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A clinical perspective of spinal cord injury

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Abstract. Spinal cord injury (SCI) results in loss of nervous tissue in the spinal cord and consequently loss of motor and sensory function. The impairments are permanent because endogenous repair events fail to restore the damaged axonal circuits that are involved in function. There is no treatment available that restores the injury-induced loss of function. The consequences of SCI are devastating physically and socially. The assessment of functional loss after SCI has been standardized in the larger part of the world. For medical care however there are no standards available. During the early phase, treatments that stabilize the patient's health and attempt to limit further neurological deterioration need to be implemented. During the later phase of SCI, the focus needs to be on prevention and/or treatment of secondary complications such as pain, pressure ulcers, and infections. Neuroprotective, axon growth-promoting and rehabilitative repair approaches are currently being tested but, so far, none of these has emerged as an effective treatment that reverses the consequences of SCI. Promising new repair approaches have emerged from the laboratory during the last years and entered the clinical arena including stem cell transplantation and functional electrical stimulation.

Keywords: Contusion, secondary injury, clinical care, neuroprotection, clinical trials

1. Introduction

Each year, many people worldwide suffer from spinal cord injury (SCI). These injuries cause death of neural cells, severance and demyelination of descending and ascending axons, and, consequently, loss of motor and sensory function. Endogenous repair efforts fail to repair the spinal cord and, as a result, the functional impairments are permanent. Most people who experience SCI are destined to spend the remainder of their life in a wheelchair [1,44,84]. Potential treatments for SCI are being tested but so far none of these have emerged as one that reverses the devastating functional consequences of SCI. Here we review SCI with an emphasis on the current status of clinical care and clinical trials.

2. Epidemiology and etiology of SCI

Inconsistent data reporting makes it difficult to accurately estimate the worldwide incidence of SCI [1, 35,69,77,79,94]. The annual incidence in the United States is about 40 cases per million population or about 12,000 cases per year [98]. Over 77% of SCI occurred among males. A number of studies profiling the epidemiology of SCI indicated that the population of SCI people has grown over 255,000 (in 2007) with estimates

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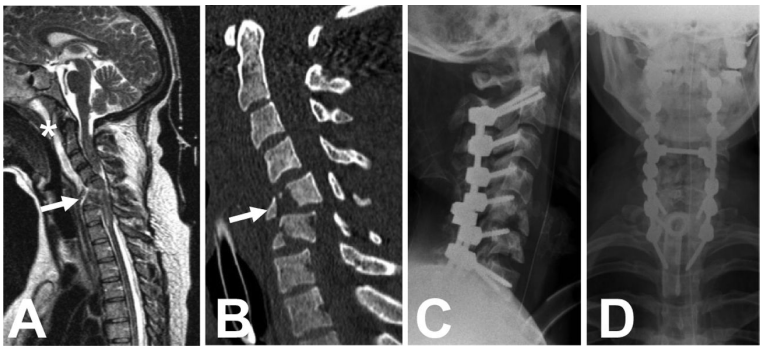

Fig. 1. Imaging of human spinal cord compressive injury. (**A**) Sagittal view of the cervical spinal cord on magnetic resonance imaging demonstrating the dislocated C5 and C6 vertebra compressing the spinal cord (arrow). The formation of a haematoma ventral to the spinal column C1-C4 indicates possible ligament damage (asterisk). (**B**) Closer view of the damaged C5 and C6 cervical vertebrae on computed tomography scan, clearly showing bony damage of the vertebrae (arrow). (**C**) Conventional X-ray lateral view of the cervical spinal column after dorsal stabilization from C2 to Th2. Because of the damage to tendons and vertebrae stabilization surgery needs to be implemented in a large number of cases of SCI. (**D**) Conventional X-ray antero-posterior view of the same patient with stabilized cervical vertebrae as in panel C.

between 227,080 and 300,938 patients. In the United States and most Western European countries, the average age at injury has increased over the last 3 decades from 28.7 to 39.5 years. Most injuries occur between the ages of 16 and 30. The percentage of people older than 60 that suffered from SCI has increased from 4.7% in 1980 to 11.5% among injuries since 2000.

In the United States, the main causes of SCI are motor vehicle crashes (42%), falls (27.1%), violence (15.3%), unknown (8.1%), sports (7.4%). These numbers are similar in other countries although the percentage of violence may be smaller [61,98,109]. Over 70% of injuries are contusive injuries [17,53].

3. Consequences of SCI

3.1. Pathophysiological and anatomical consequences

A force to the vertebral column causes damage to the ligaments and vertebrae (Figs 1A, 1B). The torn ligaments cause instability of the vertebral column. Dislocated bone fragments of damaged vertebrae may compress the spinal cord (Figs 1A, 1B). This causes immediate neural cell death, axon damage and demyelination (Fig. 2A) [46]. The cellular damage results in instant loss of motor and sensory function. After the first destructive events, a sequence of molecular and cellular pathophysiological events (Fig. 2A) including an aggressive inflammatory response within the damaged tissue leads to additional tissue loss at the injury epicenter and at distant sites (secondary injury) [8,9, 20,46,52]. On the other hand, there are also various cellular events during the early and later stages of SCI that could be interpreted as attempts to correct for the inflicted damage (Fig. 2B).

3.2. Functional consequences

The functional consequences of SCI are highly variable and depend on the degree of tissue damage, which in turn depends on the impact severity. In patients with SCI with a relatively small amount of tissue damage, some endogenous recovery of function can be observed, which is most likely resulting from plasticity of the spinal nervous tissue [27,31]. In people with SCI with large tissue damage the neurological deficits are generally major and permanent. There are very few reports of people with a large injury that regain motor function to a degree that independence can be achieved. In these few cases the injury was generally inflicted to the lower (lumbar) level of the spinal cord [54].

3.3. Social consequences

The critical-care medicine practice for people with SCI has considerably improved during the last decade and is nowadays more widely available. Accordingly, more than 95% of SCI patients survive their initial hospitalization. SCI decreases the lifespan by about 7% each year [97]. A functionally complete and high level (cervical) injury impacts the lifespan more dramatically than a functionally incomplete or low level (thoracic-lumbar) injury [97]. Together, the relatively young age when SCI occurs, the improved medical care, and the lack of effective therapies are responsible for the continually increasing number of paralyzed people with

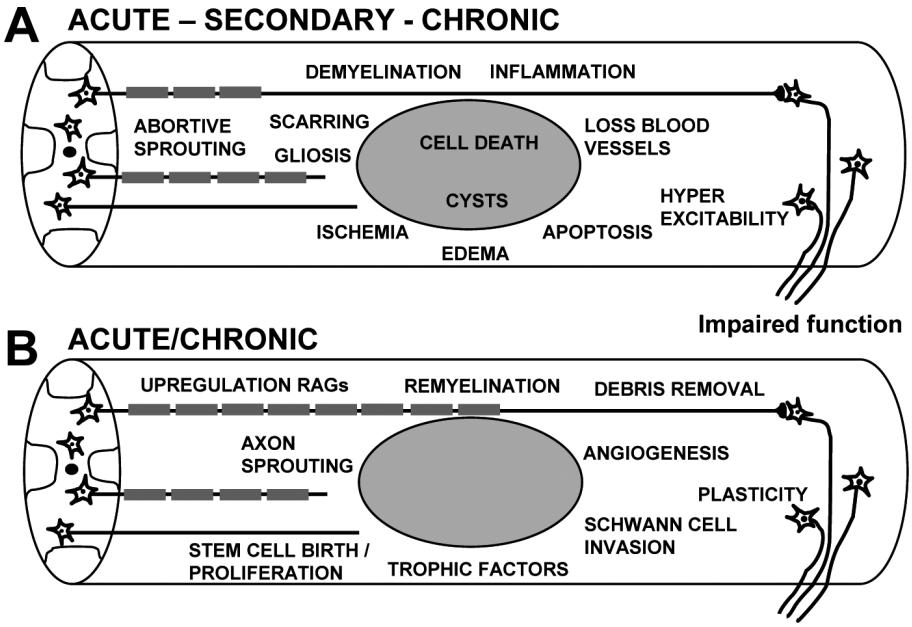

Fig. 2. Degenerative and regenerative events after spinal cord injury. Schematic representations of the degenerative (**A**) and regenerative (**B**) events that take place after spinal cord contusion injury. Rostral is to the left. In B, regeneration-supporting events that take place relatively early after injury and over a limited time period are upregulation of regeneration-associated genes (RAGs), axon sprouting, angiogenesis, trophic factor upregulation, Schwann cell invasion. Other regeneration-supporting events such as debris removal, stem cell birth/proliferation, myelination, and plasticity may also occur at later time points and over a longer time period.

SCI. This puts a high financial burden on the patient, his/her family, and society [1,41,87]. SCI is the second most expensive condition to treat in the United States after respiratory distress syndrome in infants and is ranked third in medical conditions requiring the longest stay in hospitals [104]. The costs of lifetime care for a SCI patient varies between 1 and 3 million dollars [71, 98]. The Centre for Disease Control in the United States estimated that about 10 billion dollars are spent yearly on SCI treatment excluding the management of pressure ulcers, a common side-effect of SCI, which adds another billion dollars per year [71].

4. Clinical assessment of function after SCI

The American Spinal Injury Association (ASIA) impairment scale is often used to assess the level and the completeness of SCI [2,58,45,68,70]. This scale grades the preserved dermatome for sensory function and the strength of 20 "key" muscles in the upper and lower limbs [68]. It provides clinicians with a standard for grading sensory and motor function impairment after SCI. Table 1 provides the 5 ASIA scores and their implications. Testing the intrinsic foot muscle, could complement the ASIA score as, in the majority of SCI patients, it provides an earlier and superior indicator of supraspinal influence over motoneurons projecting to lower extremity muscles [18].

Another frequently used scale is the ASIA Lower Extremity Motor Score (LEMS), an ASIA subscore, which provides a prediction of the ability to walk. The LEMS scale is commonly used together with and supplements the ASIA scale. A person without neurological deficits scores 50 on the LEMS scale. A score of 30 or more is predicative for community ambulation 1 year after injury and a score of 20 or less predicts limited ambulation [54,69,70,101].

Classification of SCI can also be achieved by measuring functional ability using the Functional Independence Measure (FIM) [29]; a 7-point scale that measures 18 items concerning mobility, locomotion, self-care, bowel and/or bladder function, communication, and social cognition. A score of 1 indicates total dependence on a caregiver and a score of 7 indicates complete independence [30,72]. Other scales to assess functional ability are the Quadriplegic Index of Function (QIF), Modified Barthel Index (MBI), and Walking Index for SCI (WISCI), Capabilities of Upper Extremity Instrument (CUE), Spinal Cord Independence Measure (SCIM) and the Canadian Occupational Performance Measure (COPM).

Table 1
Standard neurological classification of spinal cord injury. The presence of motor and sensory function per dermatome (neurological level) can be tested with the ASIA (American Spinal Injury Association) scale. A scoring sheet can be found at http://www.asia-spinalinjury.org/publications/2006_Classif_worksheet.pdf

ASIA	Classification	Level of impairment
A	Complete	No motor or sensory function preserved in the S4 and S5 segments
B	Incomplete	Sensory but not motor function preserved below neurological level and including S4 and S5 segments
C	Incomplete	Motor function preserved below neurological level and more than half of key muscles below that level have a muscle grade of < 3
D	Incomplete	Motor function preserved below neurological level and at least half of key muscles below that level have a muscle grade of $\geqslant 3$
E	Normal	Motor and sensory functions are normal

Table 2
Therapies for the injured spinal cord. Most of the listed approaches are currently under investigation using experimental models of spinal cord injury. Some are being tested clinically (indicated by asterisks)

Approach	Main objectives	Examples
Elicit neuroprotection	Limit cell/tissue loss	*MP, *minocycline, riluzole, hypothermia
Elicit axon regeneration	Axon growth/myelination	*Cetrin®, *NOGO
Supply growth substrate	Axon regeneration	SCs, *OEG, *Activated macrophages
Facilitate plasticity	Formation new circuits	*Cetrin®, *anti-NOGO-A
Restore conduction	Increase axon excitability	*4-AP
Limit spasticity	Decrease reflex activity	*Baclofen, Fampridine
Limit osteoporosis	Prevent fractures	Risedronate, vibration
Improve bowel/bladder	Limit uncontrolled release	Gut stimulants, Ditropan, Colostomy tube
Decrease pain	Decrease hyper-excitability	Amitryptaline, botulinum toxin A
Manage infertility	Erections, ejaculations	Sildenafil, vibration, levitra
Add/silence genes	Promote regeneration	Gene therapy: Viral vectors, siRNA
Stem cell grafting	Cell replacement	Stem cells/progenitors, *AIT-082 (Neotrofin)
Elicit muscle strength	Prevent muscle atrophy	*Locomat, *treadmill training
Enable movements	Facilitate muscle action	Robotic prosthetics, electrical stimulation

5. Treatment of SCI

An acute and a chronic phase can be distinguished after SCI. Since SCI is often a consequence of severe accidents, clinical care during the acute phase is generally focused on stabilization of the patient. During the chronic phase the main attention will need to be on preventing and, if unsuccessful, treating SCI consequences such as pain, infections, and pressure ulcers among others.

5.1. Clinical care acutely after SCI

To date there is insufficient evidence that would support standards of care during the acute phase of SCI. It is advised to maintain patients in an intensive care unit for close monitoring of respiratory and hemodynamic complications. For adequate spinal perfusion, which is at risk due to injury-induced edema, a mean arterial pressure of 85–90 mmHg should be maintained [11]. Depending on the type of injury, surgical interventions should be considered to relieve the spinal cord from compressing bone fragments [15,38]. The physician may decide to perform surgery to decompress or stabilize dislocated vertebrae and the vertebral column (Figs 1C, 1D). Decompression surgeries [15,38] may accelerate functional improvements and result in shorter hospitalization and rehabilitation periods [72,80]. However, it does not necessarily result in an improved final outcome [23].

The lack of standards of care during the acute phase of SCI is in part due to the large variability among injuries and makes its early management complicated. If bone fragments continue to compress the spinal cord, early surgery may be vital to prevent exacerbation of spinal cord tissue destruction. However, in cases without a clear sign of such urgency there is no consensus on whether and what type of early surgical/clinical interventions must be implemented [38]. The lack of different approaches to treat the same condition is demonstrated by a case presented in Fig. 1. Due to a fall this patient had multiple fractures of the cervical spinal cord, including dislocation fractures of the C5 and C6 vertebrae resulting in compression of the spinal cord.

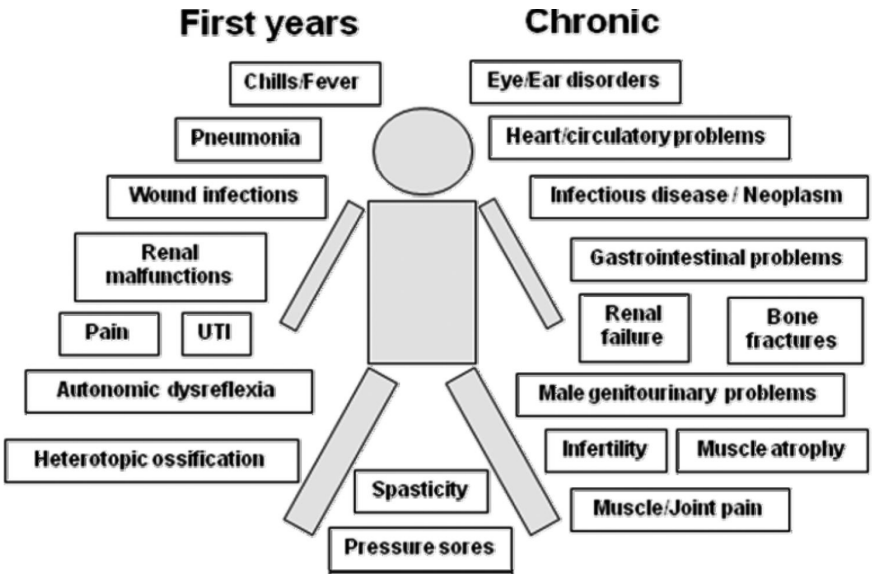

Fig. 3. Complications after spinal cord injury. The most common complications that occur during the first years after SCI are listed on the left and those that occur mostly at later (chronic) stages are listed on the right. Spasticity and pressure sores occur during the first years but are also common at chronic stages of SCI (UTI = urinary tract infection).

In the acute phase, the patient was admitted at the intensive care unit and monitored. At first, a decompression laminectomy and dorsal spondylodesis from C2-Th2 was performed. However, the C5 dislocation fracture was not repositioned sufficiently requiring a second surgery where a corporectomy C5 and C6 including a ventral spondylodesis was performed. The type of surgical intervention should be considered on a case-to-case basis, which makes it complicated to study the efficacy of intervention in the acute phase after SCI in randomized and controlled clinical trials.

Besides surgical interventions, pharmacological treatments to limit the secondary injury after SCI are often considered. The best-known treatment is a high dose of the glucocorticosteroid, methylprednisolone sodium succinate (MPSS) within 8 hours after the injury [12–14,20]. Experimentally it was demonstrated that a high dose of MPSS reduces the inflammatory response and limit tissue loss after damage to the spinal cord [78]. The effects of MPSS in patients with SCI were investigated in 3 consecutive National Acute Spinal Cord Injury Studies (NASCIS) [12–14]. The results demonstrated that MPSS treatment in the acute phase of SCI resulted in neurological improvements up to 6 months after injury. MPSS is the standard of care in the United States and other countries. After a thorough review of the results from the NASCIS studies and a more comprehensive assessment of the benefits and risks involved in high dose MPSS treatment, the therapeutic benefits are now disputed [20,62,74,75,86, 100]. Especially in patients with complete SCI high dose steroid treatment can lead to adverse effects such as myopathy and wound infection that may negatively influence functional outcome and in some cases may be life-threatening [86,100]. Currently, many SCI clinics worldwide have discontinued the ‘standard’ acute administration of MPSS after SCI. The debate on the use of MPSS should be accompanied by efforts to develop alternative treatments that counteract the early destructive events occurring during the acute phase of SCI.

5.2. Clinical care at later stages after SCI: Preventing complications

Different complications may occur during the later stages of SCI (Fig. 3) that each demands specific actions and/or interventions [61]. For instance, SCI can lead to pain [103,104], decreased fertility [82], and autonomic dysreflexia with loss of bladder and bowel control [102]. It has to be taken into consideration that many SCI patients get accustomed to the specific injury-related pain they experience and as a result reveal their distress to their physician often at a late stage [66,92]. For some SCI-related conditions, such as decreased fertility, it is the patient’s personal desire that should guide the physician’s actions.

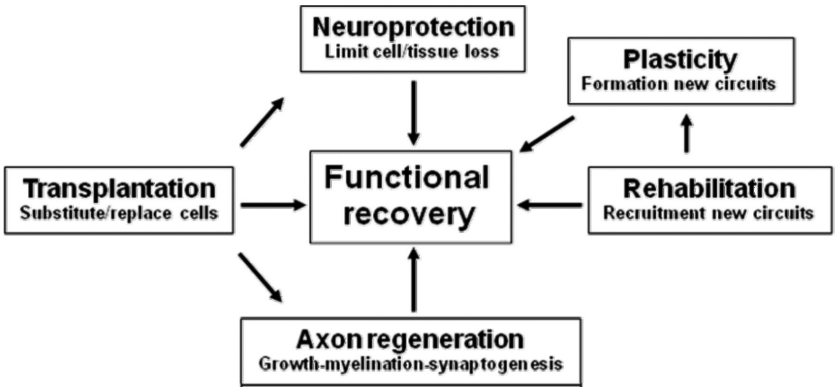

Fig. 4. Different approaches to directly and/or indirectly influence recovery after SCI.

Other common problems that arise after SCI are septicemia, respiratory insufficiency, and pneumonia (Fig. 3). These complications may cause clinical deterioration and could eventually result in death. They often occur without typical symptoms. For example, pyelonefritis can occur without flank pain or a femur fracture can occur without pain. This may lead to delay or errors in diagnosis and treatment [28,47]. It is imperative that SCI patients receive annual screenings and long-term follow-ups to prevent these secondary complications. It is advised to treat patients on a regular basis with pneumococcal and influenza vaccine to prevent opportunistic infections [55,56]. Monitoring the skin and urinary tract and implementing aggressive treatments against pressure ulcers and urinary tract infections is needed to reduce the risk of septicemia [55, 56]. Appropriate nutrition and exercise should also be incorporated in the (new) lifestyle. Rehabilitation programs should be implemented to reduce the risk of cardiovascular disease [97].

Generally, the possible medical complications of SCI patients are known, mostly recognizable, and their treatment often straightforward. It is different for the psychological problems that arise after SCI [10,95]. It may be possible to recognize some of these but treatment and responses to the treatment are depending greatly on the individual. One can expect an initial period of denial and/or inability to fully comprehend the functional consequences caused by the injury. Next a period of acceptance will have to run its course [10, 95]. The patient needs to learn to live with the disabilities and this may be accompanied by bouts of depression. The mental state of the patient can have its effect on medical treatments [103]. The psychological consequences of SCI should not be underestimated and appropriate guidance of patient and family should have an important place in the late care management of SCI [10,105].

6. Clinically tested approaches to elicit functional recovery

Continuing medical care after SCI is necessary to maintain the patient's health and quality of life. However, this generally does not result in dramatic improvements in function that would allow the patient to live an independent life. Repair-promoting pharmaceutical and/or surgical interventions will be necessary to significantly change the functional outcome after SCI (Fig. 4). Here we will review some of the current treatments that are aimed at limiting functional loss and/or improving outcome after SCI. In addition we discuss possible future treatments for spinal cord repair. Table 2 provides a list of clinical treatments for SCI.

6.1. Neuroprotective approaches

During the last 30 years, many experimental studies have targeted neuroprotection (i.e., tissue sparing) early after SCI to improve outcome. Experimental evidence has shown that the functional loss after SCI can be limited by implementing neuroprotective approaches. The best known neuroprotective approach is acute administration of MPSS. This has been tested clinically and is still being used around the world [12–14]. MPSS treatment after SCI was first thought to improve functional outcome, but at present its true therapeutic potential is intensely debated [62,74,75,86,100]. The main goal of MPSS treatment after SCI is to decrease the aggressive inflammatory response normally present within the damaged tissue. This would limit the contri-

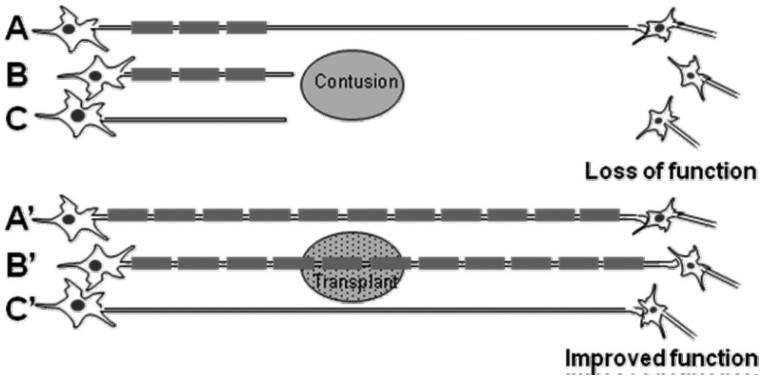

Fig. 5. Axon regeneration after spinal cord injury. Schematic representation of axon regeneration that could contribute to functional recovery after SCI. There are 3 types of damages that are inflicted to axons after SCI. Axons may be still in contact with their target neurons but demyelinated (**A**) due to immediate or delayed death of oligodendrocytes. These axons can become 'functional' and contribute to motor recovery when they are remyelinated (**A'**) by either endogenous oligodendrocytes derived from local stem cells or oligodendrocyte precursor cells, or by transplanted stem/precursor cells or Schwann cells. Axons may be severed and thereby devoid of contact with their target neurons and demyelinated (**B**). In that case, the axons need to regenerate across/beyond the injury, establish synaptic contacts with target neurons, and be myelinated by endogenous or transplanted cells (**B'**). Unmyelinated axons may be severed and without contact with target neurons (**C**). These need to regenerate and establish synaptic connections with the original or new target neurons (**C'**).

bution of macrophages and activated microglia to the secondary loss of nervous tissue.

Another example of a molecule that could elicit neuroprotective effects after SCI is the tetracycline derivative, minocycline [3–5]. Minocycline may exert its protective effects through mechanisms that decrease injury-induced glutamate-mediated excitotoxicity [3,99] and/or immunomodulatory mechanisms such as blocking microglial activation [4,32]. Moreover, minocycline may reduce oligodendrocyte and neuronal apoptosis as well as dieback of damaged axons [40,96]. These experimentally studies have established minocycline as a promising candidate for early treatment after SCI. Currently, a phase I/II clinical study is underway in the United States to assess the efficacy of intravenously administered minocycline in the acute phase after SCI [6].

6.2. Axon growth-promoting approaches

Functional improvements after SCI could be elicited by axon growth-promoting approaches as this could result in either restoration of damaged axonal circuits or elicit plastic events (Fig. 5) [43,49,90]. Examples of axon growth- or plasticity-promoting treatments are the administration of BA-210 or NOGO antibodies. BA-210 is a Rho antagonist that reduces the levels of intracellular GTPase-associated signaling proteins Rho and Rac to physiological levels [36,107]. Elevated Rho has axon growth-inhibitory effects through the above mentioned pathway [76]. NOGO antibodies neutralize axon growth-inhibitory effects of oligodendrocyte myelin-bound Nogo [6,23]. Thus, both BA-210 and NOGO antibodies may result in enhanced axon growth and/or axon plasticity after SCI. Both treatments are currently tested clinically for their efficacy to repair the injured spinal cord [6].

After SCI axons may still be intact but not functional due to injury-induced conduction block. Administration of the potassium channel blocker, 4-aminopyridine (4-AP) may restore such a conduction block and this could restore axon function and thus contribute to improved function. The efficacy of 4-AP in SCI patients has been tested clinically but so far the outcome has been modest [26,34,48].

6.3. Cell transplantation-based approaches

Neuroprotection as well as axonal regeneration could be achieved by transplanting growth-promoting cellular or a-cellular substrates. Examples of cellular substrates that are clinically tested are olfactory ensheathing cells, peripheral nerves, and activated macrophages. Grafting olfactory ensheathing cells into the spinal cord is being examined in China, Australia, and Portugal [25, 39,64]. Autologous peripheral nerves are being grafted into the injured spinal cord in Taiwan [24,50] and activated autologous macrophages in Israel [93] and Belgium [59]. Thus far, there is no clear evidence that these transplantation strategies elicit major functional changes.

7. Frontiers in treatment of SCI

A relatively new concept that does not focus on anatomical and/or functional repair but rather on supporting the patient to achieve some degree of independence is the use of robotics to enable execution of specific motor tasks. Currently, there are concerted efforts to employ cerebral (cortical) control for steering robotic devices in combination with micro-chip technologies that would enable fine-tuning of the robotic movements depending on the tasks [33,63,83].

Other comparatively novel approaches implement physical and/or electrical activity to elicit spinal cord repair. Although these approaches are generally designed to improve muscle strength/use, it has been hypothesized that these particular approaches could also elicit regenerative cellular events that could contribute to improved outcome [42,51]. Moreover, locomotor activity [7,21,89,108] and electrical stimulation [16, 85,91] may promote spinal cord repair via stimulation of plastic mechanism within existing axon circuits involved in motor function.

A relatively new concept within the more conventional field of cell-based approaches to repair the spinal cord is the transplantation of stem cells to either replace lost cells or elicit regenerative cellular events after SCI. Stem cells have been studied for their potential to restore degenerative diseases in the central nervous system, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis [60,73,81] or in traumatic injuries such as transient brain trauma [65,88] or SCI [37,57]. The challenges are to further develop these concepts to increase our knowledge and, through experimental research, develop strategies in which they could be benefited from most.

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