Sprouting, regeneration and circuit formation in the injured spinal cord: factors and activity

Irin C. Maier* and Martin E. Schwab

Brain Research Institute, University and ETH Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

Central nervous system (CNS) injuries are particularly traumatic, owing to the limited capabilities of the mammalian CNS for repair. Nevertheless, functional recovery is observed in patients and experimental animals, but the degree of recovery is variable. We review the crucial characteristics of mammalian spinal cord function, tract development, injury and the current experimental therapeutic approaches for repair. Regenerative or compensatory growth of neurites and the formation of new, functional circuits require spontaneous and experimental reactivation of developmental mechanisms, suppression of the growth-inhibitory properties of the adult CNS tissue and specific targeted activation of new connections by rehabilitative training.

Keywords: activity-dependent reorganization; Nogo-A; plasticity; regeneration; spinal cord injury; rehabilitation

1. INTRODUCTION

Repair of large lesions of the spinal cord or brain requires growth of neurites, either as compensatory growth of spared fibres or as true regenerative growth of lesioned axons. Both types of neurite growth are abundant following injuries to the newborn central nervous system (CNS). This window of opportunity closes, however, as CNS development ends within a few weeks postnatally in rodents, and in a few months in humans (Chen *et al.* 2002). Simultaneously, the cellular composition of the CNS changes dramatically by the differentiation of oligodendrocytes and the myelination of axons (Kapfhammer & Schwab 1994). The recently discovered neurite growth-inhibitory proteins in CNS myelin represent an important factor in the restriction of neurite growth and CNS repair in the adult spinal cord and brain (Fournier & Strittmatter 2001; Schwab 2004). These factors, in particular the best-studied representative Nogo-A, also suppress the endogenous growth potential of neurons (Schwab 2004). Growth capacity is lower in adult CNS neurons than during development, and overexpression of the typical growth-associated proteins can enhance the regeneration capacity of adult CNS neurons (Bomze *et al.* 2001; Schwab 2004). Furthermore, in cases of lesions which cause scar formation, scars are an additional important barrier, in particular for regenerating axons (Carulli *et al.* 2005).

Several experimental manipulations, in particular the inactivation of the myelin-associated neurite growth inhibitor Nogo-A, neurite outgrowth receptor subunit (NgR), or digestion of the proteoglycans associated with scars, can lead to long-distance regeneration of transected axons and also marked increases in compensatory fibre growth (Fournier &

Strittmatter 2001; Schwab 2004; Carulli *et al.* 2005). These fibres growing in adult CNS tissue seem to be able to recognize functionally meaningful targets; behavioural studies have shown recovery of locomotor as well as skilled forelimb movements in rats and mice in the absence of obvious malfunctions (Merkler *et al.* 2001; Bradbury *et al.* 2002; Li & Strittmatter 2003; Li *et al.* 2004). Neither the sequence of events nor the molecular mechanisms leading to the formation of new, functionally meaningful connections and circuits are presently understood. Initial molecular screens have shown the enhanced expression of neurotrophic factors, axonal guidance molecules and extracellular matrix (ECM) proteins in denervated spinal cord tissue, along with enhanced expression of growth-associated and cytoskeletal proteins in neurons (Bareyre *et al.* 2002; Bareyre & Schwab 2003). It is, therefore, conceivable that developmental guidance and targeting mechanisms are re-expressed in the adult brain and spinal cord during the repair processes. Fine tuning of the new connections may occur by mechanisms normally operating mainly during development; in particular, activity-dependent stabilization and pruning. These mechanisms, which probably form much of the basis of neurorehabilitative training in partially injured spinal cord lesioned patients or following brain injuries, may be operational during spontaneous recovery as observed in animals and humans with moderate spinal cord or brain injuries, as well as under experimental conditions which enhance neurite growth, e.g. by suppression of growth-inhibitory mechanisms. In the following sections we review the crucial characteristics of mammalian spinal cord function and injury, the current experimental therapeutic approaches, the development of spinal cord tracts and circuits, and the current observations concerning spinal cord functional repair and its underlying mechanisms.

* Author for correspondence (imaier@hifo.unizh.ch).

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2. SPINAL CORD IN HEALTH AND DISEASE

(a) *The mammalian motor system and its basic functions*

The motor system plans, coordinates and executes movements that are in turn controlled by sensory feedback. Various networks at different levels of the nervous system coordinate different motor patterns (Grillner 1981). In mammals, a high degree of motor complexity exists, including relatively automated behaviours like breathing, walking, running and swimming, as well as skilled movements, e.g. of the forepaw or hand manipulating small objects. The mammalian motor system has its centres on three main levels, spinal cord, brainstem and forebrain, containing successively more complex and hierarchically organized motor circuits (Bizzi *et al.* 2000). Basic motor patterns underlying the rhythmic limb movements as observed during running or swimming are generated by neuronal networks located within the spinal cord. Once learnt, these movements seem to be effortless. Sensory feedback loops from muscles, tendons and skin modulate spinal motor networks. Similar circuits within the spinal cord participate in more complex voluntary movements governed by higher brain centres.

The brainstem controls posture and locomotion. Voluntary movements are goal directed and often controlled by complex cognitive and motivational activities. In mammals, several interconnected cortical motor areas control the whole motor system and in particular the muscles of hand, fingers and face. They initiate and execute complex voluntary movements either via projections to the descending systems of the brainstem and the spinal cord or through direct projections from the primary motor cortex to spinal and cranial motor neurons. In order to evoke this broad variety of locomotor acts and skills, the motor system requires input of descending fibres from cortical as well as subcortical motor areas, feedback via afferent pathways and the integration of all these inputs in different spinal and supraspinal circuitries with very precise connections. The formation of such complex networks is in part genetically determined, but also formed under important activity-dependent influence during development. Different motor programmes are continuously adapted and new skills learned, trained and finally executed with ease throughout life.

(b) *Spinal cord injury*

Injury to the spinal cord results from compression of bone fragments by burst fractures or by displaced luxated vertebral bodies or disks. It is followed by loss of sensation and voluntary movements below the level of lesion. Large injuries lead to permanent disabilities and smaller lesions can be followed by various degrees of functional recovery. Dependent on their segmental level and their appearance, injuries are classified according to the American Spinal Injury Association (ASIA) as complete (ASIA A) or incomplete depending on the amount of spared sensory or motor function (ASIA B–D). High spinal lesions lead to tetraplegia or quadriplegia (paralysis of all four limbs) whereas lower lesions lead to paraplegia (paralysis of the lower part of the body). Importantly, also in ASIA A patients, complete anatomical separation of the spinal cord is

very rare. Instead, bridges of nerve tissue connecting regions above and below the lesion often persist, mostly in the periphery of the spinal cord (Kakulas 1999).

Human spinal cord injuries (SCIs) are very hard to assess, as they are variable and influenced by many different factors. In the past, a variety of animal models of SCI have been developed in order to investigate the effects of a lesion on behavioural outcome and recovery, as well as to search for the mechanisms which are involved in tissue damage and potential treatments.

Neurons in the adult mammalian CNS show a very limited ability for neuronal repair, whereas embryonic or peripheral nervous system neurons do exhibit substantial regeneration capabilities after injury. Therefore, for a long time, attempts to repair the injured adult spinal cord were considered a lost cause. Nevertheless, two decades of research, followed by rapid expansion of the field over the past few years, have now shed some light on the mechanisms involved in degeneration and tissue destruction as well as on the intrinsic neuronal mechanisms and environmental influences which are involved in the failure of axonal regrowth after SCI (Schwab & Bartholdi 1996; Schwab 2002; Ramer *et al.* 2005).

(i) *Secondary damage*

In animal models and most probably also in human SCI, the final tissue damage is much larger than that of the first mechanical insult. Additional damage accumulates within the first few hours and by a variety of reactive processes commonly described as secondary injury (Beattie *et al.* 2000; Beattie *et al.* 2002; Beattie 2004). This second phase of tissue loss can be divided into acute, subacute and late phase, and includes vascular changes, excitotoxic events, inflammation and scarring (Schwab & Bartholdi 1996; Dumont *et al.* 2001). Ischaemia is a central element; the central part of the cord often undergoes haemorrhagic necrosis. Inflammatory cells invade the lesion site in large numbers but their roles—protection, damage or both—are not well understood (Perry *et al.* 1993). Several weeks after the injury, macrophages have cleared the tissue debris at the lesion site, resulting in fluid-filled cysts surrounded by scar tissue (Schwab 2002).

(ii) *Intrinsic growth response*

Even though crushed or transected nerve fibres within the spinal cord do not regenerate, the neurons exhibit an initial growth response reflected by an upregulation of immediate early genes. Among them, L1, c-Jun and c-Fos are cytoskeletal proteins (Jenkins *et al.* 1993; Chaisuksunt *et al.* 2000a,b), and the 43 kDa is a growth-associated protein (GAP-43) (McKerracher *et al.* 1993; Tetzlaff *et al.* 1994; Caroni 1997; Mason *et al.* 2003; Wintzer *et al.* 2004). These genes are typically expressed in developing neurons (Skene 1989; Hunt & Mantyh 2001) but less in most adult CNS neurons except in regions known for their plastic potential (Benowitz & Perrone-Bizzozero 1991). Upregulation of gene expression is followed by a spontaneous growth response called regenerative sprouting (Ramon y Cajal 1928; Schwab 2002). In CNS neurons, these reactions to injury are weaker and more transient, whereas peripheral neurons enter a subsequent phase of axonal elongation

and regeneration, often up to their former target. Overexpression of GAP-43 and the related protein CAP-23 enhances the growth potential of CNS neurons (Bomze *et al.* 2001).

The absence of sufficient axonal growth stimulating cues as well as a variety of potent neural growth-inhibitory factors present in the surroundings of neurons and axons in the CNS is thought to play a key role in preventing axonal regrowth and functional circuit repair after SCI. During development of the nervous system, a variety of different cell types secrete neurotrophic factors that enhance neurite growth and can guide axons to their target regions. These factors may be absent in the adult CNS or they may have different functions and regulations. The role and relevance of endogenous neurotrophic factors for neurite outgrowth (Nogo) after injury remains to be investigated (Lacroix & Tuszynski 2000).

(iii) Myelin-associated inhibitors

Oligodendrocytes and CNS myelin were the first identified source of inhibitory factors for axonal growth and regeneration in the adult CNS (Schwab & Caroni 1988b). In the avian or mammalian spinal cord, the switch from permissive to restrictive repair states coincides with the onset of CNS myelination (Schwab 2004). A major part of the myelin-associated neurite growth-inhibitory activity in rat spinal cord is attributed to a high molecular weight protein, now called Nogo-A (formerly NI-250, IN-1 antigen; Caroni & Schwab 1988a,b). The role of myelin and Nogo-A in suppressing axon growth after SCI was first demonstrated in 1990 by antibody-mediated neutralization experiments (Savio & Schwab 1989; Schnell & Schwab 1990).

Nogo-A was purified from bovine spinal cord to homogeneity in 1998 (Spillmann *et al.* 1998) and its cDNA cloned in 2000 (Chen *et al.* 2000; GrandPre *et al.* 2000; Prinjha *et al.* 2000). Since then, a number of other myelin-associated molecules have been isolated, which can exert axon growth-inhibitory effects at least *in vitro*, and their *in vivo* relevance for CNS regeneration and repair remains to be shown. These molecules include the myelin-associated glycoprotein (MAG; McKerracher *et al.* 1994; Mukhopadhyay *et al.* 1994), oligodendrocyte myelin glycoprotein (OMgp; Kottis *et al.* 2002), semaphorin 4D (Schwab *et al.* 2005) and 5A (Goldberg *et al.* 2004), ephrin B3 (Benson *et al.* 2005) and several proteoglycans (Niederost *et al.* 1999). Nogo-A, MAG and OMgp might use a common receptor subunit, the so-called Nogo receptor NgR (Fournier *et al.* 2001; Domeniconi *et al.* 2002; Liu *et al.* 2002; Wang *et al.* 2002a; Hu & Strittmatter 2004).

(iv) Scar formation

CNS injury leads to a complicated cellular and tissue response involving glial cells, including astrocytes, oligodendrocyte progenitor cells and microglia, as well as inflammatory cells, meningeal cells and blood vessels. Rapid proliferation and hypertrophy of astrocytes around the spinal injury is a characteristic response in all mammals shortly after SCI. These reactive astrocytes form an astroglial scar which is an important part of the physical and chemical barrier to axonal regeneration (Davies *et al.* 1997; Fawcett & Asher 1999).

A number of experiments have shown that the neurite growth-inhibitory properties of astrocytes depend on the expression of chondroitin sulphate proteoglycans (CSPGs; Grierson *et al.* 1990; Meiners *et al.* 1995; Dou & Levine 1997; Asher *et al.* 2000; Schmalfeldt *et al.* 2000; Morgenstern *et al.* 2002; Rhodes & Fawcett 2004) which are strongly upregulated following injury.

(v) Axon survival

In most parts of the CNS (with the exception of retina), axotomized neurons shrink and undergo atrophy but they do not die. Corticospinal and rubrospinal neurons have been shown to survive axotomy in the spinal cord for long periods of time (Kalil & Schneider 1975; Barron *et al.* 1988; McBride *et al.* 1990). Application of neurotrophic factors could fully reverse the atrophy of 1-year axotomized rubrospinal (Kobayashi *et al.* 1997; Tobias *et al.* 2003) as well as corticospinal neurons (Giehl & Tetzlaff 1996).

(c) Recent therapeutic approaches

It is unlikely that any single therapeutic intervention will be sufficient to promote complete functional repair of a severely traumatized spinal cord. Injury and the subsequent reorganization of the nervous system are dynamic processes which will require spatially and temporally specific interventions in order to induce regeneration and guide regrowing fibres to appropriate targets. Recent therapeutic approaches mainly focus on four essential goals:

- (i) preventing secondary cell damage;
- (ii) bridging the lesion and minimizing scar formation;
- (iii) promoting regrowth of axons and enhancing plasticity; and
- (iv) restoration of function and rehabilitation.

(i) Neuroprotection

Many attempts were made to minimize secondary damage with neuroprotective agents, but animal models often gave contradictory results and clinical trials in traumatic brain injury, SCI and stroke were largely unsuccessful (Ditunno *et al.* 2003; Povlishock & Katz 2005). Corticosteroids, which reduce swelling and inflammation, show a small beneficial effect when given within the first hours after injury in human patients (Bracken *et al.* 1998). A concept of 'protective autoimmunity' (Schwartz 2004) and pharmacological blockade of the Rho GTPase (Dubreuil *et al.* 2003) are very recent experimental approaches to neuroprotection in animals after SCI.

(ii) Grafts and bridges

One of the pathological outcomes of SCI is the formation of cavities of varying sizes in the spinal cord (Bunge 1993; Bunge *et al.* 1997). Cell types that could be useful to bridge scar and cavities include olfactory ensheathing cells, Schwann cells, neural stem cells, as well as transplants from foetal spinal cord (Bregman *et al.* 1995, 1997; Olson 1997; Ribotta *et al.* 2000; Lakatos & Franklin 2002;

Santos-Benito & Ramon-Cueto 2003; Pearse *et al.* 2004). Foetal neural and genetically engineered cells as well as fibrin or hydrogel loaded with growth factors which could attract and support growing axons are promising alternatives which are being studied by various groups. However, one problem is that the regenerating fibres also have to leave the bridge to find their targets in the inhibitory environment of the adult spinal cord (Fitch & Silver 1997; Fawcett & Asher 1999; Lemons *et al.* 1999).

(iii) *Enhancing the growth response*

The ability of neurotrophic molecules to enhance an intrinsic cell response of severed neurons after injury have made them important candidates for promoting morphological as well as behavioural recovery after SCI (Schnell *et al.* 1994; Tuszynski *et al.* 1994; McTigue *et al.* 1998; Weidner *et al.* 1999; Liu & Zhang 2000; Blesch & Tuszynski 2001, 2002). Injections, pumps and grafts of genetically modified cells which can secrete these factors, or viral delivery systems, can be used to deliver neurotrophic factors to the lesion site (Lacroix & Tuszynski 2000). Application of neurotrophic factors has been shown to change the intrinsic growth ability of different neurons by upregulation of GAP-43 (Ramer *et al.* 2000, 2002), Rag and cAMP (Cai *et al.* 1999), followed by neurite elongation as well as long-distance regeneration of different motor tracts (Schnell *et al.* 1994; Grill *et al.* 1997; Liu *et al.* 1999; Horner & Gage 2000; Lacroix & Tuszynski 2000). Neurotrophic factors enhance growth through foetal spinal cord transplants, peripheral nerve grafts (Houle & Johnson 1989; Oudega & Hagg 1999; Chuah & West 2002) and Schwann cell channels (Xu *et al.* 1995a,b). Behavioural recovery has been observed in different lesion models (Grill *et al.* 1997; Jakeman *et al.* 1998; Liu *et al.* 1999).

(iv) *Inactivation of neurite growth-inhibitory factors*

Deletion of oligodendrocytes and prevention of myelin formation allows regenerative growth of transected axons in the differentiated spinal cord at normally non-permissive stages (Savio & Schwab 1990). The use of monoclonal antibodies (mAb IN-1) raised against Nogo-A in order to block its inhibitory activity allowed axonal growth on myelin substrates, spinal cord frozen sections and cultured oligodendrocytes *in vitro* (Caroni & Schwab 1988a,b; Savio & Schwab 1989; Chen *et al.* 2000). The application of IN-1 antibodies *in vivo* enhanced sprouting and long-distance regeneration of lesioned corticospinal tract (CST) fibres (Schnell & Schwab 1990). Changes in outgrowth after antibody treatment could also be observed in the rat optic nerve or cholinergic forebrain fibres (Cadelli & Schwab 1991; Weibel *et al.* 1994). An intrathecal application of Nogo-A antibodies through osmotic minipumps showed an increased regeneration of corticospinal neurons followed by behavioural improvement (Brosamle *et al.* 2000) and significant recovery of locomotion (figure 1; Merkler *et al.* 2001; Liebscher *et al.* 2005).

These functional improvements suggest that new fibres can establish meaningful functional connections. Very similar results, i.e. enhanced sprouting and long-distance regeneration of descending tracts including the CST and greatly improved behavioural recovery in adult

Figure 1. Neutralizing the myelin-associated neurite growth inhibitory activity through intrathecal application of Nogo-A antibodies *in vivo* enhances sprouting and long distance regeneration of lesioned CST fibres. Specific behavioural tests like the horizontal irregular ladder test show behavioural improvement and significant recovery of locomotion in these animals.

rats with incomplete spinal cord lesions, were obtained by inactivation of Nogo-A by intrathecal infusion of a soluble NgR fragment by blocking NgR with an antagonistically active Nogo fragment (NEP1-40) or by blocking the downstream signalling pathway of the myelin-associated inhibitory signals (Domeniconi *et al.* 2002; McKerracher & Winton 2002; Fournier *et al.* 2003; Li & Strittmatter 2003; Li *et al.* 2004).

Preventing the formation of a regeneration-inhibitory scar after SCI has not been successful yet. Nevertheless, there has been progress in the attempt to neutralize the inhibitory effects of CSPG accumulation (McKeon *et al.* 1995) following injury through an enzymatic digestion by chondroitinase ABC. Infusion or injection of chondroitinase enhanced axonal regeneration after injury and Nogo (Zuo *et al.* 1998; Moon *et al.* 2001; Bradbury *et al.* 2002). Growth of lesioned neurons was accompanied by an increase in GAP-43 expression, the restoration of postsynaptic activity and functional recovery (Bradbury *et al.* 2002).

For several of these experimental therapeutic approaches that are successful in enhancing fibre growth and functional recovery in animals, human trials are currently planned or in preparation. This is true for anti-Nogo-A antibodies, olfactory ensheathing cells, reagents to minimize scar effects and Rho-A blocking reagents. The coming few years will show whether the step from bench to bedside can be successfully achieved in SCI and CNS trauma without the danger of serious side effects or complications.

(v) *Rehabilitation*

Rehabilitative physiotherapy and ergotherapy are the only widely established and routinely used therapies for human SCI. Still, there are only very few standardized methods to assess the functional recovery after training (Curt *et al.* 2004), and only few groups use elaborate animal models to assess the effect of rehabilitative training or analyse the underlying mechanisms.

In spinal cord injured patients, training provides repeated practice, e.g. stepping with assistance from therapists or driven gait orthoses on a treadmill with body weight support (Dietz *et al.* 1994; Dietz & Harkema 2004). The beneficial effect of locomotor

training in incomplete spinal cord injured patients is well established (Barbeau & Rossignol 1994; Dietz *et al.* 1998). It can lead to significant functional improvements like the gradual increase in patients' ability to support their body weight as well as a decrease in spasticity. Furthermore, there is often a significant increase in electromyographic (EMG) activity in leg extensor muscles during training, an effect which is suggested to be connected with improvement in locomotor function (Dietz *et al.* 1994, 1995). Behavioural recovery seems to depend on the size of injury and probably correlates with spontaneous injury-induced structural rearrangements (plasticity).

A better understanding on how much potential for plastic changes persists within the adult spinal cord, the specific circuitries involved, as well as the underlying mechanisms that potentiate changes under normal conditions will help to use some of these mechanisms to increase plasticity after SCI. Some of these mechanisms can be expected to be similar or identical to those that configure and fine tune the neuronal network during development. We therefore first briefly review the essential steps of nervous system and in particular neuronal circuit formation, and then return to regeneration and plasticity in the adult CNS.

3. DEVELOPMENT OF SPINAL TRACTS

Over the past few decades, a lot of knowledge has been gained on the molecular basis of classical developmental processes such as neural induction (Wilson & Edlund 2001) and specification (Bertrand *et al.* 2002). Proper wiring of neuronal circuits during development comprises different stages; it is highly dependent on axonal outgrowth, elongation and guidance (Tessier-Lavigne & Goodman 1996; Chisholm & Tessier-Lavigne 1999; Guan & Rao 2003) as well as dendritic architecture and the establishment of precise synaptic connections (Cohen-Cory 2002).

(a) Neuronal outgrowth

Directed axonal outgrowth and pathfinding require a variety of extracellular factors acting on the axonal growth cones. There are cell adhesion molecules for proper fasciculation, especially follower axons with the pioneer fibre of a given tract (Tessier-Lavigne & Goodman 1996), neurotrophic factors which can also serve as soluble chemoattractants or repulsors (Yamamoto *et al.* 2002; Huber *et al.* 2003) and the attractive or repulsive guidance molecules, netrins, semaphorins, ephrins and slits (O'Leary & Wilkinson 1999; Kennedy 2000; Raper 2000; Wong *et al.* 2002a,b). Signalling mechanisms of these guidance cues have been studied in different systems (Guan & Rao 2003) where they can either attract or repel neurons depending on the receptors used as well as the levels of intracellular cyclic nucleotides and calcium (Hong *et al.* 2000; Zheng 2000). The retinotectal projection provides an excellent system to study topographic specificity in different animal species (Bonhoeffer & Huf 1980; Ichijo 2004), but the cues which guide retinal axons to the appropriate region of the tectum exist in other regions of the CNS as well (Constantine-Paton & Capranica 1976). In the spinal cord, the very early commissural axons

(Bovolenta & Dodd 1990; Tessier-Lavigne *et al.* 1988) as well as the late growing CST have been extensively studied (Schreyer & Jones 1982; Terashima 1995; Joosten & Bar 1999). The dorsally arising commissural axons are attracted to the ventral midline (floor plate) by netrin-1, change their responsiveness to several cues after midline crossing (Shirasaki & Murakami 2001), and are driven out of the floor plate by the slit-robo and Ephrin-Eph signals (Kaprielian *et al.* 2000; Long *et al.* 2004). Dorsal root afferents grow to and end in specific dorsoventral laminae of the spinal cord, guided by neurotrophic factors and semaphorins (Chen & Frank 1999; Masuda & Shiga 2005). The physiologically very important stretch reflex (muscle spindle Ia fibres synapsing directly onto motor neurons) involves coexpression of specific transcription factors in sensory and the corresponding motor neurons (Chen *et al.* 2003).

Descending tracts. In contrast to the brainstem motor systems, the CST reaches the cord late, i.e. in the first postnatal week (Martin *et al.* 1980; Kudo *et al.* 1993) after navigating through the internal capsule, cerebral peduncle, pons and medulla oblongata (Terashima 1995; Joosten 1997). Initially, semaphorins regulate the extension of the cortical axons towards the underlying white matter (Bagnard *et al.* 1998; Polleux *et al.* 1998). Later, the CST axons are attracted laterally towards the internal capsule through the chemoattractant netrin-1 (Metin *et al.* 1997; Bagnard *et al.* 1998) as well as Slit2 (Bagri *et al.* 2002). Finally, ingrowth into the spinal cord starts at postnatal day P0 and reaches sacral levels at P9 (Schreyer & Jones 1982; Gribnau *et al.* 1986). GAP-43 is strongly expressed during this period of caudal extension and the cell adhesion molecule L1 may be involved in fascicle formation of later arriving axons (Joosten *et al.* 1990; Fujimori *et al.* 2000).

The growing corticospinal fibres are restricted to their territory by Nogo-A and the myelin inhibitors of the dorsal funiculus as shown by anti-Nogo antibody experiments (Schwab & Schnell 1991). Several *Wnt* genes, expressed in a high-to-low gradient from cervical to thoracic spinal cord in the grey matter surrounding the dorsal funiculus, regulate anterior-posterior pathfinding of CST axons. Ryk, the vertebrate homologue of the repulsive *Wnt* receptor Derailed, is highly expressed on CST axons (Halford *et al.* 2000; Yoshikawa *et al.* 2003). Polyclonal antibodies directed against the ectodomain of Ryk blocked the repulsive effect of Wnt1 and Wnt5a (Liu *et al.* 2005). Ephrins and Eph receptors have an important role in restricting corticospinal fibres to only one side of the spinal cord. Ephrin B3 or Eph A4 knockout mice show an abnormal bilateral corticospinal termination pattern (Yokoyama *et al.* 2001; Butt & Kiehn 2003).

(b) Branching and dendrite formation

Proper wiring of neuronal circuits during development is highly dependent on the morphogenesis of dendritic trees, which is regulated by innate genetic factors and external molecular guidance cues as well as neuronal activity. The pattern as well as the number of branches determines the nature and the amount of innervation that a neuron receives (McAllister 2000). Dendritic growth is a very dynamic process of extension,

branching and retraction which has been well studied in different systems, e.g. the optic tectum (Cline 2001).

A variety of extracellular guidance cues, which were also required during neuronal outgrowth and pathfinding, can elicit changes within dendritic morphology. Semaphorin 3A (Sema 3A) affects dendritic growth mediated through Neuropilin-1 (Polleux *et al.* 2000) whereas Cpg15 enhances dendritic growth and plasticity in response to synaptic activity (Nedivi *et al.* 1998).

Bone morphogenic proteins have been shown to influence dendritic growth through an increase in the microtubule-associated protein MAP2 (Guo *et al.* 2001), whereas the cell adhesion molecule L1 regulates dendritic growth in the developing cortex (Demyanenko *et al.* 2004). Glial cells are known for the fact that they regulate dendritic growth as well as arborization (Lein *et al.* 2002; Deumens *et al.* 2004) and lately, notch signalling has been described as a potential molecular regulator for dendritic growth (Redmond *et al.* 2000).

Neurotrophins (BDNF, NGF, NT-3, NT-4) contribute to dendritic development by increasing dendritic complexity and dynamics in a spatially restricted and specific manner (Horch *et al.* 1999; McAllister *et al.* 1995; Niblock *et al.* 2000; Horch & Katz 2002). Many neurotrophic factors have been shown to be released in an activity-dependent manner, and there is strong evidence that neurotrophins are involved in activity-dependent development of dendritic circuits and their plastic changes (Kohara *et al.* 2001; Gorski *et al.* 2003; Jin *et al.* 2003; Dijkhuizen & Ghosh 2005).

Neuronal activity plays a key role in the fine tuning of dendritic growth and branching (Spitzer 2002; Libersat & Duch 2004). Visual deprivation decreases length as well as number of dendrites, and blockade of neurotransmission can dramatically affect dendritic and axonal arbor morphology (Wiesel & Hubel 1963; Hensch 2004; Ruthazer & Cline 2004). In contrast to this, exposure to enriched environment can increase dendritic growth and branching (Juraska 1982; Stell & Riesen 1987). The effect of activity on dendritic branching dynamics depends on the developmental stage of the dendrite (Wu *et al.* 1996; Rajan & Cline 1998; Wong & Ghosh 2002). Activity changes the intracellular calcium levels, which have been shown to be important for spine development (Bonhoeffer & Yuste 2002) as well as the stabilization of dendritic branches (Lohmann *et al.* 2002) through CaMKII-dependent regulation of the cytoskeleton. Furthermore, CaMKIV has been implicated in mediating calcium-induced transcriptional activation (Redmond *et al.* 2002).

(c) *Synaptogenesis*

The function of the nervous system critically relies on the establishment of precise synaptic connections (for review see Cohen-Cory 2002; Jüttner & Rathjen 2005; Waites *et al.* 2005; Zweifel *et al.* 2005). Synapse assembly is considered to be a process of multiple steps and begins when an outgrowing axon approaches its target region and establishes contacts. If correct and functionally meaningful, these initial contacts are stabilized through pre- as well as postsynaptic differentiation. The process is very complex and requires coordinated anterograde as well as retrograde signals between the axon and the target cell. Various classes of

cell adhesion molecules are involved in this process (Craig & Boudin 2001).

There is strong evidence that the same family of neurotrophic factors known for their importance during dendrite formation also play a key role in modulating synaptogenesis, as they play a key role in many aspects of synapse development and function (Poo 2001) as well as in structural plasticity within the developing brain (Prakash *et al.* 1996; Schuman 1999). Especially, brain-derived neurotrophic factor (BDNF) seems to be of outstanding importance as it regulates synapse formation and stabilization (Poo 2001), increases synaptic efficacy (Boulanger & Poo 1999), modulates the functional maturation of diverse synapses (Seil & Drake-Baumann 2000) and is involved in plastic events within neuronal circuitries (Xu *et al.* 2000).

Numerous studies support the concept that synapse formation and stabilization are highly activity-dependent processes and that activity-dependent mechanisms control the levels of neurotransmitters and their receptors (Craig & Boudin 2001).

(d) *Elimination and refinement*

One strategy used by the developing mammalian nervous system to establish neuronal circuitries is the overproduction of neurons, axons, branches and dendrites. Dendritic growth is often slow at first, but then dramatically increases with a transient overproduction of dendrites, in order to achieve the mature dendritic arborization (Luo & O'Leary 2005). Refinement occurs as specific branches and segments are selectively eliminated so that only the projections that arise from the right area connect to the appropriate targets. The elimination of excessive synaptic input is a critical step in synaptic circuit maturation.

In the developing spinal cord, outgrowing CST axon collaterals of the forelimb CST extend into deeper laminae within the grey matter than in the mature cord (Li & Martin 2000). In addition, whereas in adult animals CST neurons terminate almost exclusively contralateral to their cortical side of origin, many axon branches recross at the spinal level in development (Martin 2005). Furthermore, in newborn animals, a much higher proportion of CST axons do not cross at the pyramidal decussation but project ipsilaterally. Many of these fibres are retracted subsequently (Joosten *et al.* 1992).

It has been suggested that the developmental overproduction of connections serves to ensure that each target structure eventually receives an adequate input. The subsequent elimination is required to match the innervating neurons to the capacity of their targets and to shape precise functional connections and circuits. The cellular and molecular processes and mechanisms underlying collateral elimination are still very unclear (Luo & O'Leary 2005), but in many systems neural activity plays a key role (Goodman & Shatz 1993; Hua & Smith 2004). The activity-dependent developmental refinement of terminal arbors has been demonstrated in the kitten spinal cord for the CST (Martin 2005). These results strongly suggest an activity-dependent competition between developing corticospinal terminals and other tract

systems. When the CST was silenced during the critical period, e.g. by intracortical infusion of muscimol (a γ -aminobutyric acid (GABA) agonist), changes in termination patterns could be observed (Martin *et al.* 1999). Initially, axonal branches were not maintained, resulting in a decreased number of terminal branches and synaptic boutons. The intact, active CST not only innervated properly but also maintained its ipsilateral connections (Friel & Martin 2005). Similar changes in CST innervation pattern could be observed after an inhibition of forelimb function (Martin *et al.* 2004) or cortical stimulations (Salimi & Martin 2004). Moreover, an increased number of muscle afferent boutons was present in the cervical grey matter after early postnatal lesion of the contralateral motor cortex, suggesting competition of innervation between CST fibres and muscle afferents (Martin *et al.* 2005).

(e) *Plasticity and the critical period*

There is a certain postnatal time window when CNS circuits are formed and fine tuned, the so-called critical period (Hensch 2004). Within this time period, neuronal networks are not only highly flexible and capable of plastic changes in response to the environment, but also to destructive influences, e.g. through injury. If lesions occur within this critical period, the CNS can react through rapid neurite outgrowth and the establishment of new functional connections that can partially or fully compensate for the lost functions (Kolb & Whishaw 1989; Bachevalier & Mishkin 1994; Payne & Lomber 2001). This window of opportunity for repair closes at a certain time, which is specific for the animal species as well as the CNS area. The ability of plastic change decreases in favour of the formation of stable, reliable networks with precise circuitries and connections. In the adult CNS, the capacity for adaptive changes in response to injury is therefore rather limited.

Enhancing the ability of the CNS to react to injury through plastic changes is similar to those operating during CNS development. This could provide a powerful way to compensate for the loss of tracts or areas and form new functional connections. In order to achieve this, we need to learn more about the factors which are involved in terminating the critical period during CNS maturation. How can we modulate or repress these factors and thereby increase the potential of the CNS to revert to a plastic, developmental stage?

4. PLASTICITY WITHIN THE ADULT CENTRAL NERVOUS SYSTEM

(a) *Spontaneous plasticity within the adult central nervous system*

The view that the adult mammalian CNS is 'hard wired' and incapable of significant plasticity is no longer tenable. Throughout life, the adult brain retains a limited capacity for functional and structural reorganization in response to activity, behaviour and skill acquisition, which has been underestimated. Spontaneous reorganizations can occur at different levels including cortex, thalamus, brainstem as well as spinal cord following peripheral injury such as amputation, SCI or brain injury such as stroke. Spontaneous

injury-induced structural rearrangements may contribute in an important way to the spontaneous behavioural recovery that has been observed after smaller lesions in rodents (Goldberger 1977; Bareyre *et al.* 2004) as well as in human patients (Sanes & Donoghue 2000; Blesch & Tuszynski 2002; Raineteau *et al.* 2002; Edgerton *et al.* 2004).

The primary somatosensory cortex (S1) is characterized by a defined somatotopic organization which makes it easy to distinguish discrete topographical changes after peripheral or central trauma. In animals and humans, different techniques like positron emission tomography (PET), functional magnetic resonance imaging (fMRI) as well as transcranial magnetic stimulations (TMS) have been employed in order to investigate cortical reorganization after peripheral or central lesions. These studies show that the lack of afferent input is attributed to local anaesthesia, peripheral nerve lesion or amputation triggers a system-wide reorganization, and spatio-temporal cortical plasticity is paralleled by subcortical reorganization (Faggin *et al.* 1997). Cortical territories controlling intact body parts tend to enlarge and invade cortical regions which have lost their input (Brasil-Neto *et al.* 1992, 1993; Sadato *et al.* 1995). Patients with facial palsy revealed an enlargement of the hand representation with medial extension into the former face area (Rijntjes *et al.* 1997). Furthermore, the threshold to elicit movements was reduced (Donoghue *et al.* 1990; Sanes *et al.* 1990). In rats, changes began within hours (Sanes *et al.* 1988; Donoghue *et al.* 1990) and could be reversed after an epidural nerve block (Metzler & Marks 1979) or nerve regeneration (Wall *et al.* 1983).

Monkeys with limb amputation show a distorted sensory cortical representation and enlarged and overlapping cortical receptive fields (Merzenich *et al.* 1984; Pons *et al.* 1991; Merzenich & Jenkins 1993; Pascual-Leone *et al.* 1996). Stimulation of the deafferented motor cortex evoked movements in shoulder, trunk as well as face, whereas a deafferented hindlimb cortex evoked movements of hip, trunk and tail (Wu & Kaas 1999). Cortical reorganization might in part reflect sprouting and expansion of afferents from the remaining peripheral territories into deprived areas in spinal cord, brainstem, thalamic or cortical levels. Since the topographic representation of the body is greatly magnified in the cortex, small subcortical changes can result in dramatic cortical map changes (Jones 2000). Reorganization of S1 after amputation has been demonstrated in cats, racoons, rodents and bats (Kaas 1991) as well as in humans (Elbert *et al.* 1994; Flor *et al.* 1995). The functional significance of such reorganization events is still unclear, but an increase of cortical control of the remaining muscles and body parts may lead to compensatory movement strategies.

Reorganization is also thought to be responsible for regaining function in stroke patients affected with milder strokes. In animal studies, recovery following small cortical lesions was shown to be associated with adjacent cortical areas taking over the function of the damaged areas (Nudo 1999; Kolb 2003). After small infarcts of S1 in owl monkeys, the skin formerly represented by the infarct zone became represented in

the surrounding cortical regions (Jenkins & Merzenich 1987). Motor recovery can be mediated by the use of alternative cortical areas, in particular, the pre-motor cortex in the damaged hemisphere, a field with access to spinal motor neurons (Dum & Strick 1991; Schmidlin *et al.* 2004). Spontaneous functional improvement after an ischaemic infarct in the hand representation area of the primary motor cortex in adult monkeys has been associated with cortical reorganization. Intracortical microstimulation mapping after three months revealed an enlargement of the hand representation in the ventral pre-motor cortex, remote from the lesion site (Nudo *et al.* 1996). This enlargement was proportional to the amount of hand representation destroyed. Several authors have raised the possibility that ipsilateral motor pathways might also play a role in functional recovery from stroke (Fisher 1992; Lemon 1993; Lee & van Donkelaar 1995). In general, recovery after small- or medium-sized lesions is probably attributed to parallel pathways ipsilateral to the lesion and also owing to compensatory sprouting (Raineteau & Schwab 2001). When damage to a functional system is small, recovery within this system seems to be possible, whereas after complete destruction, substitution by a functionally related system becomes the only alternative (Seitz & Freund 1997).

The sensorimotor cortex projects to various subcortical targets (Antal 1984). Sensory as well as motor signals follow different parallel pathways which might substitute for each other. Partial lesions often impair but do not eliminate distinct functions. In adult animals, reorganization at the level of brainstem motor nuclei has been especially well illustrated for the corticorubral pathway after unilateral or bilateral corticofugal tract lesion or cortical aspiration (Lawrence & Kuypers 1968; Belhaj-Saif & Cheney 2000; Raineteau & Schwab 2001).

There are two main mechanisms to explain reorganization after peripheral as well as central injury. Changes that occur within minutes to hours following transient deafferentation in humans (Brasil-Neto *et al.* 1992, 1993; Sadato *et al.* 1995) or nerve lesions in animals (Merzenich *et al.* 1983; Donoghue *et al.* 1990) are thought to be mediated through unmasking of previously present but functionally inactive connections. The unmasking of silent synapses can be achieved by increased excitatory transmitter release, increased density of postsynaptic receptors, changes in membrane conductance as well as a decrease in inhibitory input or removing inhibition from excitatory input (unmasking excitation; Hendry & Jones 1986; Welker *et al.* 1989; Jacobs & Donoghue 1991). Long-term changes, in addition to unmasking of latent synapses, were shown to be based on long-term potentiation and long-term depression, synaptic changes which require *N*-methyl-D-aspartic acid (NMDA) receptor activation and an increase in intracellular calcium concentration as demonstrated in the motor cortex (Hess & Donoghue 1994, 1996a,b). Finally, axonal sprouting with alterations in synaptic shape, number, size and type (Kaes 1991; Florence *et al.* 1998) and growth of new horizontal connections (Das & Gilbert 1995) has been demonstrated in motor and sensory areas.

In response to SCI, synaptic plasticity as well as anatomical reorganization can also occur at cortical and subcortical regions. In spinalized cats, the deafferented

hindlimb region of S1 was incorporated into an expanded map of trunk and forelimb (McKinley *et al.* 1987). Four weeks after bilateral transection of the CST in the lower thoracic spinal cord of adult rats, microstimulations within a cortical area which exclusively evoked hindlimb muscle responses in normal adult rats did lead to responses of forelimb, whisker and trunk, thus demonstrating reorganization of the cortical motor representation (Fouad *et al.* 2001). TMS studies in human SCI patients revealed motor reorganization, as muscles immediately rostral to the lesion could be activated through bigger regions of the cortex (Levy *et al.* 1990; Topka *et al.* 1991). On the other hand, PET and fMRI studies showed that appropriate (e.g. foot, leg) motor areas can be activated by imagined movements, even in long-term paraplegic or tetraplegic patients (Corbetta *et al.* 2002; Curt *et al.* 2002).

In contrast to reorganization within cortical or subcortical sensory and motor representation areas after SCI, our knowledge about plastic changes within the spinal cord is rather limited. A first insight into the astonishing plastic potential of spinal cord circuits was provided by initial studies in spinalized cats: the isolated cord can learn through interactive training, when the body weight is partially supported and balance stabilized in order to produce or improve alternating stepping movements (Barbeau & Rossignol 1987, 1994; Edgerton *et al.* 2004). The ability of animals to place paws correctly and initiate stepping gradually improved over the training period.

In many animals and in humans, partial injury of the spinal cord is followed by functional recovery, which is often incomplete and correlates with the amount of spared descending fibres. For example, in monkeys, only 25% of the remaining white matter is sufficient for coordinated hindlimb locomotion, whereas grasping movements do not recover (Eidelberg *et al.* 1981). Anatomical reorganization of spared descending fibres is very well documented in the developing CNS after sensorimotor cortex aspiration as well as unilateral CST lesion. Here, the remaining CST fibres sprout heavily into the contralateral, denervated side followed by a high level of recovery of forelimb function (Kuang & Kalil 1990; Rouiller *et al.* 1991; Aisaka *et al.* 1999). In adults, the formation of midline crossing collaterals by spared descending fibres to the denervated side is either absent or very limited (Aoki *et al.* 1986; Woolf *et al.* 1992; Goldstein *et al.* 1997). Nevertheless, Bareyre *et al.* (2004) have shown recently that the spinal cord has the capacity to form new functional intraspinal circuits in response to injuries. Transected hindlimb CST axons sprouted into the cervical grey matter where they made contact to short and long propriospinal neurons. Synapses on the long propriospinal neurons that were spared by the lesion were stabilized. These neurons in turn increased their input on lumbar motor neurons, thus creating a new intraspinal circuit. Circuit formation correlated with the observed improvement of specific hindlimb functions.

A better understanding of the phenomena following SCI may be achieved using different imaging techniques such as fMRI or PET. In humans and animals, the application of fMRI to the spinal cord remains a considerable challenge, partly owing to the inaccessibility of the spinal cord, its small physical dimensions,

Figure 2. Compensatory fibre growth and plastic events after spinal cord injury were enhanced after Nogo-A antibody neutralization. Newly formed fibres established topographically correct terminations and synaptic contacts. Treated animals showed almost full recovery in sensory as well as motor tests including skilled forelimb reaching, whereas control animals remained severely impaired.

the distribution of white and grey matter and the surrounding CSF, all of which require high sensitivity and resolution (Stroman 2005). Despite these problems, a number of human and animal studies provide evidence that results obtained by spinal fMRI demonstrate areas of neuronal activity in the spinal cord and this technique can be used as an adequate tool for clinical trials assessing spinal cord function as well as basic research (Van Goethem *et al.* 2005; Bagley 2006; Majcher *et al.* 2006).

(b) *Regeneration, plasticity and neurite growth inhibitors*

The plasticity that exists in specific CNS areas in response to injury shows that adult axons and neurons retain a low growth potential in response to injury. Nevertheless, in comparison to the newborn CNS, adult growth processes appear very limited, especially in regard to fibre length. An intrinsic inability of adult CNS neurons to maintain long-distance growth is probably not the most important reason for this limitation as shown by the long-distance axon growth into peripheral nerve grafts placed into the adult CNS (David & Aguayo 1981; Richardson *et al.* 1984; Keirstead *et al.* 1989). Therefore, the obvious question was that of the cellular mechanisms regulating or limiting structural plasticity in the adult brain and spinal cord.

During development, oligodendrocytes appear late, and myelin formation is one of the major final stages in the formation of the CNS architecture. First insights into the role of oligodendrocytes in restricting adult CNS neurite growth and plasticity came from observations on a pronounced negative correlation between the spatio-temporal levels of GAP-43 expression and myelination in both the developing and adult CNS (Kapfhammer & Schwab 1994). Contact of growing neurites with myelin or oligodendrocytes induces long-lasting growth cone collapse via defined intracellular pathways (Schwab *et al.* 1993; Filbin 2003). This negative role of myelin on plasticity and growth has been shown *in vitro* (Schwab & Caroni 1988), followed

by *in vivo* experiments that prevented oligodendrocyte development and myelin formation by repeated local X-irradiation, a procedure that enhanced lesion induced or spontaneous sprouting, in parallel with persistent high levels of GAP-43 (Kapfhammer & Schwab 1994; Schwegler *et al.* 1995; Vanek *et al.* 1998). Active inhibition of growth and plasticity by oligodendrocytes, therefore, appears to be a key element of the restricted repair capacity of the adult spinal cord and brain.

(i) *Nogo-A and NgR*

Much recent work has focused on the identification and characterization of the factors in CNS myelin that restrict plasticity by inhibiting Nogo and inducing growth cone collapse. Using biochemical methods and bioassays, a high molecular weight component with strong neurite growth-inhibitory activity was found as the first adult CNS derived growth inhibitor (NI-250 or IN-1 antigen, now called Nogo-A; Caroni & Schwab 1988a,b; Spillmann *et al.* 1998; Chen *et al.* 2000).

Molecular cloning of the Nogo gene (Chen *et al.* 2000; GrandPre *et al.* 2000; Prinjha *et al.* 2000) revealed that its longest splice form, Nogo-A (1163 aa, 200 kDa) has a long amino terminus followed by two transmembrane domains and a short C-terminal segment. In the adult CNS, Nogo-A is synthesized predominantly by oligodendrocytes and localized in myelin within the innermost, adaxonal and in the outermost myelin membrane (Huber *et al.* 2002). The splice form Nogo-B (369 aa, 55 kDa) is found in many tissues and cell types including adult neurons, whereas Nogo-C (190 aa, 25 kDa) is expressed mainly in muscle (Huber *et al.* 2002). Functions of Nogo-B and -C are currently unknown.

All the three main products of the gene encoding Nogo share a sequence of 188 amino acids at their C-terminus. This region of the protein shares homologies with three known genes, the reticulon (RTN) proteins (Oertle *et al.* 2003a,b). RTN proteins also show a variety of splice forms but their functions are unknown. Analysis of active fragments of Nogo-A in neurite growth inhibition and growth cone collapse assays has demonstrated the existence of at least two active sites. One in the middle part of Nogo-A and a second one in a loop of 66 amino acids between the two hydrophobic domains (Fournier *et al.* 2001; Oertle & Schwab 2003). Both sites are exposed on the surface of oligodendrocytes (GrandPre *et al.* 2000; Dodd *et al.* 2005; Hu *et al.* 2005). Two intracellular components of inhibitory Nogo signalling have been identified so far: calcium and the Rho/Rho kinase pathway (Bandtlow *et al.* 1993; Niederost *et al.* 2002; Wong *et al.* 2002a,b; Fournier *et al.* 2003). It is not well understood how these messengers are linked, but inhibition of either component has been shown to prevent myelin or Nogo-A-induced growth cone collapse as well as growth inhibition (Bandtlow *et al.* 1993; Niederost *et al.* 2002; Fournier *et al.* 2003).

So far, only one binding site receptor has been identified, the 443-residue glycosylphosphatidylinositol-linked leucine rich repeat glycoprotein NgR

(Fournier *et al.* 2001; Barton *et al.* 2003; He *et al.* 2003). NgR interacts with the extracellular Nogo-66-domain (Fournier *et al.* 2001) and a short, biologically inactive Nogo-A specific site (Hu *et al.* 2005). This receptor transduces a growth-inhibitory signal in neurons via a membrane complex involving p75 and/or Troy (Naito *et al.* 1993; Wang *et al.* 2002b; Wong *et al.* 2002a,b; Shao *et al.* 2005). LINGO1, another NgR interacting protein, was found recently as an essential member of a functional NgR receptor complex (Mi *et al.* 2004). A second Nogo-A specific binding site/receptor has been demonstrated by fragment-binding studies but awaits purification and molecular identification (Oertle *et al.* 2003a,b). As mentioned in §2, several other neurite growth-inhibitory proteins have been found more recently in CNS myelin on the basis of *in vitro* assays. Their *in vivo* roles in preventing or restricting axonal plasticity and regeneration as well as functional repair after injury of the adult spinal cord or brain remain to be investigated.

(ii) *Inactivation of Nogo-A and NgR*

A neutralizing antibody against Nogo-A, the mAb IN-1, allowed a series of insights into the role of myelin-associated neurite growth inhibitors in the injured and intact adult CNS (Schnell & Schwab 1990; Schwab 2004). IN-1 is an IgM which recognizes the region specific to Nogo-A (Caroni & Schwab 1988a,b; Fiedler *et al.* 2002). Several crucial *in vivo* results have been reproduced with two new IgG anti-Nogo-A antibodies (Buffo *et al.* 2000; Wiessner *et al.* 2003; Liebscher *et al.* 2005). To investigate compensatory fibre growth and plastic events after SCI, the CST was transected unilaterally at the level of the medulla oblongata (Thallmair *et al.* 1998; Z'Graggen *et al.* 1998). In adult control animals, sprouting was minimal at the transaction site as well as in the red nucleus or basilar pontine nuclei. In contrast to this, animals with grafts of IN-1 anti-Nogo-A antibody secreting cells showed pronounced sprouting. Corticofugal fibres from the lesioned side crossed the midline of the brainstem and innervated the contralateral basilar pontine nuclei. These newly formed fibres sprouted across the pontine midline with topographically correct terminations and established synaptic contacts with the characteristics of normal corticopontine terminals (Blochliger *et al.* 2001). Fibres also grew from the unlesioned CST across the spinal cord midline and branched into the denervated dorsal and ventral part of the spinal cord (Thallmair *et al.* 1998). This sprouting occurred at all levels of the spinal cord. The animals showed almost full recovery in sensory as well as motor tests including skilled forelimb reaching, whereas control animals remained severely impaired (figure 2; Z'Graggen *et al.* 1998; Emerick & Kartje 2004).

The complete bilateral interruption of corticospinal connections can be compensated by growth of corticorubral and rubrospinal pathways. In animals treated with mAb IN-1, new collaterals sprouted from the rubrospinal tract into the cervical spinal cord in a targeted manner (Raineteau *et al.* 2002). These sprouts grew into the ventral grey matter where they contacted motor neurons of forelimb muscles which are normally

not directly innervated by rubrospinal axons (Raineteau *et al.* 2001). Cortical microstimulations induced fast muscle EMG responses like those in healthy animals. These responses were abolished after an injection of the GABA receptor agonist muscimol into the red nucleus.

Following focal cortical ischaemic lesion in adult rats, Nogo-A neutralization resulted in functional recovery of a forelimb reaching task, possibly through new cortico-efferent projections from layer V pyramidal neurons in the contralesional intact sensorimotor cortex to subcortical targets (Papadopoulos *et al.* 2002; Wiessner *et al.* 2003; Hu & Strittmatter 2004). Cortical neurons also showed increased dendritic arborization and spine density in mAb IN1 treated animals (Papadopoulos *et al.* 2005). Motor cortex stimulation of the intact side six weeks after injury showed a dramatic increase in movements of the impaired forelimb, suggesting that the newly formed midline crossing fibres are functional (Emerick *et al.* 2003). Enhanced regeneration and neuroplasticity as well as functional recovery also occurred if antibody treatment or NgR blockade was delayed (Li & Strittmatter 2003; Wiessner *et al.* 2003; Seymour *et al.* 2005).

Fibres that grow either spontaneously or through experimental manipulations in the adult spinal cord would have no function if they were not able to find their right targets. They can only lead to functional improvement once meaningful connections are established, whereas the formation of random or even wrong synaptic connections would lead to malfunctions. Almost no information is currently available on these processes. It is conceivable that fibre tracts initially sprout profusely in a widespread projection pattern, followed by refinement and stabilization of the appropriate connections in an activity-dependent manner. Expression of axonal guidance molecules and neurotrophic factors by the adult spinal cord in response to the selective loss of CST input has been shown, but the functional role of these molecules in an adult tissue environment remains to be analysed in detail (Bareyre *et al.* 2002; Zhou & Shine 2003; Zhou *et al.* 2003). The clinical experience strongly suggests that functional recovery requires specific intense training. The challenge for rehabilitation is that any axonal regeneration and all these plastic events have to be beneficial rather than detrimental, and that maximal functional recovery is obtained for a given type of injury.

(c) *Plasticity and rehabilitation*

After a large SCI, no or very little remaining tissue is left at the level of the lesion to conduct signals from the brain to neurons below the injury site, whereas local circuits above or below the lesion have lost their input but remain otherwise intact. Studies of locomotor recovery in animals with complete spinal cord transection suggest that the adult mammalian spinal cord can acquire the ability to generate stepping after all descending input is eliminated and in the absence of axonal regeneration. Locomotor movements can be initiated by a variety of stimuli such as certain postures, peripheral nerve stimulation or exercise. Rehabilitative

training has been shown to play a crucial role in teaching existing spinal pathways to generate locomotory patterns and respond appropriately to sensory feedback. Animal experiments gave rise to those which are now routine rehabilitation measures in spinal injured patients.

(i) *Treadmill training in animal models*

The first experiments were designed in order to assess the effect of treadmill training on the ability of the isolated spinal cord to generate stepping movements and standing after a complete spinal cord transaction at a low thoracic level (T12–T13) (Barbeau & Rossignol 1987; Rossignol *et al.* 1999; Edgerton *et al.* 2001; Edgerton *et al.* 2004). Locomotor recovery was compared between spinalized cats that received daily treadmill training and cats that were not trained following spinal cord transection. In the absence of training, cats did execute successful steps with both hind limbs but they frequently stumbled. In trained cats, the stepping pattern as reflected by EMG recordings was very similar to that of normal cats. They were capable of making more consistent and larger steps over a range of speeds while fully weight bearing (de Leon *et al.* 1998a,b, 1999a,b). Hindlimb standing after spinal cord transection improved with stand training for 12 weeks. These cats stood with full weight bearing on their hind limbs five times longer than control animals.

The observed plasticity and improvement of function was specific for the trained behavioural task; cats that were trained to step performed that motor task well whereas those trained for weight-bearing standing did not step well and vice versa (Lovely *et al.* 1986; Hodgson *et al.* 1994; de Leon *et al.* 1998a,b). The newly learned spinal behaviour is maintained through practice but deteriorates once exercise is stopped (de Leon *et al.* 1999a,b). Nevertheless, it can be re-established within one week of training. These results suggest that the isolated spinal cord can learn but it might forget these tasks without maintaining practice.

Functional reorganization in the spinal cord as observed after destruction of descending supraspinal input might occur at different levels and by different mechanisms. Exercise can prevent atrophy of leg muscles and spinal motor neurons and cause changes in their firing threshold and conduction velocity (Wolpaw 1997). Sensory feedback mechanisms stimulate intrinsic spinal circuitries, and the afferent feedback is essential to adjust weight support and correct leg movement (Pearson 1995). Training has also been shown to modulate glycine and GABA-mediated inhibition in the adult spinal cord of spinalized cats (de Leon *et al.* 1999a,b; Tillakaratne *et al.* 2000), suggesting that inhibition in the spinal cord was reduced via treadmill training (de Leon *et al.* 1999a,b).

Another important molecular element may be the growth and neurotrophic factors; their expression can be stimulated through increased activity (Kempermann *et al.* 2000; Cotman & Berchtold 2002). Rats that were allowed to run voluntarily for up to 7 days in a wheel showed higher levels of BDNF as well as neurotrophin 3 (NT-3) in the spinal cord and muscle (Gomez-Pinilla *et al.* 2001). mRNA levels of BDNF receptor, synapsin I, GAP-43 and cyclic AMP response element binding protein (CREB) were also increased in the lumbar spinal

cord after exercise. In turn, muscle paralysis by injection of botulinum-toxin A resulted in a decrease in BDNF and synapsin I in the spinal cord (Gomez-Pinilla *et al.* 2004).

The remarkable degree of locomotor recovery often seen after incomplete SCI may be attributed in an important way to the formation of new compensatory connections and activity-dependent reorganization of spared neuronal pathways (Basso *et al.* 2002; Bareyre *et al.* 2004). As little as 10% of descending spinal tracts are sufficient for some voluntary control of locomotion, and the number of fibres preserved in the ventral as well as lateral funiculus directly correlates with the functional outcome (Basso 2000; Schucht *et al.* 2002). Interestingly, when the spinal cord was completely cut after a certain time span, these rats were still able to retain some of the recovered locomotion (Basso *et al.* 2002). As this is never seen after an acute complete transection of the spinal cord, the result points to long-lasting reorganizations that took place in the lower spinal cord as a consequence of the first, partial lesion.

(ii) *Treadmill training after human spinal cord injury*

Treadmill training has been used with considerable success in spinal cord injured patients classified as functionally incomplete (ASIA B–D) and in stroke patients. It is now becoming routine in rehabilitation centres all over the world (Wernig *et al.* 1995; Dietz & Harkema 2004; Edgerton *et al.* 2004). The aim is to restore natural walking as much as possible which will also provide maximal sensory feedback important for modulation and adjustment of stepping (Maegle *et al.* 2002). Body weight is supported with a harness and the legs are moved by a physiotherapist or a robot.

Treadmill training rather than conventional therapy resulted in remarkable improvements of locomotor capability, however, depending on the extent and location of the injury (Wernig *et al.* 1998; Field-Fote 2001). Improvements made over several weeks were maintained for a long time period (Wernig *et al.* 1995, 1998). Nevertheless, the situation was rather different in completely injured patients. These patients did show reactivation of the spinal locomotor pattern generator and also showed a decrease of spasticity (Dietz *et al.* 1994, 1995). However, they were not able to maintain stepping movements after the training sessions were stopped. Furthermore, improvements seen on the treadmill could not be translated into independent overground walking (Wirz *et al.* 2001).

Today, robotic devices are developed to study motor recovery with high consistency in training methodologies as well as for quantitative read-outs. They have been developed for mice, rats and humans (Colombo *et al.* 2000; de Leon *et al.* 2002a,b).

(iii) *Training of forelimb function*

Research on spinal cord plasticity and neurorehabilitation has mostly focused on the recovery of hindlimb/leg function. Assessing the effect of therapeutic approaches and rehabilitative training on forelimb/hand function has proven to be more difficult as their functions are much more complex.

First experiments on the effect of increased forelimb activity on behavioural recovery were based on the observation that monkeys with lesions of the pyramidal

Figure 3. 'Constraint-induced therapy' of the forelimb in the rat. Following unilateral CST or motor cortex lesions (e.g. stroke in humans), the impaired limb shows greater recovery if the intact arm/limb is constrained by a bandage (patients) or a cast (rat).

tract failed to use their affected limb and that the use of this limb could be improved if the unaffected limb was constrained (Taub *et al.* 1999, 2002). In later experiments, somatic sensation was surgically abolished from a single forelimb. These animals did not use their limb under normal conditions. Nevertheless, they could be forced to use this deafferented limb by restricting the movements of the intact limb (Knapp *et al.* 1963; Taub 1976). Several other studies have shown that reactivation and extensive training of forelimb function (Taub *et al.* 1994) can lead to improved motor performance after neurological damage and to almost complete reversal of motor disabilities (Chambers *et al.* 1972; Taub 1976).

In order to overcome learned non-use, techniques used in monkey experiments were transferred to human patients, mostly stroke patients. These patients had to wear a sling on their non-affected side during 90% of their waking hours for 14 days (Taub *et al.* 1993) and received rehabilitative training of their affected arm. Control groups only performed passive movement exercises. After two weeks, the treated group showed a significant increase in skill and quality of movements of the paretic arm and hand, in comparison to the control group. These effects were probably dependent on the intensity of the training and not on the non-use of the impaired side (Winstein *et al.* 2003). Good success was also achieved through forelimb training with robots that do not require immobilization of the other arm (Lum *et al.* 2002a,b; Fasoli *et al.* 2003; Ferraro *et al.* 2003; Riener *et al.* 2005). Training of the affected limb (Nudo & Milliken 1996) as well as constrain-use therapy resulted in cortical reorganization. In this, the area surrounding the infarct region started to participate in specific movements (Liepert *et al.* 1998; Wittenberg *et al.* 2003).

Rats with unilateral lesion of the forelimb area of the sensorimotor cortex developed sensorimotor deficits in the contralateral limb and a compensatory hyper-reliance on the ipsilateral intact forelimb (Jones & Schallert 1992, 1994; Schallert *et al.* 1997; Jones *et al.*

1999). Behavioural changes after forelimb sensorimotor cortex lesion in adult rats resulted in numerous time-dependent structural changes in the motor cortex opposite the lesion, such as growth of layer V pyramidal cell dendrites, increase in dendritic arborization, synaptogenesis and astrocytic reactivity (Jones & Schallert 1992; Jones 1999; Jones *et al.* 1999). These changes appeared to be use dependent; immobilization of the non-impaired forelimb prevented dendritic growth and led to severe behavioural deficits (figure 3; Jones & Schallert 1994).

However, immediate intense training of the impaired forelimb shortly after the injury led to an exaggeration of the initial cortical injury, a process that could be abolished by NMDA receptor blockade (Humm *et al.* 1999). Nevertheless, complete disuse of the impaired forelimb during the first post-operative week did lead to devastating effects on the functional outcome, without exaggerating anatomical damage (Bland *et al.* 2001). This gave rise to the hypothesis that mild rehabilitative training early after injury could be beneficial, while either extreme overuse or complete disuse may disrupt reorganization and functional recovery (Leasure & Schallert 2004). The molecular mechanisms that underlay all these functional and anatomical reactions of the CNS to lesions and training remain a main research challenge for the coming years.

5. CONCLUSION

Is the repair of the injured spinal cord a recapitulation of development? Clearly, the long-held view that successful regeneration of injured fibres simply requires reactivation of developmental programmes appears too naive, in particular, owing to the fact that the tissue composition of the adult CNS is radically different from that of the developing brain or spinal cord. This is true, in particular, for the presence of oligodendrocytes and myelin, structures which actively restrict nerve fibre growth and which appear late in development simultaneously with the end of developmental fibre growth. In addition, astrocytes, which are important guidance structures in various parts of the developing CNS, have different properties and functions in the adult; their reaction to injury by the formation of a dense and growth-inhibitory scar is an important restricting factor for axon regeneration following injury. On the other hand, neurons are able to upregulate their growth machinery in response to lesions, although less in the adult than during development.

Several procedures which inactivate myelin-associated neurite growth inhibitors, in particular, Nogo-A or scar-associated inhibitory proteoglycans induce regeneration of subpopulations of injured axons and enhance compensatory growth of spared fibres. Extensive behavioural studies of injury models in rats and mice (SCI, brainstem injury, stroke) have shown remarkable behavioural recovery in the absence of detectable malfunctions. These results strongly suggest that growing fibres have formed new, functionally meaningful and correct connections. This implies the existence of mechanisms of axon guidance in the adult injured

Figure 4. Developmental circuit formation as well as successful regeneration of injured fibres in the adult CNS requires axonal guidance, target recognition, and fine tuning and stabilization. To promote optimal functional repair after CNS injury, specific interventions like neutralization of neurite growth inhibitory signals in CNS myelin and lesion scars, as well as the reactivation of growth programmes similar to developmental mechanisms help to induce regeneration and guide regrowing fibres to their appropriate targets.

CNS as well as mechanisms of target recognition and synapse formation. The fine tuning and stabilization of the new connections and circuits probably relies heavily on activity-dependent mechanisms as shown by rehabilitative training in animal models and humans. Axonal guidance and target recognition, as well as stabilization and differentiation of final axonal arbors may be highly similar to developmental mechanisms. Neurotrophic factors have been shown to be expressed in response to denervation as well as training in the spinal cord, and they can influence regenerating and sprouting axons (Bareyre & Schwab 2003; Ying *et al.* 2005). Several developmental axonal guidance and ECM molecules were also seen to reappear in the adult CNS, e.g. in areas that have lost a specific input (Bareyre *et al.* 2002; Bareyre & Schwab 2003; Ying *et al.* 2005).

In summary, mechanisms which are specifically present in the adult CNS, in particular those related to neurite growth-inhibitory signals in CNS myelin and lesion scars, as well as the reactivation of developmental mechanisms, especially with regard to axonal guidance, target selection and activity-dependent fine tuning and stabilization collaborate during the process of regeneration, plasticity and functional repair in the injured adult spinal cord or brain. The essential goals for the coming few years will be to promote optimal functional repair of the severely traumatized spinal cord through spatially and temporally specific interventions in order to induce regeneration and guide regrowing fibres to appropriate targets without side effects or complications (figure 4).

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