G. Heiner Sell Memorial Lecture: Neuronal Plasticity After Spinal Cord Injury: Significance for Present and Future Treatments

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Abstract

Summary: Recent progress in the understanding of movement control allows us to define more precisely the requirements for successful rehabilitation of patients with neurologic deficits after a spinal cord injury (SCI). Load- and hip joint position-related afferent input seems to be of crucial importance for the generation and success of locomotor training. In addition, there is accumulating evidence from animal experiments that axonal regeneration can be induced after a SCI. Consequently, in the near future, new therapeutic approaches will be developed for the treatment of subjects with SCI. Functional training and regeneration represent complimentary approaches. Regenerating spinal tract fibers needs functional training to make the appropriate connections, and training effects will be enhanced by regenerating fibers. A clinical basis for monitoring the effects of novel interventional therapies is needed. Refined and combined clinical and neurophysiologic measures are needed for a precise qualitative and quantitative assessment of spinal cord function in patients with SCI at an early stage. This is a basic requirement for predicting functional outcome, as well as for recognizing any improvement in the recovery of function caused by a new treatment. To this aim, 14 European spinal cord injury centers involved in the rehabilitation of patients with acute SCI have built a close clinical collaboration using a standardized protocol for the assessment of the outcome after SCI and the extent of recovery achieved by actually applied therapies in a larger population of patients with SCI.

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INTRODUCTION

Recovery of lost function after spinal cord injury (SCI) is in an exciting phase of research. Recovery after SCI is a multidimensional process that includes different mechanisms (Figure 1). In a clinical rehabilitation setting, recovery of sensorimotor functions is mainly achieved by “adaptation” (eg, application of an orthosis) and “compensation” (eg, change in strategy). The physical training is primarily directed to strengthen and optimize the preserved sensorimotor functions. It is directed to improve the function of both undamaged and, as far as possible, damaged neuronal structures. The “reorganization” of neuronal circuits and neuronal plasticity are also targets for specific training approaches. In particular, repetitive training sessions can optimize and improve complex upper and lower limb movements.

Although neurologic recovery is influenced by etiology and severity of injury, there is still no evidence that surgery compared with a conservative treatment leads to a favorable outcome (1,2). Standardized clinical examinations and suitable patients for new pharmacologic or surgical treatment might be identified (3). For example, recovery of locomotor function is becoming an important goal for an increasing proportion of patients with SCI. Today, most rehabilitation approaches focus on the exploitation of spinal cord plasticity below the level of lesion, for example, by locomotor training (4–6).

Animal experiments currently prepare the basis for future novel therapeutic approaches, including induction of axonal regeneration and plasticity, myelin repair, and improved neuroprotective strategies. In the future, it might become feasible to partially repair a spinal cord lesion, for example, by inducing regeneration (7,8). The effects of these new approaches observed in rat experiments seem to be potentially beneficial with respect to an improved outcome of function after SCI (9). Translating these experimental therapies to human patients is challenging and will involve integrated groups of basic and clinical scientists working together to cross

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Figure 1. Mechanisms underlying functional recovery after SCI.

almost entirely uncharted territory (10). The combination of functional training and spinal cord repair will lead to positive mutual effects. Regenerating tract fibers will require functioning neuronal circuits to make appropriate connections, and by such new rewiring, the effect of training will be enhanced.

Clinical centers dealing with patients with SCI should be prepared to include such novel approaches in their treatment procedures. They should be able to carefully monitor any regeneration effects by clinical, electrophysiologic, imaging, and behavioral examinations (11). A comprehensive protocol for the assessment of the course of a SCI is needed rather than to provide a detailed protocol of all possible clinical and neurophysiologic examinations (Figure 2). The most important aspect of such a comprehensive protocol is the combination of clinical (ASIA standards), functional (activity of daily living [ADL] scores, walking capacity), and neurophysiologic assessments (11,12). As recovery in neurologic disorders is always a complex and multidimensional process, the application of only one of these assessments is not sufficient to estimate and/or evaluate the clinical significance of any new treatment.

EXPLOITATION OF NEURONAL PLASTICITY

Functional recovery after CNS injury depends, in part, on reorganization of undamaged neural pathways (13). Spinal cord circuits are capable of significant reorganization induced by both activity-dependent and injury-induced plasticity. This plasticity becomes obvious in the ability of spinalized animals to regain a certain degree of motor function. Recent work with spinal injured humans showed that training can greatly improve the functional locomotor abilities (14). New methodologies to enhance limb movement are designed to further exploit the neuronal plasticity of the spinal cord by reinforcing appropriate connections in an activity-dependent manner. This should take place on the basis of observations made in the rat (15).

EFFECTS OF LOCOMOTOR TRAINING

As established elsewhere, the coordination of human gait seems to be controlled in much the same way as in other mammals (14,16,17). Therefore, it is not surprising that, in persons with a complete or incomplete paraplegia caused by a SCI, locomotor electromyographic (EMG) activity and movements can be both elicited and trained in a similar way as in the cat. This is achieved by partially unloading (up to 80%) patients who are standing on a moving treadmill (5,17–19). In severely affected patients, the leg movements usually have to be assisted externally, especially during the transmission from stance to swing. The approach is based on findings made in cats and rats and is directed to train functional movements. It is supposed that by moving the limbs through trajectories under physiologic conditions, spinal neuronal circuits become activated by appropriate sensory inputs. The timing of the pattern of leg muscle EMG activity is similar to that seen in healthy subjects. However, the amplitude of leg muscle EMG is considerably reduced and less well modulated. This makes body unloading necessary for locomotor training.

Analysis of the locomotor pattern in patients with complete paraplegia indicates that it is unlikely to be caused by rhythmic stretches of the leg muscles, because leg muscle EMG activity is, as in healthy subjects, equally distributed during muscle lengthening and shortening (20). In addition, recent observations indicate that locomotor movements induced in patients who are completely unloaded do not lead to leg muscle activation (21). This implies that the generation of leg muscle EMG patterns in these patients is programmed at a spinal level rather than generated by stretch reflexes (22).

During the course of daily locomotor training, the amplitude of the EMG in the leg extensor muscles increases during the stance phase and inappropriate leg flexor activity decreases. Such training effects are seen both in complete and incomplete paraplegic subjects after SCI (4,18) and even in chronic SCI (23). These

spinal pathway	method	readout	acceptance	clinical correlation
cortico-spinal ¹	MEP	amp/lat	routine	central paresis
dorsal column ²	SSEP	amp/lat	routine	proprioception
sympathetic ³	SSR	presence	routine	cardio-vascular control
spino-thalamic ⁴	LEP (laser-heat)	amp/lat	investigational	pain/temp perception
vestibulo-spinal ⁵	GVS	amp/lat	investigational	postural instability
peripheral system ⁶	NCS/reflex/EMG	amp/ncv	routine	peripheral paresis

Figure 2. Neurophysiological techniques to study the function of specific spinal tracts and of the peripheral nervous system. Electrophysiological recordings can provide quantifiable measures about the affection of different spinal pathway. Location of the spinal pathways outlined in the table are numerically assigned in the schematic diagram. LEP, laser-evoked potentials; GVS, galvanic vestibular stimulation; NCS, nerve conduction study; AMP, amplitude; LAT, latency; NCV, nerve conduction velocity.

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training effects lead to a greater weight-bearing function of the extensors (ie, body unloading during treadmill locomotion can be reduced during the course of training). After this training, the gain in ambulatory function was shown to be greater than the improvement of voluntary force in subjects with incomplete SCI (24,25). This indicates that the human spinal cord has the capacity not only to generate a locomotor pattern but also to show some plasticity. However, only patients with incomplete paraplegia benefit from the training program in so far as they can learn to perform unsupported stepping movements on solid ground (18). In complete paraplegia, the training effects on leg muscle activation are lost after training has been stopped.

There are several reports about the beneficial effect of locomotor training in patients with incomplete paraplegia (26,27), and patients who undergo locomotor training have a greater mobility compared with a control group without training (23,28). Afferent input from receptor signaling contact forces during the stance phase of gait is essential for the activation of spinal locomotor centers (21) and for achieving training effects in paraplegic patients (18). Furthermore, hip joint-related afferent input seems to be essential to generate a locomotor pattern (21).

The improvement of locomotor activity can also be attributed to some spontaneous recovery of spinal cord function that can occur over several months after an SCI. The increase of leg extensor EMG activity associated with training in individuals with paraplegia seems to occur independently from the spontaneous recovery of spinal cord function (5). Therefore, one might conclude that, in persons with SCI, specific training effects on spinal

locomotor centers lead to a similar improvement of locomotor function, as described for the spinal cat (29).

SIGNIFICANCE OF REGENERATION-INDUCING THERAPIES

To improve function in complete SCI by training, some regeneration of spinal tract fibers is required. There exists an impressive number of promising approaches based on animal experiments to induce and/or facilitate regeneration or to prevent or limit neuronal damage by neuroprotective therapies (30–32). A selection of the most important approaches, well supported by research reports, includes (a) functional blockade of molecules that inhibit axonal regeneration within the injured spinal cord (33–36); (b) enhancement of regeneration by the injection of activated macrophages (37,38); (c) facilitation of nerve growth by removing chondroitin-sulfate proteoglycans, which make scarred tissue nonpermissive for regeneration (39,40); (d) prevention of scar formation by inhibition of collagen biosynthesis using an iron chelator (41); (e) injection of human stem cells for tissue renewal around a spinal lesion (42,43); and (f) bridging the lesion site by a regeneration-facilitating tissue using either olfactory ensheathing cells (44,45) or Schwann cell bridges (46,47). Furthermore, neurotrophic factors can be applied to support regeneration in combination with the aforementioned therapies (48,49). In humans, contusion injuries result in damage of the spinal cord over several segments, leading to the induction of large cysts, and scar formation is induced. It can be expected that only a limited number of spinal tract fibers are able to regenerate through the affected zone. On the basis of animal experiments (35), regeneration over longer

distances does not seem to be required 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. Nevertheless, the distances to be overcome by regenerating fibers to establish functionally relevant connections is, in any case, longer in humans than in rodent models.

According to observations made in humans (50), and on the basis of comparisons made between the rat contusion model and human SCI (51), it can be expected that as little as 10% to 15% of functioning tract fibers (eg, pyramidal tract) may be sufficient to allow a basic (eg, locomotor) function in individuals with initially complete SCI.

On the basis of the available literature on animal experiments, it can realistically be assumed that, primarily, only a small stepwise improvement of spinal tract repair might initially be achieved. In a later, second phase, some complementary approaches will most likely be combined to improve the number of regenerating/ functioning fibers to achieve a greater success of functional recovery. For example, a neuroprotective approach could be combined with prevention of scar formation and/or, in the case of a disrupted spinal cord, a bridging by olfactory ensheathing cells in combination with the neutralization of inhibitory molecules; this approach could successfully be applied not only in the rat (52), but also in the future, in humans.

It is expected that the success of any regeneration-inducing therapy depends on combining it with a functional training approach to maintain the neuronal function below the level of lesion and to facilitate appropriate connections by regenerating tract fibers (29). The need for appropriate connections is of crucial clinical importance, because aberrant axonal sprouting might occur with unwelcome sequelae. As shown in the rat, transplantation of neuronal stem cells was shown to improve motor recovery but was associated with hypersensitivity (allodynia) of forepaws (42).

SPINAL CORD REPAIR: CHALLENGES

During the past few years, several approaches leading to spinal cord repair have been successfully established in animal models. For their translation to the human condition, specific problems have to be recognized that will affect the success of clinical trials (12). First, transection of the spinal cord is frequently applied in animal models, whereas contusion, which generally leads to injury over 2 to 3 segments, represents the typical injury mechanism in humans. The contusion injury extends over 2 to 3 segments. Second, the quadrupedal organization of locomotion in animals and the more complex autonomic functions in humans challenge translation of animal behavior into human SCI recovery. Third, the extensive damage of motoneurons 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 lesion in chronic complete SCI. The relevance of this degradation for a regeneration-inducing therapy needs to be evaluated. Fifth, the prerequisites to facilitate the appropriate reconnection of regenerating tract fibers in a postacute stage have yet to be established.

Translational Studies: Requirements for Clinical Application

In 2001, 5 European SCI centers involved in the rehabilitation of patients with acute SCI, an engineering section of neuroradiology, and a basic neurobiologic laboratory working in spinal tract regeneration decided to build a close collaboration, financially supported by the International Institute for Research in Paraplegia (IFP, Zurich, Switzerland). The same standardized assessment protocol for monitoring the extent and characteristics of recovery in SCI was applied. Today, 15 European centers are involved. Approximately 200 patients with acute SCI enter the study each year and are followed by a standardized evaluation program (11). The specific aims of a comprehensive standard protocol are (a) early diagnosis, (b) monitoring of the course, and (c) prediction of the outcome in patients with acute SCI. The combination of the assessment tools and the appropriate timing of the follow-up examinations (from acute to chronic, ie, 1 year after SCI) allows us to monitor the course of spontaneous recovery and rehabilitation-related gain in function.

Clinical Outcome Measures

The neurologic deficit caused by SCI is presently assessed by the internationally accepted and standardized neurologic examination protocol of the American Spinal Injury Association (ASIA) (53). This assessment represents a semiquantitative tool to monitor motor and sensory neurologic deficits. This protocol allows us to determine the level of the lesion, to estimate the extent of neurologic deficits, and to predict to some extent the outcome of SCI. The ASIA score describes structural deficits only indirectly, extrapolated from the neurologic deficit.

Functional Testing

The assessment of the functional outcome is most important to adequately estimate the patient's quality of life. Besides the neurologic deficit, the assessments of functional impairment, for example, walking capacity (54,55), hand function, and bladder control (56), provide essential information about the capacity of the upper and lower limbs and autonomic nervous function. The gain in function achieved during rehabilitation and by specific therapeutic approaches should be documented by specific behavioral tests. Some actual therapeutic ap-

proaches, such as the locomotor training (4), have greater effects on the walking ability than on the ASIA motor score, underlining the requirement for reliable functional tests in addition to the ASIA score (4,5,23). The walking index for SCI (WISCI) is applied for the evaluation of locomotion (57) and the spinal cord independence measure (SCIM) as a standardized rating scale of activities of daily life (ADLs) (58). Therefore, the SCIM and the WISCI scores assess the functional impairment of a task and not the neurologic deficit.

For the assessment of walking function, the WISCI walking index (57) has a good validity and reliability and includes 20 items to assess the walking ability of a patient with incomplete SCI. Because the WISCI scale does not really reflect all aspects of locomotor ability in patients with SCI, additional tests (timed up and go, walking distance in 6 minutes, time needed to traverse a distance of 10 m) have to be implemented (25). These tests allow us to quantitatively assess the walking capacity. Furthermore, they give additional information about the capacity achieved between the levels of the WISCI scale (eg, increase in walking speed while requiring the same walking aids) (59).

The SCIM rating scale estimates the impairment in ADL focused on 4 most important aspects: self-care, respiration, sphincter management, and mobility. It provides a total SCIM score of 100 points, while all the subitems (eg, feeding, bathing) are weighted (scores from 0 to 15) dependent on their relevance. Therefore, the SCIM score allows us to describe the extent of impairment and the necessary support the patient needs to cover daily life activities.

Neurophysiologic Recordings

Neurophysiologic recordings (neurography, somatosensory-evoked potentials [SSEPs], motor-evoked potentials [MEPs]) allow the assessment of ascending and descending spinal tract function. These recordings are not influenced by the cooperation of the patient and can be performed even in patients who are unconscious (eg, because of drugs), in the intensive care unit, or in spinal shock. During the last few years, it was shown that by the combination of clinical examinations and neurophysiologic recordings (neurography, SSEP, MEP, sympathetic skin response), the functional outcome of patients with SCI could be predicted with a high reliability within the first 3 weeks after the trauma (60). This enables us to plan adequate rehabilitation procedures and to initiate specific therapeutic approaches (eg, functional electrical stimulation) at an early stage (61).

Neurophysiology can be complemented by high-resolution magnetic resonance tomography (MRT) of the spinal cord to provide information about the anatomically preserved parts of spinal cord tracts, and consequently, of outcome (51). Especially with the combination of MEP, SSEP, and neurographic recordings, a highly reliable prediction of the outcome of hand

(62,63) and locomotor function (63,64) can be achieved (65,66).

Neurographic recordings have been shown to be important to assess the extent of intramedullary and peripheral nerve lesions, which represent an essential basis for the planning of rehabilitation approaches (67). The neurographic recordings within 10 to 14 days after trauma indicate whether a spastic or flaccid paralysis will develop. This, for example, determines whether functional electrical stimulation (FES) can be applied, because the FES technique is only applicable for minor damage in the peripheral part of motor pathways.

NEXT STEPS

For the successful introduction of new therapies based on neuroprotection, neuroregeneration, and/or enhancement of neuronal plasticity, it is necessary to gain further knowledge about the problems and limitations of such interventions (12). First, objective assessments and accurately predicting the spontaneous recovery of function (ie, outcome after SCI) need to be established (11). Usually, the assessment of a SCI is restricted to clinical examinations, which are, unfortunately, insufficient for reliably monitoring a therapeutic effect. Additional neurophysiologic 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 (11).

Neurophysiologic recordings can give information about the impact of any new interventional therapy on the function of specific spinal tracts and the peripheral nervous system (Table 2). Second, it will become necessary in the near future to study the course of spinal neuronal function and to recognize secondary changes in the chronic SCI animal model. Based on these models, one could develop approaches to prevent a secondary degradation of neuronal function. Third, the effect of a new interventional therapy needs to not only be studied at the level of the regeneration of tract fibers but also on peripheral neural structures. In most patients with SCI, the transition from central to peripheral nervous system is affected. Last, there is a need to improve neurorehabilitation technologies for continuous, and appropriate, training over a sufficient time in subjects with SCI (68). For any interventional therapy, functional training seems to be needed to provide the neuronal prerequisites for successful spinal cord regeneration (6,29).

CONCLUSION

In the future, new neurophysiologic examinations will be introduced, in particular to assess the function of the autonomic nervous system. The sympathetic skin reflexes (SSRs) are not yet routinely recorded in patients with SCI. By this approach, the autonomic nervous system, which is impaired in most patients with SCI, can reliably be assessed (69,70). The technique is simple but requires some experience to perform systematic recordings of skin

reflexes at different body sites in patients with different levels of SCI. For the assessment of the spinal–segmental pathway, neurographic and electromyographic parameters, as well as segmental reflex activity, can be analyzed. Furthermore, the technology of transcranial magnetic brain stimulation will be established to assess the corticospinal tract function. Although it is not yet routinely performed in paraplegic centers, it is obvious that double or triple impulses can be applied to the brain to reliably assess the remaining impulse conductivity of the corticospinal tract fibers after SCI (71), which is better than that achieved by single impulse stimulation.

An important aspect in the coming years will also be the question of how far the specific repetitive training of functional movements (hand function, locomotor ability) is able to improve the outcome compared with conventional physical therapies. The project follows the outline of the World Health Organization for the rehabilitation of patients with SCI, which aims to improve the assessment of “body structure” and “body function.” This assessment can serve as the basis to select the best therapeutic approaches to improve activities and participation. In the future, this will be reflected in a better “participation” of these patients in their social surroundings and to recognize the relevant environmental factors.

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