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Cramer, Steven C

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AN OVERVIEW OF THERAPIES TO PROMOTE REPAIR OF THE BRAIN AFTER STROKE

Steven C. Cramer, MD

Departments of Neurology and Anatomy & Neurobiology, University of California, Irvine, California.
E-mail: scramer@uci.edu

Abstract: Stroke remains a leading cause of disability. Most patients show some degree of spontaneous recovery, but this is generally incomplete. Studies on the neurobiology of this recovery are providing clues to therapeutic interventions that aim to improve patient outcomes. A number of potential such restorative therapies are reviewed. Numerous treatment strategies are under study. Most have a time window measured in days or weeks and so have the potential to help a large fraction of patients. This review considers these therapies, as well as points to consider in translating their application to human trials. © 2011 Wiley Periodicals, Inc. *Head Neck* **33:** S5–S7, 2011

Keywords: stroke; plasticity; repair; therapy; recovery.

Brain repair can be defined as a process—spontaneous or therapeutically induced—that restores some aspect of brain structure or function after an insult. Repair contrasts with other therapeutic strategies in cerebrovascular disease such as prevention or approaches that aim to limit the injury such as neuroprotection or reperfusion. Instead, repair is focused on regrowth, repair, restoration, rewiring, and rehabilitation.

The burden of disability after stroke is large. An estimated 6,400,000 American adults have had a symptomatic stroke, with a prevalence that increases with age. Note too that an estimated 13 million people in the United States have had a silent stroke. Each year, 795,000 people experience a stroke, 610,000 of which are first-ever symptomatic stroke. The mean survival after stroke is 8 years, with approximately 85% of patients living past the first year of stroke.[1]

Current therapies for a new stroke reduce disability in a limited fraction of patients. The only drug approved to treat acute stroke is tissue plasminogen activator.[2,3] A limited fraction of patients receive this medicine,[4] in large part because of the narrow time window for safe drug administration. Despite recent data supporting administration of intravenous tissue plasminogen activator up to 4.5 hours after ischemic stroke onset, it continues to be true that only a minority of patients with acute stroke receive this drug. Moreover, of those so treated, half or more have significant long-term disability.[2,3] Because most repair-based approaches have a time window measured in days rather than hours, any repair-based approach that achieves regulatory approval will likely have the potential to help a large proportion of patients affected by stroke.

Preclinical studies have characterized the neurobiology of spontaneous stroke recovery. After an experimental infarct, brain regions become excitable, in some cases showing gamma-Aminobutyric acid (GABA) receptor downregulation and increased N-Methyl-D-aspartic acid (NMDA) receptor binding. Expression changes for a number of genes, for example, resulting in increased levels of several growth factors. Angiogenesis is accompanied by structural changes in axons, dendrites, and synapses. These changes are often preferentially seen in the area surrounding an infarct and in areas with network connections to injured zones. Functional neuroimaging studies in humans in general are concordant, showing changes in network activity and reorganization in attempts to compensate. For example, increased activity is often seen in unaffected nodes of an injured brain network, behaviors that are normally highly lateralized can become more bilaterally organized, and cortical representational maps shift.[5–10]

Treating stroke recovery is a 4-dimensional issue. Thus an important consideration is that the cellular and biochemical underpinnings of recovery, many of which are potential therapeutic targets, evolve over time.[9,11,12] Targets that help the brain 1 week can be deleterious the next. For example, long-term effects of a GABA agonist or NMDA receptor blocker can be favorable if administered in the early hours after stroke[13,14]

but deleterious if initiated days later,[15–17] and the reverse may be true for matrix metalloproteinases.[18]

A number of categories of therapy are being examined in relation to promoting brain repair.[19] Many have reached the step of human study, although generally in earlier-phase trials. These therapies include growth factors, with most studies to date having a particular focus on hematopoetic growth factors. Other large molecules are also under study, such as monoclonal antibodies to block specific biochemical events. Numerous small molecules have been examined, such as amphetamine, inosine, levodopa, ropinirole, escitalopram, sildenafil, and niacin. Many of these target specific neurotransmitter systems. Cell-based therapies are receiving increased attention, with numerous types under consideration. Some therapies target endogenous neural stem cells, whereas others administer various exogenous cells including xenografts, transformed tumor cells, adult stem cells such as marrow stromal cells, stem cells with modified genes or a bioscaffold, umbilical cord cells, placental cells, fetal stem cells, and embryonic stem cells. Various intensive therapy regimens, such as constraint-induced therapy, are being examined, particularly for motor and language retraining. A range of robotic devices is under study. In some cases these act as an extension of the approach to provide intensive therapy, and in other cases these offer specific advantages such as the potential to provide telemedicine or increase use via virtual games. Brain stimulation is also being studied, including transcranial magnetic stimulation, epidural cortical stimulation, transcranial direct current stimulation, and use of laser devices. There is precedence for this, because the gold standard therapy for major depression remains a form of brain stimulation, electroconvulsive therapy. Also, with respect to the enormous cognitive potential of the human brain and building on effective interventions in healthy subjects, strategies that emphasize imagery and observation are being studied, particularly for the motor system.

The effectiveness of restorative therapies can be maximized with attention to certain issues.[20] First, brain repair is time sensitive. Some biologic targets are only relevant during a specific time period after stroke. Furthermore, as above, some therapies can have different effects on stroke depending on timing. Second, brain repair is also experience dependent. Since the classic study by Feeney et al,[21] which showed that a stimulant promoted improved motor outcome only when its exposure was paired with training, increasing evidence suggests that a restorative therapy needs the right kind of experience to produce the best results. Third, patient stratification is likely important to studies of poststroke brain repair. Numerous variables have been found to be potential predictors of stroke outcome, including location and size of injury,[22,23] genotype,[24] measures of brain function,[25] and degree of depression.[26,27] Such measures may be of pivotal value in defining the population most likely to benefit from a given therapy. Fourth, domain-specific measures might be useful to measure treatment effects.[28] Improvement in global clinical status is of course a goal of paramount importance, but a treatment that provides gains by promoting neuroplasticity might demonstrate maximum effect in brain networks that have subtotal injury. A behavior whose underlying brain regions are destroyed is less likely to improve than a behavior whose underlying regions are accessible to a restorative therapy. Thus a domain whose neural underpinnings are partially spared, such as arm motor function or language, might show substantial gains in response to a restorative therapy, with only modest effects on global measures of poststroke outcome, and this might be considered worthwhile by many patients and so worthy of measuring in clinical trials.

An additional principle that is of particular relevance to head, neck, and aerodigestive tract functions is that the nature of brain organization before stroke influences poststroke brain plasticity. For example, in healthy subjects, some behaviors such as language or hand movement tend to be highly lateralized (ie, generation of the behavior involves mainly one hemisphere), and other behaviors such as bulbar and facial movement tend to be less lateralized (ie, generation of the behavior involves both hemispheres). These differences remain apparent after stroke. Cramer and Crafton[29] found that face movement is more bilaterally organized than is shoulder or arm movement in healthy subjects (ie, before any stroke), and that this remained true after stroke. Such a difference could have functional implications. Hamdy et al[30] found that the cortical representation for swallowing is normally present in both hempisheres. Not surprisingly therefore patients with dysphagia who recovered after stroke showed an increase in their cortical pharyngeal map size within the unaffected hemisphere, whereas patients who continued to have dysphagia did not show this change.[31] For reorganization of brain maps after stroke, the pattern of brain reorganization can influence behavioral status, and this pattern is at times constrained by features of normal brain organization.

Stroke remains a major source of disability. An emerging class of therapeutics focused on repair is under study. When applied according to selected neurobiologic principles, these therapies have the potential to improve outcome for many patients after stroke.

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