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Endogenous regeneration: Engineering growth factors for stroke

Su Jing Chan [a, b], Christopher Love [a, c, d], Myron Spector [d, e, f], Simon M. Cool [b], Victor Nurcombe [b, *], Eng H. Lo [a, g, **]

[a] Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
[b] Institute of Medical Biology, Glycotherapeutics Group, 8A Biomedical Grove, #06-06 Immunos, A*STAR, Singapore 138648, Singapore
[c] Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[d] Tissue Engineering Laboratories, VA Boston Healthcare System, Boston, MA 02130, USA
[e] Department of Orthopaedic Surgery, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[f] The Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[g] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

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ABSTRACT

Despite the efforts in developing therapeutics for stroke, recombinant tissue plasminogen activator (rtPA) remains the only FDA approved drug for ischemic stroke. Regenerative medicine targeting endogenous growth factors has drawn much interest in the clinical field as it provides potential restoration for the damaged brain tissue without being limited by a narrow therapeutic window. To date, most of the translational studies using regenerative medicines have encountered problems and failures. In this review, we discuss the effects of some trophic factors which include of erythropoietin (EPO), brain derived neurotrophic factor (BDNF), granulocyte-colony stimulating factor (G-CSF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF) and heparin binding epidermal growth factor (HB-EGF) in experimental ischemic stroke models and elaborate the lost in translation of the candidate growth factors from bench to bedside. Several new methodologies have been developed to overcome the caveats in translational studies. This review highlights the latest bioengineering approaches including the controlled release and delivery of growth factors by hydrogel-based scaffolds and the enhancement of half-life and selectivity of growth factors by a novel approach facilitated by glycosaminoglycans.

Contents

List of abbreviations: AR, amphiregulin; AXIA, AX200 for the Treatment of Ischemic Stroke; BBB, blood brain barrier; BDNF, brain derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMP-2, bone morphogenetic protein-2; CAM, chorioallantoic membrane; DG, dentate gyrus; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EPO, erythropoietin; ErbB1, Erb-B2 receptor tyrosin kinase 1; G-CSF, granulocyte-colony stimulating factor; Gtn-HPA, gelatin-hydroxyphenylpropionic acid; HB-EGF, heparin binding epidermal growth factor; HIF-1α, hypoxia inducible factor-1 α; HRP, horseradish peroxidase; HS, heparan sulfate; ICV, intracerebroventricular; MCA, middle cerebral artery; NINDS, National Institute of Neurological Disorders and Stroke; NRG, neuregulin; PENUT, Preterm Erythropoietin Neuroprotection; PG, proteoglycan; pMCAO, permanent middle cerebral artery occlusion; REBIOS, Revised Research for Biomarkers in Ischemic Stroke; rtPA, recombinant tissue plasminogen activator; SGZ, subgranular zone; STEMTHER, Stem Cells Therapy for Acute Ischemic Stroke; SVZ, subventricular zone; TrkB, tropomyosin receptor kinase B; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; vWF, von Willerbrand factor.

* Corresponding author. Institute of Medical Biology, Glycotherapeutics Group, 8A Biomedical Grove, #06-06 Immunos, A*STAR, Singapore 138648, Singapore.
** Corresponding author. Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA.
E-mail addresses: Victor.Nurcombe@imb.a-star.edu.sg (V. Nurcombe), LO@helix.mgh.harvard.edu (E.H. Lo).

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1. Introduction

Intravenous recombinant tissue plasminogen activator (rtPA, alteplase) is the only FDA approved therapeutic drug for acute ischemic stroke since 1996. It was approved for administration on ischemic stroke patients within 3 h after the onset of symptoms. Subsequent analysis by the National Institute of Neurological Disorders and Stroke (NINDS) study and six other randomized trials showed a favourable outcome when treatment was given between 3 and 4.5 h (Hacke et al., 2008). Since then, several thrombolytic agents and mechanical thrombectomy using endovascular clot retrieval devices have been developed (Hacke et al., 2005, 2008; Yarbrough et al., 2015). However, the narrow therapeutic windows of such approaches limit their benefit to only small percentage of stroke patients (Hacke et al., 2008).

Reperfusion is a powerful therapy for ischemic stroke, but given the rapidly evolving pathophysiology of ischemic brain tissue, a significant number of stroke patients may always be outside eligible reperfusion treatment windows. In this context, regenerative medicine by enhancing neuroplasticity and neurorepair may provide new frontiers for both basic hypothesis-testing as well as translational stroke research (Xing et al., 2016). Regenerative medicine can be categorized into cell-based therapy and non-cell-based therapy. Cell-based therapy is defined by the rebuilding of damaged tissue through the administration of exogenous stem cells including embryonic stem cells, bone marrow messenchymal stem cells and induced puripotent stem cells. Non-cell-based therapy is the use of compounds that amplify endogenous neuroregenerative capacities after stroke, for example by inducing compensatory neurogenic mechanisms in the subventricular zone (SVZ) and subgranular zone (SGZ). Both cell-based and non-cell-based approaches require growth factors to regulate endogenous or exogenous stem cell proliferation, migration and cell fate. To date, most of the recombinant growth factors that have been tested in clinical trials have failed. A better understanding of the properties of growth factors and how they interact with the complex pathophysiology of the recovering brain post-stroke are of the utmost importance.

In this review, we first summarize the potential roles of several candidate growth factors in promoting neural protection and neuroregeneration after stroke. Second, we highlight the challenges of candidate growth factors in clinical trials. Finally, we discuss a few cutting-edge technologies that have been developed to modify the administration of growth factors that could potentially improve their application as a regenerative medicine for stroke.

2. Candidate growth factors as potential stroke treatment

In this section, we briefly summarize the beneficial effects for several candidate growth factors in animal models of stroke.

2.1. Erythropoietin

Erythropoietin (EPO) is a 30.4 kDa glycoprotein (Semenza and Wang, 1992). It is known as a hemotopoietic cytokine that acts on the EPO receptor and promotes erythroid progenitor cell proliferation, differentiation and survival (Sato et al., 2000). EPO can be transcriptionally activated by hypoxia inducible factor-1α (HIF-1α) and is responsive to brain injury (Semenza and Wang, 1992). For instance, the expression of EPO and EPO receptors were upregulated in the CNS after hypoxic injury (Siren et al., 2001). The neuroprotective effect of EPO was first reported by Brines and coworkers on a contralateral carotid artery reperfusion rat model (60 min occlusion) with permanent occlusion of both middle cerebral artery (MCA) and ipsilateral carotid artery (Brines et al., 2000). Infarct volume was reduced when recombinant human EPO (5 000 units/kg, i.p.) was given prior to ischemia, at the onset of ischemia or 3–6 h postischemia. EPO was also found to enhance angiogenesis and neurogenesis in experimental animal models. In rat models of MCAO, EPO increased BrdU-labelled cells by approximately 70% and Dcx-immunopositive cells by 80% after 7 days of administration (Wang et al., 2004).

2.2. Brain derived neurotrophic factor

Brain derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is known to play a role in brain plasticity (Hu and Russek, 2008). It is mainly synthesized by neurons and binds to the tropomyosin receptor kinase B (TrkB), triggering downstream BDNF/TrkB signalling pathways. This effect leads to the activation of the PLC-γ pathway, increase of intracellular calcium, activation of CAM kinase/PKC, and activation of the survival pathway such as PI3-kinase/AKT and MAP/ERK (Baydyuk and Xu, 2014). As a result, BDNF regulates a wide spectrum of neuronal function including neuronal development, survival, neurite extension and synaptic remodelling (Encinas et al., 1999; Orefice et al., 2013). BDNF efficacy was demonstrated by Yamashita and coworkers in a rat acute stroke model (Yamashita et al., 1997). When BDNF was administered at 15 min after permanent middle cerebral artery occlusion (pMCAO), infarct volume was reduced at 24 h after stroke (Yamashita et al., 1997). Furthermore, post-treatment of BDNF at 1 h, 3 days and 5 days after the rat photothrombotic permanent ischemic stroke model improved functional motor recovery after long term treatment at 1 and 6 weeks (Schabitz et al., 2004).

2.3. Granulocyte-colony stimulating factor

Granulocyte-colony stimulating factor (G-CSF) is a 19.6 kDa glycoprotein that has been used as the treatment for neutropenia (Cosler et al., 2007). It is a hematopoietic growth factor that is produced by monocytes, mesothelial cells, fibroblasts, neurons and endothelial cells (Schneider et al., 2005). It functions at regulating