was able to induce an increase in the newborn cells, mostly neurons, in the olfactory bulb (Kuhn et al., 1997). Intracerebroventricular administration of BDNF was also demonstrated to increase the number of new neurons in the olfactory bulb (Zigova et al., 1998), the striatum, thalamus and hypothalamus of mature rats (Pencea et al., 2001). Heparin-binding-EGF-like growth factor, an endogenous mitogenic and chemotactic glycoprotein containing an EGF-like domain, has also been shown to stimulate proliferation of neuronal precursors in the SVZ and the DG (Jin et al., 2002). Vascular endothelial growth factor (VEGF) has been shown to stimulate neurogenesis *in vitro* and *in vivo* together with the proliferation of astrocytes and endothelial cells (Jin et al., 2002). Erythropoietin (EPO) has also been shown capable of regulating the production of neuronal progenitor cells from the forebrain neurogenic region in mice (Shingo et al., 2001). Since most of the endogenous molecules described above are implicated in the pathophysiology of CNS injury, it is likely that the neurogenic status of the brain is altered after an insult.

Increases in Neurogenesis following CNS Injury

Neurogenesis has been shown to be responsive to various types of brain injury. To determine whether this is a regulated attempt at regeneration by the brain or a simple epiphenomenon is of crucial interest and remains to be elucidated. The rate of neurogenesis within the DG of adult laboratory animals was shown to increase following kainic acid administration (Gray and Sundstrom, 1998), kindling or pilocarpine-induced seizures (Parent et al., 1997), neurotoxic lesions (Gould and Tanapat, 1997), and proliferation of neuroblasts in the adult rat SVZ-olfactory bulb pathway is increased after prolonged seizures (Parent et al., 1998; Scott et al., 1998; Parent et al., 2002). Previous reports indicate that although prolonged seizure discharges stimulate DG granule cell neurogenesis, epileptogenesis may result in aberrant connections formed by these newly born dentate granule cells (Parent et al., 1997). Since it has further been shown that aberrant neural networks develop from both newly generated and existing hippocampal neurons following artificially induced seizures (Parent et al., 1999), caution must be exercised when promoting recapitulation of a developmental state with therapies designed to increase endogenous hippocampal plasticity.

In rodents, increased neurogenesis has been observed in the DG of the hippocampus after transient global cerebral ischemia (Liu and Storm, 1989) and focal cerebral ischemia (Jin et al., 2001; Takasawa et al., 2002). Ischemia-induced neurogenesis can be further increased by pharmacological manipulation with a nitric oxide donor (Zhang et al., 2001a), and it has been shown that endogenously synthesized FGF-2 is necessary and sufficient to stimulate proliferation and differentiation of neuronal precursor cells in the hippocampus after focal tran-

sient cerebral ischemia in mice (Yoshimura et al., 2001) and following TBI (Yoshimura et al., 2003). The angiogenic properties of VEGF together with its ability to stimulate the proliferation of neuronal progenitors may represent another interesting strategy to promote both angiogenesis and neurogenesis after cerebral ischemia and associated conditions such as TBI (Jin et al., 2002).

Finally, several recent studies have demonstrated alterations in neurogenesis after traumatic lesions to the CNS. Removal of afferent input via unilateral entorhinal cortex lesion has been reported to produce significantly more cell birth in the ipsilateral DG (Cameron et al., 1995). Similarly, unilateral excitotoxic or mechanical lesion of the DG results in a significant increase in proliferating cells on the lesioned side, most of which were located in the granule cell layer and expressed markers of mature granule neurons by 3 weeks after the lesion (Gould and Tanapat, 1997). After TBI, proliferation of astrocytes and activated microglia within the site of injury and hippocampus has been reported (Giordana et al., 1994; Hill-Felberg et al., 1999; Tzeng and Wu, 1999). Whether these new glial cells derive from the neurogenic regions or from parenchymal precursors remains to be elucidated. Controlled cortical impact (CCI) brain injury has been shown to induce an increase in neurogenesis in the granular cell layer of the DG of the hippocampus in rats (Dash et al., 2001). The maximal rate of proliferation was observed at 3 days post-injury and 1 month post-injury, the majority of the newly formed cells were positive for calbindin, a mature neuronal maker. An increase in proliferation in the DG has also been shown after CCI in mouse, but most of the newly generated cells differentiated into astrocytes (Kernie et al., 2001). Notably, this region has also been shown to sustain neuronal cell loss after CCI brain injury both in rats and mice (Smith et al., 1995; Colicos et al., 1996; Nakamura et al., 1999). More recently, an increase in cellular proliferation was observed 48 h after a lateral fluid percussion-induced TBI in rats both in the hippocampus and in the SVZ (Chirumamilla et al., 2002). While these proliferating hippocampal cells were positive for immature astrocyte and activated microglia markers, the proliferating cells in the SVZ seemed not to have begun to differentiate at this time point after injury. We have also observed an increase in neurogenesis following TBI in the DG of the hippocampus in rats and (in the SVZ precursors together with an ectopic migration diverging from the normal RMS pattern) in mice (Emery et al., 2001; Fulp et al., 2003). Taken together, these results suggest that TBI induces proliferation in the SVZ and the DG, recognized as neurogenic regions, and also, perhaps, in cortical regions proximal to the site of injury. However, it remains to be established whether these new cells are originating from the neurogenic regions of the brain or from local precursors. With the exception of the study of Dash et al. (2001), it is unclear whether most of the newly generated cells differentiate exclusively into neurons. However, it remains possible that the SVZ-derived cells can give rise to new neurons, and this question is of crucial interest. One can speculate that TBI-induced neurogenesis may contribute to the partial recovery observed both in animal models and in humans in terms of cognitive and motor function.

It also remains to be elucidated whether factors such as stress and anxiety or seizures that are commonly associated with TBI are implicated or can alter the pattern of neurogenesis observed after injury. Finally, pharmacological manipulation of this neurogenic potential, either by increasing the proliferation rate or inducing neuronal differentiation, represents a new strategy of tremendous interest for the treatment of TBI. Interestingly, Riluzole, a sodium-channel blocker with glutamate antagonist activity that was previously shown to be neuroprotective in experimental models of TBI (McIntosh et al., 1995; Wahl et al., 1997; Bareyre et al., 1997; Zhang et al., 1998; Wahl and Stutzmann, 1999; Stover et al., 2000), has recently been shown to enhance expression of BDNF with consequent proliferation of granule precursor cells in the rat hippocampus (Katoh-Semba et al., 2002). These observations underscore the need for further exploration of the role of growth factors in mediating neurogenesis in the adult CNS, to advance the development of neuronal replacement strategies after brain damage by pharmacologically manipulating neural precursors *in vivo*.

CONCLUSION

Treatment with exogenous trophic factors or other therapies designed to increase sprouting and expression of growth-related proteins may promote a developmental-like state and encourage plasticity. Of significant concern when manipulating factors that affect hippocampal neurogenesis or plasticity is the possibility that new neurons or new neuronal processes may contribute to aberrant sprouting and undesired neural circuitry.

In summary, increases in growth-related proteins and in neurogenesis observed following injury to the adult CNS may be viewed as reminiscent of gene expression patterns and events within the developing CNS. Although triggering events for some of these "re-"developmental processes remain elusive, numerous avenues remain for exploration. Treatments that increase the success of regenerative responses of the adult CNS following injury may be developed by capitalizing upon knowledge of ex-

ogenous factors that may increase the expression of growth-related proteins and prudently stimulate proliferation and appropriate incorporation of endogenous progenitor cells.

ACKNOWLEDGMENTS

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