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Current trends in spinal cord injury repair

W.-Y. YU, D.-W. HE

Department of Orthopaedic Surgery, the Fifth Affiliated Hospital of Wenzhou Medical University, P.R. China

Abstract. – One of the rapidly prevailing neurological disorders affecting thousands of people per year is spinal cord injury (SCI). Though, great research has been made in recent past to understand thoroughly the molecular bases of the diseases, no fully restorative treatments for SCI are available. However, various rehabilitative, cellular and molecular therapies are being tested in animal models. Some of them have shown promising results. So, the present review shall enlighten all these latest developments in the field of spinal cord injury repair.

The review shall discuss latest upcoming areas being focused for the management of SCI patients like stem cell therapy approach, cell-based approaches, combination therapeutic approaches, neuronal plasticity and possible use of omega-3 fatty acids in SCI repair.

Key Words:
Spinal cord injury, Omega fatty acids, Combination therapy, Neuronal plasticity.

Introduction

Spinal cord injury is a distressing episode in the lives of the patients suffering from it. The major causes responsible for spinal cord injury (SCI) include primarily due to vehicular accidents, secondly due to bullet wounds or some form of violence, thirdly due to accidental falls especially in elderly people[1]. Cases are also reported due to sports injury. SCI is a multidimensional disease that not only leads to loss of sensory or motor capabilities but also causes other common problems like frequent infections in bladder, kidneys, bowel problems, and cardiac and respiratory dysfunctions[2-4]. All these devastating conditions impart strong impact on the social, psychological and physiologic status of SCI patients. Moreover, lack of any specific, efficient treatment for SCI further adds to the miseries of SCI patients. The only option till now available for the SCI patients was mostly palliative in nature which included prevention of injury progression, management of pain syndromes, implementation of bowel as well as bladder training regimens, management of complications due to sensory loss.

Clinicians, scientists as well as core researchers the world over are fortunately working collectively on many key aspects in order to improve the fateful conditions of SCI patients. Moreover, ongoing research in the advance neurobiology offers to change the nature of treatment planning from palliative to more of curative in nature. This review shall provide an extensive overview of the latest developments being made in the SCI research. Latest research hotspots in SCI mainly include use of stem cell therapy via utilization of mesenchymal stem or stromal cells (MSCs). These mesenchymal stem cells have anti-inflammatory and neuro-protective effects and have been noticed to reduce secondary damage due to SCI. Also, cellular therapeutic interventions will be discussed that are primarily aimed to provide new neurons or myelinating cells and to create a favourable environment for axon regeneration. Moreover, the latest transplant therapeutic procedures will be discussed which have shown good potential for efficient management of SCI in the recent past. In the end ofreview, special attention will be given to the latest use of polyunsaturated fatty acids for management of SCI. These polyunsaturated fatty acids (PUFAs) are structural components of cell membranes and are well known for an important property: namely, the ability to modify the reaction of the nervous system to acute injury. So, the present review article will expand the knowledge from the basic biology to the current state of research and clinical areas and finish with the future trends for this field.

Stem Cell Injury in Detail

The most common cause of SCI is vehicular accidents or violence. The nature of injury observed in these victims is usually of contused or compressed nature due to strong blunt force. On the other hand, sometimes macerated spinal cord

Corresponding Author: Dengwei He, MD; e-mail: dengweihe430@163.com

by a sharp penetrating force is also noticed in these victims[5]. This sort of prime neurological damage is termed as "primary injury". This primary injury is, then, further continued by set of successive biological events leading to succession in further neurological disruption and is collectively termed as secondary injury. Time taken by secondary injury events is of tune of few minutes to several weeks. This is followed by onset of chronic phase of spinal cord injury that usually takes several days to years and this phase results in impairments in orthograde as well as retrograde directions along with brain regions[6]. Secondary injury is accompanied by following these detrimental events:

Lipid peroxidation: Lipid peroxidation is the prime event widely spread across the spinal cord after SCI, leading death of neurons due to oxidative shock. It also hampers blood flow that ultimately causes edema and inflammatory reaction. Further, important enzymes like Na+ K+ ATPase lose their activity due to aldehyde formation during lipid peroxidation process.

Vasuclar damage: Vascular damage mainly include hemorrhage, vasospasm, thrombosis, loss of auto-regulation, breakdown of blood brain barrier andinfiltration of inflammatory cells resulting in edema, necrosis and ischemia.

Apoptosis: Apoptosis is programmed cell death that immediately follows above two prime events in secondary injury and finally causes cell death in variety of neuro-sensory cells including neurons,oligodendrocytes, microglia, and, perhaps, astrocytes. These all process collectively leads to next successive deterioration event that is termed as post-injury demyelination.

Finally, the chronic phase comprises events such as whitematter demyelination, gray matter dissolution, connective tissue deposition and reactive gliosis that lead to glial scar formation[7]. In most of the cases glial scar formation is further associated with pain syndrome, depression and related mood disorders.

Stem Cell Therapies

The latest technological advances in each and every research area in today's world involve use of latest approach of stem cells therapies. The basic theme of stem cell therapy is use to peculiar property of stems cells to regenerate into any desired cell type[8]. This helps in creation altogether new set of cells in a damage area in any kind of pathological state. This unique property of stem cells made them amazingly applicable as well quite feasible in almost many important medical research areas including cancer and off course spinal cord injury. In the condition like SCI it is very crucial to recover neuro sensory cells, so stem cells offer an option as they have ability to regenerate into any cell type, thus, hold promise as a novel treatment modality for SCI[9]. However, the the conversion of stem cells into neural cells is still a debated topic.

Neuronal stems cells (NSCs) are able to differentiate into wide variety of neural cells including neurons, oligodendrocytes, and astrocytes due to their multipotent nature. They are mainly isolated from developing central nervous system in fetus. Moreover, they have been also reported to secrete several neurotrophic factors like brain-derived neurotrophic factor, glial derived neurotrophic facts and nerve growth factor[10]. However, due to negative reports pertaining to NCSs remaining undifferentiated or differentiated predominantly into glial cells, is a potential problem that prevents their direct transplantation into the injured spinal cords. Moreover, ethical issues due to isolation from fetal CNS and other practical issues limited their use in both clinical trials as well as in biomedical research.

Multi potent mesenchymal stem cells (MSCs) is the latest version of stem cell approach being explored worldwide for the betterment of varied pathological states including cancer, cardiovascular diseases, and spinal cord injuries. Main pros of MSCs are their regenerative effects but in addition to these MSCs are quite easy to isolate along with efficient *ex vivo* expansion, lack of ethical concerns, and acceptable safety profile[11-12]. MSCs can be isolate from bone marrow, adipose tissue, umbilical cord. Moreover, MSCs are also unique in having desirable properties such as anti-inflammatory, immune-modulatory, anti-apoptotic, trophic and angiogenic[12].

Studies in recent past have clearly shown beneficial role played by MCSs in modulating detonate effects of acute as well as chronic spinal cord damage[13,14]. Voulgari- Kokota et al[15] observed protective effects by MCSs during glutamate toxicity, reduction in stress associated proteins and pro-inflammatory cytokines damage. Other important protective modulatory effects observed by use of MSCs included, secretion of

neurotrophic factors[16], enhancement of neural stem cell oligodendrogenic fate and remyelinization[17]. Also, there are reports[18] which suggested that MSCs have ability to transdifferentiate into glial and neuron-like cells by themselves.

In latest development in the field of researchers are trying to exploit MCS for the management of secondary events during SCI as these events are responsible for permanent progression of SCI into chronic syndrome. This shall help SCI patients in the recovery process following SCI secondary damage.

Surgical and Related Approaches

Although the available surgical and the other clinical interventions are so far not the ultimate solution to the problems faced by SCI patients, they still provide relief to some extent by stabilization and decompression of spinal cord along with methylprednisolone therapy[19,20]. However, there are controversies about these procedures which have posed much debate in the neuronal plasticity community, due to the complexity and individuality of SCI that do not allow standardization of uniform surgical procedures for SCI management. On the other hand, there have been as many positive reports on the benefits of surgical interventions as those negative ones[21].

Use of methylprednisolone therapy[22] is a part of pharmacological interventions being explored for the management of SCI. The pharmacological avenues have shown promising effects in improving neurological function and/or support neurological recovery, when given timely with the help of efficient delivery routes. Methylprednisolone has been reported as the most widely used pharmacological agent in clinical practice; however, in recent past its use is now limited due to reported side effects and controversies. It is basically corticosteroid and is able to scavenge free radicals, inhibit lipid peroxidation, helps in blood-spinal cord barrier, stimulate blood flow in spinal cord and regulate inflammation. In other words, it manages most of the secondary injury events prevents the spinal cord deterioration further to chronic syndromes. The severity of side effects associated with the above drug limited its application. Moreover, another recent option to use methylprednisolone with the least side-effects has been suggested. It involved the use of high doses of drug for shorter time periods through efficient drug delivery mechanism, for instance, nano particle based drug delivery system[23].

Other treatment options exist like monosialotetrahexosylganglioside (GM-1) which is a naturally occurring compound found in cell membranes. This drug showed potential therapeutic effects in acute SCI injury[24-26]. Moreover, another pharmacological agent, namely thyrotropin-releasing hormone (TRH), has been explored and reported to show antagonistic effects against secondary injury mediators such as excitotoxic amino acids, peptide-leukotrienes, endogenousopioids, and platelet-activating factors in experimental studies[27,28]. None of the pharmacological agents are confirmed as certain treatment for SCI injury. Ongoing research has focused on the developing of pharmacological agents with superior therapeutic features for SCI patients.

Polyunsaturated Fatty Acids in SCI Management

Research reports revealed that the natural compounds, polyunsaturated fatty acids (PUFAs) of the omega-3, have the peculiar ability to modify the reaction of the nervous system in acute injury. The severity of SCI instantaneously necessitates a treatment that could shield spinal cord right in the acute phase; thereby, helps in beneficial regeneration and neuroplasticity in order to restore some of the basic functions for better quality of life for SCI patients. Docosahexanoic acid (DHA), a polyunsaturated fatty acid, has been recently explored for SCI management[29], DHA given within 1 hour of SCI via intravenous injection resulted in increased neuronal and oligodendrocyte survival and decreased the microglia/macrophage responses. Moreover, in another set of experiment, DHA was also supplemented in diet in addition to injection. It showed better neurological recovery. The possible mechanism may involve that DHA acted by invading oxidative stress associated with SCI along with inhibition of lipid peroxidation as well as oxidation of nucleic acids. This may ultimately led to myelin protection by moderating damage to white matte in SCI. Furthermore, DHA treatment also reduced axonal accumulation of b-amyloid precursor protein (b-APP)[30]. Eicosapentaenoic acid (EPA) is another long chain PUFA, which is synthesized through desaturation and elongation reaction from its precursor, alpha-linolenic acid (ALA), which is available in the diet. EPA also has been shown to be neuro-protective in rat compression SCI[31]. These observations confirmed that the acute administration of long-

chain PUFAs in the immediate aftermath of SCI offers significant neuro-protection. Furthermore, DHA and EPA have been recently reported[32-35] to increase synaptic connectivity that could be another mechanism of action of PUFAs to restore neuro-plasticity.

Future Prospects

The above review of trends in SCI management showed varied medications in use to manage differential aspects of spinal cord injury. These include medications to control primary injury, secondary injury events, control pain and muscle spasticity, as well as medications that improved day to day functioning of life. Besides this, few inventive medical devices have been recommended these days for a spinal cord injury that make them more self dependent and improvise their quality of lives. These includemodern wheelchairs that are making SCI patients more mobile and more comfortable. Computer adaptations are being explored for SCI patients withlimited hand function and voice recognition. Electronic aids to daily living are the latest electronic devices being recommend for SCI patients as they can be turned on or off by voice-controlled and computer-based remotes for day to day living. Functional electrical stimulation (FES) systems are another technological advancement that utilizes electronic stimulators to control arm as well as leg muscle to allow SCI patients to stand, walk and grip. Robotic gait training is another emerging technology which is being employed for retraining walking ability after spinal cord injury.

Conclusions

The available literature and current trends in SCI management research has shown that utilization of single target with specific approach or in other words use of only one specific therapy cannot handle the huge deteriorations offered to SCI patients. So, the future of research in this filed should be combination approach involving multiple approaches on multiple targets within acute phase of SCI. The combination therapy should target controlling aspects of neuroprotection, neuroinflammation, and regeneration. All these, physiological mechanisms can collectively provide the much desired ultimate solution to burning problem of SCI.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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