Modulation of Neural Plasticity as a Basis for Stroke Rehabilitation

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Current understanding of the mechanisms underlying neural plasticity changes after stroke stems from experimental models as well as clinical studies and provides the foundation for evidence-based neurorehabilitation. In this review, we first describe the main structural and functional constituents of neural plasticity that are believed to contribute to recovery of function after stroke. Next, we discuss selected behavioral manipulations and adjuvant therapies that can stimulate neural plasticity and improve recovery of function, particularly when applied in combination with task-specific physiotherapy and in a stimulating environment.

Neural Plasticity After Brain and Spinal Cord Injury

Experience-Dependent Plasticity of the Cerebral Cortex

Cerebral cortex is an assembly of neuronal cells that are highly interconnected. The morphology as well as function of these complex and spatially distributed networks are modulated or even controlled by the glial component of the central nervous system (CNS). The ability to adapt in response to the changing environment is the most fundamental property of the nervous tissue and constitutes the basis for learning. Neural plasticity is the neurobiological basis for the ability to adapt and learn in an experience-dependent manner. At the structural level, neural plasticity could be defined in terms of dendritic and axonal arborization, spine density, synapse number and size, receptor density, and in some brain regions also the number of neurons. These structural constituents of neural plasticity jointly determine the complexity of neuronal networks and their activity and contribute to recovery of function after stroke and other CNS injury.

Spontaneous Recovery of Function After Stroke

Loss of function attributable to stroke is caused by cell death in the infarcted region as well as cell dysfunction in the areas surrounding the infarct. In addition, the function of remote brain regions, including the contralateral areas that are connected to the area of tissue damage, is compromised because of hypometabolism, neurovascular uncoupling, and aberrant neurotransmission, jointly called diaschisis. Some recovery of function occurs spontaneously after stroke in humans as well as in animal models. It is believed that this functional recovery involves 3, to some extent overlapping, phases: (1) reversal of diaschisis, activation of cell genesis, and repair; (2) changing the properties of existing neuronal pathways; and (3) neuroanatomical plasticity leading to the formation of new neuronal connections. The basic processes underlying phases 2 and 3 also are involved in normal learning and it has been recognized that functional improvement after CNS injury is a relearning process.

Cortical Map Rearrangements

As stated, the brain, and especially the cerebral cortex, has a capacity to alter the structure and function of neurons and to reorganize its neural networks in response to the changes in input and output demands. Thus, when the normal input to a particular area of the primary somatosensory cortex is lost because of injury, rapid structural and functional reorganization results in this area being activated by sensory stimulation of the surrounding intact body regions. Thus, spinal cord injuries lead to both unmasking of existing latent connections as well as changes in somatosensory cortex anatomy attributable to the growth of new lateral connections. Similarly, the motor maps in the primary motor cortex change in response to task-specific training or after injury. Training human subjects or animals to perform a specific task leads to an increase in the area of motor cortex that controls the muscles used during the task. Injury to the motor cortex leads to the recruitment of motor areas that were not making significant contribution to the lost function before the injury. For example, in macaque monkeys, recovery of dexterity after unilateral motor cortex lesion is mediated by the ipsilesional premotor cortex. Inactivation of this region abolishes recovered movement, whereas it does not affect the performance in uninjured monkeys. The notion that the activity of cortical areas recruited after injury plays a role in functional recovery in humans is supported by a study showing that in well-recovered stroke patients, the ipsile-
Contralesional Hemispheric Involvement

The contralesional hemisphere has the capacity to contribute to movement on the ipsilateral side but does not make any significant contribution in healthy subjects.12 However, significant increases in contralesional motor cortex activity can be observed in stroke patients during movement of the affected foot or arm.13–15 These and other studies have demonstrated that in the early phase of stroke recovery process, there is an increased activation of the motor areas in both hemispheres but is substantially more pronounced on the contralesional side. The contralesional activation is often reduced in the later stage of recovery. Although there is no general consensus concerning the role of contralesional somatosensory and motor area activation in recovery of function, it appears that the best recovery is associated with an early recruitment of the supplementary motor areas on the ipsilesional side, whereas persistent activation of the contralesional prefrontal and parietal cortex predicts a slower and less complete recovery and also is often associated with larger infarct.16,17 Notably, a recent functional magnetic resonance imaging study has shown that the pattern of brain activation present in the early phase after stroke could be predictive of subsequent recovery of motor functions.18

Contralesional Axonal Remodeling of the Corticospinal System

Whereas the capacity for functional and structural rearrangements has been studied for decades and is well-documented for the neural networks within the cerebral cortex, the plasticity responses induced by stroke at the level of the spinal cord have been demonstrated only recently. Using a rat stroke model, Liu et al19 showed that the spontaneous behavioral motor recovery highly correlates with the remodeling of corticospinal tract axons in the cervical spinal cord as well as the reorganization of pyramidal neurons in the cerebral cortex of both hemispheres. Consistent with conclusions from human imaging studies, they further showed that functional recovery is highly correlated with contralesional cortical wiring only in the acute phase, with a negative correlation later.19 Although the capacity for remodeling of the corticospinal tract axons at the spinal cord level remains to be demonstrated in stroke patients, these findings add a new dimension to the rehabilitative efforts for improved functional recovery after stroke.

Cell Genesis

In the adult human brain, neural stem cells keep producing new neurons, astrocytes, and oligodendrocytes in 2 defined regions, the dentate gyrus of the hippocampus and the subventricular zone, albeit at a much lower rate than during earlier ontogenetic stages.20 A structure analogous to the rostral migratory stream in rodents connecting the subventricular zone with the olfactory bulb exists also in the human brain.21 Having originated from dividing neural stem cells, differentiating cells migrate through the rostral migratory stream to the olfactory bulb. In the rodent stroke models, some of these cells divert from the rostral migratory stream and reach the ischemic penumbra, where some of them transiently persist and others turn into neurons and astrocytes.22 We do not know yet the functional significance of the adult mammalian neurogenesis because no animal models exist in which neurogenesis could be specifically inhibited without simultaneous inhibitory or modulatory effects on other plasticity responses. However, an enriched environment applied to adults of various vertebrate species stimulates both baseline and ischemia-triggered neurogenesis. Thus, it is possible that newly formed neurons, astrocytes, or oligodendrocytes positively affect brain plasticity and functional recovery after stroke. In a mouse CNS, gap junctional coupling occurs between introduced neural stem cells and residential neuronal cells, and is essential for the neuroprotective effect of neural stem cells on the endogenous neuronal cells.23 Thus, apart from the plasticity-promoting “trophic” effects of newly born and partially differentiated neuroectodermal cells, these cells also might protect the ischemic penumbra by a direct cell–cell transfer of signaling and other molecules.

Angiogenesis, the formation of new vessels, plays an important role in remodeling of ischemic brain tissue after stroke through enhanced perfusion as well as blood flow–independent mechanisms.24

Increasing Neural Plasticity Through Behavioral Manipulations and Adjuvant Therapies

Evidence accumulated during the past 2 decades together with recent advances in the field of stroke recovery clearly show that the effects of neurorehabilitation can be enhanced by behavioral manipulations and combination with adjuvant therapies that stimulate the endogenous neural plasticity. However, the dose, timing after stroke, and coupling with appropriate physical therapy may be critical for the outcome.

Enriched Environment and Multimodal Stimulation

A large number of animal studies have demonstrated that experience in an enriched environment (housing conditions that facilitate enhanced sensory, cognitive and motor stimulation) stimulates all the structural and functional components of neural plasticity and cognitive performance in healthy animals as well as promotes recovery of sensorimotor function after experimental stroke.25,26 Human equivalents of the environmental enrichment are multimodal stimulation and multisensory training protocols. These have been shown to be more effective for learning in healthy subjects.27–29 However, we are only beginning to understand how to translate the positive effects of enriched environment in experimental animal
research to humans. Specific examples of multisensory neurorehabilitation are mirror therapy and action observation, motor imagery and mental training, virtual reality training, and music-related therapies.

In mirror therapy, the illusion of movement in the affected limb is created by the reflection of the moving unaffected limb while the affected arm is hidden behind the mirror. The strongest evidence in support of the effectiveness of this approach has come from a study of subacute stroke patients who received 30 minutes of mirror therapy program per day consisting of wrist and finger flexion and extension movements in addition to a conventional program for 4 weeks. Compared with a control group who received a sham instead of mirror therapy, the mirror training patients showed a more improved distal hand functioning at the end of therapy period and at 5-month follow-up. Similarly, severely hemiparetic patients who received mirror therapy regained more distal function after 6 weeks of training 30 minutes per day, 5 days per week, for 6 weeks. However, little is known about which patients are likely to benefit from mirror therapy and how such a therapy should be preferentially applied. Action observation for 4 weeks also led to enhanced motor performance in stroke patients, and this functional improvement was still present at 8 weeks of follow-up. Action observation on motor training in combination with concurrent physical training of the observed action enhanced the positive effects of task practice alone.

Mental training is based on conscious activation of brain regions and networks involved in movement preparation and execution. In a placebo-controlled trial of chronic stroke patients, therapist-guided mental practice was associated with increased dexterity and changes in patterns of cortical activation. Because motor imagery is not dependent on the actual ability to execute movements, mental training can be used early in the rehabilitation process and even in severely paretic patients, although it can be difficult in patients with left parietal or left lateral prefrontal lesions.

Virtual reality technologies provide multimodal, interactive, and realistic 3-dimensional environments with a high level of control of the sensory input to suit each user’s needs. The evidence of the effectiveness of virtual reality training in stroke rehabilitation thus far is limited, with most studies underpowered and lacking controls. However, recent reports show that Nintendo Wii gaming technology represents a potentially effective alternative to promote motor recovery, and a rehabilitation gaming system facilitates the functional recovery of the upper extremities as compared with intense occupational therapy or nonspecific interactive games for stroke patients who received this adjuvant therapy in combination with conventional rehabilitation.

A number of studies suggest that listening to music can enhance a variety of cognitive functions, such as attention, learning, communication, and memory, both in healthy subjects and in various patient groups. Music also can affect the mood and motivation of the subject, and thus could be an easy-to-conduct and inexpensive means to facilitate cognitive and emotional recovery in numerous neurological and psychiatric disorders. A recent study of listening to music after stroke demonstrated that patients who listened to self-selected music had better cognitive recovery and mood compared with those who listened to self-selected audio books or those with no listening material. Further, listening to music or speech in the acute phase after ischemic stroke induced long-term plastic changes in early sensory processing that correlated with improvement in verbal memory and focused attention. Patients with chronic poststroke visual neglect who performed tasks while listening to music of their choice showed enhanced visual awareness of contralesional targets relative to when tasks were performed either with preferred music or in silence.

**Noninvasive Brain Stimulation**

Noninvasive brain stimulation can be performed using repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS). These therapies have the potential to enhance neuroplasticity during stroke rehabilitation, thereby supporting recovery of motor and cognitive impairments. The differences between tDCS and transcranial magnetic stimulation are based on presumed mechanisms of action in which transcranial magnetic stimulation acts both as a neurostimulator and a neuromodulator, whereas tDCS acts as a neuromodulator. Depending on the frequency, duration of the stimulation, the strength of the magnetic field, and the shape of the coil, transcranial magnetic stimulation can activate or suppress the activity in different cortical regions. The tDCS delivers weak polarizing currents to the cerebral cortex, which induce sustained changes in neural cell membrane potential, leading to either hyperpolarization or depolarization. The basic cellular mechanisms underpinning the effects of noninvasive brain stimulation are only partially known. Animal studies indicate that the effects of transcranial magnetic stimulation could be analogous to other interventions inducing long-term potentiation or long-term depression in the hippocampus. Different neurotransmitters and neuromodulators such as γ-aminobutyric acid, glutamate, dopamine, and serotonin are altered in defined regions of the brain after stimulation with both repetitive transcranial magnetic stimulation and tDCS. Further, immediate early genes like c-fos and genes coding for neurotrophic factors like brain-derived neurotrophic factor are expressed in the rat brain after repetitive transcranial magnetic stimulation.

In humans, both repetitive transcranial magnetic stimulation and tDCS are shown to induce long-term effects on cortical excitability that last for months after the intervention, which may, in turn, lead to long-lasting behavioral modifications. These effects are believed to engage mechanisms of neural plasticity, rendering noninvasive brain stimulation well-suited to promote recovery of cognition and motor functions, especially in combination with other types of rehabilitative interventions. Results from several studies show, for example, that active stimulation of either the affected or the unaffected motor cortex in combination with physical and occupational therapy improves motor outcome after stroke.
Pharmacological Modulators of Neural Plasticity

Recently, several promising approaches that promote the recovery of function after stroke through the stimulation of neural plasticity have been identified through experimental animal research. Importantly, some of these compounds are already in clinical use for other indications or are already being tested in clinical trials.

D-Amphetamine

There is large body of laboratory work showing that administration of amphetamine, a potent psychomotor stimulant that induces neuronal release of norepinephrine, dopamine, and serotonin, coupled with motor practice can enhance motor recovery in animal models of stroke or other brain injury and these functional improvements are associated with increased axonal plasticity and the formation of new anatomical pathways.49,50

Several double-blind placebo-controlled clinical studies have evaluated the effects of amphetamine on poststroke motor recovery in humans.39 A meta-analysis concluded that there is no indication for the routine use of amphetamines to improve recovery after stroke.51 Given the potentially critical differences in trial designs, however, the interpretation of the results of this meta-analysis is not clear.49 As pointed out by Goldstein,49 several principles pertinent to the trial design have been elucidated by the animal studies. First, the dose–effect relationship for amphetamine-promoted motor recovery has an inverted “U” shape. The drug is relatively ineffective at lower and higher doses. Second, the effects of certain drugs (eg, amphetamine) on recovery are dependent on concomitant behavioral experience. Third, the timing of the drug administration/experience intervention is critical and also varies with the number and frequency of treatment sessions. Fourth, some drugs (eg, haloperidol) impair recovery. Thus, the clinical value of D-amphetamine in combination with physiotherapy remains to be determined through new clinical trials. The National Institute of Health–sponsored Amphetamine-Enhanced Stroke Recovery trial to evaluate the impact of the timing and duration of therapy was started in 2003. Regrettably, this trial was put on hold in 2009 pending application for further funding and the data remain unanalyzed. Recently, a pilot randomized clinical trial involving 16 patients showed that 10 mg amphetamine administered 2 days per week before physiotherapy augments the positive effects of physiotherapy on recovery of activities of daily living and arm function.52

Levodopa

Levodopa (L-3,4-dihydroxyphenylalanine) is the precursor of dopamine that is further converted to norepinephrine. Delayed treatment with levodopa in combination with physiotherapy improves functional motor recovery in ischemic stroke patients.53 Although the positive effects of levodopa (and amphetamine) on recovery are mostly ascribed to the increased levels of norepinephrine at the synapse,53,54 there is also experimental evidence in support of the role of astrocytes and dopamine signaling in recovery-enhancing actions of levodopa.55

Sigma-1 Receptor Agonists

The expression of 1 receptor is upregulated in brain tissue from rats that were housed in enriched environment after focal cerebral ischemia.56 A more detailed analysis of the involvement of 1 receptor in recovery after stroke showed that the expression of 1 receptor is upregulated in the surviving cells, particularly astrocytes, in the peri-infarct region of animals with good recovery of neurological function.56 The 1 receptor is located in membrane rafts of astrocytes and neurons and plays an essential role in membrane raft trafficking and neurite outgrowth. Importantly, a potent and selective 1 receptor agonist SA45031 enhanced functional recovery in rat models of stroke when administered within 2 days after stroke induction.56 This promising compound is presently investigated in a stroke clinical phase II trial.56

Fluoxetine

Acute increases in the amount of synaptic monoamines induced by antidepressants produce secondary long-term neuroplastic changes and involve transcriptional and translational changes that mediate molecular and cellular plasticity.57 In the posts ischemic brain, selective serotonin reuptake inhibitors are neuroprotective through their anti-inflammatory effects and improve ischemia-induced spatial cognitive deficits by promoting hippocampal neurogenesis in the rat.58 A clinical study, fluoxetine for motor recovery after acute ischemic stroke (FLAME), demonstrated in a larger cohort of patients (n=118) with moderate to severe hemiplegia after ischemic stroke that physiotherapy in combination with early treatment with fluoxetine enhances motor recovery and reduces the number of dependent patients compared with physiotherapy alone.59 These interesting results call for even larger and more comprehensive trials with an extended focus on functional outcome parameters. Because selective serotonin reuptake inhibitors are not a homogeneous category of drugs, additional experimental and pharmacological studies are needed to further deepen the understanding of their mechanism of action.

Niacin

Niacin (nicotinic acid, vitamin B3) is the most effective drug currently available for the treatment of dyslipidemia.60 Treatment with Niaspan, a prolonged-release formulation of niacin, starting 24 hours after focal brain ischemia improved functional outcome in rats, conceivably through a combination of its effects on angiogenesis,61 arteriogenesis,62 and increased synaptic plasticity and axon growth.63 The clinical usefulness and efficacy of niacin in treatment of stroke remain to be shown.

Inosine

Inosine is a naturally occurring purine nucleoside. Intracerebral infusion of inosine starting immediately after unilateral stroke induction stimulated neurons on the undamaged side of the brain to extend new projections to denervated areas of the midbrain and spinal cord and improved behavioral outcome in rats.64 Inosine altered gene expression in neurons contralateral to stroke and enhanced the ability of these neurons to form connections on the denervated side of the spinal cord.65
Inosine combined with a Nogo receptor blocker or with environmental enrichment augmented the effects of these 2 treatment modalities on the restoration of skilled forelimb use after stroke.66 These results demonstrate that the combination of behavioral and pharmacological adjuvant therapies may have additive or even synergistic effect in promoting the recovery of function after stroke. A 2-year inosine treatment was safe and well-tolerated in multiple sclerosis patients.67 Because inosine is currently in clinical trials for Parkinson disease, it appears to be a particularly attractive candidate for increasing brain plasticity and improving outcome in stroke patients.

Nogo-A Inhibition

Nogo-A is a myelin-associated protein that limits plasticity and recovery after CNS injury through neurite outgrowth inhibition. Anti-Nogo-A antibody treatment enhanced functional recovery and promoted reorganization of the corticospinal tract and axonal plasticity originating in the contralesional sensorimotor cortex.71 Genetic manipulation of the Nogo–Nogo receptor system or the use of peptides that block the signaling through the Nogo receptor have similar effects on axonal plasticity and recovery of function after experimental stroke.72 A recent study showed that Nogo-A immunotherapy also leads to the improvement of chronic neurological deficits and enhancement of neuronal plasticity and that this therapy may be used to restore function even when administered intracerebroventricularly for 2 weeks starting 9 weeks after stroke.73 An obstacle in using the anti-Nogo-A antibodies or peptide blockers could be their limited delivery into the brain parenchyma after systemic administration because of the inability to cross the blood–brain barrier. This hindrance to clinical testing of therapeutic strategies based on Nogo–Nogo receptor inhibition now may have been removed by a generation of a biologically active Nogo receptor blocker NEP1–40 fusion proteins that cross the blood–brain barrier after systemic delivery.74 A phase I clinical trial applying anti-Nogo-A antibody to subjects with acute spinal cord injury has been successfully conducted, and a phase II trial is in preparation.74

Reducing Tonic Inhibition

After stroke, the peri-infarct zone shows increased neuroplasticity which allows sensorimotor functions to remap from damage areas.76,77 However, this peri-infarct neuroplasticity, critically important for rehabilitation, is counteracted by tonic neuronal inhibition mediated by extrasynaptic \( \gamma \)-aminobutyric acid \( \gamma \)-receptors and is caused by an impairment in the ability of astrocytes to take-up \( \gamma \)-aminobutyric acid.78 L-655 708 is a cognition-enhancing drug that acts as benzodiazepine inverse agonist–specific for the \( \alpha 5 \) subunit of \( \gamma \)-aminobutyric acid receptors.79 Chronic treatment with L-655 708 starting 3 days after stroke counteracted the excessive \( \gamma \)-aminobutyric acid–mediated tonic inhibition and resulted in an early and sustained recovery of function in mice. In contrast, stroke volume was increased in mice treated with L-655 708 from stroke onset, showing that tonic inhibition in the acute phase is neuroprotective and the timing of drug delivery therefore is critical for the treatment outcome.78 These results provide a rational basis for the development of novel pharmacological strategies to promote recovery after stroke.

Phosphodiesterase 5 Inhibitors

Phosphodiesterase 5 is an isoenzyme that catalyzes the hydrolysis of a second messenger molecule cyclic guanosine monophosphate. Phosphodiesterase 5 is expressed in smooth muscle cells of blood vessels as well as in neural cells. Pharmacological inhibition of phosphodiesterase 5 leads to vasodilation and is used for the treatment of erectile dysfunction.80 Phosphodiesterase 5 inhibitors (sildenafil, tadalafil) administered orally for 6 to 7 days starting 24 hours after stroke onset improved functional recovery in young and aged experimental animals, conceivably through improved cerebral blood flow, enhanced angiogenesis, neurogenesis, and synaptogenesis.81–83 In case studies, compassionate use of sildenafil caused notable functional improvement in a patient with locked-in syndrome84 and in a patient with spastic quadriplegia.85 Two-week treatment with sildenafil (25 mg daily) appeared to be safe in patients with mild to moderately severe subacute ischemic stroke.86

Growth Factors

Several proteins or polypeptides from the growth factor family have shown beneficial effects on neural plasticity and recovery of function after stroke. For example, vascular endothelial growth factor, a protein with angiogenic properties, is both neuroprotective and exerts positive effects on neurogenesis and angiogenesis function,87 although an early administration of vascular endothelial growth factor can promote blood–brain barrier leakage and hemorrhagic transformation.88 Erythropoietin (EPO), a growth factor used for the treatment of anemia, was shown to be neuroprotective when administered within the first 2 hours after stroke;89 however, in combination with tissue plasminogen activator (tPA) treatment, EPO administered outside the therapeutic window induces blood–brain barrier permeability, exacerbates hemorrhagic transformation, and negates any neuroprotective effect of EPO.90,91 The deleterious effects of combined tissue plasminogen activator and EPO treatment are conceivably the reason for the negative outcome of a phase III EPO Stroke Trial on the efficacy and safety of EPO treatment in stroke.92 Neuroprotection aside, a recent study demonstrated that EPO treatment started 3 days after stroke induction improves functional recovery by promoting neuronal survival and angiogenesis in the perilesional tissue as well as contral-esional pyramidal tract plasticity.93

The hematopoietic growth factor granulocyte colony-stimulating factor is used for the treatment of chemotherapy-induced neutropenia. In experimental stroke, granulocyte colony-stimulating factor appears to have multiple effects that lead to enhanced functional recovery, including neuroprotection, stimulation of neurogenesis and angiogenesis, and modulation of immune response and bone marrow mobilization.84 Clinical studies showed that granulocyte colony-stimulating factor treatment for 5 days starting within 12 hours and 3 to 30 days after onset of ischemic stroke, respectively, is safe and leads to mobilization of hematopoietic stem/precursor
cells. Also, in chronic stroke patients with concomitant vascular disease, a 10-day treatment with granulocyte colony-stimulating factor was safe and well-tolerated. Clinical efficacy of granulocyte colony-stimulating factor with regard to functional recovery poststroke remains, however, unproven.

Daily intravenous treatment with brain-derived neurotrophic factor improved behavioral outcome after experimental stroke by increased neurogenesis and migration of SVZ progenitor cells and transient upregulation of binding densities of excitatory glutamate receptors. High serum levels of insulin-like growth factor 1 after stroke are associated with neurological recovery and better functional outcome. In experimental stroke, insulin-like growth factor 1 treatment improved motor recovery, paralleled by enhanced neovascularization and neurogenesis. However, because of its inability to pass through blood–brain barrier, insulin-like growth factor 1 was administered intranasally starting 10 minutes after stroke induction or by adeno-associated virus-mediated gene transfer 3 weeks before stroke. The clinical applicability of these results remains to be determined.

Basic fibroblast growth factor (fibroblast growth factor-2, terafemin) is a mitogenic factor for a variety of cell types, including neural progenitor cells, glia, and endothelial cells. In addition to its role in cell proliferation, basic fibroblast growth factor supports neuronal cell survival and axonal growth. Despite strong neuroprotective effects of basic fibroblast growth factor demonstrated by a number of experimental studies, phase III clinical trials were terminated because they did not demonstrate benefit of basic fibroblast growth factor over placebo when administered within 6 hours from stroke onset and showed higher incidence of adverse effects and mortality. However, because of its positive effects on neural plasticity, the possible enhancement of recovery by delayed administration of basic fibroblast growth factor could be worth testing.

**Cell-Based Therapy**

The therapeutic potential of cell transplantation for stroke recovery has been shown in a number of animal studies. In particular, bone marrow stromal cells, a mixed population of stem and progenitor cells, have long-lasting positive effects on recovery neurological function and a range of structural and molecular plasticity parameters. However, in diabetic animals, such a cell therapy did not improve function but increased mortality, blood–brain barrier leakage, and brain hemorrhage. This study pointed to the limitations and potential risks of these and possibly other adjuvant neural plasticity modulating therapies and the need to take into consideration the associated diseases. Intravenous transplantation of autologous bone marrow–derived mesenchymal stem cells is safe and feasible in stroke patients followed-up for 12 months, although the efficacy remains to be shown. Importantly, this study also showed that these cells can be rapidly expanded in autologous serum, reducing cell preparation time and the risk of transmissible disorders.

A recent animal study demonstrated that intravenous administration of human umbilical tissue–derived cells 24 hours after stroke induction improves functional outcome along with increased angiogenesis, synaptogenesis, and reduction of apoptotic cell death. Similar positive effects on motor function recovery and brain plasticity were observed when these cells were transplanted directly into the ischemic cortex. Thus, the umbilical tissue–derived cells could represent an interesting cell-based therapy alternative, especially for patients from whom autologous bone marrow–derived cells could not be obtained. Also, peri-lesion injection of genetically engineered neural stem cell line (CTX0E03) 14 to 28 days after stroke induction improved behavioral dysfunctions in a dose-related manner. A first clinical safety trial, in which the CTX0E03 cells are delivered intracranially in chronic stroke patients (Pilot Investigation of Stem Cells in Stroke [PISCES]), has recently started (ClinicalTrials.gov/NCT01151124).

**Astrocytes and the Innate Immune System**

The emergence of astrocytes as an interesting target in stroke intervention is intriguing. Astrocytes control blood flow, a function highly relevant for both physiological and pathological situations such as stroke. In the ischemic brain lesions, astrocytes stimulate the formation of new blood vessels through the secretion of vascular endothelial growth factor and thus are strong contributors to neurorestorative processes, including synaptogenesis. Astrocytes are of major importance in the detoxification process of different reactive oxygen species after cellular stress, which is a major component of ischemic stroke. Beta-lactam antibiotics had a neuroprotective effect in in vitro models of ischemia, conceivably through the stimulation of the glutamate transporter GLT1 (EAAT2) in astrocytes. Stroke leads to massive activation of astrocytes and prominent reactive gliosis in the ischemic penumbra. Attenuation of reactive gliosis in ischemic stroke by genetic ablation of GFAP and vimentin (proteins that constitute the highly dynamic astrocyte intermediate filament system) leads to increased infarction, suggesting that reactive astrocytes play an important role in the protection of the ischemic penumbra. Thus, modulation of astrocyte activity may provide novel therapeutic paradigms for ischemic stroke. Astrocytes directly control the number and function of neuronal synapses. Mice deficient in GFAP and vimentin exhibit a more pronounced loss of synapses in the hippocampus in the acute phase after partial deafferentation of the dentate gyrus of the hippocampus by entorhinal cortex lesion, but show remarkable synaptic recovery later. They also exhibit improved integration of neural grafts or neural stem cells transplanted in the CNS, improved axonal regeneration and increased baseline and injury-induced hippocampal neurogenesis. An interesting link exists between astrocytes, thrombospondins, and synaptic response and axonal sprouting in ischemic stroke. Thrombospondins 1 and 2 are extracellular glycoproteins with synaptogenic properties secreted by astrocytes. Their deficiency leads to reduced synaptic density during development. Astrocyte expression of thrombospondin 1 and 2 is increased after experimental stroke, and mice deficient in thrombospondin 1 and 2 exhibit synaptic density and axonal sprouting deficit associated with impaired motor function recovery after stroke. Astrocytes also play a role in the elimination of superfluous synapses during development and also possibly in a...
pathological context. Immature astrocytes are a source of a signal that triggers the expression of complement component C1q in developing neurons. C1q localizes to synapses that are thus tagged for elimination through the activation of the complement cascade and deposition of C3b, an opsonin derived from the proteolytic activation of the third complement component (C3). The complement-mediated elimination of synapses seems to be reactivated in neuropathologies such as glaucoma. The possible implications of these findings for modulation of synaptic plasticity after stroke need to be experimentally addressed.

Conclusion

Given the complexity of the CNS response to brain ischemia, and the role of neural plasticity in functional recovery, it is likely that future treatment and rehabilitation protocols for stroke survivors will target multiple molecular pathways, will aim at adjusting multiple equilibria, and will be based on both pharmacological and nonpharmacological neural plasticity modulating approaches. Possible negative effects of comorbidities such as diabetes need to be carefully taken into consideration when tailoring such combination treatments for each patient.

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