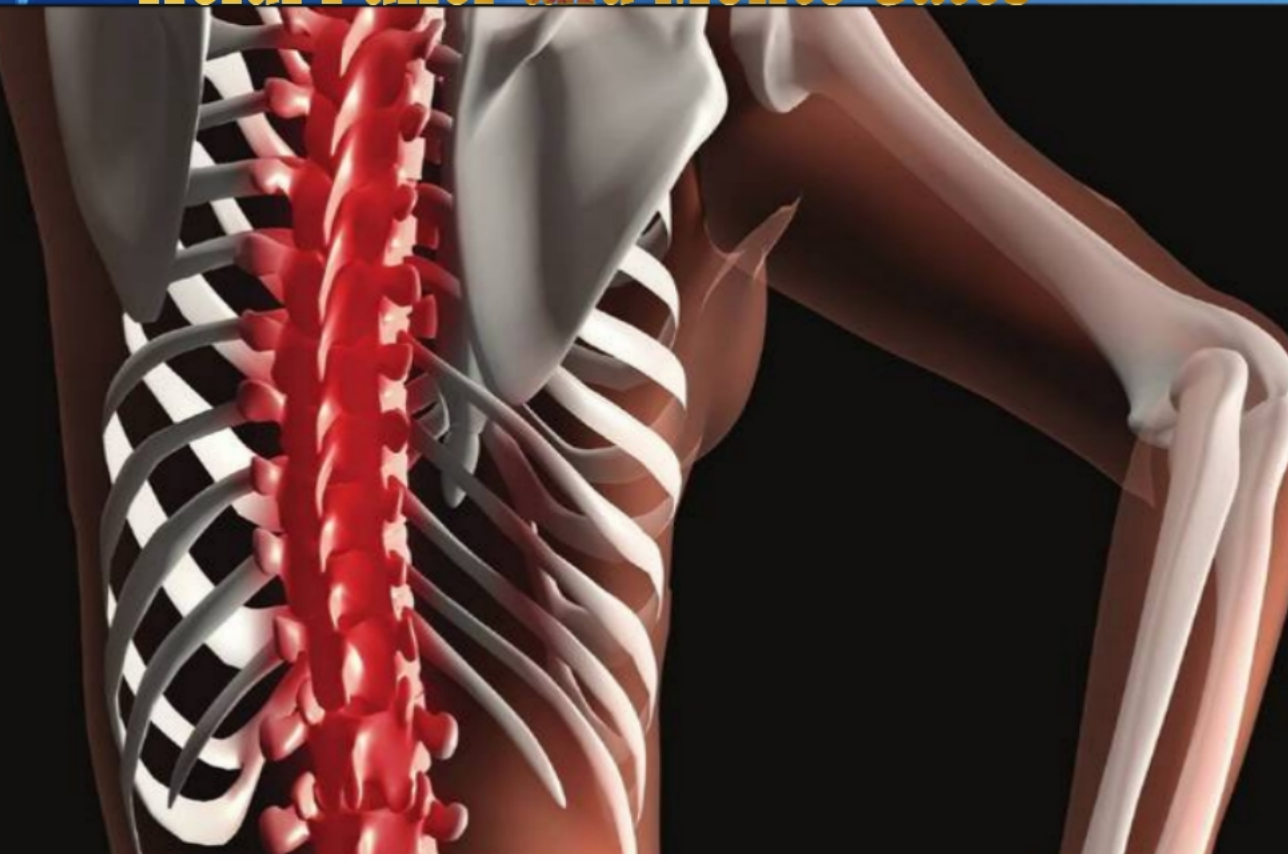
RECOVERY OF MOTOR FUNCTION FOLLOWING SPINAL CORD INJUR

Heidi Fuller and Monte Gates



Recovery of Motor Function Following Spinal Cord Injury

Edited by Heidi Fuller and Monte Gates

Recovery of Motor Function Following Spinal Cord Injury

Edited by Heidi Fuller and Monte Gates

Published by ExLi4EvA

Publishing Process Manager
Technical Editor AvE4EvA MuViMix Records
Cover Designer

ISBN-10: 953-51-2498-6
ISBN-13: 978-953-51-2498-6

Print
ISBN-10: 953-51-2497-8
ISBN-13: 978-953-51-2497-9

Contents

Preface

Chapter 1 Experimental Spinal Cord Injury Models in Rodents: Anatomical Correlations and Assessment of Motor Recovery
by Christina F. Vogelaar and Veronica Estrada

Chapter 2 In Vitro Models of Spinal Cord Injury
by Lucia Slovinska, Juraj Blasko, Miriam Nagyova, Eva Szekiova and Dasa Cizkova

Chapter 3 Protective Role of the Immune System in Spinal Cord Injury: Immunomodulation with Altered Peptide Ligands
by Paola Suárez‐Meade and Antonio Ibarra

Chapter 4 Role of the Neuroinflammation in the Degree of Spinal Cord Injury: New Therapeutic Strategies
by Irene Paterniti, Emanuela Esposito and Salvatore Cuzzocrea

Chapter 5 Normal Distribution and Plasticity of Serotonin Receptors after Spinal Cord Injury and Their Impacts on Motor Outputs
by Mengliang Zhang

Chapter 6 Docosahexaenoic Acid Promotes Recovery of Motor Function by Neuroprotection and Neuroplasticity Mechanisms
by John V. Priestley and Adina T. Michael-Titus

Chapter 7 Role of JAK-STAT Signalling on Motor Function Recovery after Spinal Cord Injury
by Victor S. Tapia and Juan Larrain

Chapter 8 Bridging Defects in Chronic Spinal Cord Injury Using Peripheral Nerve Grafts: From Basic Science to Clinical Experience
by Sherif M. Amr

Chapter 9 Stem Cell Therapies for Cervical Spinal Cord Injury
by Vanessa M. Doulames, Laura M. Marquardt, Bhavaani Jayaram, Christine D. Plant and Giles W. Plant

Chapter 10 Orthoses for Spinal Cord Injury Patients
by Mokhtar Arazpour, Monireh Ahmadi Bani, Mohammad Ebrahim Mousavi, Mahmood Bahramizadeh and Mohammad Ali Mardani

Chapter 11 Non-invasive Brain Stimulation to Characterize and Alter Motor Function after Spinal Cord Injury
by Aaron Z. Bailey, Hunter J. Fassett, Tea Lulic, Jenin El Sayes and Aimee J. Nelson

Chapter 12 Emerging Techniques for Assessment of Sensorimotor Impairments after Spinal Cord Injury
by Filipe Barroso, Diego Torricelli and Juan C. Moreno

Preface

Restoration of motor function following spinal cord injury is a complex and challenging task. By reviewing emerging cellular, pharmacological, rehabilitative, as well as surgical approaches, this book seeks to highlight promising therapeutic strategies for the repair and regeneration of motor circuitry. The multidisciplinary nature of these approaches illustrates various routes to bridging the gap between the bench and the bedside and to identify the challenges that must be overcome in order to bring about a viable therapeutic strategy for spinal cord injury patients.

Chapter 1

Experimental Spinal Cord Injury Models in Rodents: Anatomical Correlations and Assessment of Motor Recovery

Christina F. Vogelaar and Veronica Estrada

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62947

Abstract

Human traumatic spinal cord injury (SCI) causes disruption of descending motor and ascending sensory tracts, which leads to severe disturbances in motor functions. To date, no standard therapy for the regeneration of severed spinal cord axons in humans exists. Experimental SCI in rodents is essential for the development of new treatment strategies and for understanding the underlying mechanisms leading to motor recovery. Here, we provide an overview of the main rodent models and techniques available for the investigation of neuronal regeneration and motor recovery after experimental SCI.

Keywords: spinal cord injury, regeneration, plasticity, rodent, motor recovery

1. Introduction

The challenge of spinal cord injury (SCI) research is to find the right model for testing new treatment strategies. Although rodents differ from humans in many aspects, the research on primates is prohibited in many countries, and there are very strict regulations on experimenting with nonhuman primates [1]. Therefore, rodent models are the first choice for testing the effectiveness and mechanisms of new potential treatments for SCI. Rodents, especially mice, provide the additional advantage of transgenic technologies (knock out and knock in) that can be helpful in SCI research. In this chapter, an extensive description is provided on the currently available rodent SCI models, methods of treatment application, histological analysis of regenerating axons, and functional analysis of motor recovery.

2. Anatomy of the longitudinal axon tracts in rodents and humans

In order to understand the impact of SCI, it is important to have some basic knowledge about the long axon tracts that are interrupted by the lesion. Descending tracts control various motor functions. Sensory information from ascending tracts is also essential for posture, balance, and coordination of movements. Here, the main projections from the brain to the spinal cord and vice versa are summarized.

2.1. Descending motor tracts

The descending tracts in the spinal cord (**Figure 1**, left-hand side) run from the brain and brainstem to the spinal cord and are all involved in motor control [2].

2.1.1. Corticospinal tract (CST)

The corticospinal tract (CST) is variable between species. The motor cortex in rodents, generally referred to as the sensorimotor cortex (a rostrocaudal gradient of motor and sensory areas), is not as well defined as it is in humans, who have separate areas for sensory and motor cortex. The CST is responsible for the control of fine movements of distal musculature (e.g., fingers). Pyramidal neurons in layer V of the motor area give rise to the corticospinal axons that run via the internal capsule to the brainstem pyramids where they cross. It then depends on the species which path the majority of CST axons follow. In primates, almost all crossed fibers run in the lateral CST, located in the dorsolateral part of the lateral column. In rodents, most fibers are located in the dorsal CST (dCST), running in the ventral part of the dorsal columns. In some species, a ventral CST (vCST) is also observed. The CST axons terminate mainly in lamina 3–6 of the grey matter. In humans, up to 20% of CST axons terminate directly on motoneurons in lamina 9. CST terminals are glutamatergic.

2.1.2. Rubrospinal tract (RST)

The rubrospinal tract (RST) plays a role in general locomotion and in some species controls more skilled motor tasks together with the CST. It arises from the caudal magnocellular part of the red nucleus and crosses in the ventral tegmental decussation. The RST descends in the dorsal part of the spinal cord lateral column. The axons terminate in laminae 5 and 6 (sometimes 7) in the cervical and lumbosacral enlargements corresponding to the limbs. In rats, direct termination on lamina 9 motoneurons has been reported. The RST is prominent in rodents, whereas in animals with a large lateral CST (e.g., primates and humans), the RST is smaller. RST axons use glutamate as neurotransmitter.

2.1.3. Reticulospinal tracts (ReST)

The reticular formation in the brainstem plays a role in the preparation of movements and postural control. Reticulospinal tracts run medially and laterally in the ventral part of the spinal cord white matter. Whereas the medial reticulospinal tract (ReST) remains uncrossed, part of the lateral ReST fibers cross to the contralateral side. The ReST does not form a clear bundle

but intermingles with fibers from other tracts, for example, the vestibulospinal and spinothalamic tracts. The axons terminate in laminae 5–9 and can be either glutamatergic or GABAergic [3].

2.1.4. Vestibulospinal tracts (VeST)

The medial and lateral vestibulospinal tracts (VeSTs) are responsible for the initiation of limb and trunk extensor activity, which is important for posture. The lateral VeST arises from the lateral vestibular nucleus and does not cross, whereas the medial VeST originates from both the medial and the spinal vestibular nuclei and partially crosses to the contralateral side. Both run in the ventral white matter and terminate in laminae 7–8, providing glutamatergic input [3].

2.1.5. Raphespinal and coeruleospinal tracts

The Raphe nuclei give rise to the raphespinal projections, which together with the coeruleospinal projections (from the locus coeruleus) modulate (among others) motor functions. The raphespinal projections include a non-serotonergic component that runs in the dorsolateral funiculus and is involved in gating pain, as well as a serotonergic component that runs in the ventrolateral white matter, terminating in the intermediate grey and on motoneurons in the ventral horn. The noradrenergic coeruleospinal fibers run without crossing in the ventral funiculus and project throughout the grey matter.

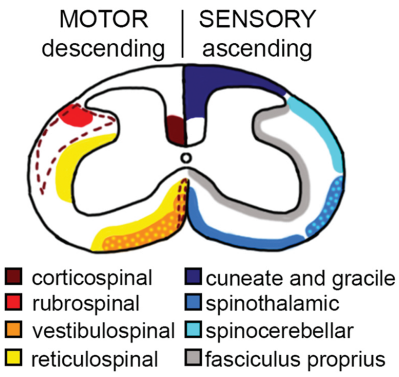


Figure 1. Spinal cord anatomy: schematic representation of the main ascending sensory tracts (right) and descending motor tracts (left) in a transverse section of the rodent spinal cord. Dotted areas represent locations where tracts are intermingled. Dashed lines indicate the location of the corticospinal tract in humans.

2.2. Ascending sensory tracts

The ascending tracts in the spinal cord (**Figure 1**, right-hand side) convey sensory information from the periphery to central nervous system (CNS) areas involved in walking, posture, and information processing about noxious stimuli [4].

2.2.1. Gracile and cuneate tracts

These two large ascending pathways contain axons from the dorsal root ganglia (DRGs) and provide sensory information from the limbs and trunk. In rodents, an additional dorsal column nucleus contains afferent axons from the tail. The tracts synapse in the gracile and cuneate nuclei located in the medulla oblongata. The second-order axons then cross the midline and run through the medial lemniscus to the thalamus. A subpopulation of DRG neurons synapses locally on dorsal horn neurons, whose axons also project to the gracile and cuneate nuclei. This is called the post-synaptic dorsal column pathway, whereas those DRG axons that do not synapse locally constitute the direct dorsal column pathway.

2.2.2. Spinothalamic, spinoreticular, and spinovestibular tracts

Several sensory tracts run in the ventrolateral funiculus of the spinal cord. These include the spinothalamic tract that conveys nociceptive, thermal, crude touch, and pressure information from the DRGs to the thalamus. The spinoreticular tract provides pain information to brainstem nuclei of the reticular formation. The spinovestibular tract is important for bringing proprioceptive signals to the vestibular nuclei. Several other tracts are present in the ventrolateral funiculus, such as the spinomesencephalic, spinoparabrachial, spinohypothalamic, and spinocervical tracts, each providing information to specific brain regions, that is, mesencephalon, parabrachial nuclei, hypothalamus, and lateral cervical nucleus in the upper cervical cord, respectively.

2.2.3. Spinocerebellar tracts

Projection axons from the spinal cord to the cerebellum are located in the dorsolateral and ventrolateral funiculi (**Figure 1** right-hand side). They carry proprioceptive information from the muscles and tendons to the cerebellum, so that adjustments of posture and coordination of movements can take place.

2.3. The propriospinal system

The spinal cord's "own" projection system refers to neurons that are located in the spinal cord, whose axons interconnect various spinal cord levels [5]. This so-called propriospinal system constitutes a large part of the white matter. It comprises interneurons that are connected to either other interneurons or directly to motoneurons. With respect to locomotor control, short-axon propriospinal neurons are also called premotoneurons, because they modulate corticospinal and sensory input to motoneuron pools controlling fore- and hindlimb activity. The long-axon propriospinal neurons form connections between the cervical and lumbosacral enlargements and are responsible for coordination of fore- and hindlimbs. These axons run in the fasciculus proprius (**Figure 1**, right-hand side).

The propriospinal neurons also modulate input to the lumbar central pattern generator (CPG), a local system involved in reflexive stepping in total absence of supraspinal input [5]. Serotonin from brainstem neurons has been shown to play a major role in CPG activation [6, 7].

http://dx.doi.org/10.5772/62947

3. Rodent spinal cord injury models

The choice of SCI models is important in view of comparability with human SCI, but practical issues should also be considered. Although human lesions are usually compressions (but some may be sharp wounds as well or a mixture of both), from the experimental point of view it might be important to have a more "clean" and reproducible cut. Treatment strategies that fail to cause regeneration through a spinal cord transection lesion will probably have equally small effects after contusion lesions. On the contrary, treatments that induce regeneration in a transection model should then be tested and optimized in a contusion model. Partial injury models are useful for the investigation of the locomotor recovery over time, since not only regeneration but also sprouting from spared axon tracts can occur (see Section 5). Models of complete transection are used to study regeneration without the possibility of plasticity processes bypassing the lesion. While the complete transection of the spinal cord is a very reproducible injury, disadvantages of this lesion model are the poor degree of regenerative

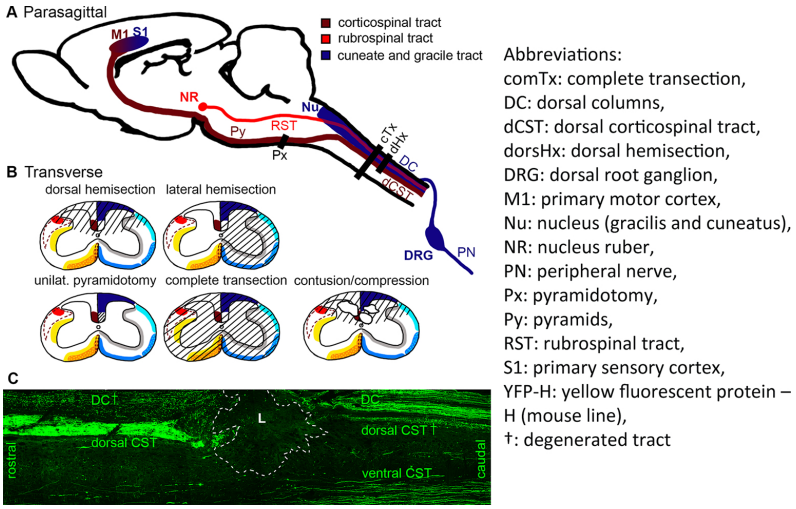


Figure 2 Spinal cord lesions in rodent models of SCI: (A) schematic representation of a parasagittal section through the brain and spinal cord (modified from Paxinos & Watson, The Rat Brain in Stereotaxic Coordinates, 6th Edition). Tracts with clear localizations are indicated. It should be noted that these do not run in the same spinal cord section, with the RST (red) running more laterally than the CST (brown) and the cuneate and gracile tracts (blue). The dorsal hemisection, complete transection, and the pyramidotomy lesions are represented as black bars. (B) Schematic drawings of transverse sections through the spinal cord with bilateral motor tracts depicted left and bilateral sensory tracts depicted right (for exact description of the tracts see **Figure 1**). Dashed areas represent the extent of tissue damage produced by the different injury paradigms. Note that motor and sensory tracts run in both spinal cord hemispheres but are depicted separately for better understanding. (C) Histological parasagittal section through the spinal cord of YFP-H mice (The Jackson Laboratory) 7 days after a dorsal hemisection (compilation of 2 sagittal sections). Descending CST axons are intact rostrally and have degenerated caudally from the lesion site (dashed white line). Ventral CST fibers are not lesioned (plane of section causes apparent lack rostrally). Ascending dorsal column axons are intact caudally and have degenerated rostrally.

growth of the severed axons and the general inadequacy for most motor tests. In this section, the technical principles of each model in rats and mice are described.

3.1. Dorsal hemisection (Hx)

Spinal cord transection lesions are generally applied using scissors, scalpel blades, or fine retractable wire knives. The advantage of wire knives (McHugh Millieux) is that a SCI can be performed with high precision, because they can be attached to a stereotactic frame. The dorsal Hx (Figure 2A–C) is the most used SCI paradigm for the investigation of the regeneration of CST and, depending on the extent of lateral lesion, it also includes the RST. It is mostly performed at thoracic level 8 (T8) and involves the laminectomy at T8-9, opening of the dura mater and subsequent lesioning of the spinal cord [8, 9]. For mice, microdissection spring scissors (Fine Science Tools) are used to hemisect the spinal cord. Since this procedure is inherently variable, the experimenter needs to test various depths to determine the desired extension of the lesion. A more controlled technique for dorsal Hx in mice was described by Hill et al. (2009) who used a so-called Vibraknife (LISA-Vibraknife; Louisville, KY) [10, 11]. Dorsal hemisection lesions are usually applied at thoracic spinal cord levels and result in the formation of a dense inhibitory scar [12, 13]. Depending on the severity of the lesion, the animals spontaneously recover a certain degree of walking that can be further ameliorated by regeneration promoting treatments.

3.2. Lateral Hx

For lateral Hx, the lateral half of the spinal cord is transected in mostly the same technical procedure as the dorsal Hx, with the difference that the tracts on one side are left intact (Figure 2B). These lesions provide the advantage of an internal control situation [14], which is also reflected in the behavioral testing, where paw preferences are often scored (see Section 7.5.). Lateral Hx experiments are usually performed at cervical levels, allowing the analysis of both fore- and hindlimb recovery. Mostly, a lesion at cervical level C5 is produced, but some groups have specialized on the analysis of breathing musculature after a lesion at C2 [15].

3.3. Complete transection (Tx)

For a complete transection (Figure 2B), small scissors are generally used to transect the spinal cord after having cut the meninges. Alternatively, the dura mater is opened just enough to allow the insertion of a spinal cord hook (Fine Science Tools) between dura and spinal cord. The hook is then used to lift the cord in order to completely cut the spinal cord. The dura mater can be closed with fine sutures (10-O) after the procedure. The complete Tx model is useful to investigate the effect of treatments on the axonal regeneration, and on (limited) recovery of locomotor function. After a complete SCI in rats, there is usually the development of fluid-filled cavities, whereas in mice this is generally not the case [16].