Neurorestorative Treatment of Stroke: Cell and Pharmacological Approaches

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Summary: There is a compelling need to develop cell and pharmacological therapeutic approaches to be administered beyond the hyperacute phase of stroke. These therapies capitalize on the capacity of the brain for neuroregeneration and neuroplasticity and are designed to reduce neurological deficits after stroke. This review provides an update of bone marrow–derived mesenchymal stem cells (MSCs) and select pharmacological agents in clinical use for other indications that promote the recovery process in the subacute and chronic phases after stroke. Among these agents are 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins), erythropoietin (EPO), and phosphodiesterase type 5 (PDE-5) inhibitors and nitric oxide (NO) donors. Both the MSCs and the pharmacologic agents potentiate brain plasticity and neurobehavioral recovery after stroke. **Key Words:** Stroke, neuronal plasticity, angiogenesis, neurogenesis, synaptogenesis, MSC, pharmacotherapy.

INTRODUCTION

The time window for effective treatment to enhance stroke recovery is likely to be far longer than that for acute neuroprotective stroke treatments: perhaps days or weeks, rather than minutes or hours after stroke. The extended therapeutic window creates an opportunity to treat most, if not all, stroke patients. Thus, the search for novel cellular and pharmacological therapeutic approaches to be administered beyond the hyperacute phase of ischemia, amplifying the intrinsic properties of the brain for neuroplasticity and subsequent neurological recovery, becomes critical.[1] Poststroke recovery treatments are likely to enhance structural and functional reorganization (i.e., plasticity) of the damaged brain. This review provides an update of select cellular and pharmacological agents that facilitate neurobehavioral recovery and brain plasticity following stroke.

BIOLOGICAL BASICS OF NEURORESTORATIVE THERAPY

Neurorestorative events include neurogenesis, angiogenesis, and synaptic plasticity, all of which contribute to functional improvement after stroke. The adult rodent brain generates neuronal progenitor cells in the subventricular zone (SVZ) and in the dentate gyrus of the hippocampus throughout the life of the animal. The persistence of neurogenesis in the adult mammalian brain suggests that endogenous precursors are a source for neuronal replacement after brain injury. After stroke in the adult brain, the neuroblast population is greatly expanded in the SVZ, and these cells are recruited to areas bordering the infarct, where they can differentiate into neurons and thereby replace lost neurons.[2,3] In addition, neuroblasts may act synergistically with the microvasculature to stimulate angiogenesis and synaptic activity in the local microenvironment and thereby promote neurological recovery.

Synaptic plasticity is related to behavioral change and functional recovery after brain injury.[4] Increasing dendritic arborization and spine density are potential morphological strategies for enabling the brain to reorganize its neuronal circuits.[5] Functional alterations in motor cortex organization are accompanied by changes in dendritic and synaptic structure, as well as by alterations in the regulation of cortical neurotransmitter systems.[5,6] After a stroke, synaptic activity is increased in the ischemic boundary zone, as evidenced by increased expression of synaptic proteins such as synaptophysin and growth-associated protein 43. These proteins are amplified with successful neurorestorative treatments.[7]

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Angiogenesis in the ischemic border creates a hospitable microenvironment for neuronal plasticity, leading to functional recovery.[8] Greater microvessel density in the ischemic border correlates with longer survival in stroke patients.[9] Angiogenic vessels express trophic factors (e.g., brain-derived neurotrophic factor, BDNF) and other soluble factors that stimulate recruitment of new neurons and synaptic function.[10,11] After stroke, neuroblasts are concentrated around blood vessels.[12] Thus, vascular signaling via angiogenesis influences neuroblast migration and survival.[12] Neuronal recruitment and angiogenesis are therefore mechanistically linked.

Angiogenesis, neurogenesis, and synaptogenesis comprise an interrelated set of neurorestorative events that facilitate recovery of neurological function. Thus, cellular or pharmacological agents that promote one or more of these restorative events may improve neurological outcome after a stroke. The cellular approach includes a variety of cells, including neural stem and progenitor cells, cord blood, and mesenchymal stem cells (MSCs).[13–18] The search for pharmacological therapies that potentiate the recovery process after a neurological injury has intensified during the last decade. Many therapeutic agents already marketed have been shown to promote functional outcome after stroke,[7,19–22] including trophic and growth factors (e.g., vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF), and BDNF), granulocyte colony-stimulating factor (G-CSF), angiopoietin 1 (ANG1), angiotensin modulators, minocycline, and thiazolidinediones. In addition, various agents with widespread application for other medical indications have neurorestorative effects on injured cerebral tissue. Among these are statins, erythropoietin (EPO), and phosphodiesterase type 5 (PDE-5) inhibitors.

We now review the use of select cellular and pharmacological agents, all of which stimulate neurogenesis, angiogenesis, and synaptogenesis and appear to possess neurorestorative properties. The eventual movement of these agents into clinical use will depend on the rigorous demonstration of efficacy in preclinical models of stroke, clinical safety, and realistic dosing protocols. Here, we focus on a particular cell-based therapy, MSC, and on three categories of neurorestorative agents: (1) the 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins); (2) EPO; and (3) PDE-5 inhibitors. This is by no means an exhaustive list, but simply represents classes of cellular or neurorestorative agents, some of which are likely candidates for clinical use. A common thread in the neurorestorative therapies is that they increase parenchymal cell expression of VEGF and angiogenesis.

MSC TREATMENT OF STROKE

MSC neurorestorative therapy

The regenerative potential of MSCs has been demonstrated in myocardial, limb, and brain ischemia.[23] MSC administration starting 24 hours after stroke promotes functional outcome after stroke, whether by intracerebral, intravenous, or intra-arterial route.[17,18] In addition, delayed treatment of stroke with MSCs at 7 days or at 1 month after stroke onset also increases brain plasticity and improves long-term functional outcome.[17,24,25]

Mechanisms of MSC neurorestorative effect

MSCs are multipotential, and can differentiate into various tissue lineages, including astrocytes, neurons, and endothelial cells in the brain.[18,26] When MSCs are administered 24 hours after stroke, functional outcome is significantly improved from 7 days after treatment.[27] This benefit is probably not attributable to the very few MSCs that differentiate into brain cells. Instead, the active principle seems to be that MSCs secrete various growth factors (e.g., VEGF, bFGF, and BDNF) that promote functional outcome after stroke,[28–32] thus amplifying their endogenous brain levels. These growth factors support and amplify angiogenesis, neurogenesis, and synaptic plasticity.[33,34] MSCs thus behave as small biochemical and molecular factories and catalysts, producing and inducing within parenchymal cells many cytokines and trophic factors that enhance angiogenesis and vascular stabilization in the ischemic boundary (which is where the majority of MSCs that survive in the brain are located).[35]

In addition, neurogenesis in the SVZ and synaptogenesis are greatly amplified by MSC treatment. MSCs also induce other agents within injured brain, such as bone morphogenetic proteins BMP2 and BMP4 or connexin 43 expression in astrocytes.[36] In concert with enhancing angiogenesis, neurogenesis, and synaptogenesis, MSCs significantly decrease glial scar formation and promote glial–axonal remodeling.[24] Thus, MSCs act in a pleiotropic way to stimulate brain remodeling.

Basic and clinical data support the translation of MSC therapy to clinical trials. Stroke patients treated with autologous MSCs (i.v.) show improved functional recovery after stroke.[37] The procedures of *ex vivo* expansion of autologous MSCs and of transplantation are safe and well tolerated.[37,38] MSCs are not immunorejective, and allogeneic cells can be used.[39,40] Thus, MSC treatment is poised for clinical trials in stroke. Preclinical data point to other cell therapies that appear highly efficacious in reducing neurological deficits after stroke,[15,22,41] and we expect that these cells will also enter the clinical arena.

A major benefit of cell-based therapy is that cells administered via a vascular route distribute themselves throughout the entire region of compromised tissue. They serve as a distributed network of polypharmacy and a catalysis for neurorestoration. Benefit derives essentially from stimulating and amplifying the endogenous restorative mechanisms residing in brain. It is likely that feedback loops sensitive to the microenvironment of the

compromised tissue titrate the restorative response to exogenous cells to safe and effective levels.

PHARMACOLOGICAL TREATMENT OF STROKE

Statins

Statins are potent inhibitors of cholesterol biosynthesis and also benefit stroke. The mechanism by which statins provide benefit against stroke is likely multifactorial, involving reduction of low-density lipoprotein cholesterol along with stabilization of vulnerable plaques. Statins also render cortical neurons more resistant to NMDA-induced excitotoxic death. Many of the pleiotropic effects of statins are cholesterol independent, such as improvement of endothelial function, increased NO bioavailability, antioxidant properties, inhibition of inflammatory responses, immunomodulatory actions, upregulation of endothelial nitric oxide synthase (eNOS), decrease of platelet activation, and regulation of progenitor cells.[42,43] Pretreatment of stroke with statins reduces brain infarct size and improves neurological outcome by directly upregulating brain eNOS.[44,45] Combination atorvastatin and recombinant human tissue plasminogen activator (rhtPA) treatment 4 hours after stroke induces downregulation of tissue factor, protease-activated receptor 1, intercellular adhesion molecule 1, and matrix metalloproteinase 9 (MMP 9); concomitantly, it reduces cerebral microvascular thrombosis and enhances microvascular integrity.[46] Patients who had taken statins prior to the onset of stroke have significantly decreased mortality and improved outcome after acute ischemic stroke.[47,48] The results of the recently reported in stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial indicate that atorvastatin is likely efficacious in reducing the incidence of recurring stroke.[119]

Neurorestorative effects of statins. Low-dose statin administered 24 hours after stroke promotes angiogenesis, neurogenesis, and synaptic plasticity and improves neurological functional outcome after stroke in young and in older retired breeder rats (middle age).[49,50] Treatment of patients within 4 weeks after acute ischemic stroke with statins significantly increased favorable outcome at 12 weeks.[51] In addition, the efficacy, safety, and tolerability of statins have been confirmed in randomized, controlled, multicenter trials involving large numbers of patients aged ≥65 years.[52] Elderly patients taking lipid-lowering agents, such as statins, at the time of an ischemic stroke have lower poststroke mortality and a lower risk of worsening during hospitalization.[48]

Mechanisms of statin-induced neurorestoration. Molecular mechanisms underlying the role of statins in the induction of brain plasticity and subsequent improvement of neurological outcome after treatment of stroke include the statin-mediated increase of eNOS, VEGF–VEGFR2, BDNF, tPA, phosphatidylinositol 3′-kinase (PI3K)–AKT, and small G proteins in the ischemic brain.[53] These proteins play an important role in regulating vascular and neurogenic, neuroprotective, and neurorestorative effects.[54,55]

Specific cell populations and neurorestorative processes are targeted by statins. Statins increase brain endothelial cell expression of VEGF–VEGFR2 and eNOS and thereby activate the PI3K–AKT pathway, which regulates endothelial cell proliferation and migration and increases angiogenesis.[56] Statins also increase vascular stabilization and decrease blood–brain barrier (BBB) permeability after stroke.[57] The effect of statins on the induction of angiogenesis, however, is dose dependent and biphasic.[58] Some authors particularly highlight the proangiogenic effects of statins caused by low, nanomolar concentrations and regarded as beneficial for the treatment of vascular diseases.[58] Others have found that a high dose of statins promotes endothelial cell death and inhibits experimental angiogenesis induced by growth factors or tumor, laying a foundation for developing statin-based angiopreventive strategies.[59]

In addition to their effects on cerebrovascular function, statins increase neurogenesis in ischemic brain, protect cortical neurons from excitotoxicity, and increase neurite outgrowth and synaptic plasticity.[50,53,60,61] Atorvastatin treatment after stroke induces endogenous SVZ progenitor cell proliferation and migration to the ischemic border and neuronal differentiation.[50,53] Statins increase the expression of BDNF and synaptic proteins and also increase neuroblast migration to blood vessels.[53]

Neurogenesis and synaptic reorganization are important for functional improvement after stroke. Neurogenesis declines with advancing age. Thus, repairing the aged ischemic brain and promoting functional outcome may be significantly more challenging than in the young brain. Several signaling cascades play important roles in the regulation of statin-induced neurogenesis. Transcription factors with basic helix–loop–helix (bHLH) motifs are essential elements in neurogenesis. The Mash1 protein encodes a bHLH transcription factor, which controls the correct timing of differentiation during neuronal development.[62] Atorvastatin increased Mash1 gene and protein expression in the ischemic brain, and promoted neuronal differentiation in retired breeder rats.[49] Thus, the molecular mechanisms by which statins alter vascular and neurogenic status in young and older brains are becoming more clear.

Given the wide use of statins, their favorable safety profile in patients, the extensive preclinical data showing both neuroprotection and neurorestoration, and provocative positive clinical data in stroke patients, clinical studies are warranted to determine neuroprotective and neurorestorative properties of statins after stroke.

Erythropoietin

EPO as a neurorestorative agent. EPO is a hematopoietic growth hormone that regulates survival, proliferation, and differentiation of erythroid progenitor cells. EPO is widely used in the treatment of anemia in cancer patients undergoing chemotherapy. EPO and EPO receptor (EPOR) are weakly expressed in normal adult brain, but they are dramatically upregulated in response to brain hypoxia and metabolic distress of neurons.[63]

EPOR is important for adult neurogenesis and for migration of regenerating neurons during postinjury recovery.[64] EPO can pass the BBB,[55] and is well tolerated and safe in the stroke patient.[65,66] In preclinical studies, treatment with EPO at 24 hours after onset of stroke significantly improved functional outcome.[67] EPO treatment in rodent initiated 1 day after experimental traumatic brain injury is neurorestorative (by enhancing neurogenesis) and neuroprotective, and it significantly improves spatial memory function.[68] EPO inhibits axonal degeneration and therefore may be therapeutically useful in a wide variety of human neurological diseases characterized by axonopathy.[69]

In clinical studies, stroke patients receiving recombinant human EPO (rHuEPO) within 5 hours of the onset of cerebral ischemic symptoms showed a significantly improved clinical progress, as well as a reduced infarct size as measured by MRI, compared with placebo-treated patients.[65] The Gottingen EPO Stroke Study, a multicenter pilot study for proof of concept (preceding the necessary phase III trial), is ongoing in Germany.[65,70] EPO is the first compound with a favorable safety profile to show significant beneficial effects in stroke patients. Although the use of rHuEPO is not without side-effects (e.g., hypertension, thrombosis, and increased hematocrit), the clinical benefits of rHuEPO in other applications cannot be ignored. Recently introduced, carbamylated erythropoietin (CEPO) does not stimulate erythropoiesis but retains the antiapoptotic and neuroprotective effects of EPO.[71,72] Treatment with CEPO 24 hours after stroke reduces perifocal microglial activation and white matter damage, and significantly improves functional outcome after stroke.[73]

Mechanisms of EPO-induced neurorestoration. EPO is a pleiotropic cytokine that is proangiogenic.[74] EPO and EPOR are expressed in the vasculature during embryogenesis. EPO regulates endothelial cell proliferation and migration and it increases angiogenesis, erythropoiesis, and vascular resistance.[75] EPO also engages diverse cellular pathways, such as those involving Janus kinase 2 (JAK2), signal transducers and activators of transcription (STATs), mitogen-activated protein kinases (MAPKs), Bcl-x_L, protein kinase B, protein kinase C, and cysteine proteases to provide plasticity to vascular systems through highly conserved mechanisms.[76] Moreover, EPO upregulates ANG1 expression under normoxic conditions[77] and protects the *in vitro* BBB against VEGF-induced permeability.[78]

Treatment of stroke rats with EPO increases angiogenesis in the ischemic border.[67] EPO promotes endothelial cell secretion of MMP 2 and MMP 9, which are chemotactic for neuroblast migration.[79] VEGF and BDNF expression in the ischemic brain are increased in response to EPO, and may provide a vascular niche, a microenvironment supporting migrating neuroblasts. EPO infusion into the adult lateral ventricles increases the number of newly generated cells migrating to the olfactory bulb, and thereby increases new olfactory bulb interneurons.[80] The JAK2–STAT3 and PI3K–AKT pathways activated by EPO may also underlie the EPO-mediated neuronal regeneration.[81] Thus, multiple signaling pathways may regulate the EPO-induced angiogenesis and neurogenesis that promote neurorestorative effects after stroke.

PDE-5 inhibitors, cGMP, and NO donors

cGMP is a molecular messenger involved in diverse cellular processes, including regulation of cellular proliferation.[82] Increases in cGMP levels enhance proliferation of endothelial cells and motor neurons.[83] Thus, increased cGMP production may facilitate neuroprotection and neurorestoration after stroke. cGMP levels in brain may be increased by cGMP production via increases in NO or inhibition of cGMP hydrolysis. NO activates soluble guanylyl cyclase and leads to the formation of cGMP in target cells. PDE-5 inhibitors are a new class of vasoactive drugs (including sildenafil, vardenafil, zaprinast, and tadalafil) developed for treatment of erectile dysfunction in patients.[84] These drugs competitively inhibit cGMP hydrolysis by PDE-5, thereby fostering cGMP accumulation and relaxation of vascular smooth muscle.[85] Sildenafil significantly increases cerebral cGMP.[86,87]

Neurorestorative effect of PDE-5 inhibitors. Chronic treatment of stroke-prone, spontaneously hypertensive rats with DA-8159, a new PDE-5 inhibitor, increases cerebral blood flow in the ischemic brain, plasma NO, cGMP, and the total antioxidative status and attenuates endothelial dysfunction.[88] Treatment of stroke with sildenafil starting at 24 hours after stroke significantly increased brain levels of cGMP, evoked neurogenesis, and reduced neurological deficits after stroke in both young adult and aged rats.[86,89] Increasing age decreases the number of new neurons in the dentate gyrus and the SVZ.[90] Sildenafil not only enhances angiogenesis and neurogenesis in young adults, but also augments angiogenesis and neurogenesis in aged ischemic rats.[91]

Molecular mechanisms underlying functional benefit include a sildenafil-mediated increase in phosphorylated AKT, which increases phosphorylation of glycogen synthase kinase 3.[92] Sildenafil also attenuates learning impairment induced by blockade of cholinergic muscarinic receptors in rats by modulating NO-cGMP signal transduction, a

pathway implicated in age-related cognitive decline and neurodegenerative disease.[93] Therefore, in addition to promoting neuroregeneration after stroke treatment, sildenafil may also enhance cognitive function, and can be used to treat cholinergic dysfunction in age-related cognitive decline and Alzheimer's dementia (AD).

Neurorestorative effect of NO donors. NO donors produce neurorestorative effects after stroke both by increasing cGMP and through other complementary pathways. In the CNS, NO is an important physiological messenger involved in the modulation of brain development, synaptic plasticity, neuroendocrine secretion, sensory processing, and cerebral blood flow.[94]

Cerebrovascular protection by various NO donors after experimental stroke has been reported in rat.[95] NO promotes angiogenesis and neurogenesis, and increases neuroblast migration. Stroke rats exhibit significant improvements of neurological outcome during recovery from ischemic stroke when administration of DETA-NONOate to rats is initiated at 24 hours after stroke.[96,97] NO has a prominent role in the regulation of cerebral blood flow and the modulation of cell-to-cell communication in the brain.[98] L-arginine increases cerebral blood perfusion and improves vasomotion of microvessels by enhancing NO levels.[99] Systemic administration of a low dose of the NO donor DETA-NONOate to rats 24 hours after stroke significantly induced angiogenesis in the ischemic boundary regions.[96]

NO donors such as SNAP, GSNO, and NOC also regulate HIF-1-mediated *VEGF* gene activation and promote angiogenesis.[100] In addition, NO upregulates expression of $\alpha_v\beta_3$ integrin (a critical mediator of cell–matrix adhesion and cell migration) on endothelial cells and promotes angiogenesis.[101] NO also increases vascular stabilization[96,100] via upregulation of the ANG1–Tie2 pathway[102] and mediates mural cell recruitment and vessel morphogenesis in murine melanomas and tissue-engineered blood vessels.[103]

NO regulates neurogenesis in the adult brain.[97] DETA-NONOate promotes neuronal differentiation and neurite outgrowth in both young and older SVZ neurospheres.[104] DETA-NONOate modulation of SVZ cell differentiation is controlled by N-cadherin, β-catenin, and neurogenin 1 gene expression.[104] The NO–cGMP–protein kinase G (PKG) signaling pathway facilitates communication between neurons and glia,[105] and enhances neurotrophin-induced neurite outgrowth.[106] As described above, EPO and EPOR promote adult neurogenesis and migration of regenerating neurons during postinjury recovery.[64] NO modulates hypoxic stimulation of EPO production[107] and L-arginine rescues decreased EPO gene expression by stimulating GATA-2 with NG-monomethyl-L-arginine.[108] Therefore, NO upregulation of EPO production may also play an important role in promoting brain plasticity. Thus, agents that chronically increase NO in brain appear to be neurorestorative and may be candidates for clinical development.

VASCULAR ENDOTHELIAL GROWTH FACTOR

VEGF is a trophic factor common to both cell and pharmacological neurorestorative therapy.

Administration of MSCs and agents such as statins, EPO, or PDE-5 inhibitors (e.g., sildenafil and tadalafil) and NO donors (e.g., DETA-NONOate) after stroke all significantly increase ischemic brain VEGF expression and promote functional recovery without affecting lesion volume.[53,67,86,96,97] Thus, induction of VEGF is likely a major contributor to neurorecovery after stroke. Direct administration of VEGF or indirect upregulation of VEGF in ischemic brain by cell or pharmacological means may promote functional recovery after stroke.

VEGF is an angiogenic protein with a wide variety of physiological and molecular effects; it has therapeutic potential in ischemic disorders, including stroke. VEGF increases endothelial cell proliferation, migration, and angiogenesis after stroke; it also modulates the PI3K–AKT–nuclear factor kappa B signaling pathway, inhibits caspase-3 activity, and reduces ischemic neuronal apoptosis.[109,110] However, early postischemic (1 hour) administration of recombinant human VEGF165 (rh-VEGF165) to ischemic rats increased BBB leakage and infarction volume in the ischemic brain.[111] In contrast, late (48 hours) administration of rhVEGF165 to ischemic rats enhanced angiogenesis in the ischemic penumbra and significantly improved neurological recovery,[111] and combination ANG1–VEGF treatment decreased BBB leakage and promoted angiogenesis.[112]

VEGF stimulates angiogenesis and neurogenesis, and improves functional outcome after stroke, through multiple mechanisms.[113,114] Among other effects, VEGF is a chemoattractant for bFGF-stimulated neural progenitors.[115] VEGF increases ischemia-induced tyrosine phosphorylation of Kv1.2 potassium channel proteins via activation of the PI3K pathway, enhances proliferation and migration of neural progenitors in the SVZ, and improves striatal neurogenesis, neuronal differentiation, and maturation of neuroblasts in adult rat brains after stroke.[109,116,117]

VEGF can be induced in ischemic brain by both cell-based and pharmacological restoration therapies. In most preclinical and clinical studies, however, the introduction of these factors as single agents has resulted in the formation of stabilized blood vessels of only limited duration.[118] Drawbacks of administering VEGF directly include the potential adverse effects of inducing hemorrhage. To our knowledge, no clinical trials are planned or proposed to treat stroke using VEGF. A more reasonable approach to capitalizing on the potential benefit of VEGF is through pharmacological agents that stimulate endogenous production of VEGF.

CONCLUSION

Here we have partially summarized the use of MSCs and pharmacological agents in clinical use that have potential to improve neurological function when administered, after stroke, or later. All of these agents increase VEGF levels and activate signal transduction pathways that remodel brain by inducing neurogenesis, angiogenesis, synaptic plasticity, and structural changes that augment functional improvement after a stroke. MSCs and many of these therapeutic molecules have long and safe medical histories from their use in treatment of other medical conditions. The literature reviewed here shows that the injured brain can be stimulated to improve neurological function. Many of these restorative events, such as angiogenesis, neurogenesis, and synaptic plasticity occur naturally after stroke, but they can also be amplified by cell and pharmacological interventions to restore neurological function after a cerebral insult.

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