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Mechanisms of Brain Adaptation in Post-Stroke Motor Recovery

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Abstract: After the initial cerebrovascular event, around one-third of stroke patients experience ongoing disability; the majority of poststroke disability is caused by motor deficits. After a stroke, motor function has long been restored by exercise and training. For poststroke impairment, improved training methods and treatments are presently being developed to maximize the benefits of these rehabilitative procedures. This effort depends on expanding our knowledge of the inherent processes of healing and the neuroplastic alterations linked to poststroke motor dysfunction. To further expand the scope of poststroke rehabilitation, pharmaceutical, biological, and electrophysiological therapies that enhance neuroplasticity are being investigated. Potential motor rehabilitation therapies, such as stem cell therapy, exogenous tissue engineering and brain–computer interface technologies, could be integral in helping patients with stroke regain motor control. As the methods for providing motor rehabilitation change, the primary goals of poststroke rehabilitation will be driven by the activity and quality of life needs of individual patients. This Review aims to provide a focused overview of neuroplasticity associated with poststroke motor impairment, and the latest experimental interventions being developed to manipulate neuroplasticity to enhance motor rehabilitation.

Keywords: Brain Adaptation, Motor Recovery, Neuroprosthestics, Poststroke Rehabilitation

Introduction

One of the most common neurological disorders in the world, particularly among the elderly, is stroke. Numerous symptoms may be caused by this cerebrovascular disease, which in extreme circumstances may be fatal. One of the primary disabilities linked to stroke is motor impairment, which can significantly lower a patient's quality of life if their surroundings have not been adjusted to accommodate their functional limitations, such as the lack of assistive devices to help with everyday tasks.

The ability of training and physical activity to restore motor function after neural injury has long been appreciated. This observation has led to the establishment of rehabilitation and, notably, neurorehabilitation as clinical disciplines. Innate physiological and anatomical plasticity are important processes that underlie substantial gains in motor function after stroke, and the combination of task-specific training and general aerobic exercise is still the gold-standard treatment for poststroke rehabilitation. Nevertheless, even with intensive task-specific training and physical activity, 15–30% of patients with stroke are permanently disabled. As a result, research aiming to develop novel therapies that enhance neuroplasticity is currently being conducted to allow rehabilitation of these patients.

This area of research can be divided into three different arms, all of which are at relatively early stages of development. The first research arm relates to the study of the molecular and cellular mechanisms of normal movement and the pathophysiological processes involved in poststroke

paresis. An in-depth understanding of the pathophysiological mechanisms of stroke-related paresis should lead to improvements in prognostic indicators of functional recovery, and more effective interventions to improve relearning of lost motor function than are currently available. The second research arm is concerned with the development of pharmacological, biological and electrophysiological techniques that can augment training-induced plasticity. Both of these research arms aim to understand and enhance innate plasticity in the adult CNS, so that this neural process can be harnessed to aid poststroke rehabilitation. Nevertheless, the degree of neuroplasticity that can occur in the adult brain is unknown, and the extensive neural reorganization that is observed in children after hemispherectomy might not be inherently possible in adults. Thus, the third research arm aims to utilize advances in biomedical and tissue engineering to promote functional recovery within the brain. Of note, attempts have been made to promote neural repair or replacement through use of innate or exogenous stem cells. Another prominent research avenue involves developing neuroprosthestics and brain–computer-interface technologies to bypass injury via adaptive remote neuroplasticity, whereby part of the nervous system not originally dedicated to a particular task can be harnessed to provide the neural substrate that interacts with the neuroprosthesis or brain–computer device.

Socioeconomic, political and environmental factors need to be accounted for to fully address the complex issues associated with poststroke disability; however, this review only focuses on the biological aspects of motor impairment after stroke, and the therapies being developed to restore motor function. Unlike other reviews that have critically assessed the efficacy of poststroke treatments or have focused on the contributions of neuroprotection and reperfusion to functional recovery, this article examines research aiming to enhance neuroplasticity after stroke. By assessment of the biological aspects of voluntary movement and neural plasticity that are being translated into the field of poststroke motor rehabilitation, we will highlight the most consistent and significant findings in the three arms of neurorehabilitation research outlined above. In this article, special emphasis is given to studies of the pathophysiology of poststroke paresis and the development of electrophysiological interventions that, when combined with customary training-based protocols, could aid motor rehabilitation in patients with stroke.

Current standard of care

Poststroke rehabilitation requires managing the disability and the chronic diseases that cause or accompany the stroke. International guidelines have been developed on the basis of available data to promote best clinical practice in poststroke rehabilitation. For the rehabilitation of motor functions, dedicated rehabilitative strategies involving both physical and occupational therapy, among other treatments, are recommended. These treatments should preferably be undertaken in a specialized rehabilitation unit. The guidelines also emphasize the use of general aerobic exercise to regain physical endurance and intense task-directed training to attain specific functional gains. Few comprehensive systematic reviews have evaluated the effectiveness of the various training techniques; however, some of these therapies are associated with marked improvements in motor function. For example, constraint-induced movement therapy—a regimen involving comfortable restraint of the nonparetic limb in conjunction with ‘forced’ use of the paretic limb in activities of daily living, and in intensive functional training—has been shown to be associated with an immediate decrease in disability rating scores in several meta-analyses. By contrast, while individual trials have shown that body weight-supported treadmill training is associated with gains in motor function, a systematic review of the literature relating to this approach came to a different conclusion. Other techniques such as motor imagery, bilateral arm training and robot-assisted therapy might also improve motor function in patients with stroke, but the limited number of studies that have investigated these techniques precludes the formulation of meaningful guidelines for their use. A previous assumption that expensive and complex rehabilitative methods could not be tested in randomized clinical trials has been proved incorrect by the implementation of several large, well-designed clinical studies, and systematic reviews examining these trials have led to improvements in evidence-based approaches of poststroke rehabilitation.

Poststroke physiology

Preclinical studies provide a means of exploring the cellular and molecular pathophysiological processes associated with hemiparesis and/or stroke and the physiological processes underlying spontaneous recovery after experimental brain injury. Studies in rodent models of stroke indicate that synaptogenesis increases substantially after experimental lesioning, and that dendrite number and shape are altered following infarction. Furthermore, both synaptogenesis and dendrite remodeling are associated with increases in neurological activity in the 'motor map' in the ipsilesional and contralesional cerebral cortices. Axonal reorganization has also been demonstrated in rodent models of stroke, indicating that this process might be critical for spontaneous recovery after infarction. Data from animal models also support the use of task-specific training and generalized aerobic exercise in poststroke rehabilitation, and show that these measures can activate molecular pathways—such as the upregulation of brain-derived neurotrophic factor—that are important for neurogenesis as well as learning and memory. Furthermore, task-specific training in animal models of brain injury has been shown to induce changes in neural architecture, such as neural sprouting, synaptogenesis and dendritic branching. Anatomical and physiological changes are also known to occur with other types of motor training in rodents; for example, endurance training increases metabolic demand and leads to angiogenesis, while skill-specific training induces synaptogenesis and synaptic potentiation.

In humans, structural and metabolic brain imaging and electrophysiological recording of the primary motor cortices have been used to document reorganization of neural activity after stroke, with both ipsilesional and contralesional primary motor cortices and the dorsal premotor cortex having been identified as areas that can undergo substantial poststroke neuroplasticity. Evidence of this neural activity has led researchers to investigate ways of predicting potential poststroke recovery. As a result of these investigations, among patients with stroke, those with low contralesional primary motor cortex activity and evidence of ipsilesional motor cortex-evoked potentials to transcranial magnetic stimulation maybe considered more likely to recover from stroke-associated motor deficits than those who do not exhibit such phenomena.

Evidence of neural reorganization after stroke might also lead to the development of novel interventions that promote poststroke rehabilitation. Studies using neuroimaging and neurophysiological techniques to identify changes in both metabolic activity and anatomical connections in the brain to investigate poststroke motor network dynamics indicate that non-primary motor areas might contribute significantly to movement of the paretic limb after stroke. Transient disruption of activity in the contralesional premotor cortex through use of transcranial magnetic stimulation (TMS) has been shown to briefly alter hand movements in patients with stroke. A limitation of neuroimaging techniques such as functional MRI or PET is that although they can identify abnormal brain network activity after stroke, they are unable to determine whether such activity is inhibitory or excitatory in nature. By contrast, intracellular and extracellular electrophysiological recordings can identify poststroke changes in neural activity and determine whether these changes are inhibitory or excitatory. These approaches are limited, however, in relation to the number of networks that can be examined at any one time.

Strategies to promote plasticity

Pharmacological interventions

Pharmacological interventions that act on neurotransmitter systems might promote neural plasticity and could potentially enhance the effectiveness of poststroke motor therapies. Preclinical studies involving decerebrated cats or rodent models of brain injury have revealed that amphetamine treatment—through increased presynaptic release of dopamine and norepinephrine, and inhibition of neurotransmitter reuptake—may have therapeutic effects following brain injury. Basic forms of motor training in humans can be enhanced by amphetamines, and these findings are consistent with the results of several small clinical trials of these drugs, which have shown that amphetamine treatment can decrease the level of motor impairment on tests such as the Fugl-

Meyer score in patients with cerebral infarction. Enthusiasm for amphetamine treatment has waned, however, since larger trials of this therapy yielded mixed results: while four trials showed that amphetamine treatment was associated with some rehabilitative benefit in patients with stroke, four other trials indicated that this treatment provided no benefit in this patient group. Furthermore, a meta-analysis determined that, given the detrimental cardiovascular effects associated with amphetamines, insufficient data existed to support the use of amphetamine therapy in the treatment of stroke. Some investigators argue that the inconsistent results associated with this treatment might reflect the use of inappropriate animal models in preclinical studies, heterogeneity in brain lesions, use of inappropriate doses of amphetamines, and/or administration of such drugs at suboptimal time points during clinical studies. Future clinical trials will benefit from a re-examination of these issues and use of more homogeneous strategies than were employed in previous.

Complex behavioral factors such as motivation, which might not be easily translated from animal models to human patients, might account for inconsistencies observed between clinical trial data and predictions arising from the results of preclinical studies. This hypothesis might explain why inconsistent results have been associated with the use of levodopa in patients with stroke. Drugs that enhance the activity of the cholinergic system, which is known to modulate neural activity throughout the cortex, are also being tested for their ability to enhance poststroke motor rehabilitation. In addition to their proven ability to enhance memory and executive function in patients with Alzheimer disease, these compounds have also been associated with improvements in sensorimotor function and overall activities of daily living in case studies and small trials involving patients with stroke. Whether such enhancement of motor rehabilitation is a direct consequence of improvements in motor learning or simply a reflection of the drugs' cognitive effects is not fully understood. Nevertheless, further research into the use of pharmacotherapy in poststroke motor rehabilitation, and its potential impact on disability, is required before pharmacological treatment is employed in clinical care.

Nervous system stimulation

Therapies that directly stimulate the PNS or CNS may enhance neuroplasticity during poststroke rehabilitation, and might help patients with stroke overcome their motor impairments. For example, devices that provide electrical stimulation to peripheral nerves and muscles might assist stroke patients with hemiparesis move their affected limbs. Furthermore, PNS stimulation can influence the CNS via afferent pathways, and some PNS stimulation protocols have been designed specifically to induce cortical plasticity. For example, repetitive peripheral nerve stimulation has been shown to improve both strength in paretic limbs and learning of a sequential finger-tapping sequence in patients with stroke.

Stimulation of the CNS, specifically the primary motor cortex (M1), might directly enhance motor rehabilitation after stroke. TMS and direct current stimulation (Figure 1) offer noninvasive approaches of stimulating the cortical surface of the brain, while epidural electrodes can be surgically implanted to stimulate the motor cortex directly. Since 'normal' limb movement is accompanied by a transient increase in excitability in the corticospinal tract, numerous research groups have investigated the use of electrical stimulation—either applied transcranially or through implanted epidural electrodes—to exogenously increase the excitability of the stroke-affected ipsilesional M1 in order to improve function. Most studies of ipsilesional M1 stimulation have demonstrated an improvement in at least one motor ability, such as an active range of motion, or have demonstrated improved performance on specific functional rehabilitation tests. Interventions that stimulate the M1 are still at the experimental stage and, consequently, have not been subjected to large, well-controlled clinical trials that test their effects on patient activity and/or participation. Nevertheless, a double-blind, controlled, multicenter clinical trial that aims to investigate the efficacy of transcranial direct current stimulation combined with physical therapy to enhance rehabilitation after stroke is under way. The exact mechanisms of action of these techniques are under investigation, but improvements in motor function that are associated with stimulation of the CNS might occur as a direct result of changes in synaptic activity and gene expression, and

increases in neurotransmitter, receptor and neurotrophin levels. Furthermore, the efficacy of these techniques seems to be highly dependent on the intensity, duration and frequency of the electrical stimulation, as well as on the area of the brain being stimulated.

The combination of PNS and CNS stimulation to promote neuroplasticity has been investigated in preclinical studies and in a small trial involving patients with stroke, and promising results for this approach have been reported. In one study of patients with stroke, repetitive low-intensity peripheral stimulation of the paretic limb with subsequent transcranial direct current stimulation of the affected primary motor cortex resulted in improved procedural learning of a finger-tapping sequence. Furthermore, paired associative stimulation, whereby peripheral stimulation and central stimulation are timed to coincide in such a way as to induce spiketiming-dependent plasticity, has been used to promote motor recovery in a rodent model of stroke, but this technique has only demonstrated electrophysiological effects in patients with stroke to date.

Taken together, most early clinical studies of nervous system stimulation (reviewed above) have demonstrated some positive effects on poststroke motor rehabilitation. Nevertheless, the overall effect sizes observed in these studies have not been significantly greater than those demonstrated with behavioral therapy alone. To address the issue of treatment efficacy for nervous system stimulation, new trials are being designed that extend the duration of treatment, combine complementary methods of stimulation, and identify patients most likely to benefit from each intervention. Treatment effect sizes may improve when patients with similar stroke-related impairments are enrolled in large studies and when the most effective stimulation protocol and clinically relevant functional outcome measures are identified. Nevertheless, our understanding of the dynamics of inhibition and excitation within the motor system, upon which stimulation studies are based, is still incomplete. Thus, a better understanding of the connectivity and interactions within the motor system might lead to more-efficacious stimulation protocols. Such therapies will all need to be assessed with regard to their outcomes on patient activity and quality of life before becoming part of clinical practice.

Novel treatments

Stem cells

Above, we have reviewed the areas of research that aim to enhance innate repair mechanisms within the CNS after stroke, but there might be a limit to how much endogenous regeneration can be augmented and supported. These issues might be circumvented through replacement of damaged neural tissue by use of artificial or exogenous materials to improve neural regrowth, or bypassing stroke-related impairment by developing prosthetics that are directly connected to the CNS (for example, an orthosis that moves a paralyzed limb by taking instructions directly from the brain). Preclinical success with neural stem cell therapy, despite limited understanding of the mechanisms of action, dosing and possible adverse effects, has led to the first clinical trial of such therapy for poststroke hemiparesis, which is being conducted in the UK.

In preclinical studies, both human-derived and rodent-derived stem cells were transplanted into rodents with experimentally induced stroke, where they migrated to the location of the lesion and developed into electrophysiologically and anatomically mature neurons (Figure 1). One area of preclinical research attempting to improve the success of this treatment approach is focusing on how exogenous scaffolding or modulation of the local environment might improve the proliferation and growth of stem cells. By providing an artificial extracellular environment that promotes appropriate cell growth, nanotechnology could have a role in improving and modifying stem cell therapy.

Neuroprosthetics

Prosthetics and orthotics have generally been designed to provide support for a weak limb, and only indirect effects on function have usually been associated with these kinds of devices. However, if orthotics could be developed that enable patients with stroke to achieve their intended motor goals, such as walking unaided, these devices could serve a more functional purpose (Figure

1). Research into both invasive and noninvasive brain–computer and nerve–computer interfaces has shown that patients with stroke can control exogenous systems through training. In one study, magnetoencephalography was used to record the sensorimotor μ rhythm over the affected M1 region of patients with chronic hemiparesis. These patients successfully learned to use motor imagery to control the mu rhythm and, through the brain–computer interface, to control an orthotic device that opened and closed their paralyzed hand (Figure 2). In addition, a single case report has shown that an EEG brain–computer interface enabled a patient with chronic stroke to control functional electrical stimulation of her paretic limb, leading to voluntary finger extension. Interestingly, the neuroprosthetic methods highlighted above are being explored not only as a means to bypass injury, but also as a means by which to encourage training and practice; for instance, robotic devices have been used as training tools to promote neuroplasticity (Figure 1).

Defining rehabilitation goals

As research into poststroke neuroplasticity and motor rehabilitation evolves, assessment of the motor outcomes that benefit patient activity and participation, and the patients own rehabilitative goals, will be important. We should anticipate that interventions that restore body functions and those that increase participation might not be viewed equally by patients, and that patient satisfaction may itself depend on a balance between restoring body functions and increasing participation. In the case of interventions that are associated with marked success in clinical studies, patients may not always feel that the benefits of such treatments are worth the sacrifices and effort required to see such rewards. Thus, future clinical research into poststroke rehabilitation should employ assessments of quality of life and patient satisfaction.

Defining the specific purpose of rehabilitative treatments, both before such therapies are tested in trials and once they are used clinically, is important, since the goals of one particular intervention may actually conflict with the goals of a different intervention. For example, training protocols that focus on relearning how to perform a particular motor task in the same manner to how it was carried out before the stroke might be substantially different from treatments that aim to teach the patient how to execute a task through a set of adaptive strategies. Furthermore, the choice of one strategy over another approach might determine which aspect of neuroplasticity is enhanced, and could limit the efficacy of other forms of plasticity. We will probably find that patient preferences as well as genetic and social factors will affect each patient's responses to rehabilitative therapies; thus, customization of poststroke therapies will probably be required in the future.

Conclusion

Motor rehabilitation after stroke continues to be an area in need of substantial financial and scientific investment. Our understanding of the mechanisms underlying stroke-induced paralysis is increasing and, with this knowledge, our ability to modulate the neural structures affected by stroke and to stimulate neuroplasticity is improving. Advances in technology are aiding the development of therapies that can augment innate repair mechanisms or, even, bypass such processes, thereby providing alternate methods to carry out tasks of daily living. As the number of methods for modulating stroke-related physiological processes increase, so must the emphasis on measuring both functional outcomes and quality of life in patients. Poststroke neurorehabilitation is evolving into a field dominated by multidisciplinary interactions and collaborations, as therapists, molecular biologists, engineers, physiologists, physicians and patients work together towards the goal of improving the quality of life of patients with stroke.

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