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Moving Towards a Cure for Paralysis

Potential Treatments for Spinal Cord Injury

By Shiv Gaglani

You wake up in a hospital bed to the beeping of your vital signs; dazed, confused and with tubes coming out of your arms and face. Immediately you try to arise from the bed so that you can find out how you got there. However, you find that you cannot move your legs. Your nose is itching, so you try to scratch it, but you discover that your arms are immobile as well. You hear your parents outside of the room talking to a doctor and the only word you pick up is enough to stun you – paralyzed. For thousands of people, this dramatic scenario is not confined to the imagination. After an accident, they wake up only to find that they have lost the ability to feel and move. Each year, 11,000 people incur spinal cord injuries that result in quadriplegia or paraplegia, the loss of movement and sensation in all four limbs or from the waist down, respectively; today over 250,000 Americans live with spinal cord injuries that have forced them to change their lifestyles dramatically (1).

This change in lifestyle starts with a change in neural signal conduction. The central nervous system (CNS) includes the brain and spinal cord, which are responsible for initiating and controlling muscular activity. Motor neurons projecting from the spinal cord send signals that engender voluntary movement in the limbs. A break at any level of the pathway prevents signals from reaching their destination, leading to paralysis. The area of the brain responsible for movement can be damaged by a stroke, the interruption of the blood supply to the brain. Typically, severe cases result in hemiplegia, paralysis affecting one side of the body. In amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, rapid degeneration of motor neurons leads to the development of a fatal paralysis that precludes breathing. Repairing damage at these levels would be a complex process, involving restoration of a neural network in one case and preventing the death of neurons in another.

Spinal cord injury presents a deceptively simple obstacle: learning how to reconnect neurons. Signaling down the spinal cord is commonly disrupted by a contusion injury, in which part of the spinal cord is bruised. In transection events, the spinal cord is cut so that the nerves become disconnected. Yet the cure for paralysis remains elusive, with many biochemical pathways impeding neural regeneration. Scientists have nevertheless made significant progress in developing therapies to address these problems.

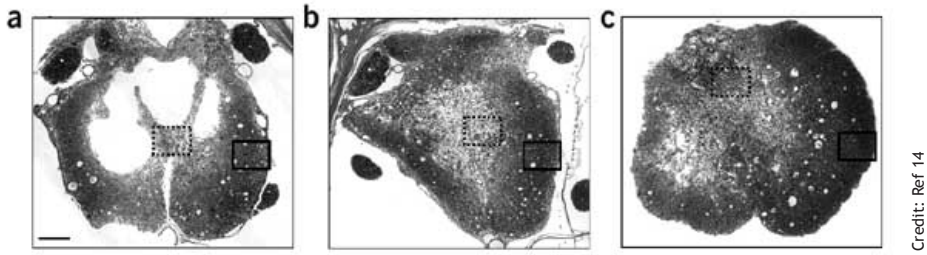
Obstacles

Everyone has experienced the regenerative ability of his or her body. Common examples are that of our skin healing after a cut and our broken bones becoming whole again. Many tissues in our body are capable of growing back or, like our blood, being continually replaced by a source of stem cells within us. Unfortunately, this is generally not the case for neurons in the central nervous system. Shortly after we are born, our neurons stop dividing and regenerating for the most part. There have been some studies demonstrating that there is some regeneration in the peripheral nervous system, but not nearly comparable to that of skin or bone cells (2).

Therefore, drugs promoting regeneration or cell replacement therapy are needed to overcome spinal cord injury.

Blows to the spinal cord initiate changes to the biochemical environment that result in large-scale damage

credit: Cindy Ung, HSR



Credit: Ref 14

Figure 1. Transverse sections of injured rat spinal cords 11 weeks after injury and acute treatment. (a) injured control spinal cord without treatment, (b) with Schwann cell graft transplantation, and (c) with Schwann cell graft and rolipram and cAMP elevation. Notice the extent of regeneration.

to, or loss of, neurons in the CNS. These changes, referred to as secondary damage, include restriction of blood flow, inflammation, free radical damage, neurotransmitter toxicity and scar tissue formation (3). Generally, inflammation acts as a protective mechanism, concentrating immune system cells at the compromised site. However, in spinal cord injury, swelling cuts off blood flow to the damaged area, killing even more neurons because of oxygen deprivation. Inflammation also stimulates some cells in the CNS to produce free radicals, namely, highly reactive and damaging forms of oxygen molecules. In addition, a neurotransmitter called glutamate is released in excess and consequently destroys more neurons. Once all of these acute biochemical changes take place and the chemical environment returns to equilibrium, scar tissue forms, precluding the regeneration and reconnection of CNS neurons.

By exploring different therapeutic mechanisms, scientists have achieved some success in countering paralysis induced by spinal cord injury. These treatments can be grouped into a few major categories, including drug administration, cell transplantation, combination therapies, and other innovative techniques.

Drug Therapy

Administered immediately after an accident, some drug therapies can effectively treat acute spinal cord injury so that the patient sustains less secondary damage. The only clinical treatment available for this purpose is a steroidal drug called methylprednisolone (MPS). It has demonstrated a small protective effect on the human spinal cord reducing inflammation if administered within eight hours after injury (4). However, the effectiveness of MPS therapy has been the subject of recent debate, with some scientists claiming that it may do more harm to the cord (5).

Though MPS administration is still the clinical standard for treating acute spinal cord injury, researchers are trying to find other drugs that can reduce inflammation, decrease free radicals, and elevate regenerative factors in animal models. These pharmaceutical agents include the sulfur amino acid taurine, sodium channel blocker riluzole, minocycline, polyethylene glycol, and the tissue-protective hormone erythropoietin (6, 7).

Cell Transplantation

Cell transplantation is another promising treatment for replacing lost tissue and damaged neurons in the spinal cord. Olfactory ensheathing glial cells (OEGs) and Schwann cells (SCs), the cells responsible for producing myelin to cover the neurons, have been effective in restoring tissue and promoting regeneration in the chronically injured spinal cord when transplanted (9). However, since a large number of cells are needed for transplantation, these cells have to be obtained from a human donor and may be rejected by the immune system of the host.

Stem cells have also received a lot of attention in the field of spinal cord research. Defined by the ability to replicate themselves in a process called self-renewal and to differentiate into other cell types, these cells could provide a large source of cells for replacement therapy. Embryonic stem (ES) cells are capable of differentiating into neurons and show promise for repairing spinal cord injuries (10). Hendricks and colleagues demonstrated that the transplantation of ES cells into mice with spinal cord injuries relieved their pain and restored sensory function (11). Another recent study by Keirstead and others demonstrated that transplantation of oligodendrocyte progenitor cells derived from human embryonic stem cells into paralyzed rats remyelinated the axons in the spinal cord and improved their ability to move (12). Such transplantation therapies have yet to be assessed in human studies.

Two Treatments Are Better Than One

Some researchers have combined pharmacological and cell-based therapies to achieve impressive results in rats. An exciting biochemical pathway that is being explored is the role of cyclic adenosine monophosphate (cAMP) in regeneration post-injury. Shortly after an injury there is a dramatic increase in the levels of phosphodiesterase 4 (PDE 4), which degrades cAMP, and therefore inhibits regeneration. One strategy, therefore, is to administer a PDE 4 inhibitor, such as rolipram, additional cAMP, and embryonic spinal tissue to promote repair of the spinal cord (8). Along similar lines, a promising study by Pearse and colleagues showed that combining the elevation of cAMP with Schwann cell transplantation restored function in spinal cord-injured rats by 70% (14). Figures 1 and 2 show pictures of injured rat spinal cords after the combination treatment.

A landmark paper by Kerr and his colleagues at Johns Hopkins University studied the effects of transplanting motor neurons derived from mouse embryonic stem cells into paralyzed rats. In addition to the transplantation, they administered rolipram and cAMP to further promote regeneration. They concluded that "in adult paralyzed rats, functional restoration of motor units with ES cell-derived motor neurons is possible, and ES cells represent a

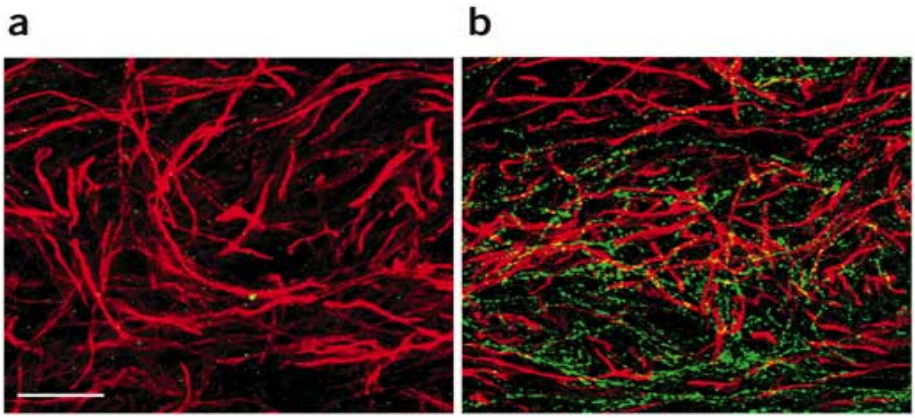


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Figure 2. Regeneration of specialized nerve fibers. Serotonergic nerve fibers (green dots) are important for movement and are susceptible to secondary damage after spinal cord injury. These pictures show the importance of cAMP elevation for successful regeneration of serotonergic fibers. (a) Schwann cell (red strands) transplantation only in the injured rat spinal cord and (b) Schwann cell transplantation with cAMP elevation and rolipram treatment. There are significantly more serotonergic fibers in the latter treatment group.

potential therapeutic intervention for humans with paralysis" (13). Combination therapies are harder to get approved for clinical use by the FDA because each factor in the therapy has to be thoroughly studied for potentially harmful side effects.

"Combining the elevation of cAMP with Schwann cell transplantation restored function in spinal cord injured rats by 70%"

Other innovative strategies

Other scientists are exploring innovative therapies such as functional electronic stimulation (FES) systems and repetitive transcranial magnetic stimulation (rTMS) to promote recovery in chronically paralyzed patients. FES systems stimulate the muscles by applying electric current so that the patient is able to bypass their injured spinal cord (15), while rTMS is an interesting technique that is used to excite neurons in brain regions such as the motor cortex. Furthermore, rTMS was shown to improve the clinical and functional outcome of patients with spinal cord injury (16). More testing is required, however, to confirm how beneficial these promising approaches are before they can be applied clinically.

Fortunately, many researchers are working continuously to find therapies to restore function after spinal cord injury. We now have a good understanding of the physiological barriers that make the effects of spinal trauma so hard to reverse. Scientists are targeting each of these obstacles and have obtained very promising results in animal models and some success in human trials. Any research advances in treating spinal cord injury will help us approach other debilitating CNS disorders because they share similar causes. However, many years of work are still required before these therapies can transition from the lab bench to the bedside because several of them need to be clinically tested. Nevertheless, it is reassuring that the general consensus among scientists is that finding a cure is not a question of "if," but of "when." H

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