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Acute Spinal Cord Injury: Pharmacological Interventions

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Abstract: *Researchers are wary of giving people false hopes that a magic bullet for curing spinal cord injury is just around the corner. However, with accelerating progress in scientific research, there is renewed vitality and growing optimism that, with continued effort, the problems of spinal cord injury will be overcome. Although many years of intensive study have contributed to the development of the prostheses now being tested, they are really the first generation of useful devices. Better materials and enhanced technology can refine these devices to provide much better function. Rehabilitation techniques can greatly improve patients' health and quality of life by helping them learn to use their remaining abilities. Studies of problems that spinal cord injury patients experience, such as spasticity, muscle weakness, and impaired motor coordination, are leading to new strategies that may overcome these challenges. Overcoming spinal cord injuries will require general progress in many fields of neuroscience as well as specific studies in animal models of spinal cord injury and in patients themselves.*

Keywords*: spinal cord, regeneration, neural prosthesis*

I. Introduction

Spinal cord injury (SCI) is a global epidemic. Based on conservative average annual incidence of 22 people / million population in the western and developing world [1] it is estimated that over 130,000 people each year survive a traumatic spinal cord injury and begin a "new and different life" bound to a wheelchair for 40 years or more. With an average age at injury of 33.4 years and most injuries occurring at the age of 19[2] and life expectancy diminished only by an average less than 10 %, and advances in health maintenance and emergency healthcare, it is clear that the population of people living with spinal cord injuries is steadily increasing around the world. By 2005, NEW injuries will swell the total world population of people living with spinal cord injury induced paralysis to over 2.5 million. The economic impact on the community, in terms of the long-term cost of care and cost of social welfare support reaches in excess of tens of billions of dollars each year.

Reliable reports have estimated the cost in the United States alone at $ 7.7 billion dollars annually. In Canada that figure is $1.5 billion, over $500 million British Pounds in the United Kingdom and Australia around $1 billion.[3, 4]

One of the present areas of research is in axon regeneration. In 1988, Martin Schwab discovered two myelin-associated proteins that inhibit growth in the damaged mammalian spinal cord, a revolutionary finding. Until then, it was believed that the cord's inability to regenerate was due only to the absence of nerve growth factors. He has followed up his research with many published articles including this one published in 2009 on the differential effects of anti-Nogo-A antibody treatment and treadmill training in rats with incomplete spinal cord injury. Nogo-A is the myelin associated neurite growth inhibitory protein and lesioned rats treated with antibodies against Nogo-A, showed increased regeneration, neuronal reorganization and behavioral improvements.[5] His research also induced nerve regeneration in the rat spinal cord by blocking damaging proteins with an antibody called IN-1. With this treatment, regenerating axons grow about 11 millimetres; without treatment, they do not grow even one millimeter.[6] He also reported dramatic regrowth of nerves in partially severed rat spinal cords after treatment with a combination of the antibody IN-1 and the growth-promoting factor NT-3.[7]

Effective drug therapy for spinal cord injury first became a reality in 1990, when methylprednisolone, the first drug shown to improve recovery from spinal cord injury, moved from clinical trials to standard use. The NASCIS II (National Acute Spinal Cord Injury Study II) trial, a multicenter clinical trial comparing methylprednisolone to placebo and to the drug naloxone, showed that methylprednisolone given within 8 hours after injury significantly improves recovery in humans. Completely paralyzed patients given methylprednisolone recovered an average of about 20 percent of their lost motor function, compared to 8 percent recovery of function in untreated patients. Paretic (partially paralyzed) patients recovered an average of 75 percent of their function, compared to 59 percent in people who did not receive the drug. Patients treated with naloxone, or treated with methylprednisolone more than 8 hours after injury, did not improve significantly more than patients given a placebo. [11]

The applicability of corticosteroids for acute spinal cord injury has been investigated for more than 30 years. Although many animal studies have supported the administration of steroids in experimental spinal cord injury, it is important to realize that not all have demonstrated a beneficial effect. Coticosteroids are thought to provide neuroprotection in several ways (Table 1)

Table 1 Potential Mechanism of Action for Corticosteroids after Central Nervous System Injury

- Inhibition of lipid peroxidation
- Improved micro vascular perfusion
- Prevention of calcium influx into cells
- Suppression of pro inflammatory cytokine expression
- Attenuation of the effects of inflammatory cytokines
- Inhibition of nitric oxide production,
- Inhibition of apoptosis

The inhibition of lipid peroxidation has been hypothesized to be the most important neuroprotective property in preventing lipid peroxidation when compared with other glucocorticoids.[8,9]

The NASCIS II (National Acute Spinal Cord Injury Study II) trial, a multicenter clinical trial comparing methylprednisolone to placebo and to the drug naloxone, showed that methylprednisolone given within 8 hours after injury significantly improves recovery in humans. Completely paralyzed patients given methylprednisolone recovered an average of about 20 percent of their lost motor function, compared to 8 percent recovery of function in untreated patients. Paretic (partially paralyzed) patients recovered an average of 75 percent of their function, compared to 59 percent in people who did not receive the drug. Patients treated with naloxone, or treated with methylprednisolone more than 8 hours after injury, did not improve significantly more than patients given a placebo. [11]

The successful clinical trial of methylprednisolone revolutionized thinking in the medical community. The trial showed conclusively that there is a window of opportunity for acute treatment of spinal cord injury. Some doctors are now using this idea to guide surgical treatment as well as drug therapy. Today, most patients with spinal cord injuries receive methylprednisolone within 3 hours after injury, especially if the injury is severe. This shows that emergency rooms and acute care facilities are aware of the drug's value and are capable of providing rapid treatment for spinal cord trauma. Success in delivering this drug on a widespread basis shows that health care systems are capable of providing rapid treatment. The NASCIS II trial also proves that well-designed trials of acute therapies for spinal cord injury are feasible and provides a model for testing other interventions.[10, 12]

Other drugs are now being tested in clinical trials. A recently completed trial suggested that 48-hour regimen of methylprednisolone may be warranted in some patients. Preliminary clinical trials of another agent, GM-1 ganglioside, have shown that it is useful in preventing secondary damage in acute spinal cord injury, and other studies suggest that it may also improve neurological recovery from spinal cord injury during rehabilitation. [9]

Although many years of intensive study have contributed to the development of the prostheses now being tested, they are really the first generation of useful devices. Better materials and enhanced technology can refine these devices to provide much better function. Among the recent technical advances are extremely small probes that fit 16 electrodes on a shaft finer than a human hair. Integrated into a neural prosthesis, this type of electrode could provide extremely selective stimulation within the CNS, allowing the patient much more refined muscle control and a greater range of function. Future clinical development may allow easier, faster, and more natural movements; improve the longevity and reliability of components; and eliminate external cabling systems and external mounting of sensors.

A major motivation behind spinal cord research has been Christopher Reeve. Injured in a horseback riding incident, Christopher Reeve suffered a cervical spinal cord injury that left him quadriplegic. Christopher Reeve began the Christopher Reeve Paralysis Foundation (CRPF). CPRF funds research to treat or cure paralysis resulting from spinal cord injury or other CNS disorders. CPRF supports a Research Consortium, which collaborates the work of nine laboratories, as well as funds an international individual grants program. Several of the labs involved in the Research consortium focus on stem cells, making a lot of progress. The Salk Institute, run by Dr. Fred Gage examines the progenitor cells differentiating into glial cells. Someday they hope to manipulate these progenitor cells, inducing differentiation into neural cells.

Scientists believe another common motor problem, muscle in coordination, may result in part from the substantial brain reorganization that occurs after injury to the CNS. With a better understanding of how the spinal cord changes following injury, researchers may be able to use drugs or physical therapy to promote reorganization when it is useful and block it when it is harmful.

Rehabilitation strategies will continue to play an important role in the management of spinal cord injury, and they will increase in importance as the ultimate goal of functional spinal cord regeneration is realized. Studies in animals with spinal cord injuries have shown that recovery of movement is linked to the type of training the animals receive. Physical therapy and other rehabilitation strategies also are crucial for maintaining flexibility and muscle strength and for reorganizing the nervous system. These factors will be vital to recovering movement following regeneration as well as maximizing the use of undamaged nerve fibers.[14]

Electrical stimulation and Neural Prosthesis

Electrical stimulation is also used as a method of nerve regeneration but it is still in the human clinical trials. Researchers at Purdue University's Centre for Paralysis Research and Indiana University School of Medicine are using low-level electrical stimulation on paralyzed dogs. They implant a small battery pack, known as an extra spinal oscillating field stimulator (OFS), near the dog's spine. It sends a weak electrical signal (thousandths of a volt) to the site of injury. This helps regenerate cells and guide growth in the damaged nerves. In about a third of the cases, the dogs improved significantly.[15]

Neural prostheses are complex and contain many intricate components, such as implantable stimulators, electrodes, leads and connectors, sensors, and programming systems. There are many technical considerations in selecting each component. The electronic components must be as small as possible. Biocompatibility between electrodes and body tissue is also necessary to prevent the person from being harmed by contact with the device and to prevent the device from being harmed by contact with the person. Other challenges include finding ways to safely send currents into the body, to reliably record neural activity, and to cope with changes in muscle properties due to the injury. Neural prostheses also must be evaluated for usefulness and long-term safety. [16]

Further research to improve components and increase understanding of brain circuits may yield prostheses that can provide sensory information to the brain. This will improve both the safety of the devices and the patient's performance of tasks. Devices now being developed May eventually enable people with spinal cord injury to stand unassisted and to use signals from the brain, instead of muscles, to control movement. Other types of neural prostheses currently being developed around the world aim to improve respiratory functions, bladder control, and fecal continence. Ultimately, researchers may be able to harness reflexes or the innate pattern-generating abilities of the spinal cord's central pattern generators to help people with spinal cord injuries walk.

Therapies for spinal cord injury have improved substantially in the last few years. Drugs for treatment of acute injury, neural prostheses, and advanced rehabilitation strategies are improving the survival and quality of life for many patients. However, there are still many opportunities for improvement. These include finding ways to build on CNS reorganization and comparing the usefulness of different rehabilitation strategies. Investigators must also develop improved animal models for spinal cord injury to allow testing of new or improved therapies.

A lot of research is still ongoing in the field of spinal cord injury and regeneration. For many years it was assumed that spinal cord regeneration was not possible. Paralysis, often resulting from damaged spinal cords, was likely to be permanent, and many peoples' lives were forever altered by a spinal cord injury. This is still the case today, but what has changed is the degree of optimism many people hold about someday being able to use medical techniques to fix spinal cord injuries and restart the damaged nerves that have lost function after an injury has occurred. A recent study conducted at the Korea University Medical Centre suggests that implants of exogenous neural stem cells may promote regeneration in aging organisms through stimulation of endogenous neurogenesis.[17]

Spinal cord injury (SCI) in adults often leads to permanent functional deficits because the regeneration of injured axon and the reorganization of the remaining circuitry are insufficient in the human central nervous system. Therefore promoting axonal regeneration is one of the essential goals to be achieved for effective repair from SCI. Wnt ligands are a family of glycoproteins that have diverse and essential roles in the development, cell growth and human diseases. Experimental work done in rats suggested the neurological recovery after SCI in rats were improved by Wnt secreting fibroblasts which were injected intramedullarily at 1 week after SCI. ME – MRI shows that axonal regeneration was better in Wnt group through the injured site in spinal cord.[18]

Cell transplantation therapies have been developed experimentally for some CNS disorders. It also came to be realized that adult mammalian CNS has some regenerative capacity. Thus regeneration of the damaged CNS is becoming feasible from the clinical aspect, although it still remains primitive. Therefore it is obvious that both 1) activation of the endogenous regenerative capacity and 2) cell replantation therapy are very important strategies for CNS repair. Elucidation of the molecular and cellular mechanisms of the stem cell regulation and normal CNS developmental process in combination with molecular – targeted drug discovery would be essential for future development of innovative therapeutic interventions of various CNS damages including SCI, stroke and neuro degenerative disorders.[17]

II. Conclusion

Spinal cord injury research has now come of age. Because of general progress in neuroscience, as well as specific advances in spinal cord injury research, researchers can test new ideas about how changes in molecules, cells, and their complex interactions in the living body determine the outcome of spinal cord injury. Scientists are learning, for example, how processes such as oxidative damage, excitotoxicity, and apoptosis contribute to spinal cord injury and how this damage might be minimized. Inspired by demonstrations that spinal cord nerve cells can regrow, researchers are learning to manipulate trophic factors, intrinsic growth programs, and growth inhibitors to encourage regeneration.[18]

One of the most exciting aspects of the neurosurgical research is the potential for applying findings from other fields, such as development, immunology, and stroke research, to spinal cord injury. There is increasing recognition that similar processes contribute to a diverse range of neurological disorders, including spinal cord injury, stroke, brain trauma, and neurodegenerative diseases. New insights about how the nervous system develops are also suggesting ways to encourage regeneration. Researchers may debate how directly these insights will apply to the adult spinal cord, but they agree that testing these hypotheses in animal models of spinal cord injury ultimately will lead to better treatments. Scientists are studying several growth factors and how they can be used in treating spinal cord injury. Each growth factor has very specific target cells that it works on. They include NT-3 (Neurotrophin 3); BDNF (brain derived neurotrophic factor); aFGF (acidic Fibroblast Growth Factor) and NGF (nerve growth factor). [20]

Another component of nerve regeneration, which researchers are working on, is with different substances to guide nerve growth so nerves grow past the injury site and reconnect with the proper nerve. Netrins are proteins produced in the brainstem that "attract" nerve cells. They encourage nerve cells to migrate to and grow branches toward a "target." Dr. Mark Tessier-Lavigne of Stanford University has identified netrins in several animal models and is evaluating their use with spinal cord injury.[21]

Overcoming spinal cord injuries will require general progress in many fields of neuroscience as well as specific studies in animal models of spinal cord injury and in patients themselves. Key areas for research include:

- Secondary damage and intrinsic repair processes, including oxidative damage, excitotoxicity, calcium-mediated damage, proteases, apoptosis, immune responses, stem cells, and plasticity and reorganization.
- Development and regeneration, including trophic factors, axonal pathfinding, growth inhibitors, and synapse formation.
- Applied studies in animal models of spinal cord injury, including tests of trophic factors and grafting and transplantation strategies.
- Clinical research in human patients, including studies to describe anatomical and functional changes that follow spinal cord injury, to refine existing supportive and rehabilitation therapies such as neural prostheses, and to test new therapies that emerge from basic and applied research.

Researchers are wary of giving people false hopes that a magic bullet for curing spinal cord injury is just around the corner. However, with accelerating progress in scientific research, there is renewed vitality and growing optimism that, with continued effort, the problems of spinal cord injury will be overcome[22]. Research in spinal cord regeneration is catching up attention by the clinicians and basic scientists. It would almost revolutionize the life and disease outcome of these unfortunate patients if we can work out a cost effective and practical treatment regimen for these victims who are unfortunately in the prime of their productive years. It was gratifying to learn that nerves in peripheral nervous system (PNS), which are outside the brain or spinal cord, did regrow. It is exciting to learn that the prospects of regrowth of spinal cord improve when these PNS cells are implanted in damaged spinal cord. Spinal cord injury is a global epidemic. A lot of research is going on in this field. Axonal regeneration, electric stimulation, Netrins, stem cells etc are few exciting fields in the area of research. It is ongoing research whereby the ability to grow human motor neurons in the laboratory will provide new insights into disease processes and could be used as alternative to animal models for finding therapeutic targets and testing drugs.[23]

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