Neurological aspects of spinal-cord repair: promises and challenges

Volker Dietz, Armin Curt

During the past few years, several approaches to spinal-cord repair have been successfully established in animal models. For their use in trials of spinal-cord injury (SCI) in human beings, specific difficulties that affect the success of clinical trials have to be recognised. First, transection of the spinal cord is commonly applied in animal models, whereas contusion, which generally leads to injury in two to three segments, represents the typical injury mechanism in human beings. Second, the quadrupedal organisation of locomotion in animals and the more complex autonomic functions in human beings, challenge translation of animal behaviour into recovery from SCI in people. Third, the extensive damage of motor neurons and roots associated with spinal-cord contusion is not addressed in current translational studies. This damage has direct implications for rehabilitation strategies and functional outcome. Fourth, there is increasing evidence for a degradation of neuronal function below the level of the lesion in chronic complete SCI. The relevance of this degradation for a regeneration-inducing treatment needs to be investigated. Fifth, the prerequisites to enable appropriate reconnection of regenerating tract fibres in a postacute stage have still to be established.

Introduction

Spontaneous recovery from a spinal-cord injury (SCI) is hindered by the limited ability of the mammalian CNS to re-establish functional neuronal connections. SCI leads to sensorimotor loss and disruption of autonomic nervous-system control caudal to the level of injury. During the past few years, progress has been made in understanding the behaviour of neuronal circuits within the human spinal cord, and functional training approaches have become established and been optimised. Provision of appropriate afferent input in patients with incomplete SCI improves functional outcome. However, in severely affected patients or those with complete SCI (complete loss of sensory and motor functions below the level of the SCI), functional recovery becomes feasible only if some regeneration of injured spinal-tract fibres can be achieved.

Basic research in spinal-cord repair is promising, and translational studies in human SCI have already been introduced or will be within the next decade. Some of these clinical trials have already moved or are about to move from rodents directly to human beings without a larger animal (eg, dog, cat, or monkey) intermediate (eg, recombinant derivative of C3 transferase or autologous incubated macrophage). Such rapid progressions are not without substantial risk and, indeed, may fail because of unresolved scientific concerns. For example, most new treatments focus on the restoration of functions provided by the long spinal pathways. However, in human SCI the distribution and extent of segmental damage is also of great clinical relevance. Contusion injuries inherently represent the combined damage of both central and peripheral neural structures. Furthermore, a preserved function of neuronal circuits below the level of the lesion—ie, the target for rewiring by regenerating tract fibres—is essential for a successful regeneration-inducing therapy. Lastly, assessment of new interventions has to follow internationally acknowledged rules as outlined by the American Academy of Neurology to obtain a solid control basis for their efficiency (ie, evidence-based therapy). Thus, several previously reported treatments of human SCI might need to be reassessed in this light.

Regeneration-inducing treatments

To improve function in complete SCI by training, some regeneration of spinal-tract fibres is needed. There are an impressive number of promising approaches based on animal experiments to induce or improve regeneration or to prevent or limit neuronal damage by neuroprotective treatments. A selection of the most important approaches, well supported by research, includes: functional blockade of molecules that inhibit axonal regeneration within the injured spinal cord; enhancement of regeneration by the injection of activated macrophages; facilitation of nerve growth by removal of chondroitin-sulphate proteoglycans, which make scarred tissue non-permissive for regeneration; prevention of scar formation by inhibition of collagen biosynthesis with an iron chelator; injection of human stem-cells for tissue renewal around a spinal lesion; and bridging of the lesion site by a regeneration-facilitating tissue with either olfactory ensheathing cells or Schwann-cell bridges. Furthermore, neurotrophic factors can be used to support regeneration in combination with the aforementioned therapies. In human beings, contusion injuries result in damage to the spinal cord over several segments, leading to the induction of large cysts and scar formation. Only a few spinal-tract fibres are able to regenerate through the affected zone. On the basis of animal experiments, regeneration over long distances does not seem to be needed to build up functionally relevant neuronal connections. Regeneration over short distances to the long propriospinal neuronal circuits might be sufficient, for example, to mediate a locomotor function (figure 1).
Nevertheless, the distances to be overcome by regenerating fibres to establish functionally relevant connections are, in any case, longer in human beings than in rodent models.

According to observations in people, and on the basis of comparisons made between a rat contusion model and human SCI, as few as 10–15% of functioning tract fibres (eg, pyramidal tract) may be sufficient to allow a basic (eg, locomotor) function in patients with initially complete SCI.

On the basis of the available published work on animal experiments, primarily only a small step-wise improvement of spinal tract repair might initially be achieved. In a later second phase, some complementary approaches will probably be combined to improve the number of regenerating and functioning fibres to achieve increased success of functional recovery. For example, a neuroprotection approach could be combined with prevention of scar formation or, in the case of a disrupted spinal cord, bridging by olfactory ensheathing cells in combination with the neutralisation of inhibitory molecules could successfully be applied not only in rats, but also, in the future, in people.

The success of any regeneration-inducing therapy depends on combination with a functional training approach to maintain the neuronal function below the level of lesion and to improve appropriate connections by regeneration of tract fibres. The need for appropriate connections is of crucial clinical importance because aberrant axonal sprouting might occur with unwelcome sequelae. As shown in rats, transplantation of neuronal stem-cells improved motor recovery, but was associated with a hypersensitivity (allodynia) of forepaws.

** Appropriateness of animal SCI models**

Many features of an SCI can adequately be investigated in a rodent spinal-cord contusion model. In a study that compared functional outcome, neurophysiological recordings, and imaging in SCI contusion of rats and people, most outcome measures obtained in the rat SCI model could be translated to the human condition. The transection models in animals, however, allow only a limited comparison with the human contusion injury where the region of spinal-cord damage is much more extensive. Contusion injuries represent a combination of a direct traumatic compression and secondary local haemodynamic effects due to impaired vascular supply leading to post-traumatic ischaemia. A spinal-cord contusion with bleeding and oedema usually affects two to three segments and causes extensive damage to all structures of the spinal cord, including ventral horn cells and roots. Therefore, any regeneration would certainly be more hindered in such a natural condition than in an artificially-induced transection lesion.

There are basic differences between rats and human beings concerning the mode of locomotion (ie, bipedal versus quadrupedal) and the autonomic nervous system.
system function, which has a much greater role in people than in rats. In rats SCI, a basic automatic self-training prevails, which facilitates recovery of locomotor function. In complete SCI in people, changes in neural structures are likely to occur, probably due to both the lack of activation of neuronal circuits and to trans-synaptic degradation. Furthermore, there are only a few animal studies of the dysfunction of the autonomic system and of pain (eg, induced by aberrant tract fibres); ie, these impairments are insufficiently modelled in rodents. Lastly, if a regeneration-inducing therapy becomes available, the question will arise as to whether such a therapy can be successfully used not only in patients with acute but also in those with chronic SCI.

Peripheral nervous system in SCI

Most experimental studies of SCI in rodents damage the thoracic cord, whereas injury to the cervical cord is most common in people. However, there are essential differences between the thoracic and the cervical type of SCI. In cervical and thoracolumbar spinal contusions, the spinal damage involves not only tract fibres, but also closely packed motor neurons and roots, usually over two to three segments that supply arm and leg muscles, respectively (figure 2). Therefore, a large part of the motor deficit has to be attributed to the peripheral nervous system. In rodents, around 40% of triceps brachii and about 30% of quadriceps femoris motor neurons are lost after a C7 and L2 contusion, respectively. In human beings, damage to the peripheral nervous system associated with SCI (in about a third of tetraplegic patients, the ulnar compound action motor potential is lost) is important with respect to two problems. First, such damage leads to a flaccid paresis. The functional outcome is an insufficient development of muscle tone, which frequently underlies problems in grasping (tenodesis grasp), walking, and bladder functions in patients with incomplete SCI. Second, if a large part of the damage concerns the peripheral nervous system, the application of functional electrical stimulation of paralysed muscles becomes impossible. In denervated muscles, functionally relevant muscle contractions can hardly be achieved by functional electrical stimulation.

The proportion of peripheral-nerve damage associated with an SCI also has significant implications for future regeneration-inducing therapies. These therapies aim for the repair or regeneration of longitudinal spinal-tract fibres. Thus, the effects of such new interventions on motor neurons and roots, as well as on the connections between central and peripheral neural structures, have not yet been sufficiently studied in animal experiments. Consequently, regeneration of spinal-tract fibres could potentially occur without improvement of peripheral muscle paresis. In cervical lesions this applies to the arm and hand functions and in thoracolumbar lesions to ambulatory and bladder functions.

The peripheral-nerve deficit in cervical or thoracolumbar SCI can reliably be assessed by neurographic, electromyographic, and reflex recordings. Also the differentiation from flaccid paresis due to spinal shock at an early stage after SCI can be achieved by this technique. Such assessments can be made early for optimum planning of appropriate rehabilitation procedures.

Course of neuronal activity in SCI

Although acute animal models used for regeneration-inducing therapies are well established, limited
experience exists with subacute and chronic SCI.  

Furthermore, if regeneration can be successfully introduced in acute human SCI, such an effect can certainly not automatically be extrapolated to the chronic condition. The possible problems arising in chronic SCI need to be carefully considered and systematically studied.

There are several aspects that, in particular, have to be taken into account. For most of the current clinical approaches, a delayed therapeutic intervention with a time window after injury of up to 10 days is foreseen. Already, after some weeks (ie, in a subacute stage) with a regeneration-inducing intervention the therapeutic effect might be affected by scar formation.  

In the chronic stage of SCI, the course of neuronal function below the level of lesion in complete (or almost complete) SCI has to be recognised. There are indications in human SCI that both a demyelination around the injury cavities and a degradation of neuronal function below the level of the lesion occur over time—ie, a year after an SCI (figure 3). In the latter study, degradation was associated with rapid exhaustion of neuronal activity underlying assisted locomotor movements of patients with complete SCI and could not be reversed by 3 months of locomotor training. Such a mechanism would fit with the observation of a trans-synaptic degeneration of neuronal systems in the rat that strongly depends on the input, which is lost. From the existing studies, whether this degradation is reversible is unclear. Additionally, no test is available to make this distinction.

There is a need for an animal model of chronic SCI for the assessment of the course of neuronal function after a complete SCI and, consequently, for an improved understanding of neuronal plasticity and degradation. This model could help in the identification of approaches whereby neuronal function could be maintained after a severe SCI (figure 3). Such a goal might be achieved by specific early-onset functional training. There is convincing evidence in spinal-cord transected animals and patients with SCI that a use-dependent plasticity of spinal neuronal circuits exists, which could potentially be maintained to the chronic SCI stage. Such training might be used in conjunction with the application of implants leading to a release of neurotransmitters, in accordance with findings from studies in mice. However, even if adequate animal models of chronic SCI can be established, the extent to which these models match human chronic SCI needs to be investigated. The course of neuronal function below the level of the lesion should be assessed as a prerequisite for a successful regeneration therapy in chronic human SCI. Functionally relevant neuronal reconnections can be achieved only when the function of neuronal circuits below the level of the lesion is basically preserved.

What is needed for the future?

The aim of this review was to elucidate the main problems and hazards associated with a move of preclinical trials from rodent models to human SCI. These concerns have to be distinguished from

---

**Figure 3:** Schematic illustration of the behaviour of spinal neuronal circuits underlying locomotion that might occur after an SCI and possible countermeasures

Neuronal behaviour in a healthy patient, early (<1 year) after an SCI, in a chronic SCI (>1 year) not trained, and in a chronic SCI with an early onset of training.

Reproduced with permission of Oxford University Press.
experimental trials that follow neither any standard of preclinical nor clinical trial planning. For the successful introduction of new therapies based on neuroprotection, neuroregeneration, or enhancement of neuronal plasticity, further knowledge is needed about the problems and limitations of such interventions. First, objective assessments that accurately predict the spontaneous recovery of function (ie, outcome after SCI) need to be established. Usually, the assessment of SCI is restricted to clinical examinations, which are, unfortunately, insufficient for reliably monitoring a therapeutic effect. Additional neurophysiological and functional assessments allow some differentiation between compensation, neuronal plasticity, and regeneration as factors underlying an improvement of functions over the course of an SCI. Neurophysiological recordings, in particular, can give information about the effect of any new interventional therapy on the function of specific spinal tracts and the peripheral nervous system (figure 4). Second, it will become necessary in the near future to study the course of spinal neuronal function and to recognise secondary changes in the animal model of chronic SCI. Based on these models, approaches could be developed to prevent a secondary degradation of neuronal function. Third, the effect of a new interventional therapy needs not only to be studied at the level of the regeneration of tract fibres, but also on peripheral neural structures. In most patients with SCI, the transition from the central to the peripheral nervous system is affected. Last, there is a need to improve neurorehabilitation technologies for continuous and appropriate training over a sufficient time in patients with SCI. For any interventional therapy, functional training seems to be needed to provide the neuronal prerequisites for successful spinal-cord regeneration.

---

**Figure 4: Neurophysiological techniques to study the function of specific spinal tracts and of the peripheral nervous system**

The clinical neurological examination can be complemented by electrophysiological recordings to obtain quantifiable measures about the affection of different spinal pathways. The location of the spinal pathways outlined in the table are numerically assigned in the schematic diagram. MEP=Motor evoked potentials; SSEP=Somatosensory evoked potentials; SSR=Sympathetic skin response; LEP=Laser evoked potentials; GVS=Galvanic vestibular stimulation; NCS=Nerve conduction study; EMG=Electromyography; AMP=Amplitude; LAT=Latency; NCV=Nerve conduction velocity.

<table>
<thead>
<tr>
<th>Pathway/ system</th>
<th>Method</th>
<th>Readout</th>
<th>Acceptance</th>
<th>Clinical correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Corticospinal</td>
<td>MEP</td>
<td>Amp/lat</td>
<td>Routine</td>
<td>Central paresis</td>
</tr>
<tr>
<td>2 Dorsal column</td>
<td>SSEP</td>
<td>Amp/lat</td>
<td>Routine</td>
<td>Proprioception</td>
</tr>
<tr>
<td>3 Sympathetic</td>
<td>SSR</td>
<td>Presence</td>
<td>Routine</td>
<td>Cardiovascular control</td>
</tr>
<tr>
<td>4 Spinotalamic</td>
<td>LEP</td>
<td>Amp/lat</td>
<td>Investigational</td>
<td>Pain/temp perception</td>
</tr>
<tr>
<td>5 Vestibulospinal</td>
<td>GVS</td>
<td>Amp/lat</td>
<td>Investigational</td>
<td>Postural instability</td>
</tr>
<tr>
<td>6 Peripheral</td>
<td>NCS/reflex/IMQ</td>
<td>Amp/ncv</td>
<td>Routine</td>
<td>Peripheral paresis</td>
</tr>
</tbody>
</table>

---

**Search strategy and selection criteria**

References for this review were identified by searches of MEDLINE between 1990 and May, 2006, and references from relevant articles with the search terms “spinal cord injury (SCI), “regeneration”, “spinal tracts”, “neuroplasticity”, “degeneration”, “neural repair”, “SCI animal model”, “motoneurons”, “spinal neuronal function”. Articles were also identified through searches of the extensive files of the authors. More recent publications were preferred. Only papers published in English were reviewed. The final list was generated on the basis of originality and relevance to the topics covered in the review.

---

**Contributors**

Both authors have contributed equally to the writing of this review.

**Conflicts of interest**

We have no conflicts of interest.

**Acknowledgments**

This work was supported by the Swiss National Foundation (NCCR Neuro and grant no. 3200B0-105324). We thank R Jud for editorial assistance and W Tetzlaff for his help with figure 3B.

**References**


