Conferences and Reviews

Neuroplasticity
Key to Recovery After Central Nervous System Injury

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After an injury to the central nervous system, physical and cognitive impairments and disabilities often abate. These gains may be partly mediated by mechanisms that allow reorganizing of the structure and function within gray and white matter. The potential to enhance neurologic recovery by manipulating the brain and spinal cord must now be considered in clinical practice. Today's rehabilitation routines may not encourage maximum recovery. Indeed, some commonly used physical and pharmacologic methods could inhibit the restoration of motor activities such as walking. On the other hand, therapies that use our expanding knowledge of neuroplasticity could lead to better results for patients.

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Each year more than half of the 300,000 survivors of stroke, the 100,000 survivors of serious traumatic brain injury, and most of the 10,000 victims of spinal cord injury will have paralysis or impaired motor control that leads to disability. The cardinal goal of early treatment is to prevent or treat complications that add to morbidity and death. New pharmacologic approaches such as the use of high-dose steroids and gangliosides may decrease neuronal and tissue damage after ischemic, hypoxic, and traumatic injury.[1-3] These will become the first step in neurologic restoration. The next step includes inpatient and outpatient physical, occupational, speech, cognitive, psychosocial, and vocational rehabilitation to reduce disability and reintegrate the patients into the community. Because clinical trials in rehabilitation are often not scientifically designed and interventions are poorly defined,[4,5] none of the numerous retrospective and prospective uncontrolled studies of general neurologic rehabilitation nor the few controlled clinical trials that compared types of programs or training techniques have clearly shown efficacy.[6,7] Most rehabilitation specialists, however, believe that most patients improve in function over the 3 to 18 months after injury, even though paresis and sensory and cognitive loss may remain the same. The spontaneous recovery of reversibly injured, edematous, and metabolically depressed tissue, compensatory behavioral training, strong motivation, a supportive milieu, and assistive devices are among the more easily recognizable influences that may account for gains.*

One of the most challenging goals in neurologic rehabilitation is to increase recovery of motor control for walking and for reaching and fine coordinated movements of the upper extremity. Here, too, traditional theories and activities in physical therapy often rest on scientifically unsubstantiated grounds. The potential for some restoration after injury probably lies within the anatomic and physiologic reorganization of the cortical, subcortical, and spinal circuits that control motor output.

*See also the editorial by M. E. Selzer, "A Scientific Basis for Neurologic Rehabilitation," on pages 91-92 of this issue.

Sensorimotor Pathways and Recovery

Increasing evidence from neurophysiologic studies points to numerous parallel systems that cooperate to manage the diverse information necessary for the rapid, precise, and yet highly flexible control of multijoint movements. These circuits might contribute to spontaneous and training-induced recovery of function.

The primate motor cortex has separate clusters of output neurons that can facilitate the same spinal motor neuron. Also, a single cortical motor cell can project to the spinal motoneurons for several muscles, even those that might act across a joint. This overlapping organization contributes to the control of the complex muscle synergies for voluntary movement.[8] These motor and neighboring cortical sensory neurons are sensitive to inputs from the periphery and can adapt in remarkable ways during training. In adult and developing animals and in humans, these representations are capable of much physiologic and perhaps structural reorganization.[9] Merzenich and colleagues showed that the cortical sensory representation of hand skin of primates trained to use that hand spread into the previously mapped area of nearby neurons that had, before training, served the skin that surrounded the stimulated area.[10] Similar cortical representational changes were especially likely to arise during training that involved learning and the acquisition of specific skills.[11]

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Many other lines of research in animals suggest that compensation after a central or peripheral injury can be due to a functional shift to neighboring neurons.[12-14] In humans, cortical sensory reorganization has occurred within four weeks after amputation of an arm.[15] When the patient's face was touched, the patient experienced the sensation in the missing hand, suggesting that the sensory input from the face had invaded the cortical hand area. This plasticity probably arises by the unmasking of previously silent synapses from thalamocortical and intracortical circuits that are mediated by acetylcholine and norepinephrine, but in some instances might arise from the sprouting of dendrites over short distances.[16] Studies by magnetic and electrical cortical stimulation,[17] as well as of regional cerebral blood flow and metabolism by positron emission tomography, also reveal evidence of anatomical and functional reorganization after injury similar to that found in experiments in animals. For example, after a subcortical striatocapsular infarction that produced a right hemiparesis, but from which the patients recovered hand use, finger tapping and right-handed squeezing showed bilateral rather than contralateral activation of cortical motor neurons.[18] Also, regions related to selective attention and intention were activated, which suggests that they must come into play when a movement reorganizes.

The failure to use a weakened upper extremity is common after stroke and head trauma. In studies of both animals and humans, the quality of movements by the involved limb improved simply by not allowing the subject to use the unaffected limb.[19] This forced-use strategy could lead to reaching and grasping that is accomplished by an alternative strategy, such as substituting whole-body movements for the loss of supination and pronation of the arm.[20] Plasticity in behavior presumably has a neural substrate that might include reorganization of cortical representation, increased efficiency of residual pathways, and a greater use of alternate descending pathways. Can rehabilitation specialists incorporate this modulation of cortical centers into treatment strategies? The inherent adaptability offers the possibility that specific training plans and drugs that increase local synaptic activity might augment remodeling and, in turn, improve sensorimotor and higher cognitive functioning.

Descending Pathways

The premotor, supplementary motor, and primary motor cortices exert what Hughlings Jackson (the neurophysiologist who proposed the theory of hierarchic control in the nervous system) called "the least automatic control" over voluntary motor commands. Each area receives a separate and independent set of signals from adjacent and remote regions and sends parallel but separate signals to the brain stem and spinal cord.[21] This schema accounts for some of the nuances of impairments in motor control after a cortical injury, such as difficulty in starting a movement or in controlling bimanual and sequential movements. Other pathways also exert great influence. In primates, cortical, thalamic, limbic, and brainstem signals feed into the basal ganglia and contribute to a motor behavior by direct projections to the midbrain motor region and by indirect projections to the thalamus. The basal ganglia influence motor circuits through their myriad miniloops to help specify the combination, sequence, and direction of movements.[22] These parallel arrangements occur in cerebellar and most other sensory and motor projections.[23]

After an injury, the balance of activities of these networks is reset. The intact, parallel systems from cortical and especially subcortical areas might partially compensate or substitute for injured ones. This might require specific cognitive and motor retraining. For example, skeletal muscle strength was shown to increase by having normal persons imagine that they were contracting a hand muscle.[24] A neural process was postulated for this increase in strength. Positron emission tomographic studies suggest that the strengthening is made possible by the activation of central motor planning areas outside of the primary motor cortex that increase the coordination of outputs to the muscle.[25]

Bilateral Descending Pathways

The primary motor cortex contributes about 40% of the 1 million corticospinal fibers that enter each medullary pyramid. From 70% to 90% of pyramidal fibers decussate into the lateral corticospinal tract, and 10% to 30% remain uncrossed and form the ventral corticospinal tract.[26] Sparing of only 17% of the crossed fibers was enough in one human study to allow clinically useful improvement in hand, finger, and toe function.[27] Axons of the uncrossed ventral tract, as well as from the vestibulospinal and reticulospinal tracts, are especially likely to connect to bilateral spinal motoneurons associated mostly with axial and proximal girdle muscles. Even some of the crossed lateral corticospinal tract fibers will connect within the cord's gray matter with interneurons of the opposite side. Although attempts to demonstrate the actions of residual pyramidal pathways after a brain injury in adults has met with variable success,[28,29] it is likely that some pyramidal and especially nonpyramidal fibers from the brain stem contribute redundancy for motor control. This may account for how persons with hemiplegia regain modest arm function and enough use primarily of their antigravity muscles on the paretic side to advance the legs for walking.

Primitive Centers for Automatic Movements

The brain stem and spinal cord have their own intrinsic centers for locomotion. The descending message to start the process of walking seems to be carried by reticulospinal pathways from specific areas of the midbrain and pons that synapse with lumbar spinal neurons.[30] Electrical stimulation of these regions and cholinergic agonists and excitatory amino acids like glutamate are among the neurotransmitters that cause a decerebrate cat to step when placed on a treadmill. In cats, monkeys, and humans, hemisection of the upper lumbar spinal cord is followed by considerable recovery of locomotion, mediated at least in part by descending reticulospinal fibers on the intact

side that cross at a segmental level below the transection.[31] The use of systemic drugs that increase or block the neurotransmitters of this pathway might enhance or inhibit the ability of patients to step.

While cortical and peripheral sensory input is essential for smooth, normal locomotion, the starting and timing of stepping appears to be primarily the task of a self-oscillating lumbar interneuronal network. Even an isolated section of lumbar spinal cord can produce cyclical outputs that rhythmically flex and extend a joint.[32] The circuits of the lumbar stepping motoneurons are especially influenced by descending serotonergic and noradrenergic pathways from brain-stem nuclei. They set the gain for sensory and motor neuronal activation and modulate both the oscillatory behavior of spinal neurons and specific aspects of the locomotor pattern.[33]

After a complete lower thoracic spinal cord transection, adult cats and other mammals can be trained on a treadmill so that their paralyzed hindlimbs fully support their weight, rhythmically step, and increase their walking speed toward what a normal cat can do.[34] Serotonergic and noradrenergic drugs can enhance the stepping pattern; strychnine, through a glycinergic path, quickly induces it. Additional studies on adult spinal-transected cats that were trained only to stand and then encouraged to step on a moving treadmill showed that postural support alone was detrimental to subsequent locomotion.[35] Thus, the lumbar spinal cord of adult cats, in the absence of supraspinal input but with peripheral sensory input, retains the capability to generate hind-limb stepping. Static physical therapies in cats impede recovery, whereas rhythmic alternating movement of the limbs with joint loading seems critical to the recovery of locomotor output.[36] In other experimental models of spinal cord injury, physical exercise also seems to contribute to the recovery of locomotion. For example, in adult rats who had a three-quarter section of the midthoracic spine that spared only the lateral aspect, those who were allowed to roam freely achieved motor recovery and locomotion and those who were immobilized for three weeks did not.[37] Most physical therapies emphasize standing and static balance early after the start of hemiplegia and paraparesis before a patient proceeds to training in walking. Can rehabilitation specialists make use of these findings in animals and of the intrinsic properties of locomotor centers?

Strategies to Enhance Recovery of Locomotion

Using a protocol similar to treadmill stepping in the thoracic-spinalized cats, several groups have trained subjects with chronic paraplegia to step. As much as 50% of their body weight was suspended in a harness connected to an overhead hydraulic lift. Therapists manually assisted their legs so that they could step on a slowly moving treadmill belt. The aim was to gradually achieve full weight-bearing at increasing treadmill velocities. In at least 20 patients who probably had some residual descending neural input but who had been able to walk little or not at all, independent treadmill walking was achieved and the subjects became able to walk overground.[38-40] In addition, in subjects with complete thoracic spinal cord injuries, rhythmical flexor and extensor electromyographic activity can develop in their paralyzed leg muscles during assisted stepping with body weight-supported treadmill training, but they cannot step independently.[41] Greater sensory input such as increased loading of the joints and cutaneous electrical stimulation that was timed to the gait cycle enhanced this effect and could evoke hip flexion. Serotonergic and noradrenergic drugs also altered motor output.[42] When this training strategy was applied to six patients with chronic hemiplegia, treadmill and overground velocity increased.[43] These findings offer yet another mechanism for gains in walking after a brain or spinal injury. More important, they suggest new physical and pharmacologic strategies that can influence residual descending cortical and subcortical pathways and spinal circuits to enhance the ability to walk.

Neurotransmitter Effects on Recovery

Studies in animals and a small clinical trial have provided preliminary evidence that a variety of pharmacologic agents might increase or decrease the rate or degree of recovery of sensorimotor function and walking after a cerebral injury. After being given dextroamphetamine, rats and cats that underwent a unilateral or bilateral ablation of the sensorimotor or frontal cortex had more rapid recovery of the ability to walk across a beam than did controls. This endured well past the single or intermittent dosing schedule of the drug.[44] The use of amphetamine also seemed to work in a small group of patients shortly after they had a stroke, though these results have not been replicated.[45] In both instances, the drug worked only when combined with physical activity and practice, the equivalent of training and motor experience. The dopamine blocker, haloperidol, prevented this recovery in the animals. Investigators have speculated that noradrenergic drugs might alleviate a functional depression in remote, transsynaptically connected regions of the brain.[46] Such physiologic inactivity of intact neurons, called diaschisis, is revealed by positron emission tomography as regions of hypometabolism.

Other neurotransmitters, including acetylcholine, norepinephrine, dopamine, γ-aminobutyric acid, and serotonin, have enhanced motor recovery whereas phenytoin, scopolamine, clonidine, neuroleptics, and benzodiazepines have slowed gains in specific experimental designs. Benzodiazepines have also been associated with poorer and slower 30-day recovery of sensorimotor function in patients with a stroke.[47] It is not surprising that some drugs could improve one function but be associated with another type of motor or cognitive dysfunction.[48] Some drugs have more clear-cut mechanisms of action. For example, the conduction of action potentials along demyelinated axons could be restored by pharmacologic agents like 4-aminopyridine, which blocks potassium channels and improves impulse conduction.[49]

Drug studies in humans are complicated. The type, location, extent, and age of the lesion; the specific drug, its

dosage, time of initiation, duration of use, and adverse effects; and the accompanying physical or cognitive therapy that might add to a drug's effect must be determined. It is clear that clinicians must select medications with special care in the months after a cerebral injury and monitor for effects that seem to speed or impede recovery.

Biologic Mechanisms of Restoration

Motor learning can produce the arborization of dendrites and the growth of synapses in the cerebral and cerebellar cortex in animals.[50,51] After a unilateral injury to the sensorimotor cortex serving the forelimb of adult rats, one study showed the growth of neuronal dendrites in the sensorimotor cortex of the normal opposite side. This was associated with early disuse of the impaired forelimb and an increased use of the normal forelimb as it compensated for the paretic one.[52] As the paretic limb improved, the increased dendritic growth of the uninjured cortex was pruned back in parallel with less demand for its use.

We can begin to imagine how a combination of neurobiologic measures might increase connections and perhaps allow axons to regenerate. This research is especially applicable to spinal cord injury because less than 10% of residual supraspinal input seems needed to recover the ability to walk.[53,54] To regain even one more level of useful upper extremity function, even to go from a C-5 to a C-6 quadriplegia, would greatly add to a patient's independence.

Possible Therapies From Molecular Biology and Biotechnology

Tissue culture and vertebrate models have shown that substances in the extracellular matrix tend to inhibit axonal elongation at the site of injury. Peripheral nerve[55] and fetal tissue transplants[56] have been used with some success to bridge areas of spinal gliosis. Antibodies have been directed against molecules on glial cells that block neuritic extension.[57] Neurotrophic growth factors have been used to protect neurons and to signal neuronal machinery to make the substances necessary for extension. Direct transplantation of motor neurons and cells that produce a specific neurotransmitter to replace lost noradrenergic projections has met with some success.[58,59]

The techniques to manipulate the promoters and inhibitors of neuroplasticity are still in early development. As with the other possible mechanisms for neurologic restoration, their effectiveness will depend in part on strategies developed by rehabilitation specialists to boost activity along neural circuits.

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