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Ischemia-Induced Neurogenesis: Role of Growth Factors

Robert J. Dempsey[a,b,*], Haviryaji S.G. Kalluri, PhD[a]

[a]*Department of Neurological Surgery, University of Wisconsin, CSC K4/818, 600 Highland Avenue, Madison, WI 53792, USA*

[b]*Cardiovascular Research Center, University of Wisconsin, Madison, WI 53792, USA*

Stroke is the leading cause of death and disability in the United States. It continues to be a problem of vast clinical significance. Approximately 3.9 million Americans are stroke survivors. The aftereffects of stroke require more than $51 billion in health care costs annually.

Treatment of stroke has emphasized prevention and protection, but little has been done in the brain to repair stroke. At present, tissue plasminogen activator (tPA) is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of acute ischemic stroke [1]. In other studies, kallikrein, a serine proteinase, was shown to provide neuroprotection even when administered 24 hours after the onset of stroke [2]. The treatment of stroke may involve protecting the tissue from ongoing damage, but an approach to functional repair would be replacing the damaged tissue with new cells. One such approach to tissue repair involves the generation of new cells from stem cells in vitro and transplanting them into the site of injury [3]. With regard to stem cell transplantation, there exist concerns regarding ethical issues, a limited supply of tissue, and immunologic compatibilities, however. An alternate approach to tissue repair involves the stimulation of an endogenous neurogenic response using exogenous growth factors [4]. Hence, boosting endogenous neurogenesis using exogenous growth factors has emerged as a potential therapy for stroke.

Neural stem/progenitor cells in the adult brain are located in the dentate gyrus of the hippocampus and the subventricular zone and can differentiate into various cell types. These cells proliferate in response to growth factors, such as fibroblast growth factor (FGF)-2 [5], epidermal growth factor (EGF) [6] and insulin-like growth factor (IGF)-1 [7,8]. The proliferation of stem/progenitor cells has been shown to be upregulated in a variety of pathologic conditions [9]. Although the stem cells respond to the repair process by proliferation and differentiation, this response is not adequate to overcome the damage incurred to the tissue. The finding that neurogenesis occurs persistently in the adult brain has provided hope that tissue repair can be stimulated in these neurogenic regions after a survivable stroke.

In this article, the authors discuss the role of growth factors in stroke-induced neurogenesis and attempt to summarize some of the work performed in this fascinating area, emphasizing its effects on cerebral ischemia.

Growth factors and neurogenesis

Neurogenesis involves the proliferation, differentiation, and maturation of neural progenitor/stem cells into different types of cells in the brain and the integration of the resulting cells into the brain circuitry. Although several growth factors promote neurogenesis by stimulating the proliferation and inducing the differentiation of neural progenitor/stem cells [4,10], the exact sequence of

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* Corresponding author.
E-mail address: dempsey@neurosurg.wisc.edu (R.J. Dempsey).

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events that stimulates differentiation after proliferation in vivo is not clear. Most growth factors bind to their receptors and activate mitogen-activated protein kinase or PI3 kinase pathways to initiate signal transduction.

The activation of mitogen-activated protein kinase by growth factors mediates the proliferation of cells, whereas the activation of the PI3 kinase pathway supports their survival (Fig. 1). In general, the response to a growth factor depends on the expression of its receptors on the target cells [9,11]. Hence, neurogenesis occurs in a temporal and spatial manner because of the intrinsic differences in the expression of growth factor receptors on the progenitor/stem cells or restricted availability of growth factors in the germinal niche.

Stroke-induced neurogenesis

Ischemia-induced neurogenesis has been well studied in a variety of animals and stroke models [12,13]. The progenitor cells in the subventricular zone and the dentate gyrus proliferate in response to cerebral ischemia. Neurogenesis after ischemic damage may be attributable to the release of endogenous growth factors or chemokines by the ischemic tissue. Gene expression analysis using DNA microarrays identified the differential regulation of several genes after ischemia [12]. The transcripts that are affected in ischemic brain include inflammatory mediators, heat-shock proteins, transcription factors, neuroprotective genes, growth factors and their receptors, apoptotic genes, and cell-signaling molecules [14]. Changes in the expression of these genes might be responsible for the neurodegenerative, neuroprotective, and neurogenic effects observed after stroke. To maximize the neurogenic response after ischemia, it is essential to block the inhibitory and apoptotic molecules while stimulating the neuroprotective and neurotrophic machinery. Cerebral ischemia upregulates the expression of several growth factors, such as brain-derived neurotrophic factor (BDNF), glial cell line–derived neurotrophic factor (GDNF), basic fibroblast growth factor (bFGF), and IGF-1; hence, the authors discuss the role of these growth factors in ischemia-induced neurogenesis.

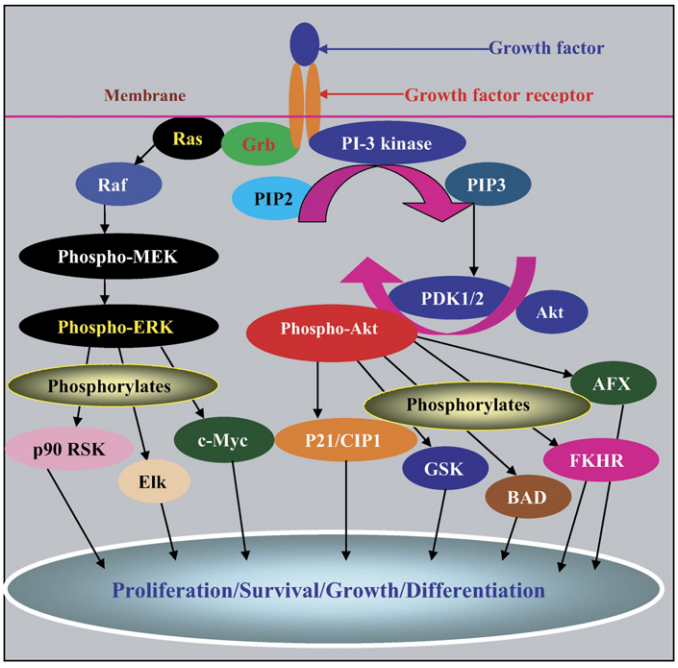

Fig. 1. Growth factor–mediated signal transduction. On growth factor binding and autophosphorylation of its receptors, hierarchic phosphorylation initiates the activation of PI3 kinase/Akt and Ras/Raf/MEK/ERK pathways and induces the proliferation, survival, and differentiation of cells.

Brain-derived neurotrophic factor

BDNF, a member of nerve growth factor (NGF) family of neurotrophic factors, is required for the proliferation, differentiation, and survival of specific neurons in the brain. In the adult brain, ischemia increases the expression of BDNF [15] and its receptor, trk B, [16] to enhance neuroprotection and neurogenesis [17]. Consistent with this observation, BDNF knockout mice produced larger infarcts [18], whereas blockade of endogenous BDNF decreased the survival of neurons after an ischemic insult [19].

Overexpression of BDNF induced the recruitment of progenitor cells in the adult brain [20]. Intrastriatal infusion of BDNF before ischemia in adult rats increased the survival of neurons and improved functional recovery [21]. Intravenous infusion of human mesenchymal stem cells expressing BDNF gene, even if given 6 hours after permanent middle cerebral artery occlusion (MCAO), has been shown to reduce the infarct volume [22]; however, long-term delivery of high levels of BDNF increased the vulnerability of interneurons to stroke-induced damage, although potentiating the neurogenic response during the early stages [23]. Long-term delivery of BDNF was shown to attenuate intrinsic neurogenerative responses [24]. Hence, it was proposed that low and moderate levels of BDNF are neuroprotective but that the beneficial neurogenic response is only observed during the early stages of ischemia [23].

Glial cell line–derived neurotrophic factor

GDNF is a potent neurotrophic factor belonging to the transforming growth factor-β superfamily, which is involved in the survival and differentiation of neurons [25]. Cerebral ischemia has been shown to upregulate the GDNF content [26,27] and induce neuroprotection in the ischemic brain [26,28]. Conflicting studies have shown that long-term treatment with GDNF may increase the infarct size after ischemia, however [29]. In addition, pretreatment with GDNF was shown to enhance the death of neurons deprived of oxygen and glucose in hippocampal slice cultures [30]. Administration of Sendai virus carrying GDNF gene was shown to be neuroprotective in postischemic gerbil brain [31]. The neuroprotective effect of viral GDNF was shown to be effective even when administered 4 to 6 hours after ischemia and was proposed to have a therapeutic effect by preventing delayed neuronal death induced by global ischemia.

A recent study has demonstrated the expression of GDNF as a delayed event, however, and has suggested that it may be related to protection from delayed neuronal death [27]. Therefore, it is possible that delayed administration of GDNF after 4 to 6 hours of ischemia may have a beneficial effect [31]. Intracerebroventricular infusion of GDNF increased the MCAO-induced progenitor cell proliferation in the ipsilateral dentate gyrus and enhanced survival up to the third week [8]. Hence, it seems that GDNF may be involved in the survival of cells, maintaining the number of newly formed cells in the brain.

Epidermal growth factor

EGF is a mitogen known to be involved in the proliferation of adult neural progenitor/stem cells. Previous studies using exogenous EGF in ischemic animals have demonstrated replacement of 20% of the interneurons that would have died after ischemia, suggesting the potential to use EGF for manipulating endogenous neurogenesis and to promote brain repair [32]. Heparin-binding epidermal growth factor–like growth factor (HB-EGF-GF) is a hypoxia-inducible protein involved in neurogenesis. Studies have shown that HB-EGF-GF binds to EGF receptors with higher affinity to promote neurogenesis [33]. Postischemic administration of HB-EGF-GF contributes to the recovery of cerebral injury by enhancing neuroprotection and increasing neurogenesis [34]. Experiments using the viral delivery of HB-EGF-GF have demonstrated a significant improvement in neurologic function after MCAO, however, without altering the infarct volume [33]. The increased functional recovery was attributed to enhanced neurogenesis and angiogenesis.

It is interesting to note that spironolactone, an aldosterone antagonist, decreased the infarct size and mRNA content of EGF receptors in stroke-prone spontaneously hypertensive rats (SPSHRs), indicating that the upregulation of EGF receptor content in SPSHRs may play a role in increasing the infarct size in these rats [35]. Because EGF receptors were shown to be upregulated, it is expected that spontaneously hypertensive rats (SHRs) may show an enhanced response to EGF. Consistent with this assumption, a previous study has observed an increase in neurogenesis in SHRs as compared with the Sprague-Dawley strain [36]. Thus, it seems that stroke and the associated neurogenic response depend on the strain of the animal.

Fibroblast growth factor-2 or basic fibroblast growth factor

FGF2 or bFGF is a heparin-binding protein involved in the regulation of neurogenesis in the brain [5,37]. In normal rat brain, deletion of the FGF2 gene reduces the progenitor cell population by 50% in the anterior subventricular zone (SVZa), supporting a role for FGF2 in neural progenitor proliferation [38]. Previous studies have shown upregulated expression of FGF2 in the brain after ischemic injury [39]. Deletion of the FGF2 gene decreased the total number of newborn cells in the dentate gyrus after ischemia as compared with wild-type mice [37]. However, pre-ischemic delivery of the viral FGF2 gene increased the total number of new born cells following ischemia in the FGF2 deficient mice. The resulting cells show colocalization with 5-bromo-2′deoxyuridine (BrdU) and neuronal nuclear protein (NeuN), which are markers for proliferating cells and neurons, respectively, implicating a role for FGF2 in postischemic neurogenesis. Consistent with this observation, several studies have shown an increase in ischemia-induced neurogenesis after FGF2 delivery to brain [13,40].

Administration of bone marrow stromal cells engineered to produce FGF2 [41] and recombinant adenovirus vector expressing FGF2 [42] has been shown to decrease infarct size. Hence, FGF2 may have a role in cell proliferation and neuroprotection after ischemia. Several mechanisms have been proposed for the neuroprotective effects of FGF2. These include downregulation of the glutamate-binding subunit of the *N*-methyl-D-aspartate (NMDA) receptor [43] and induction of GDNF [44]. Focal cerebral ischemia produced larger infarcts (75%) in FGF2 knockout mice as compared with wild-type litter mates and was associated with the downregulation of BDNF and trkB mRNA expression [45]. Because BDNF was shown to be neuroprotective, it seems that the neuroprotective effects of FGF2 may be mediated by the upregulation of BDNF gene expression. These observations are consistent with the fact that cerebral ischemia upregulates the content of FGF2 and BDNF [15,39].

Insulin-like growth factor-I

IGF-I plays a major role in the growth and development of the brain [7,10]. Although IGF-I is primarily produced in the liver, the brain can also synthesize this peptide [46], implicating a role for endogenous IGF-I in neurogenesis. Several studies have shown that administration of IGF-I reduced neuronal loss [47] and enhanced neurogenesis [8,48] after cerebral ischemia. In contrast, an earlier study demonstrated the lack of neuroprotection by IGF-I and implicated the disruption of the IGF signaling pathway after ischemia [49]. Like FGF2, IGF-I was also shown to be upregulated after stroke [50]. In gerbils, ischemia induced the upregulation of mechano–growth factor (MGF), an alternatively spliced variant of IGF-I (IGF-I Ec in human beings or IGF-I Eb in rodents), in the neurons resistant to ischemic insult [51]. Hence, it is essential to study the differential expression of IGF-I splice variants after ischemia, because various forms have been shown to have diverse effects ranging from proliferation to differentiation [52]. Although IGF-I variants may have a differential role in the same tissue, individual forms of IGF-I may also have differential effects in a tissue-specific manner. For instance, IGF-I enhances the proliferation of myoblast precursors but promotes differentiation and induces hypertrophy of myotubes [53]. Hence, the response of growth factors to proliferation, differentiation, and survival depends on the duration and strength of the stimulus as well as the cell type.

Most of the studies carried out so far have shown that IGF-I can enhance the proliferation of cells in the brain [7,8]. Because of the in vivo nature of these studies, it is difficult to ascertain whether the proliferative effect of IGF-I was attributable to its direct stimulation of neural stem/progenitor cells or to the involvement of neighboring cells. In vitro studies have demonstrated the activation of an IGF-I–mediated ERK pathway and implicated IGF-I in the proliferation of neural progenitor cells [7]. Conversely, other studies have demonstrated the lack of activation of ERK by IGF-I [54,55] and suggested a role for IGF-I in differentiation [10].

Proteins that regulate the content of IGF-I by sequestering or releasing it may also regulate neurogenesis by controlling the bioavailability of IGF-I in the cellular environment [56]. IGF-binding proteins (IGFBPs) form a 150-kDa ternary complex on binding to IGF-I and function as carrier proteins. This forms a storage reserve and also an inhibitor of IGF-I by preventing access of free IGF-I to IGF-I receptors. IGFBP proteases degrade IGFBPs from the IGF-IGFBP complex, however, and release IGF-I in the circulation. Consequently, a balance in IGFBPs and IGFBP

proteases is essential in maintaining IGF-I homeostasis in the tissue (Fig. 2; IGF-IGFBP3). It is suggested that IGFBP3 enhances the half-life of circulating IGF-I; however, if IGF-I is not released from the IGF-IGFBP3 complex at the appropriate time, it can result in the inhibition of IGF-I–mediated neurogenesis. Hence, studying the expression of these regulators after ischemia is also important in understanding IGF-I–mediated postischemic neurogenesis.

Platelet-derived growth factors

Platelet-derived growth factors (PDGFs) are a family of dimeric ligands composed of four polypeptide chains (PDGF-A, PDGF-B, PDGF-C, and PDGF-D) that bind to their receptors PDGFR-α and PDGFR-β. PDGF-B and its receptor, PDGF-β, are highly expressed in the neurons of the central nervous system, however, which are implicated in nerve regeneration and glial cell proliferation [57,58]. Thus, a role for PDGF in neuroprotection was proposed [59]. These studies are supported by a recent report demonstrating that PDGFR-β mutant mice develop normally but are vulnerable to injury [60]. Ischemia-induced upregulation of PDGF receptors was observed in a variety of studies [61–64]. Although PDGF was shown to have a positive role in angiogenesis and neuroprotection, it also plays an important role in restenosis [65] and many cancers [66]. Indeed, a recent study suggested that PDGFR signaling may be involved in the neoplastic transformation of neural stem cells [67]. Although all these studies indicate that PDGFR may be a potential pharmacologic target for stroke patients, because of its role in cancer

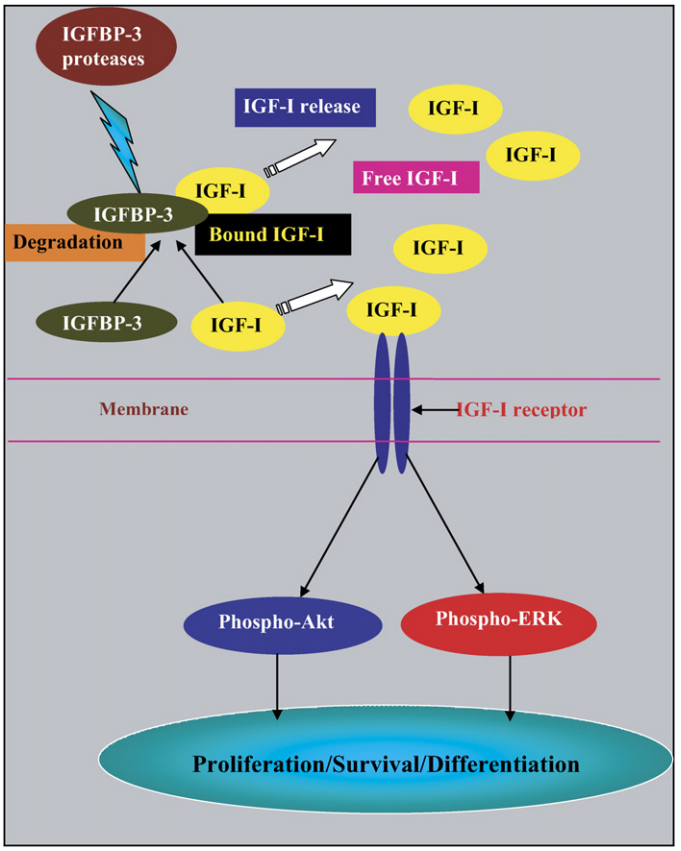

Fig. 2. Regulation of IGF-I–mediated cell proliferation, survival, and differentiation. Free IGF-1 binds to IGF-1 receptors and activates Akt and ERK pathways, which are involved in proliferation, survival, and differentiation. IGFBP-3 binds to IGF-1 and regulates the activation of its signaling pathways. Likewise, IGFBP-3 proteases degrade IGFBP-3 and release free IGF-I.

and clogging of arteries, further studies are required to establish its beneficial effect.

Summary

The neurogenic response in ischemic brain to growth factors is the net result of cell division and cell survival in specific regions of the brain. To increase the cell number, these physiologic processes should be active. Hence, when growth factors are infused into the brain, they might stimulate survival, cell division, or both to enhance neurogenesis. It should be noted that the withdrawal of growth factors (mitogens) in vitro leads to the differentiation of progenitor cells. Because the brain is a rich source of several factors, the infused mitogen(s) might show their effect in conjunction with the endogenous growth factors, chemokines, and cytokines. Hence, the end result is the interplay of all the endogenous factors with the infused exogenous factors. This scenario is more active in ischemic brain, wherein an abundance of several endogenous factors is observed because of an inflammatory response to ischemia. This ischemic response depends on the age, strain, species, and physical condition of the animal under study. It is essential to understand the growth factors and their regulators that are expressed after ischemia if one is to pharmacologically enhance neurogenesis. It seems that a combinational therapy of factors or their inhibitors may provide powerful therapeutic potential for enhancing stroke-induced neurogenesis and restoring the damaged tissue to function.

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