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Novel medical management of spinal cord injury

Abstract

Spinal cord injuries are well known for causing permanent disability and for not having effective treatments. Many promising studies are going on to formulate new pharmacological agents or to use existing medications that are indicated for entirely different pathological processes. Stem cell therapy and gene therapy have always been at the center of research but have not successfully established as a treatment of choice. Microtubule stabilizing anti- cancer drugs and chondroitinase ABC are other interventions currently under study. Pharmacological agents under investigation should be evaluated in detail to determine correct timing for use. Most recent researches focus on cellular receptor level modulation to promote the healing process. Remyelination agents and axonal regeneration stimulators that function by affecting the molecular biological level functioning of the cells require further studies to enable them to be used commercially. This article reviews various aspects of newer pharmacological agents in the management of spinal cord injury and the factors determining the success of concomitant use of these agents with traditional or non-pharmacological management.

Keywords: spinal cord injury, mesenchymal stem cell therapy, chondroitinase, gene therapy, anticancer drugs, sulfonylureas, neutrotrophic factor, rapamycin

Roy Sebastian,[1] Theresa M Meloche,[2] Tony L Brown[3]

[1]Baylor Scott and White Medical Center, USA
[2]Major General Hugh G Robinson Center for Neuropsychiatric Studies, USA
[3]Department of Neurology, College of Physicians and Surgeons, USA

Correspondence: Tony L Brown, Department of Neurology, College of Physicians and Surgeons, Columbia University, USA, Email tbrown@post.harvard.edu

Abbreviations: SCI, spinal cord injury; hUCB-MSCs, human umbilical cord b blood-derived mesenchymal stem cells; OPCs, oligodendrocyte precursor cells; NPC, neural progenitor cells; PBS, phosphate buffered saline; CSPG, chondroitin sulfate proteoglycans; ChABC, chondroitinase ABC; SUR1–TRPM4, sulfonylurea receptor 1–transient receptor potential melastatin 4; PTEN, phosphate and tensin homolog; mTOR, mammalian target of rapamycin; SOCS3, suppressor of cytokine signaling 3; BDNF, brain -derived neurotrophic factor; LINGO-1, leucine rich repeat and Ig domain containing 1; Trk , tyrosine kinase; NT-3, neurotrophic factor-3; NT4/5, neurotrophin-4; NGF, nerve growth factor; p75NTR, P75 neurotrophic receptor; GFRα, GDNF family receptor alpha; KLF, krüppel- like factors

Introduction

The latest statistical data estimated that the annual incidence of spinal cord injury (SCI) was approximately 40cases per million population in the U.S. or about 12,500 new SCI cases each year.[1] The average age at injury had increased to 42years. The cure for the spinal cord injury sequelae has remained elusive. Current treatment has been limited to the early administration of high-dose steroids and acute surgical intervention, to minimize spinal cord edema. Recent studies have been instituted in order to find more effective treatments for spinal cord injuries. There has not been an indication that a single cure is on the horizon, but the correct combination of traditional management and novel pharmacological agents is expected to be the future of spinal cord injury treatment.

Pathophysiological features after SCI

The pathophysiological processes of SCI consist of primary and secondary phases of injury. Initially, there is the formation of a central hemorrhagic lesion devoid of healthy neurons, glial cells, oligodendrocytes and astrocytes in the white matter near the impact site, with an estimated 50% reduction within 24hours post injury. The extent of damage to the spinal cord is dependent upon the site of injury, degree of impact, availability of nutrient supply, and physical manipulation of the person after the injury. The factors that limit the recovery following spinal cord injury (SCI) are axonal damage, demyelination, and scar formation.

Mesenchymal stem cells in SCI

Neural stem cells have been used for the treatment of neurological diseases such as SCI[2] or stroke. Clinical application of these cells, however, has been limited for multiple reasons, including the lack a sufficient cell supply, a risk of immune rejection, and ethical issues. Mesenchymal stem cells (MSCs) are relatively a better option since they are easy to isolate, multiply *in vitro*, and differentiate into several types of mature cells that include neurons, adipocytes, cartilage, and skeletal hepatocytes under appropriate conditions.[3] This therapeutic strategy has been a valuable therapy source for central nervous stem (CNS) diseases and injuries, and has proven to make a significant impact on the recovery process. Human umbilical cord blood-derived MSCs (hUCB-MSCs) have significant therapeutic potential and are preferred because of their availability and poor immunogenicity compared to other sources of stem cells, such as bone marrow or adipose.[3] Another strategy of stem cell therapy is the protection of injured cells and the promotion of endogenous cell regeneration. Stem cells provide a better environment for damaged tissue and protect the remaining neurons by neurotrophic factors or cytokines. Various studies have considered MSC treatment of SCI as a leading candidate that supplies angiogenic, antiapoptotic, and mitogenic factors, as well as one that exhibits migration toward the damaged tissue. Recently, MSCs have been used in the clinical treatment of various pathologies and were shown to be effective despite the lack of a known, unique therapeutic mechanism.[4]

Cellular therapies for SCI repair may involve modification or recruitment of endogenous cells *in vivo*, or harvest and alteration *ex vivo* of endogenous cells that are subsequently implanted as an allogeneic graft or transplanted into the injured organism as allogeneic or xenogeneic grafts. Transplanted stem cells have proven

to facilitate healing through neural regeneration promotion and impaired neural function rescue after SCI by secreting permissive neurotrophic molecules at the site of the lesion. This process enhanced the regenerative capacity, which thereby provided a scaffold for the regeneration of axons and the replacement of lost neurons and neural cells.

The normal spinal cord contains oligodendrocyte precursor cells (OPCs) and endogenous neural progenitor cells (NPC). Injury, though, may restrict production of new neurons and oligodendrocytes by endogenous cells into the spinal cord. Some cell transplantation studies have demonstrated reduced differentiation of exogenous stem cells compared to the endogenous differentiation after grafting to a spinal cord.[5] Thus, the environment of the spinal cord has a restrictive or inhibitory action related to the differentiation of OPCs. If this environmental restriction can be overcome hUCB- MSC in SCI, OPCs may be able to provide new neurons and oligodendrocytes.

Unknown, though, is whether or not the transplanted hUCB-MSCs influence survival and differentiation that is generated from the endogenous cells. One study revealed that the transplantation of hUCB-MSCs conferred therapeutic effects in a rat experimental SCI model. In this study, hUCB-MSCs that were transplanted after SCI, survived in and around the injured site.[3] Also, the cavities of the MSC -treated rats were much smaller than those of the PBS-injected rats. Transplanted MSCs after SCI demonstrated a neuroprotective effect by reduction of the cavity volume. The transplantation of hUCB-MSCs, however, could not solely be responsible for functional recovery after SCI.

The collective results supported the view that hUCB-MSCs transplantation has benefit in SCI via secreting growth factor and also by physical support for the growing axons. Further investigations are needed to confirm that the benefit obtained from hUCB-MSCs persists at later time points, the long-term efficacy of the transplanted hUCB-MCSs, and to identify the mechanisms underlying functional recovery after transplantation of hUCB- MSCs. Cell-based therapy continues to face numerous application challenges that include the selection of an SCI model, timing and mode of cell implantation, location of cellular injection, and their subsequent migration, survival, transdifferentiation, immune incompatibility and rejection, and tracking of implanted cells.

Chondroitinase ABC injection and gene therapy

An approach that holds promise for enhancement of the regenerative response following an SCI is the neutralization of inhibitory factors in the post-injury environment. Many different inhibitory elements can be neutralized post- injury. Significant progress has been reported related to the development of agents to counteract the inhibitory influence of either chondroitin sulfate proteoglycans (CSPGs) or myelin debris. CSPGs expressed in and around the glial scar are considered a primary reason for the lack of axonal regeneration and Remyelination following an SCI. The inhibitory nature of the CSPGs, though, can be neutralized using the enzyme chondroitinase ABC (chABC), which is produced by the bacteria Proteus vulgaris and is a catalyst for the removal of the glycosaminoglycan side chains from the central core protein. Studies have shown that by treating a CNS lesion site with the enzyme chABC both axonal growth and axonal sprouting into and around the lesion are significantly increased.[6] The use of this agent has been shown to reverse CSPG inhibition efficiently

and promote axonal sprouting and outgrowth as well as to enable the migration and differentiation of endogenous OPCs.[7] ChABC breaks down quickly, so beneficial effect maintenance for an extended period requires repeated invasive administration of the enzyme to the spinal cord.

To overcome this hurdle, researchers recently began the exploration of gene therapy as a method to efficiently coax spinal cord cells to produce the enzyme in order to coax the spinal cord cells to produce and secrete ChABC in large quantities over areas spanning the injury epicenter, as well as to assist in the maintenance of the overall health of the damaged spinal cord. ChABC gene therapy was shown to have altered the inflammatory cells' response in the region of injury. Typically, after an acute injury to the spinal cord, immune cells invade the injured area and cause destructive and irreparable tissue damage. ChABC gene therapy, though, both decreased the presence of inflammatory cells and increased the presence of M2 macrophages that assist in the reduction of inflammation and the enhancement tissue repair. Chondroitinase ABC enzyme degrades the chondroitin sulfate proteoglycans, and then removes the barrier to regeneration from the glial scar while increasing CNS plasticity by eliminating perineuronal nets. This mechanism of action is unique and does not interfere with other treatment strategies, which highlights ChABC as an attractive candidate as a therapeutic agent in combination with other methods of therapy.[8]

Microtubule stabilizing anticancer drugs

Microtubule stabilizing anticancer drugs interferes with the cellular division and has shown promise in the field of axonal regeneration. Two such drugs are paclitaxel (Taxol), and Epothilone B. Taxol was shown to prevent the formation of retraction bulbs after injury, stabilize the cytoskeleton of the reactive growth cone, and promote the regeneration of axons in an injured optic nerve model.[9] Systematic administration of Epothilone B in rodents demonstrated decreased glial scarring and increased microtubule polymerization in the tip of the axon.[10] Induction of microtubule polarization in the growth cone appears to drive the growth of the axon at the site of the lesion. Importantly, not only do both Taxol, and Epothilone B have the potential to enhance axonal growth following injury, but also they are currently enjoy FDA approval for cancer therapy. Epothilone is superior to other cancer drugs while it provides a a similar effect because of its ability to penetrate the blood -brain barrier, enter into the central nervous system, and reach the damaged axons directly. Epothilone inhibits the formation of microtubules in the cells that form the scar tissue. Therefore, they do not migrate to the spinal cord lesion and result in wound scarring. At the same time, Epothilone causes microtubules to grow into the damaged axon tips, which promotes growth and regeneration of the nerve cells. Through the same effect, namely microtubule stabilization, Epothilone can inhibit directional movement in scar-forming cells while stimulating active growth in nerve cell axons.[11]

Sulfonylureas after acute spinal cord injury

Within hours of spinal cord injury, an up regulation of the sulfonylurea receptor 1–transient receptor potential melastatin 4 (SUR1-TRPM4) channels at the site of the lesion has been observed. After CNS injury, the SUR1–TRPM4 channel has been detected in neurons, astrocytes, oligodendrocytes, and micro vascular endothelium at the site of damage.[12] Increased expression of this cation channel has been linked to the development of vasogenic

and cytotoxic edema, as well as to subsequent hemorrhagic conversion. Inhibition of expression of the SUR1- TRPM4 channel would minimize the progression of the damage. Glibenclamide is an antidiabetic agent from the class of sulfonylureas that acts as an inhibitor of SUR1. Accumulating evidence has indicated that the beneficial effects of glibenclamide might be related to the protection of micro vascular endothelium, reduced edema formation, secondary hemorrhage, and ant apoptotic and anti-inflammatory mechanisms. Importantly, penetration of glibenclamide into the CNS is enabled after focal injury.[12] Clearly, the SUR1–TRPM4 channel deserves further investigation as a drug therapy in SCI.

Stimulation of axonal regeneration

Axonal regeneration may be stimulated or inhibited after injury through direct modulation of molecular signaling pathways within the axons. These molecular signaling pathways are very complex, and have the ability to facilitate axonal growth. One such molecular signaling target is Phosphate and Tensin homolog (PTEN), which is a negative regulator of the mammalian target of rapamycin (mTOR). Recent studies have shown that silencing the mTOR molecule resulted in significant axonal growth.[13] Besides PTEN, suppressor of cytokine signaling 3 (SOCS3), a known negative regulator of Janus kinase/signal transducers and activators of transcription (JAK/STAT), has been depicted as inhibitory to axonal regeneration. The suppression of the SOCS3 pathway, it would appear, will facilitate axonal regeneration. Pharmacological research should focus on drugs that are highly specific to inhibit PTEN and SOCS3 pathways.

Another target for axonal regeneration therapy is the Krüppel-like factors (KLF) family of transcription factors. These transcription factors play a significant role in the regulation of neural regeneration and growth through either suppression or enhancement of axonal growth abilities. KLF family members known to be inhibitory to axonal growth (KLF 4 and 9) had been found to be upregulated postnatally while those that are growth promoting (KLF 6 and 7) were down regulated.[14] Research should focus on both suppression- and enhancement-specific transcription factors to facilitate axonal regeneration.

Neurotrophic factor supplementation

Neurotrophic molecules consist of a group of proteins that are structurally similar and bind to one of the three tyrosine kinase (Trk) surface receptors or to the p75 neurotrophic receptor (p75NTR). Members of the NT family include brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT4/5), which preferentially bind to TrkB, nerve growth factor (NGF), which binds TrkA, neurotrophic factor-3 (NT-3), and its receptor TrkC.[15] While NTs bind to a specific Trk receptor, all of the NT molecules can bind to p75NTR, which has important physiological implications for neurons. Further investigation should be done to enhance the expression of the appropriate Trk receptors in order to maximize neuronal regeneration and minimize harmful effects. Glial- derived neurotrophic factors are another family of growth promoting molecules which require two surface receptor components. The GDNF family of molecules directly binds to one of four GDNF family receptor alphas (GFRα), which then complex with the Ret receptor tyrosine kinase. Members of this family include glial-derived neurotrophic factor (GDNF) which binds GFRα1, nurturing which binds GFRα2, artemin which binds GFRα3, and persephin which binds to GFRα4.[15]

Promoting remyelination

One study focused on the promotion of Remyelination of spared axons through the use of antibodies to block the protein Leucine Rich Repeat and Ig Domain Containing 1 (LINGO-1). LINGO-1 is selectively expressed in both oligodendrocytes and neurons and is highly inhibitory to the myelination process. Following CNS disease or injury the expression of the LINGO-1 protein is up regulated, and it inhibits the differentiation and maturation of OPCs via the activation of RhoA pathway.[16] Demonstrated was that utilization of LINGO-1 knockout animals or administration of anti -LINGO-1 antibodies resulted in significantly increased levels of Remyelination in animal models of demyelization (autoimmune encephalomyelitis or lysolecithin-induced).[17] Use of anti-LINGO-1 as a method of medical treatment for multiple sclerosis (MS) cleared phase I clinical trials in April 2012 and has since moved into phase II.[18] Clinical trials and findings for anti-LINGO-1 antibodies have revealed usefulness in demyelinating conditions such as MS. Anti-LINGO-1 does present another potential therapeutic opportunity for the treatment of SCI.

Conclusion

Spinal cord injuries historically have caused permanent disability in most of the affected population. There is currently promising research related to facilitation of recovery after SCI, which utilize various pharmacological agents. Formulation of a protocol that can be applied to most of the patient population in order to minimize the damage and aid the recovery process, though, is essential. Stem cell therapy with hUCB-MSCs may facilitate functional recovery after spinal cord injury by reducing the cavity volume, increase cell proliferation and endogenous oligogenesis, and decrease apoptosis. Clinical trial completion for sulfonylurea treatment might prove beneficial in the effort to limit the damaging effect of the acute inflammatory reaction, which then has the potential to be followed by administration of therapeutic agents that stimulate axonal regeneration and Remyelination. In sub acute stages of the injury, chondroitinase ABC may be beneficial.

Medication management cannot solely treat spinal cord injury successfully; appropriate rehabilitation is also key. Rehabilitation using physical and occupational therapy are based on neural plasticity. The benefit of a combined pharmacological and rehabilitative approach should be studied for identification of any particular therapy combination, in relation to the time frame and the extent of the injury. Drug and Remyelination-promoting agents that are in various stages of clinical trials hold promise that there is a method on the horizon to minimize the extent of disability caused by spinal cord injury.

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Conflict of interest

The author declares no conflict of interest.

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