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Plastic Spinal Motor Circuits in Health and Disease

Uwe Windhorst in collaboration with Payam Dibaj

© **Uwe R. Windhorst,** Dr. med. habil., former Professor of Physiology at Centrum Physiology and Pathophysiology, University of Göttingen, Germany; Departments of Clinical Neuroscience and Physiology, University of Calgary, Canada; Arbetslivsinstitutet associated with the University of Umeå, Sweden; Center for Musculoskeletal Research, University of Gävle, Sweden; E-mail: siggi.uwe@t-online.de

Payam Dibaj, Dr. med., Neurologist, Geriatrician and Medical Coordinator. Center for Rare Diseases (ZSEG), University Medical Center Göttingen, Germany; Max-Planck-Institute for Multidisciplinary Sciences, Göttingen, Germany; Department of Neurology, Hospital Weser-Egge, Höxter, Germany; E-mail: payam.dibaj@med.uni-goettingen.de

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Abstract. In former times, the spinal cord was considered a hard-wired network for spinal reflexes and a conduit for long-range connections. This view has changed dramatically over the past few decades. It is now recognized as a plastic device whose structures and functions adapt to changing circumstances. While such changes also occur under physiological conditions, the most dramatic alterations take place during or after various pathological events. It is astonishing what mechanisms the musculo-skeletal system has evolved to come to grips with the damages. Many of these changes are maladaptive, but some appear to help adapt to the new conditions. Although myriads of studies, using manifold methods, have been devoted to elucidating the underlying mechanisms, in humans and animal models, the etiology and pathophysiology of various diseases are still little understood, due to a number of reasons. We will here try to summarize some results and remaining problems in a selection of diseases, in particular spinal muscular atrophy (SMA), amyotrophic laterals sclerosis (ALS), and predominantly spinal cord injury (SCI) with occasional relations to stroke. Especially the changes in SCI (and stroke) depend on the cause, site and extent of the afflicted damage and are therefore multifarious. At the end, we will briefly summarize results indicating that operant, classical and instrumental conditioning can be used to produce plastic changes in healthy people, with potentials for applications to patients with spinal cord injury. In order not to overload the article, we will not delve deeply into sub-cellular processes.

Keywords: Spinal plasticity, spinal neuronal networks, spinal muscular atrophy, amyotrophic lateral sclerosis, spinal cord injury, stroke, spasticity, classical conditioning, instrumental conditioning, operant conditioning

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1 Introduction

Animals must adapt their actions and operations to changing conditions of the surroundings, as well as to those of the own body. This requires learning from action outcomes and adapting to changes, at very different levels of organization and time scales, and using as much sensory information as available at any time. This in turn requires their neuronal networks, including motoneurons (MNs) and their inputs, to be plastic rather than rigid. The structures subject to plasticity are manifold and distributed throughout the neuraxis, even extending to the neuromuscular junction (Christensen et 2017; Grau 2014; Grau et al. 2020; Schouenborg 2004).

The musculo-skeletal system is a plant of extreme complexity with which the nervous system yet deals easily and elegantly. How does it do so? The most promising strategy has been suggested to be "...based on trial-and-error learning, recall and interpolation of sensorimotor programs that are good-enough rather than limited or optimal" (Loeb 2021). But this general strategy must be realized by flexible mechanisms that are only partly understood so far.

Plastic adaptations occur throughout normal life, from birth to old age (Christensen et al. 2017). But dramatic examples are provided by adaptations to pathological processes. The primary emphasis of this selective review lies on plastic processes in the spinal sensory-motor system during and after various pathological states, including spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), and various lesions to the nervous system, particularly spinal cord injury (SCI). Multifarious and complex plastic changes are known to happen in the dorsal spinal cord (and beyond) during nociceptive processing, but are beyond of the scope of the present review which concentrates on processes in the sensory-motor system.

2 Plastic Changes in Motoneuron Diseases

Neurological diseases change bodily conditions and enforce adaptive changes in the operation of neuromuscular (and other) systems. Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are two pathological conditions that originally were considered to simply result from MN degeneration, but over time have been recognized to be multi-systemic diseases affecting not only different areas inside but also outside the nervous system (Al-Chalabi et al. 2016; Yeo and Darras 2020). In addition, multi-factorial mechanisms have emerged over time, taking into account the pathophysiology of MN diseases, which include a complex interplay of genetic factors and molecular signaling pathways (Vucic et al. 2014).

ALS and SMA do differentially affect α-motoneurons (α-MNs) innervating extrafusal muscle fibers, γ-motoneurons (γ-MNs) innervating intrafusal muscle-spindle fibers, or ß-MNs innervating both extra- and intrafusal muscle fibers (Banks 1994, 2005, 2015; Manuel and Zytnicki 2011). (For simplicity, α-MNs and ß-MNs are here called α-MNs). In both SMA and ALS, the largest α-MNs innervating fast-contracting, fast-fatiguing muscle fibers (type FF) are the most vulnerable and degenerate first, followed by the α-MNs innervating fast-contracting, fatigue-resistant (type FR) muscle fibers, with the α-MNs innervating slowly contracting, fatigue-resistant muscle fibers (type S) being the last, if any, to degenerate (Brownstone and Lancelin 2018; Falgairolle and O´Donovan 2020; Kanning et al. 2010; Nijssen et al. 2017; Powis and Gillingwater 2016; Pun et al. 2006), γ-MNs are affected less or later, at least in ALS (Limanaqi et al. 2017).

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2.1 Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy (SMA) is one of the most common neuromuscular disorders of childhood with a high morbidity and mortality (Nicolau et al. 2021). It is characterized by degeneration of α-MNs in the spinal cord and brainstem (other cell types are also affected; for details see Quinlan et al. 2019). 90-95% of SMA cases involve a group of autosomal-recessive disorders caused by loss-of-function mutations in the survival α-MN 1 (SMN1) gene on 5q13 (Peeters et al. 2014; Wurster and Petri 2022). Thus, the majority of SMA cases is caused by low levels, not the complete absence, of the essential SMN protein. SMN1-associated SMA (5q-SMA) comes in varieties of different severity: severe (type I) with the highest disease incidence, and more prevalent milder forms with intermediate (type II) and mild (type III) SMA. SMA leads to progressive symmetrical muscle atrophy, weakness and hypotonia, and the inability to sit, stand or walk (Arnold and Fischbeck 2018; Kolb and Kissel 2015; Wirth 2021). Therapy has advanced towards the development of drugs, such as nusinersen, onasemnogene abeparvovec, and risdiplam (Nicolau et al. 2021), which when applied presymptomatically, now allow the children to achieve the above motoric abilities and almost age-based development (Wirth 2021). The non-SMN1 SMA (or non-5q SMA) is a heterogeneous group of very rare neuromuscular disorders with autosomal recessive and dominant as well as X-linked recessive inheritance (Karakaya et al. 2018; Peeters et al. 2014).

Mouse (and other) models of SMA have led to deeper insights into the pathophysiology of MN degeneration (Hua et al. 2015). The precise cellular and molecular mechanisms mediated by SMN deficiency are still unclear, however. SMA is not a MN autonomous disease (Rindt et al. 2015). Its pathology is not restricted to α-MNs and dysfunction is more widespread, particularly within the brainstem and spinal circuits in which the α-MNs are embedded. In a mouse model, mutant SMNΔ7 mouse, the α-MN degeneration leads to motor deficits, such as weakness and an inability to right themselves. These mice eventually die at 2 weeks of age. The proximal muscles are more affected than the distal muscles, with the epaxial and hypaxial muscles being the most severely weakened (Falgairolle and O´Donovan 2020).

The vulnerability of α-MNs and their synaptic connections is evidenced by the fact that increasing the expression of SMN restricted to α-MNs is sufficient to rescue α-MN survival, maintain excitatory synapses from sensory afferents onto α-MNs, and increase the lifespan of the mice. But in systemic SMN reduction, deficiencies in other cell types also contribute to SMA pathology (for references see Quinlan et al. 2019). SMA is likely a non-cell autonomous disease with a critical impact when considering the pathophysiology of the disease, through the interactions of MNs and other cell types in the nervous system, particularly glial cells (Abati et al. 2020; Ilieva et al. 2009; Rindt et al. 2015). Different glial cells exhibit many functions to maintain MN integrity: trophic support, minimization of excitotoxicity, synaptic remodeling, and immune surveillance, to name a few.

2.1.1 Changes in Motoneuronal Excitability

α-MN excitability depends on a number of factors, including intrinsic properties such as MN size, input impedance etc., as well as extrinsic modulatory influences, exerted, for example, by descending monoaminergic signals. Thus, serotonin [5-hydroxytryptamine (5-HT)] and noradrenaline (NA) enhance certain ion channels in α-MNs (Binder et al. 2020; ElBasiouny et al. 2010; Leech et al. 2018). One way that serotonin influences α-MN excitability is via persistent inward currents (PICs).

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Persistent Inward Currents (PICs) contribute to the operation of endogenous and conditional oscillators and increase the gain of the input/output relationship leading to an increase in the firing rate of α-MNs. PICs are activated by depolarization and carried by sodium (Na^+) and calcium (Ca^{2+}) ions through Nav1.6 and nifedipine-sensitive L-type Ca^{2+} channels, Cav1.3, respectively. The channels mediating the Na^+ PIC appear to be located on the soma and/or proximal dendrites and contribute to both the initiation of action potentials during rhythmic firing and maintenance of normal repetitive firing of α-MNs. Channels mediating the Ca^{2+} PICs are situated in close proximity to synapses in mid-dendritic locations supporting a role for amplification of synaptic inputs. This distribution of Cav channels on dendrites is consistent with that of serotonergic [5-hydroxytryptamine (5-HT)] and noradrenergic (NA) boutons on α-MN dendrites, and a higher innervation occurs in extensor compared with flexor α-MNs. This might explain the bias toward extensor α-MNs for facilitating expression of PICs by an increase in monoaminergic effects (Binder et al. 2020; ElBasiouny et al. 2010; Quinlan et al. 2019).

α-MN Hyper-excitability. In two mouse models of severe SMA, α-MN excitability was increased as indicated by hyperpolarization of the threshold voltage for action potentials and faster action-potential firing rates, among many other changes in α-MNs. In $Smn^{2B/-}$ mice at P9-10, the hyperpolarized action-potential threshold is most likely due to alterations in persistent inward currents (PICs). Hence, in $Smn^{2B/-}$ mice, an increase in these currents is likely to underlie altered α-MN excitability. The PICs showed increased amplitudes and more hyperpolarized threshold activation. In $Smn^{2B/-}$ mice at P9-10, α-MNs were larger in size, which might compensate for the greater excitability because of decreased input resistance. α-MN hyper-excitability and changes in α-MN size were also found in pre-symptomatic mouse models of amyotrophic lateral sclerosis (ALS) (Sect 2.2). It has been hypothesized that the hyperexcitability involves an altered function of aberrant voltage-gated Na^+ channels and probably occurs early in the disease process at an age before α-MN loss, and would initiate a series of compensatory changes, including loss of glutamatergic synapses, changes in α-MN size, and finally cell death. Also, motor-unit loss occurred after these changes in α-MN properties at P9-10, at earliest two weeks after birth (Quinlan et al. 2019).

2.1.2 Changes in Proprioceptive Reflexes

In SMA mouse models, α-MNs have reduced proprioceptive reflexes that correlate with decreased numbers and functions of synapses on α-MN somata and proximal dendrites (Mentis et al. 2011). One of the first pathological changes is a decline in the strength of synaptic input to α-MNs from group Ia afferents from muscle spindles. This decline is due to a decrease in the amount of glutamate released from the afferents onto α-MNs. In addition, in SMNΔ7 mice, the number of vesicular glutamate transporter (VGLUT)2^+ terminals on α-MNs is reduced, which can be derived from local or descending glutamatergic interneurons. The decreased glutamate release from group Ia afferents triggers several secondary changes in the α-MN properties, including an increase in input impedance and a down-regulation of the Kv2.1 potassium channel, these responses being probably compensatory. In contrast to α-MNs, Renshaw cells (Sect 4.4) in SMNΔ7 neonatal mice receive an increasing number of VGLUT1 primary afferent terminals (which disappear later) as well as of vesicular acetylcholine transporter (VAChT)+ terminals from α-MNs, which could be due to sprouting of proprioceptive afferents and of motor-axon collaterals of the remaining α-MNs, respectively. Restoration of the SMN protein in afferents, but not in α-MNs, normalized Kv2.1 expression and partially restored the firing of α-MNs to current injection. Although secondary, the motoneuronal changes contribute significantly to the

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motor deficits in SMA. Inhibitory inputs to α-MNs are less affected than excitatory inputs (Falgairolle and O´Donovan 2020).

2.2 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a complex, multi-factorial neurodegenerative disease often associated with pathobiological features of fronto-temporal dementia (McKenna et al. 2021; van Es et al. 2017). About two thirds of the patients have a spinal form of the disease, which initially manifests with arm or leg weakness (limb-onset) (Casas et al. 2016; Kiernan et al. 2021). Most of the remaining cases are bulbar-onset, which initially manifests with speech and swallowing problems. Most commonly, ALS starts at varying advanced age (up to 80 years), with a mean age of about 60 years at onset of sporadic disease (about 50 years in familial disease), shows progressive muscle weakness and atrophy leading to paralysis, loss of the dexterity, ability to move,, talk, eat, and breathe, is often accompanied by spasticity (Sect 3) and pain, and ends with death 3 to 5 years after disease onset (Chiò et al. 2017; Delpont et al. 2019; Kiernan et al. 2011; Kiernan et al. 2021; Riancho et al. 2021; Verschueren et al. 2021). The term `lateral sclerosis´ refers to an anatomo-pathological hardening of the anterior and lateral spinal cord (Charcot and Joffroy 1869), indicating degeneration of mainly the cortico-spinal tract (CST) but also other tracts within the antero-lateral spinal white matter (Dibaj et al. 2011b; Yamanaka et al. 2006). There are two broad classes of etiologies: familial (ca. 5-10%) and sporadic (idiopathic), with the first being related to mutations in specific causative genes (C9ORF72, SOD1, TARDBP, FUS among others), which directly induce α-MN degeneration, and sporadic ALS cases considered to be secondary to the interactions between the individual genetic risk and developmental factors and environmental conditions (Al-Chalabi et al. 2016; Hulisz 2018; Mejzini et al. 2019; Riancho et al. 2019, 2021; Turner et al. 2013; van Damme et al. 2017).

Traditionally, as of the first description by Jean-Martin Charcot in 1869, ALS was considered an α-MN disorder characterized by the selective degeneration of upper and lower MNs (Casas et al. 2016). More recently, views have changed such that ALS is now considered a multi-system disease in which degenerative pathology has also been detected in the cerebral cortex, cerebellum, basal ganglia, spino-cerebellar tracts, dorsal columns, serotonin-containing neurons in the raphé, noradrenergic neurons in the locus coeruleus, peripheral nervous system, neuromuscular junction and other synapses, as well as gastrointestinal, autonomic and vascular systems, with early and frequent impacts on cognition, behavior, sleep, pain and fatigue (Bae and Kim 2017; Casas et al. 2016; Dibaj et al. 2011b; Dibaj et al. 2012; Dibaj and Schomburg 2022; Fang et al. 2017; Limanaqi et al. 2017; Mahoney et al. 2021; Mazzocchio and Rossi 2010; Philips and Rothstein 2015; Riancho et al. 2021; Sábado et al. 2014; Tremblay et al. 2017; Verde et al 2017). There is also evidence for immune dysregulation in the pathogenesis of ALS (Beers and Appel 2019; Dibaj et al. 2011b; Lyon et al. 2019; Ruffoli et al. 2017).

The underlying pathogenesis and pathophysiology are complex and incompletely understood, but probably affected by manifold genetic, epigenetic, developmental and environmental factors (Dolinar et al. 2018; Mejzini et al. 2019; Oskarsson et al. 2018; Quinn and Elman 2020; Riancho et al. 2019; Saberi et al. 2015; Turner et al. 2013; van Damme et al. 2017; van Es et al. 2017; Zhao et al. 2018).

Impairment of several crucial cellular pathways, such as gene-processing disorders, proteostasis and axonal transport impairments, hyperexcitability and excitotoxicity, or functional deficits of surrounding glial cell (with immunological and trophic consequences for the motoneuronal integrity), have been associated with degeneration of α-MNs (Casas et al. 2016; Dibaj et al.

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2011b, Dibaj et al. 2012; Ilieva et al. 2009; Riancho et al 2019). In particular, energy homeostasis is compromised in patients with ALS, which has notable clinical implications such as weight loss, hypermetabolism, and hyperlipidaemia. More recently, alterations have been described in all the compounds of the neuro-vascular unit. In addition to MNs, considering the non-cell autonomous pathophysiology of ALS, other cells are considered as determinants of ALS onset and progression, such as astrocytes, microglia, oligodendrocytes, Schwann cells, muscle cells, or as contributors, such as lymphocytes, pericytes, and interneurons (Casas et al. 2016, Dibaj et al. 2011b, Dibaj et al. 2012; Ilieva et al. 2009).

A number of animal models have been developed to study the genetic and molecular mechanisms (Alrafiah 2018; Bonifacino et al. 2021; Casas et al. 2016; Lutz 2018; Mejzini et al. 2019; Philips and Rothstein 2015). The first intraspinal changes in ALS appear to differ from those in SMA, at least in mouse models (Brownstone and Lancelin 2018; Falgairolle and O´Donovan 2020). There are several mouse models, but the one on which most work has been done is the superoxide dismutase SOD1-G93A model (in addition to G93A mutation of SOD1 gene, mice with other mutations of SOD1 such as G37R and G85R were also examined, but to a much less extent), which survives much longer (up to 150 days) than the SMNΔ7 model of SMA (two weeks). In transgenic mouse models of ALS (expressing mSOD1), the PIC amplitudes are altered and may contribute to α-MN dysfunction. Na^+ PICs are increased and show a rapid recovery from fast inactivation, allowing α-MNs to fire at higher rates (ElBasiouny et al. 2010).

2.2.1 Progression of ALS

It may be instructive to start with a hypothesis based primarily on data from animal models (Brownstone and Lancelin 2018).

In ALS, the successive death of α-MNs, from FF-type α-MNs over FR-type α-MN to S-type α-MNs, leads to consequent loss of muscle forces. But since the disease becomes symptomatic only after the degeneration of at least 30% of an α-MN pool, there should be some homeostatic mechanisms that compensate for the early loss. It is proposed that, in pre-symptomatic ALS, a key compensatory mechanism lies in increasing excitation of α-MNs by premotor circuits, which would lead to increased co-activation of functional α-MNs and γ-MNs (Brownstone and Lancelin 2018).

Homeostatic mechanisms would include increased input to α-MNs from spinal segmental and supraspinal circuits to ensure that force production is preserved. Thus the input to co-activated γ-MNs would also increase, leading to increased contraction of intrafusal muscle fibers out of proportion to extrafusal fibers. This α-γ imbalance would result in an increase in muscle spindle afferent input to α-MNs. The increasing glutamatergic excitation from these inputs would initially maintain the homeostatic response despite a reduction of activity of F-type α-MNs whose muscle fibers produce high forces. The loss of particularly type-F α-MNs would simultaneously, in motor pools with recurrent inhibition via Renshaw cells (Sect 4.4), reduce the recurrent inhibition of α-MNs and γ-MNs, which would be initially compensated by increased α-MN activity particularly from type-S α-MNs. Together, these processes would lead to increased glutamatergic excitation of vulnerable α-MNs and, hence, excitotoxicity, via elevated intracellular Ca^{2+} concentrations. That is why ablation of primary afferents exerts a protective effect on α-MNs. In symptomatic stages, the processes that started in pre-symptomatic stages would continue, there would be runaway from homeostatic processes, and further excitotoxicity would lead to disease progression. It would no longer be possible to maintain muscle contraction, compounding the α-γ imbalance, and the resulting loss of input to

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Renshaw cells would reduce recurrent inhibition of α-MNs and also diminish γ-MN inhibition, thereby contributing to increased excitation of remaining α-MNs but a further imbalance of α-γ output (Brownstone and Lancelin 2018). This hypothesis needs experimental testing and scrutiny.

2.2.1.1 Proprioceptive Inputs to α-MNs

"You can only control what you sense" (McCloskey and Prochazka 1994). The impacts of different sensory inputs on CNS networks are diverse and complicated, but sensory deficits certainly severely interfere with motor control (and kinesthesia). In particular, proprioception is of great importance for motor control (Prochazka and Ellaway 2012) and kinesthesia (Proske and Gandevia 2012, 2018).

Sensory impairments at early stages of ALS have been underestimated. In both ALS patients and mouse models, sensory neurons reveal abnormalities (Limanaqi et al. 2017; Riancho et al. 2021; Tao et al. 2018). There are three categories: (a) sensory peripheral nervous system; (b) sensory ascending spinal tracts; and (c) somato-sensory cortex (Riancho et al. 2021).

Proprioceptive afferents of groups Ia and II from muscle spindles appear to be damaged in ALS, probably because of their monosynaptic connections to α-MNs (at least in cats: Kirkwood and Sears 1974; Stauffer et al. 1976) while group Ib afferents from Golgi tendon organs are not. The latter may also apply to some group II cutaneous afferents which signal proprioceptive information on joint position and movements (Edin and Abbs 1991). The degeneration of Meissner corpuscles needs explanation because they do not monosynaptically connect to α-MNs.

In two lines of transgenic mice (SOD1-G93A and TDP43-A315T), there was no difference in the total number and size of proprioceptive sensory neuron somata in dorsal-root ganglia (DRG) between symptomatic (SOD1-G93A) and control mice. Group Ia and II sensory terminals around the equatorial region of intrafusal fibers of muscle spindles revealed early alterations before the symptomatic phase of the disease. During the symptomatic phase, these sensory endings underwent degeneration, in parallel with degeneration of the central endings on α-MNs, when the neuromuscular junction was denervated. By contrast, group Ib proprioceptive afferents from Golgi tendon organs and γ-MN nerve endings were mostly spared at all ages examined. Spinal nerve endings terminating on α-MNs were affected during the symptomatic phase and after peripheral nerve endings had begun to degenerate. This indicates that cells directly contacting α-MNs are preferentially affected in ALS. In muscles, α-MN terminals at neuromuscular junctions undergo bouts of degeneration and regeneration in young asymptomatic mice expressing mutant SOD1. Later in life, α-MN axons degenerate via a process termed `dying back´, resulting in the appearance of neurological symptoms from denervation of muscle fibers and loss of α-MNs (Pun et al. 2006; Vaughan et al. 2015). It should also be mentioned that another crucial mechanism of α-MN degeneration, namely a `dying forward´ mechanism (Eisen and Weber 2001; Vucic et al. 2013) has been assumed. The main assumption is the anterograde glutamate-mediated excitotoxic process responsible for α-MN degeneration.

In the SOD1-G93A mouse, large proprioceptive neurons in the dorsal-root ganglion (DRG) accumulated misfolded SOD1 and underwent a degenerative process involving the inflammatory recruitment of macrophagic cells, and degenerating sensory axons occurred in association with activated microglial cells (Dibaj et al. 2011a, 2011b). As large proprioceptive DRG neurons project monosynaptically to ventral horn α-MNs, it was hypothesised that a prion-

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like mechanism might be responsible for the transsynaptic propagation of SOD1 misfolding from ventral-horn α-MNs to DRG sensory neurons (Sábado et al. 2014).

As to changes in the muscle-spindle loop, animal models of ALS have provided some relevant data. In ALS mice models, VGLUT1 immunoreactivity, presumably originating from proprioceptive afferents, was reduced in the ventral horn of the spinal cord at day 110 and was almost absent at day 130, indicating loss of muscle spindle afferent input to α-MNs. This may have been due to the initial degeneration of proprioceptive nerve endings in the periphery, which was followed by the loss of their central projections onto α-MNs. Proprioceptive afferents in the mesencephalic nucleus of the SOD1 mouse were less excitable at P11 due to reduced expression of Nav1.6-type Na^+ currents, which could lead to compensatory increases in the excitability of their target α-MNs (Falgairolle and O´Donovan 2020). Elimination of group Ia fiber synapses protects α-MNs, implicating that this excitatory input is involved in α-MN degeneration. The reduction of group Ia afferent activation by targeted reduction of γ-MNs delays symptom onset and prolongs lifespan. All this suggests that group Ia excitatory inputs contribute to α-MN degeneration, so that silencing these inputs improves α-MN survival (Lalancette-Hebert et al. 2016). But there are other excitatory inputs to α-MNs.

2.2.1.2 Other Sensory Inputs

In transgenic mice, expressing a human SOD1 mutant (hSOD1-G93A), exhibited significant sensory damage, including Wallerian-like degeneration in axons of the DRG and dorsal funiculus, and mitochondrial damage in DRG neurons (Guo et al. 2009). SOD1-G93A mice display small-diameter fiber pathology, as measured by loss of intra-epidermal nerve fibers and Meissner corpuscles (Rubio et al. 2016; Sassone et al. 2016)

Cutaneous Small-diameter Fibers are primarily involved in nociception and thermosensibility. One third of ALS patients reported cutaneous sensory symptoms. Sural sensory response amplitudes were reduced in a similar proportion of patients. Sural nerve biopsy showed that predominantly large-diameter myelinated fibers were affected while small-diameter myelinated fibers were affected less frequently (Hammad et al. 2007). About 16% of pure ALS patients complained of sensory disturbances with different distributions, and most ALS patients showed a loss of intra-epidermal small-diameter nerve fibers (Dalla Bella et al. 2016). ALS patients showed a significant reduction in intra-epidermal nerve fiber density as well as a significant loss in Meissner´s corpuscles (Nolano et al. 2017; Ren et al. 2018).

Muscle Small-diameter Fibers. What about small-diameter fibers from skeletal muscles, which are also involved in nociception, thermosensibility and some mechano-reception of muscle events?

Pain. Noxious stimulation of cutaneous or muscular free nerve endings with afferents in groups III and IV elicit motor (e.g., withdrawal reflexes), cardio-vascular and respiratory reactions, as well as arousal, pain and stress, the latter in turn influencing pain sensations. Primary causes of pain include pain with neuropathic features, spasticity, and cramps, with the latter being the major cause, while spasticity typically starts at advanced stages. Secondary causes develop during progressive paresis, which induces immobility and degenerative changes in connective tissue, bones, and joints, leading to musculo-skeletal pain (Chiò et al. 2017; Delpont et al. 2019; Riancho et al. 2021; Verschueren et al. 2021). Rhythmic stimulation, treadmill training, and cycling enhance the expression of brain-derived neutrophic factor (BDNF) and counters the development of nociceptive sensitization (Grau et al. 2020).

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Pain and Stress. While the importance of pain in ALS patients has attracted increasing attention, that of psychic stress has not. Pain powerfully activates systems involved in emotional stress responses, such as anxiety, fear and frustration. Chronic pain can indirectly contribute to all categories of stress. Conversely, stress may influence the generation, maintenance and perception of pain. There are significant differences between acute and chronic states of pain and stress. While the acute states are frequently beneficial in ensuring survival, chronic pain and stress are generally detrimental and may have adverse effects on health, depending on various factors including genetic predisposition, early life experience and other factors (de Kloet et al. 2005; Gunnar and Quevedo 2007; Schaeuble and Myers 2022). Stress deserves more attention.

2.2.1.3 Ascending Sensory Systems

Ascending Spinal Tracts. Spinal sensory tracts ascend through the dorsal (light touch, vibration, and proprioception) and antero-lateral (pain and temperature) columns. Sensory evoked potentials (SEPs) and laser evoked potentials (LEPs) showed that, compared to healthy controls, a substantial proportion of ALS patients had prolonged nerve conduction latencies. Also, diffusion tensor imaging (DTI) and MT MRI sequences have demonstrated spinal alterations in both dorsal and antero-lateral tracts (Riancho et al. 2021). Using DTI of the dorsal columns at C5-T1 levels and SEPs after median and ulnar nerve stimulations in ALS patients with moderate disability indicated anatomical damages of ascending sensory fibers in about 60% of patients (Iglesias et al. 2015).

Somato-sensory Cortex. Compared with control subjects, ALS patients contain smaller numbers of neurons in the primary motor (MI) and primary somato-sensory (SI) cortex (Mochizuki et al. 2011). The median survival time was significantly shorter in patients who had larger somato-sensory cortical amplitudes in SEPs, suggesting that sensory-cortex hyperexcitability predicts short survival (Shimizu et al. 2018). Evidence suggests that the motor cortex is hyperexcitable in response to transcranial magnetic stimulation and that marked disinhibition is present in the somato-sensory cortex as of >2 years after disease onset (Nardone et al. 2020).

2.2.1.4 Interneuronal Inputs to α-MNs

Excitatory Interneuronal Inputs. Other excitatory inputs to α-MNs derive from interneurons. Loss of V2a interneurons in ALS has been suggested to deplete the direct connectivity to α-MNs, which might be what drives V2a loss. A similar mechanism might cause the loss of $V0_c$ interneurons, a small compact group of interneurons close to the central canal. This is supported by the finding that the percentage loss of the $V0_C$ and α-MNs are tightly correlated. $V0_C$ neurons provide direct neuromodulatory input α-MNs, being more frequent on FF-type α-MNs than S-type α-MNs via large so-called `C-bouton´ synapses and thereby regulate α-MN excitability in a task-dependent manner by reducing afterhyperpolarization (Falgairolle and O´Donovan 2020; Miles et al. 2007; Zagoraiou et al. 2009). Changes in the C-boutons found in both ALS patients and in transgenic mice that carry the mutant form of superoxide dismutase 1 (mSOD1-G93A), suggest that they play a role in ALS disease progression. C-boutons are necessary for behavioral compensation in mSOD1-G93A mice. Symptomatic mSOD1-G93A mice showed significantly higher C-bouton activity than wild-type mice during low-intensity walking. Also, C-bouton silencing in combination with high-intensity training worsened gross weight but improved fast-twitch muscle weight and was beneficial for the behavioral capabilities of mSOD1-G93A mice and prolonged their lifespan in over-untrained mSOD1-G93A mice with silenced C-boutons,

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but not over-untrained mSOD1-G93A mice. The presence of C-boutons also significantly worsened fast-twitch muscle innervation over time. The $V0_C$ interneurons, and thus C-boutons, were active in a task-dependent manner and in symptomatic mSOD1-G93A mice.

Nonetheless, there is evidence to indicate that another alternative modulatory system must be involved in compensating for the loss of C-bouton modulation, namely the serotonergic system, for three reasons: 1) The serotonergic system modulates α-MN excitability by increasing persistent inward currents (PICs); 2) it slows disease progression and improves motor function in ALS; 3) the $V0_c$ interneurons also receive serotonergic input. Thus the serotonergic modulatory system might be up-regulated when the $V0_c$ interneurons fail (Wells et al. 2021).

Inhibitory Interneuronal Inputs. The role of Renshaw cells mediating spinal recurrent inhibition in ALS has been studied in humans and animals (Sect 4.4). There is evidence that recurrent inhibition is reduced in ALS patients (Sect 4.4). In animal models of ALS, the innervation of Renshaw cells by α-MNs is lost early on and is associated with a down-regulation of VAChT in α-MNs. At this time, Renshaw cells appear to produce axonal sprouting leading to transient up-regulation of glycinergic synapses on α-MNs. However, as the disease progresses, Renshaw cells receive progressively less input from α-MNs, with some Renshaw cells being completely denervated. A proportion of Renshaw cells then dies during disease advance. Thus there is evidence that a reduction in α-MN inputs to Renshaw cells leads to a reduction in recurrent inhibition, but that Renshaw cells initially compensate by sprouting on remaining viable α-MNs (references in Brownstone and Lancelin 2018; Falgairolle and O´Donovan 2020). It has been argued, however, that on various grounds the loss of Renshaw cells plays a decisive role in making α-MNs more susceptible to glutamate excitotxicity, and moreover, that in cats and humans, it is sparse or absent in α-MN pools that innervate distal limb muscles in which initial wasting is prominent in human ALS (Mazzocchio and Rossi 2010).

In mutant SOD1-G93A mice, inhibitory spinal circuits exhibit abnormalities early on. For example, the GABA equilibrium potential in α-MNs is more depolarized than in wild-type animals, indicating an alteration in chloride homeostasis at E17.5. At this early stage, inhibitory synaptic terminals on α-MNs show a deficiency, which persists into postnatal life. The loss of glycinergic function appears to be specific for large α-MNs because it is not observed in small, fatigue-resistant (S-type) α-MNs and presumed γ-MNs. The reduced inhibitory input could be due to loss of inhibitory interneurons or to weaker inputs from inhibitory neurons (Falgairolle and O´Donovan 2020).

Changes in inhibitory interneurons were also found in the spinal cord of mice (ALS model low-copy Gurney G93A-SOD1), in which the expression of markers of glycinergic and GABAergic neurons were reduced. This suggests that, in mutant SOD1-associated ALS, pathological changes may spread from α-MNs to interneurons early on. The degeneration of spinal inhibitory interneurons may in turn facilitate degeneration of α-MNs and contribute to disease progression (Hossaini et al. 2011). SOD1-G93A α-MNs showed a decrease of surface postsynaptic glycine receptors, which may contribute to inhibitory insufficiency in α-MNs early in the disease process (Chang and Martin 2011).

2.2.2 Comments and Questions

A MN is a neuron in the brainstem or spinal cord that innervates muscle fibers, extrafusal and/or intrafusal. Any neuron that innervates MNs is a premotor neuron. What are `lower´ and `upper´ MNs?

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The question as to the origin of ALS processes has been speculated upon from the beginning.

About half of the ALS patients show cognitive-behavioral deficits. Together with other degenerative brain diseases, such as Alzheimer´s disease and Parkinson´s disease, ALS shares the histo-pathological phenomena of aggregation of abnormally altered endogenous proteins in the nervous system. A so-called staging model of the abnormally phosphorylated protein TDP-43 (pTDP-43) pathology in sporadic ALS proposes that four stages can be distinguished, where pTDP-43 inclusions are found in different places. Stage 1: agranular motor cortex and α-MNs of the brainstem and spinal cord. Stage 2: pre-frontal cortex (middle frontal gyrus), reticular formation, and pre-cerebellar nuclei. Stage 3: other areas of the pre-frontal cortex (gyrus rectus and orbito-frontal gyri), post-centrally located sensory cortex, and basal ganglia. Stage 4: antero-medial temporal lobe including the hippocampus. Accordingly, a cortico-fugal spreading of pathology has been hypothesized (`dying forward´), whereby pathology starts in the primary motor cortex and spreads from there via axonal projections to sub-cortical structures and α-MNs (Verde et al. 2017).

Another hypothesis lets pathology start in the periphery, at the other end of the motor-control system, and harks back to the α-γ loop (Sect 2.2.1). It proposes that the primary target of ALS lies in the muscle, not only in extrafusal, but also intrafusal muscle fibers, resulting from oxidative stress, mitochondrial and myogenic pathology. The ensuing reduction of neurotrophic factors would lead to the pre-symptomatic degeneration of motor and sensory axons as a `dying-back´ axonopathy ending in MN death (Limanaqi et al. 2017).

Whether a third (intermediary) proposal, attempting an integrative view, will solve the priority problem is uncertain. It poses “synaptic failure as a converging and crucial player to ALS etiology. Homeostasis of input and output synaptic activity of MNs has been proved to be severely and early disrupted and to definitively contribute to microcircuitry alterations at the spinal cord. Several cells play roles in synaptic communication across the MNs network system such as interneurons, astrocytes, microglia, Schwann and skeletal muscle cells” (Casas et a. 2016).

So, the question of what comes first and is the origin of it all remains open. But how can we be sure about the start within a multi-system disease whose elements and entagled interactions are not completely known as yet? Time may tell.

3 Brain and Spinal Cord Lesions

The following discussion will concentrate on spinal cord injury (SCI) with occasional mention of higher brain damage. The consequences after SCI in humans go through several stages, beginning with acute effects.

3.1 Acute Effects of SCI

SCI is caused by a primary mechanical insult, e.g., acute compression, sharp injury, missile, laceration, shear etc. This is followed by a secondary injury, comprising an acute, a sub-acute and a chronic phase.

The primary insult of SCI arises from the loss of directly damaged gray matter and neural pathways, as well as tissue damage beyond. The acute phase within the first 48 hours after primary injury is associated with spinal ischemia, vasogenic edema, and glutamate

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excitotoxicity. The sub-acute phase within the first two weeks after primary injury involves mitochondrial phosphorylation and neuro-inflammation. The chronic phase extends from days to years and includes apoptosis and necrosis, acute axonal degeneration and glia scar formation (Donnelly and Popovich 2008; Hachem and Fehlings 2021).

At the cellular level, the following changes occur. Immediately after injury, the perished and dying neurons release death signals which exacerbate the injury. The immediate tissue damage activates the innate and adaptive immune response (Donnelly and Popovich 2008). Monocyte-derived macrophages and activated microglia remove the debris from the initial primary insult. These immune cells remain long after debris is removed and continually release inflammatory cues that initiate secondary injury in areas rostral and caudal to the injury epicenter. Reactive astrocytes limit the spread of inflammation, compensate for a leaky blood-brain barrier, and reduce lesion expansion by forming a glial scar, which may also prevent axonal regeneration through the lesion. Evidence supports astrocytic release of growth-promoting factors, such as laminin, but the cumulative effect is detrimental to recovery. Other processes also contribute to the inability of damaged axons to regenerate after injury. Wallerian degeneration of the distal axons and myelin results in debris releasing Nogo (or Rtn4), MAG (myelin-associated glycoprotein) and OMgp (oligodendrocyte myelin glycoprotein, or Omg), which have all been shown to inhibit regeneration and sprouting. Collectively, these impediments limit the efficacy of spontaneous recovery (Lee et al. 2010; Walker and Ryan-Detloff 2021).

Behaviorall, the acute effect of a complete SCI in humans is a spinal shock in which neither locomotor nor spinal reflexes can be evoked. Muscles are paretic and flaccid (Dietz 2010; ElBasiouny et al. 2010). The main reason for spinal shock is the sudden loss of supraspinal influences on spinal networks, that is, the damage of cortico-spinal (CST) glutamatergic signalling, as well as the loss of bulbo-spinal monoaminergic pathways and their powerful descending modulation of spinal excitability (Leech et al. 2018; Perrin and Noristani 2019).

In animals, the spinal shock is associated with a dramatic reduction of extensor muscle tone and of spinal reflexes, including postural limb reflexes (PLRs). One factor responsible for the reduced efficacy of spinal reflexes is a decrease in the excitability of spinal α-MNs. Another factor is a decrease in the activity of most spinal interneurons, including PLR-related interneurons.

For example, in decerebrate rabbits in which the head and the vertebral column and pelvis were rigidly fixed, anti-phase flexion/extension movements of the hindlimbs caused by roll tilts of a supporting platform elicited postural limb reflexes (PLRs). Neurons in spinal segments L5–L6, which presumably contributed to the generation of PLRs, could be divided into three groups: F-interneurons activated during flexion of the ipsilateral limb, E- interneurons activated during extension of this limb, and a group of non-modulated interneurons. In decerebrate rabbits acutely spinalized at T12, postural functions were lost, including the disappearance of PLRs in response to roll perturbations of the supporting platform. The three interneuron groups named above reacted differently to spinalization. The proportion of non-modulated interneurons in spinal rabbits was larger than in control animals (33% *vs* 18%). This was probably due to the fact that, after elimination of supraspinal drive, part of the modulated interneurons became non-modulated. Spinalization affected the distribution of F- and E-interneurons in segment L5 across the spinal gray matter, caused a significant decrease in their activity, as well as disturbances in processing of posture-related sensory inputs. The decrease in activity (mean frequency, burst frequency, and depth of modulation) of F- and E-interneurons could be caused by three factors: (1) a decrease in excitability of spinal interneurons; (2) a decrease in efficacy of sensory input from limb mechano-receptors; (3) a decrease in the value of sensory input due to a strong reduction in the forces developed by extensor muscles and monitored by load receptors, as well

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as due to inactivation of γ-MNs, leading to a decrease in signals from muscle spindles. Spinalization affected the contribution of sensory inputs from the ipsilateral and contralateral limbs to modulation of F- and E-interneurons. Thus, there was an almost two-fold increase in the proportion of interneurons modulated by sensory input from the ipsilateral limb and a corresponding decrease in the proportion of interneurons with a contribution of input from the contralateral limb. This was caused by a significant reduction in the efficacy of tilt-related sensory inputs from the contralateral limb to both F- and E-interneurons across the entire gray matter. Most likely, commissural interneurons (CINs) transmitting signals from the contralateral limb are inactivated by acute spinalization. Spinalization affected differently the efficacy of sensory inputs from the ipsilateral limb to F- and E-interneurons. These changes in the operation of postural networks underlie the loss of postural control after spinalization, and represent a starting point for the development of spasticity (Zelenin et al. 2019).

3.2 Chronic Effects of SCI

After the initial spinal shock, locomotor activity and early spinal reflexes reappear in response to appropriate sensory input. In the subsequent 4-8 months, clinical signs of spasticity appear (Dietz 2010), but deficits in excitation of spinal α-MNs by descending pathways remain and conrtibute to weakness. In incomplete SCI, sensory afferent inputs may assume a disproportionately larger influence on volitional activation than in normal adults, as during volitional upper extremity tasks or standing and stepping. After incomplete SCI, specific changes contribute to spasticity, including changes in α-MN excitability and sensitivity to serotonin (5-HT) (Sect 4.2.1), decreased reciprocal inhibition (Sect 4.3), recurrent inhibition (Sect 4.4) and presynaptic inhibition (Sect 4.5), sprouting of descending (cortico-, bulbo-, and propriospinal) pathways, as well as alterations in interneuronal pattern-generating networks (Martin 2022). Beyond these spinal alterations, plasticity in sub-cortical networks and sensory-motor cortices develop, probably to partially compensate for muscle weakness that is due to loss of whole muscle and muscle fiber size (i.e., atrophy), alterations in fiber phenotype, and increased fatiguability (Leech et al. 2018).

In patients with incomplete SCI, spinal excitability is increased during the performance of strong voluntary contractions compared with that in healthy subjects. In intact subjects, maximal voluntary contractions (MVCs) that fatigue a muscle result in reduced volitional output, but the opposite holds in SCI patients. In intact subjects, twenty repeated isometric MVCs of the knee extensors resulted in an immediate and sustained decline in peak torque production (~30–35% decrease), while individuals with incomplete SCI produced increased peak torque and electromyographic (EMG) activity by the third contraction (15–20%). In SCI patients, these gains in muscle activation over repeated MVCs were partly due to increased central excitability during maximal contractions, consistent with the presence of PICs (Sect 2.2.1). Thus, in SCI patients, elevated reflex activity typically characterized as spasticity may boost motor performance during both static and dynamic tasks (Leech et al. 2018).

3.3 Spasticity

Spasticity is a long-term symptom of brain and spinal cord damage. It has tradidionally been defined as an augmented resistance of skeletal muscle at rest to passive stretch in a velocity-dependent way. But this definition is based on a fast and simple clinical test and not on a comprehensive description of spasticty and its underlying mechanisms. In fact, the term spasticity is now mostly used in a wider sense (Nielsen et al. 2020).

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Spasticity can occur subsequent to traumatic brain injury, stroke, cerebral palsy, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), spinal cord injury (SCI), and in many other disorders (Bose et al. 2015; Chiò et al. 2017; D´Amico et al. 2014; Dietz 2010; Dietz and Sinkjaer 2012; Eldahan and Rabchevsky 2018; Ganguly et al. 2021; Hachem and Fehlings 2021; Haefeli et al. 2017; Jean-Xavier et al. 2018; Mukherjee and Chakravarty 2010; Nielsen et al. 2020; Sheean and McGuire 2009; Trompetto et al. 2014; Wolpaw 2018). For simplicity, we will here emphasize SCI-related and occasionally mention stroke-related syndromes. Spasticity goes along with the following chronic symptoms.

Increased muscle tone (hypertonus) with muscle stiffness

Sustained involuntary muscle contractions

Hyperexcitable muscle stretch reflexes associated with velocity-dependent resistance to passive muscle stretch

Increase in short-latency stretch reflexes with enhanced tendon-tap reflexes

Clonus

Clasp-knife reflex

Loss of long-latency reflexes

Synkinesia: co-contraction of normally independently controlled muscles

Long-lasting exaggerated cutaneous reflexes (e.g., flexor or withdrawal reflexes)

Severe uncontrollable muscle spasms

Impaired voluntary activation of multiple muscles

Sensory disturbances such as enhanced abnormal sensation, dysesthesia and pain

Secondary changes in mechanical muscle-fiber properties, collagen tissue, and tendon properties (e.g., loss of sarcomeres, subclinical contractures)

Autonomic and immune dysfunctions

The specific syndromes differ with different causes. For example, unilateral stroke in the forebrain may leave intact various tracts descending to the spinal cord. By contrast, spinal cord injury (SCI) damages one or the other tract (in in-complete SCI) or all tracts (in complete SCI) and can thus produce manifold primary anatomical and pathophysiological changes, associated with secondary changes including neurotoxicity, vascular dysfunction, glial scarring, neuro-inflammation, apoptosis and demyelination (Sandrow-Feinberg and Houlé 2015). The effects of SCI depend on the species, completeness, extent and site of the lesion, and the state of the animal (Darian-Smith 2009; ElBasiouny et al. 2010; Jean-Xavier et al. 2018; Zholudeva et al. 2018). A problem in elucidating these processes is that they differ considerably between rodents, non-human primates and humans (Filipp et al. 2019).

Prominent chronic features after SCI are excessive spasms in extensor and flexor muscles with lesser expression of increased muscle tone (Ganguly et al. 2021) as compared to the opposite pattern after stroke, indicating different underlying mechanisms (ElBasiouny et al. 2010; Hachem and Fehlings 2021). Some of these changes have formerly been considered maladaptive, particularly those leading to involuntary motor behaviors, such as spasticity, spasms, and clonus (Sect 4.1.1.2). However, animal models of incomplete SCI and human studies also suggest that increased spinal excitability underlying hyperexcitable reflexes may facilitate motor function, particularly when utilized during voluntary tasks (Leech et al. 2018).

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Autonomic and Immune Dysfunctions. Without delving into details here, it needs emphasis that the disruption of descending tracts also causes a number of autonomic abnormalities, including compromised cardiovascular, respiratory, urinary, gastro-intestinal, thermo-regulatory, and sexual activities. In brief, high thoracic or cervical SCI often causes life-threatening disordered hemodynamics and respiratory dysfunctions due to de-regulated sympathetic outflow, while the parasympathetic (vagal) control remains intact. With injuries below the 5th thoracic segment, both the sympathetic and parasympathetic control of the heart and broncho-pulmonary tree are intact (Eldahan and Rabchevsky 2018; Hachem and Fehlings 2021; Hou and Rabchevsky 2014; Krassioukov 2009). Moreover, SCI disrupts the neural and humoral control of immune cells. Autonomic dysfunction and impaired neuro-endocrine signalling are instrumental in determining the so-called `SCI-induced immune deficiency syndrome´, in which mature leukocyte dysfunction plays a sigificant role and the development and mobilization of immune cell precursors in bone marrow are impaired (Rodgers et al. 2022).

3.4 Quiet Standing and Sitting in Humans with SCI and Stroke

Without sensory feedback, no upright stance and its maintenance. The sensory inputs of importance derive from a number of peripheral receptor systems. Here we concentrate on inputs processed at spinal level and their change after SCI.

Covarrubias-Escudero et al. (2019) used body-worn accelerometers positioned at L5 to measure characteristics of body sway, such as the amplitude, frequency, and smoothness, during quiet upright stance in incomplete SCI (iSCI) patients. These patients presented with increased postural sway as measured by altered initial values of jerk (time derivative of acceleration) as compared to normal subjects. Although they were able to generate postural adaptations to environmental challenges, these patients could not fully compensate for the postural control changes caused by their sensory and motor impairments. It has been argued that incomplete SCI patients might have increased postural sway consequent to deficient motor responses related to timing muscle contractions, which in turn would be the consequence of the diminished motor pathways, thus being insufficient to react and generate appropriate postural adjustments. Postural sway could also increase due to damaged somato-sensory pathways, which are often compromised after SCI and subsequently reflect noisy somato-sensory feedback from foot pressure, muscle proprioceptors, and joint receptors. Damaged somato-sensory pathways could thus provide inaccurate information about body position in space. Together, these possible consequences of incomplete SCI could generate frequent, abrupt corrections of postural sway direction and might be responsible for higher jerk values as compared to healthy individuals (Covarrubias-Escudero et al. 2019).

Due to partial muscle paralysis, incomplete SCI patients tend to have atrophy and weakness in the ankle pantar-flexor muscles and consequently reduced standing balance. A potential compensatory strategy to reduce instability during quiet upright stance is to co-contract ankle plantar-flexor and dorsi-flexor muscles, which increases the ankle-joint stiffness, which in turn increases postural sway. These co-contractions may be a strategy used by older adults as well as by subjects with incomplete SCI to compensate for muscle weakness at the ankle joint and thus their upright posture. Indeed, an incomplete SCI group exhibited more co-contractions than an able-bodied group, and postural sway was larger during ankle muscle co-contractions than during no co-contraction in the SCI-group. It has been hypothesized that the increased co-contraction in the SCI-group may be due to a switch of reciprocal inhibition (Sect 4.3) to facilitation. Both recurrent inhibition (Sect 4.4) and presynaptic inhibition (Sect 4.5) operate incorrectly after SCI which influences reciprocal inhibition. After SCI, reciprocal

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inhibition has been shown to be replaced with facilitation, which might increase co-contractions of ankle plantar- and flexor muscles (Lon Fok et al. 2021).

During quiet standing, subjects with incomplete SCI showed larger postural sway than did able-bodied subjects, primarily due to larger ankle-joint acceleration. Also, while in able-bodied subjects the ankle- and hip-joint accelerations were in anti-phase to minimize the postural sway, this interjoint coordination was not affected in SCI patients, which could therefore not help reduce the large center-of-mass (COM) accelerations (Lee et al. 2021).

Patients with spasticity of different etiologies and degrees stood quietly upright on a force platform. The body sway measured was not correlated with muscle tone, muscle strength, tendon reflexes, plantar responses, or duration of the disease. On average, as compared to normal subjects, all patient groups showed a forward shift of the center of pressure (COP) under the feet. Moreover, paraparetic and to a much larger extent hemiparetic patients showed a lateral shift of COP. Sudden rotations of a supporting platform, in a toe-up or toe-down direction to stretch the soleus muscle or the tibialis anterior (TA) muscle, respectively, evoked short-latency (SLR) and medium-latency (MLR) reflex responses [The former is assumed to be mediated by muscle-spindle group Ia afferents and the second by group II afferents (Schieppati and Nardone (1997)]. As compared to normals, soleus SLR was increased in all patients. TA SLR was often seen in both patients with ALS and paraparetic patients, but only rarely in normal subjects and hemiparetic patients. By contrast, the MLRs of soleus and TA in the affected leg were diminished in hemiparetic patients, which could contribute to increased body sway. These responses were decreased in size and not modulated by background EMG in the affected leg of hemiparetic patients, suggesting a disturbed control of spinal reflexes fed by spindle group II afferent fibers (Nardone et al. 2001).

In post-stroke patients with spastic hemiparesis standing upright on a force platform, the center of pressure (COP) under the feet is shifted toward the unaffected limb. This stance asymmetry can predict deficits in gait resulting from increases in the time and effort needed to shift body weight toward the affected limb (Nardone et al. 2009).

Thoracic spinal cord injury (SCI) can negatively affect the ability to maintain unsupported sitting. Subjects with high- and low-thoracic SCI swayed more than did able-bodied control subjects regardless of upper-limb support. The level of injury was correlated with postural performance insofar as those with higher injuries swayed more and faster. Unsupported sitting was more unstable in comparison to supported sitting posture, especially in the anterior-posterior direction. The way subjects with high-thoracic SCI achieved stability was different from that of subjects with low-thoracic SCI, suggesting different postural regulation strategies (Milosevic et al. 2017). Similar reductions in postural stabilty have been observed in subjects with motor-complete thoracic SCI who showed a trunk postural sway constraint to maintain the suboptimal unsupported sitting balance (Ilha et al 2020). In another study on seated subjects, the SCI group had greater center of pressure (COP) sway than the controls, with no difference in the postural sway between the SCI subgroups, suggesting that the impairment in individuals with SCI results from disturbed supraspinal and peripheral mechanisms (Shin and Sosnoff 2017).

3.5 Quiet Stance and Responses to Stance Perturbations in Spinal Animals

Many aspects of the specific pathophysiology remain unclear. To elucidate underlying mechanisms, various experimental animal models of spasticity have been developed,

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categorized based on the mechanism of injury into contusion, compression, distraction, dislocation, transection or chemical models (Cheriyan et al. 2014).

3.5.1 Quiet Stance in Spinal Cats

The extent to which spinal circuits contribute to the maintenance of upright stance has been studied in cats after spinalization. Adult cats chronically spinalized at mid-thoracic level can be trained to stand for a short while, with the body parallel to the support surface and the hip held at normal height (Fung and Macpherson 1999; Macpherson and Fung 1999; Pratt et al. 1994). This demonstrates that the spinal cord can define set points regarding limb geometry, and in so doing, regulate extensor muscle lengths at knee, ankle, and metatarsal-phalangeal joints (Fung and Macpherson 1999). However, although this mechanism may contribute significantly to weight support, it is not sufficient for balancing the body (Macpherson and Fung 1999) because the direction-specific muscle synergies are absent (Chvatal et al. 2013).

3.5.2 Postural Responses to Surface Motions in Spinal Cats

The intact cat can maintain balance during unexpected stance perturbations through automatic, stereotyped and rapid postural responses. Responses were elicited to 16 directions of linear translation in the horizontal plane and various variables measured before and after spinalization at the T(6) level. After spinalization, four cats were trained to stand on a force platform. All cats were able to support their full body weight. However, the cats usually required assistance for balance in the horizontal plane, provided by gentle lateral force at hips. Perturbations were delivered during the periods of independent stance in three cats and during assisted stance in the fourth. A response to translation occurred only in those muscles that were tonically active to maintain stance and never in the flexors. Latencies were increased and amplitudes of EMG activation were diminished compared with normal cats. Hence, the spinal cat can achieve good weight support, but cannot maintain balance during stance except for brief periods and within narrow limits, centers above the lumbosacral cord being required for full automatic postural responses. This limited stability is probably provided by the stiffness of tonically active extensor muscles and spinal reflex mechanisms (Macpherson and Fung 1999).

3.5.3 Interneurons Mediating Postural Reflexes

In the decerebrate rabbit in which the head and the vertebral column and pelvis were rigidly fixed, anti-phase flexion/extension movements of the hindlimbs caused by roll tilts of a supporting platform elicited postural limb reflexes (PLRs). Neurons in spinal segments L5-L6, which presumably contributed to the generation of PLRs, could be divided into two groups: F-neurons activated during flexion of the ipsilateral limb, E-neurons activated during extension of this limb. There was also a group of non-modulated neurons. F- and E-interneurons were intermingled and scattered across the whole cross-section of the gray matter. The phase of modulation of a neuron was determined mainly by sensory input from the ipsilateral limb. The majority of neurons received mono- and polysynaptic sensory inputs from both limbs, with the inputs being linearly summated. Sensory inputs from the receptive field of a neuron (determined at rest) can be responsible for the tilt-related modulation only in some of the neurons (Zelenin et al. 2015).

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On a longer time base, spinalization of rabbits triggers two kinds of plastic changes: 1) rapid restoration of normal activity levels in interneurons, which takes days, 2) slow recovery of α-MN excitability, which takes months. Most likely, recovery of interneuron activity underlies re-appearance of α-MN responses to postural stimuli. However, the absence of recovery of normal processing of postural sensory signals and the enhancement of oscillatory activity of interneurons result in abnormal PLRs and loss of postural functions. The relative number of F- and E-interneurons activated from receptive fields from skin/fur receptors increased up to 60% vs. 7% in control and 4% after acute spinalization. Chronic spinal rabbits often show spasms of long duration appearing spontaneously or caused by unspecific sensory stimuli, for which multiple mechanisms have been suggested: changes in biophysical properties of α-MNs; reduced presynaptic inhibition (Sect 4.5) of afferents; changes in inhibition efficacy. Furthermore, excitatory (glutamatergic) interneurons may be important in triggering and sustaining the spasms; in particular, V3 interneurons may initiate spasms (Zelenin et al. 2019). The changes are probably due in part to specific loss of supraspinal inputs but also to plastic processes whose cellular and molecular underpinnings are not yet well understood.

3.6 Locomotion

In principle, locomotor rhythms can be generated by spinal central pattern generators (CPGs), which are autogenous in the sense that they do not depend on afferent sensory feedback (fictive locomotion) or spinally descending signals for their basic rhythm-generating function (Rossignol et al. 2006). But the autonomy of the isolated spinal cord for generating locomotor rhythms is far greater in the spinalized rat or cat than in primates, including humans.

Spinal rhythm generation by CPGs require the coordinated activities of many neuron groups that organize the basic rhythmic spinal outputs as well as the spatio-temporal patterns of muscle activities, which must be capable of answering the varying demands of internal goals and the environment. The spatio-temporal patterns include flexion–extension alternation in intra-limb coordination and left–right coordination of different limbs. The underlying neuronal mechanisms have begun to be unravelled over the past few decades using anatomical, developmental, genetic, molecular, anatomical and electrophysiological methods, particularly in mice (Arber 2012; Côté et al. 2018; Gosgnach et al. 2017; Haque and Gosgnach 2019; Kiehn 2016; Rancic and Gosgnach 2021; Steuer and Guertin 2019; Ziskind-Conhaim and Hochman 2017), but also in cats. CPGs most probably exist in man, but are much less known than in mice and other mammals (Grillner and El Manira 2020; Klarner and Zehr 2018; Minassian et al. 2017).

Sensory inputs have diverse roles in locomotion. Proprioceptive feedback reinforces ongoing motor output, shapes muscle activities and contributes to timing the transitions between the different locomotor step phases. It also plays an important role in adjusting the basic locomotor rhythm to environmental conditions and in compensating for unexpected perturbations. Various sources of sensory feedback change throughout the gait cycle, and all known spinal reflex pathways are modulated during locomotion: stretch reflexes and H-reflexes (Sect 4.1), and presynaptic inhibition (Sect 4.5). Sensory information most appropriate for the particular step phase is gated by the CPGs (Duysens and Forner-Cordero 2018; McCrea 2001; Pearson 2000, 2008; Rossignol et al. 2006; Windhorst 2007). Presynaptic inhibition is modulated by supraspinal centers and primary afferents in order to filter sensory information, adjust spinal reflex excitability, and ensure smooth movement (Quevedo 2009; Rudomin 2009; Rudomin and Schmidt 1999; Stein 1995; Sect 4.5).

In animal models and humans with SCI, sensory afferent feedback is important, if not critical, to the locomotor output. The influence of spastic motor behaviors on MN discharge and on

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different muscles suggests that the altered sensory input-motor output relationships could either facilitate or antagonize the intended motor command (Leech et al. 2028).

3.6.1 Locomotion in Spinal Cord Injured Humans

In incomplete SCI patients, the ability to walk is compromised by lower limb paresis, increased spasticity, poor coordination, impaired postural control. Body-weight support during treadmill training (BWSTT) increases muscle strength, kinematics, and spatio-temporal gait parameters (Brumley et al. 2018; Covarrubias-Escudero et al. 2019; Smith and Knikou 2016; Torres-Espín et al. 2018; Yu et al. 2019). Locomotor training promotes the plasticity of neural spinal circuits (Sect 4.11). The mechanisms contributing to functional recovery overlap with those underlying spasticity. Specific changes that contribute to spasticity include both decreased reciprocal inhibition (Sect 4.3.) and presynaptic inhibition (Sect 4.5), muscle afferent and interneuron collateral sprouting, partially resulting from the loss of competition from cortico-spinal tract (CST) terminals, and changes in MN excitability and sensitivity, particularly in response to residual serotonergic (5-HT) inputs (Leech et al. 2018; Martin 2022).

3.6.2 Locomotion in Spinalized Cats

Cats with partial low-thoracic spinal transections recovered voluntary quadrupedal locomotion with treadmill training (3-5 days/wk) over several weeks. The locomotor pattern showed left/right asymmetries in various kinematic parameters, such as homolateral and homologous interlimb coupling, cycle duration, and swing/stance durations. When partial recovery was stationary, cats were spinalized. Thereafter, the hindlimb locomotor pattern rapidly re-appeared within hours, but left/right asymmetries in swing/stance durations could disappear or reverse. Hence, after a partial spinal lesion, the hindlimb locomotor pattern was actively maintained by new dynamic interactions between spinal and supraspinal levels but also by intrinsic changes within the spinal cord (Barrière et al. 2010).

Spinalized and decerebrate cats while walking on treadmills adjust their hindlimb stepping rate to a considerable speed range between 0.1 and 1 m/s. At higher speeds, walking/trotting sometimes gives way to galloping. Increased step rate is achieved primarily by shortening the stance phase, while the flexion phase remains nearly constant. These adjustments indicate a substantial role for sensory feedback in switching between different locomotor phases, especially in regulating the stance phase duration (Pearson 2008).

In cats with a complete spinal cord injury, hindlimb locomotion is inhibited by inputs from the lumbar region but facilitated by inputs from the perineal region. In cats with a complete SCI, these inputs also exert opposite effects on cutaneous reflexes from the foot in that lumbar inputs increase the reflex gain while those from the perineal region decrease it. Moreover, spinal cord injury can lead to a loss of functional specificity through the abnormal activation of functions by somato-sensory feedback, such as the concurrent activation of locomotion and micturition (Merlet et al. 2021).

3.7 Reach-and-Grasp Movements

Reach-to-grasp movements to obtain or manipulate objects are synchronous and composed of several observable components, including limb lifting, aiming, and advancing the limb, and followed by opening the digits, pronating the wrist, grasping the object, and supinating to orient

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the object for release into the mouth. After incomplete or complete SCI at cervical level, this delicately organized sequence is disrupted or impossible, respectively. The consequences of incomplete SCI depend on the site and degree of damage.

In humans, fine motor control of the digits is largely controlled by the descending lateral cortico-spinal tract (CST), which decussates and crosses midline at the pyramids in the brainstem, and then continues through the spinal dorso-lateral white matter. These lateral CST fibers synapse in cervical MN pools to control proximal and distal muscles of the limb and digits. The MN pools for the shoulder and arm are located at levels C4-6, and the MN pools of the forearm and digits are located in C7-T1. In addition to CST control in non-human primates, there is evidence of the involvement of descending rubro-spinal and reticulo-spinal tract (RST) fibers in controlling which upper extremity muscles execute the reach and grasp of a target object. Also, direct excitatory projections from the deep cerebellar nuclei to the ipsilateral cervical spinal cord appear to be involved in the control of the reach-to-grasp movement. Mice with silenced ipsilateral cerebello-spinal projection neurons took longer to touch the food pellet and failed to successfully grasp it. After SCI, recovery or compensatory reaching and grasping is mediated by several spared systems that respond after injury. Plasticity of primary sesosry afferent fibers also contribute to improved function post-injury (Walker and Ryan-Detloff 2021).

4 Neuromuscular Changes in Spasticity

The neural control of muscles is heavily compromised during spasticity and depends on the etiology (stroke, SCI, multiple sclerosis), experimental paradigm and condition (rest, static muscle contraction, sitting, standing, locomotion, voluntary movement) and methods used. We will here emphasize SCI and mention other conditions in passing.

Loss of supraspinal signals leads to an abundance of changes below (and in fact above) the SCI site. They include changes in the number of specific neurons, adult neurogenesis, dendritic spine growth, re-distribution of sensory and descending inputs to α-MNs and interneurons, augmented sprouting of descending (cortico-, bulbo-, and propriospinal) pathways, aberrant rewiring of spinal circuits, changes in the use of afferent sensory input, dysfunctions of short- and long-latency reflexes, alterations in interneuron pattern-generating networks; increase of α-MN excitability and sensitivity to serotonin (5-HT), synaptic plasticity, and changes in skeletal muscle, tendon and ligament properties.

Chronic spinal subjects often show spasms of long duration appearing spontaneously or caused by unspecific sensory stimuli, for which multiple mechanisms have been suggested: changes in biophysical properties of α-MNs; reduced presynaptic inhibition of sensory afferents; changes in inhibition efficacy. Furthermore, excitatory (glutamatergic) interneurons, in particular V3 interneurons may be important in triggering and sustaining the spasms (Darian-Smith 2009; Dietz and Sinkjaer 2012; Edgerton et al. 2004; Fong et al. 2009; Leech et al. 2018; Nardone et al. 2015; Rossignol and Frigon 2011; Taccola et al. 2018; Zelenin et al. 2019; Zholudeva et al. 2018). Although a number of potential causes for the neuromuscular changes after SCI have been suggested, it is still not clear how these plastic and/or compensatory changes come about.

Clinically, spasticity is often defined as an increased velocity-dependent resistance to passive muscle stretch. This reflex is elicited by sensory receptors excited by muscle stretch, processed by spinal networks as the interface and ends in muscle contraction. In the following, we will discuss the various elements.

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4.1 Changes in Muscle Stretch Reflexes

Muscle stretch reflexes are much more complicated than instigated by the relatively simple tendon-tap responses of manually exerted stretches used by neurologists. And they are more complicated than the phasic H-reflex which generates a short-latency EMG wave in response to electrical stimulation of group Ia muscle spindle afferents in the parent muscle nerve. After complete SCI, the amplitude of H-reflexes in hindlimb muscles is greatly increased, but can be reduced by locomotor training (Takeoka 2020).

The notion of augmented stretch reflexes requires the consideration of various neuronal networks. Several mechano-receptors and their afferents are involved: group Ia and II afferents from muscle spindles modulated by fusimotor control by γ-MNs, group Ib afferents from Golgi tendon organs (GTOs) responding particularly to active muscle contraction, and group III and IV muscle afferents responding in part to mechanical events in muscles (Sect 4.1.2), as well as their complex central connections to α-MNs. Important special networks include: reciprocal Ia inhibition (Sect 4.3), recurrent inhibition (Sect 4.4), presynaptic inhibition (Sect 4.5), group Ib connections (Sects 4.1.1.3, 4.1.2), and connections of group III and IV afferents (Sect 4.1.1.4; review: Windhorst 2021).

These spinal interneuronal networks are under descending modulating influences from various, differentially connected descending tracts (e.g., Windhorst 2021). So, any impairment of these descending influences must be expected to derange and shift spinal network functions including the muscle stretch reflex.

When discussing muscle stretch reflexes, it is important to note that the total mechanical response of a contracting muscle to a stretch is the sum of the response from the passive tissues, the response from the properties of the muscle fibers contracting prior to the stretch (intrinsic properties), and the response from the stretch reflex-mediated contraction of the muscle fibers (Sinkjaer and Magnussen 1994).

4.1.1 Human Work

Resistance to stretch of a muscle is determined by three mechanisms: passive and intrinsic properties of the intact and active muscle system around the joint (`non-reflex component´), force generated by the stretch reflex (`reflex component´), and supraspinal control of the stretch reflex.

4.1.1.1 Length Feedback

Compared with healthy human subjects, the ankle mechanics and stretch reflexes of spastic hemiparetic stroke patients showed changes in various variables, as determined by using a nonlinear delay differential equation. Mechanically, stiffness in spastic ankle joints was higher across plantar-flexion and dorsi-flexion torque levels, and the more spastic plantar-flexor muscles were stiffer than dorsi-flexors at comparable torques. Increased stiffness in spastic ankle joints was mainly due to passive stiffness increase, indicating increased connective tissues/shortened fascicles. Viscous damping in spastic ankle joints was increased across the plantar-flexion torque levels and at lower dorsi-flexion torques, reflecting increased passive viscous damping. The more spastic plantar-flexor muscles showed higher viscous damping than dorsi-flexors at comparable torque levels. Spasticity was associated with decreased threshold

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and increased gain of tendon reflexes. The gain of the phasic component of the stretch reflex in spastic plantar-flexor muscles was higher and increased faster with plantar-flexor contraction. The gain of the tonic stretch reflex was increased in spastic ankle muscles at rest (Zhang et al. 2013).

Upright Stance. In normal subjects, muscle stretch and H-reflexes are modulated dependent on task and step phase in walking. Task-dependency is evidenced by the reduction of soleus H-reflex gain from standing to walking to running and is thought to be due to increased presynaptic inhibition (Sect 4.5; references in Thompson et al. 2019) caused by supraspinal (including cortico-spinal, CST)) control, and so is phase-dependent modulation of the H-reflex. Patients with spasticity of different etiologies and degrees stood quietly upright on a supporting force platform. Sudden rotations of the platform, in a toe-up or toe-down direction to stretch the soleus muscle or the tibialis anterior (TA) muscle, respectively, evoked short-latency (SLR or M1) and medium-latency (MLR or M2) reflex responses. As compared to normals, soleus SLR was increased in all patients. TA SLR was often seen in both patients with ALS and paraparetic patients, but only rarely in normal subjects and hemiparetic patients. These responses were decreased in size and not modulated by background EMG in the affected leg of hemiparetic patients, suggesting a disturbed control of spinal reflexes fed by spindle group II afferent fibers (Nardone et al. 2001).

In standing human subjects, foot dorsi-flexion evoked a short-latency (SLR or `M1´) and a medium-latency (MLR or `M2´) EMG response in the soleus muscle. SLRs are thought to be mediated by spindle group Ia afferents, while group II fibers contribute to MLRs through an oligosynaptic circuit. Achilles tendon vibration had different effects on both SLR and MLR responses in spastic hemiparetic patients and normals subjects. While there were no differences between normals and patients in the size of control SLR or MLR, vibration decreased SLR to 70% in normal subjects, but increased it to 110% in patients, in both affected and unaffected leg. Vibration did not affect MLR in normals, but increased it to 165% on the affected and 120% on the unaffected side of patients. In hemiparetics, therefore, the lack of the inhibitory effect of vibration on SLR indicated that inhibition of the monosynaptic reflex was reduced, but the increased MLR indicated a disinhibition of group II pathway in patients, connected to the loss of descending control on group II interneurones. Spastic hypertonia depends on release of group II rather than group Ia reflex pathways (Nardone and Schieppati 2005).

Locomotion. Phase-dependent modulation of the H-reflex during locomotion of normal humans is likely to be generated by presynaptic inhibition (Sect 4.5; references in Thompson et al. 2019). In spastic stroke patients, the input-output properties of the soleus stretch reflex during sitting and walking showed differences from healthy subjects. In the early swing phase, the threshold of the input-output relation was significantly lower in the patient group. There was a significant correlation between the stretch reflex threshold in the early swing phase and the clinical spasticity score. It has been suggested that in the early swing phase, the reduced soleus stretch reflex threshold prevents the stroke patients from making fast foot dorsi-flexion and thereby impairs the walking speed (Nielsen et al. 1998). In chronic incomplete SCI patients, the swing-phase H-reflex, which is absent or very small in neurologically normal subjects, is abnormally large, but can be down-regulated by operant conditioning (Thompson and Wolpaw 2021; Sect 6.2).

In spastic patients with hemiparetic stroke and age-matched healthy volunteers, three types of ankle perturbations during treadmill walking were applied. Fast dorsi-flexion perturbations elicited short-latency stretch reflex in the soleus muscle, which were facilitated in the patients. Fast plantar-flexion perturbations, applied during the stance phase to unload the plantar flexor muscles and remove the afferent input to soleus α-MNs, decreased soleus activity that was

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significantly smaller in the patients than normals. Slow-velocity, small-amplitude ankle trajectory modifications, which mimicked small deviations in the walking surface, generated gradual increments and decrements in the soleus EMG in the healthy volunteers, but significantly depressed modulation in the patients. This was taken to indicate that, although the stretch reflex response was facilitated during spastic gait, the contribution of afferent feedback to the ongoing locomotor soleus activity was depressed in patients with spastic stroke (Mazzaro et al. 2007).

In normal subjects and patients with spasticity due to chronic incomplete SCI, unexpected ankle dorsi-flexion perturbations and soleus H-reflex were elicited throughout the gait cycle. In normal subjects, spinal short-latency M1 (mainly elicited by group Ia muscle spindle afferents), spinal medium-latency M2 (presumably mediated mainly by group II muscle spindle afferents), and long-latency M3 reflexes (probably mediated via transcortical or sub-cortical pathways) were modulated throughout the step cycle. The responses were largest in mid-stance and almost completely suppressed during the stance-swing transition and swing phases. In SCI patients, M1 and M2 responses were abnormally large in the mid–late-swing phase, while M3 modulation was similar to that in normal subjects. The H-reflex was also large in the mid–late-swing phase. Elicitation of H-reflex and stretch reflexes in the late swing often triggered clonus (Sect 4.1.1.2) and affected the soleus activity in the following stance phase. The large M1 enhancement in SCI patients has been suggested to result from reduced inhibition of group Ia excitatory pathways, while the enhancement of the M2 component could be due to increased oligo- or polysynaptic group Ia excitation, reduced inhibition of excitation from group II spindle pathways, and/or changes in pathways containing excitatory and inhibitory interneurons that receive inputs from group Ib afferents (Sects 4.1.1.3, 4.1.2), and/or increased excitation of interneuronal pathways fed by other afferents. It has also been suggested that, at least partly, the firing of group II and Ib afferents and an altered modulation or excitability of Ib/II interneurons (Sect 4.1.2) may explain abnormal swing-phase bursts in the soleus EMG or abnormally large M2 responses in the late-swing phase. Group Ib feedback interacts with other reflex pathways (Sect 4.1.2) and cutaneous reflexes, which are also altered after SCI. Other interneuronal networks are likely also involved. Reduced cortico-spinal (CST) activation of the TA muscle results in weak dorsi-flexion and foot drop and would reduce reciprocal inhibition (Sect 4.3) of the soleus even if reciprocal inhibition itself were normal. Yet in SCI patients, reciprocal inhibition between the plantar-flexors and dorsi-flexors is often abnormal (Sect 4.3), and would further reduce the suppression of the soleus α-MN excitability in the stance-swing transition through the late-swing phase. Recurrent inhibition (Sect 4.4) inhibits α-MNs, γ-MNs and reciprocal inhibitory interneurons and is modulated by sensory afferents (not well investigated; Windhorst 2021) and signals descending from supraspinal sources. Thus, it is probable that multiple inhibitory mechanisms are altered during walking, resulting in disorganized and ineffective activation of multiple muscles in SCI patients (Thompson et al. 2019). These suggestions make an important point by emphasizing the potential involvement of complex interneuron networks, which are almost all influenced by descending fiber tracts (Windhorst 2021; Sect 4.1.2).

In hemispheric stroke patients, increased drives via the vestibulo-spinal (VeST) and/or reticulo-spinal tracts (ReST) contribute to spasticity on both sides (Li et al. 2021). After hemispheric stroke, alterations in the activity of the reticular nuclei affect both sides of the spinal cord, and thereby should contribute to increased α-MN excitability on both paretic/spastic and contralateral sides, as compared to neurologically intact subjects. Experiments measuring stretch reflex threshold showed that both contralateral and affected sides exhibited increased α-MN excitability as compared to intact subjects, including a reduction in stretch reflex thresholds in the contralateral limb. This would be in line with ReST activation, which has bilateral descending influences. Spasticity may thus be due to a different strongly lateralized pathway,

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such as the vestibulo-spinal tract.. There may also be changes in neuromodulation (Sect 4.2.1) at the spinal level (Afzal et al. 2019).

4.1.1.2 Clonus

Ankle clonus is an involuntary 5- to 7-Hz joint oscillations (Ganguly et al. 2021; Wallace et al. 2005) and commonly occurs at the ankle in patients with motor-incomplete SCI and other forms of CNS pathology. Clonus may be promoted by increased soleus α-MN excitability, reduced post-activation depression of repeated stretch activations and antagonist co-activation. Clonic soleus activity may impede walking progression and compromise independent walking. Ankle clonus probably results from the loss of descending inhibition of soleus stretch reflexes and maladaptive re-organization of spinal reflex pathways. The latter comes with other abnormalities, such as co-activation and reciprocal facilitation of tibialis anterior (TA) and soleus MNs (S) (Sect 4.3). Operant conditioning (Sect 6) can increase muscle TA activation and decrease H-reflexes in patients with SCI (Manella et al. 2013; below).

Computer simulations of the reflex circuit involving ankle muscles and monosynaptic spinal connections between spindle afferents and α-MNs showed that oscillations such as clonus occur when the α-MN excitability increases in a reflex pathway containing long delays. This change in excitability is mediated by a reduction in α-MN firing threshold, rather than by an increase in feedback gain (Hidler and Rymer 1999).

4.1.1.3 Force Feedback

In stroke patients, constant velocity stretches elicits, after movement onset, active reflex force progressively increasing with increasing joint angle. However, after the reflex force magnitude exceeds a particular level, it begins rolling off until maintaining a steady-state value. The magnitudes of these force plateaus are correlated with the speed of stretch, such that higher movement speeds result in higher steady-state forces. These force plateaus could result from a force-feedback inhibitory pathway.

A simple model representing the elbow-reflex contained two separate feedback pathways, one representing the monosynaptic stretch reflex originating from muscle spindle excitation, and another representing force-feedback inhibition arising from force sensitive receptors. The force-feedback inhibition altered the stretch-reflex response, resulting in a force response that followed a sigmoidal shape similar to that observed experimentally. Moreover, simulated reflex responses were highly dependent on force-feedback gain, in that increases in this gain predicted that reflex force plateauing would begin at decreasing forcce levels. The parameters from the model fits indicate that the force threshold for force-sensitive receptors is relatively high, suggesting that the inhibition may arise from muscle free nerve endings rather than Golgi tendon organs (GTOs). The experimental results together with the simulations of elbow-reflex responses suggest that after stroke, the effectiveness of force-feedback inhibition may increase to a level that has functional significance (Hidler and Schmitt 2004).

4.1.1.4 A Special Stretch-reflex Component: Clasp-Knife Reflex

The clasp-knife reflex is one sign of spasticity. It can also be evoked in decerebrate and spinalized (T12) cats by muscle stretches or contractions. Stretch of a hindlimb extensor muscle evoked inhibition in homonymous and synergistic extensor muscles, but only if the

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stretch was of large amplitude and produced large forces. The reflex effects extended to other muscles. Extensor muscles were inhibited and flexor muscles were excited throughout the hindlimb. Stretch of the tibialis anterior muscle generated the same spatial pattern and time course of reflex action as stretch of an extensor muscle - inhibition of extensor muscles and excitation of flexor muscles throughout the hindlimb (Cleland and Rymer 1990). The receptors responsible for the reflex are group III and IV muscle afferents from free nerve endings. In decerebrate and spinalized (T12) cats, group III and IV muscle afferents are sentivive to muscle stretches of large amplitude that produce considerable passive force. In response to ramp stretches, their discharge began after a brief latency, attained its maximum at the ramp end and then showed a rapid and complete decay during static stretch, and the discharge adapted to repeated stretches. Isometric muscle contraction also excited the afferents. Thus, the afferents responded to both length and force. Stimulation of free nerve endings by squeezing the Achilles tendon in cats exhibiting the clasp-knife reflex evoked strong homonymous inhibition and a flexion/withdrawal pattern of reflex action, i.e., inhibition of extensor and excitation of flexor muscles throughout the hindlimb, which parallels the spatial divergence of the clasp-knife reflex (Cleland et al. 1990). Muscular free nerve endings activated interneurons in laminae V-VII of the cat L5-S1 spinal segment. These interneurons were held responsible for mediating the clasp-knife reflex because the time course and magnitude of their responses to stretch and contraction paralleled the time course and magnitude of the clasp-knife reflex (Cleland and Rymer 1993).

Comments. These simulations suggest that Golgi tendon organs (GTOs) play no great role in force feedback in spasticity, but that muscle group III and IV afferents from free nerve endings assume the role. What then would be the role of GTOs? Hints may be gleaned from the following discussion.

4.1.2 Intricacies of Spinal Networks in Cats

Stretch of active muscles activates muscle receptors other than muscle spindles, e.g., Golgi tendon organs (GTOs). It is therefore important to estimate what GTO afferent contribution to the reflex might be, in health and disease. Unfortunately, this is not so easy because, firstly, group Ib afferents from GTOs have complex spinal effects via interneurons, and, secondly, these effects are state-dependent (review: Windhorst 2021).

Group Ib Input-Output Distribution. In cats, group Ib afferents from flexor and/or extensor muscles provide the dominant excitatory monosynaptic or both mono- and disynaptic effects on so-called `Ib-INs´ (but see below). Inhibitory Ib-interneurons exert widespread oligosynaptic actions that reach almost all α-MN pools of the ipsilateral hindlimb. Most intermediate-zone `Ib-interneurons´ receive convergent inputs from sensory afferents in groups I to IV and from descending tracts (Schomburg 1990). Conversely, α-MNs receive oligosynaptic inhibitory inputs from group Ib fibers originating in various muscles, implying that group Ib input from one muscle diverges to different α-MN pools. `Ib-interneuron´ terminals producing inhibitory postsynaptic potentials (IPSPs) in homonymous and synergistic α-MNs are subject to presynaptic inhibition (Sect 4.5), which gates autogenetic Ib inhibition of active homonymous α-MNs and is rhythmically modulated by CPGs during locomotion (Côté et al. 2018; Jankowska 1992; Schomburg 1990).

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Group Ia-Ib Convergence. In cats, group Ia and group Ib afferents converge on 30-50% of intermediate-zone interneurons (so-called `Ia/Ib interneurons´; below) in which they exert co-excitatory, co-inhibitory or mixed effects. Convergence occurs for afferents from the same muscle, or from different muscles acting at the same joint or at different joints. Interneurons with Ia/Ib convergence may project to all α-MN pools in the hindlimb and to contralateral pools. Excitatory intermediate-zone interneurons project ipsilaterally, bilaterally or contralaterally while all inhibitory neurons project only ipsilaterally (Jankowska and Edgley 2010).

Positive Force Feedback. At rest, e.g., in reduced immobile preparations, group Ib afferents exert di- or trisynaptic inhibition on homonymous α-MNs and closely related synergistic α-MNs (autogenetic inhibition) as well as di- or trisynaptic excitation on antagonist α-MNs. During locomotion, extensor group Ib and Ia afferents activate ipsilateral extensor α-MNs and inhibit flexor α-MNs, thus switching to positive force feedback to extensors widely distributed in the cat hindlimb (review: Windhorst 2021). Excitatory force feedback is active and predominant during both locomotion and quiet standing in cats (Pratt 1995). However, inhibitory and excitatory force feedback coexist during locomotion, with inhibition being re-distributed towards more distal muscles (Nichols 2018).

Group III and IV Afferents originate from free nerve endings and are in part nociceptive and their activation reflexly elicits, for example, nocifensive flexor and withdrawal reflexes. Group III and IV afferents of muscle origin are in part nociceptive and in part ergoceptive, and have wide-ranging central effects and diverse functions. They exert modulatory effects on most spinal interneurons and thereby reflexes, may contribute to adjust muscle contractions during muscle fatigue (Decherchi and Dousset 2003; Laurin et al. 2015; Windhorst 2007) and to adjust ventilation, heart rate, blood pressure and vascular resistance during physical exercise (Laurin et al. 2015; Gandevia 2001; Murphy et al. 2011).

Group III muscle afferents are more mechano-sensitive than group IV afferents during skeletal muscle contraction, force production, dynamic/static muscle stretch and local intramuscular pressure. Muscle group IV afferents are more sensitive to metabolites released into the interstitium by muscle activity because their activation usually starts after a delay during prolonged muscle contraction and continues to discharge until the withdrawal of muscle metabolites (Laurin et al. 2015). In particular, group III and IV muscle afferents appear to elicit the clasp-knife reflex (Sect 4.1.1.4).

All the interneurons intercalated in the above connections receive modulating inputs from various descending tracts and sensory afferents (Windhorst 2021). The partial or complete interruption of descending tracts should thus have complex effects on the operation of these interneurons.

In humans, such intracate spinal connections are much more difficult to investigtae, requiring indirect methods.

4.1.3 Stretch Reflexes in Animal Models of Spasticity

In adult decerebrate spinalized cats, reflexes elicited by ramp-hold-return stretches of the triceps surae muscles were abolished in the acute spinal state. In chronic spinal cats (4 weeks after spinalization), reflex force had partly recovered, but soleus and lateral-gastrocnemius activity remained fairly depressed, despite the fact that injecting clonidine (α_2-adrenoceptor agonist) could activate these muscles during locomotor-like activity. By contrast, other ankle extensor muscles not activated in the intact state, such as medial gastrocnemius (MG), plantaris, flexor

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hallucis longus and the peroneal muscles as well as muscles that cross other joints, such as semimembranosus and biceps femoris, were strongly activated by stretching the triceps surae muscles in chronic spinal cats (Frigon et al. 2011). Hence, the reflex pattern is re-organized after spinalization.

Several types of sensory receptors contribute to stretch reflexes. First, muscle stretch activates group Ia and group II muscle spindle afferents. Electrically stimulating triceps surae muscle afferents at group I (i.e., Ia and Ib) strength evokes similar or larger homonymous and heteronymous excitatory postsynaptic potentials (EPSPs) in chronic spinal cats (>6 wk) than in cats with intact spinal cords, immediately after spinalization, group I-evoked EPSPs are increased in triceps surae α-MNs. Second, group II inputs from secondary muscle spindle endings in cat and human stretch reflexes could contribute to the observed stretch reflex changes, but their effects are complicated because they are mainly mediated by complex interneuron networks (Frigon et al. 2011; Windhorst 2021). Contributions from group II, III, and/or IV muscle afferents from free nerve endings can be excited by muscle stretch and could contribute as well. Finally, the clasp-knife reflex (Sect 4.1.1.4) could play a role. Stretching triceps surae muscles after an acute dorsal hemisection in a decerebrate cat evoked inhibition in ankle and knee extensors, i.e., the clasp-knife response, while eliciting activity in muscles such as semitendinosus, tibialis anterior and iliopsoas. Hence, triceps surae muscle stretch activates muscles throughout the hindlimb, particularly in chronically spinalized animals (Frigon et al. 2011).

Functional re-organization of stretch reflex pathways after spinalization likely occurs at the pre-motoneuronal level, that is, within a complex interneuron network (Frigon et al. 2011; Windhorst 2021). For example, in the intact state, triceps surae group II inputs readily excite interneurons and transmit signals to ankle extensor α-MNs, whereas those that project to semitendinosus and sartorius α-MNs are tonically inhibited. After spinalization, the excitability of interneurons reverses such that interneurons receiving group II inputs from triceps surae and projecting to ankle extensor α-MNs are inhibited while those projecting to semitendinosus and sartorius α-MNs are disinhibited (Frigon et al. 2011).

Finally, inhibitory mechanisms within the spinal cord are particularly affected by SCI. Disynaptic reciprocal inhibition (Sect 4.3) between ankle flexors and ankle extensors can be altered following SCI in humans. Spinalization also changes presynaptic inhibition (Sect 4.5). After spinalization, collaterals from the same muscle afferent can be differentially regulated by other segmental inputs. Changes in presynaptic regulation of triceps surae muscle afferents could explain why the same muscle stretch fails to activate some muscles after spinalization, which were strongly activated in the intact state (e.g., soleus and lateral gastrocnemius) while activating muscles that were inactive before spinalization (e.g., semitendinosus and sartorius).

Descending monoaminergic influences likely participate in the re-organization of stretch reflexes. Depressed stretch reflexes after acute spinalization may be due to the loss of serotonergic drive because selective activation of 5-HT_2 receptors restores triceps surae excitability, as does clonidine (Frigon et al. 2011).

All in all, stretch reflex pathways from triceps surae muscles to multiple hindlimb muscles undergo functional re-organization after spinalization. Altered activation patterns by stretch reflex pathways could explain some sensory-motor deficits observed during locomotion and postural corrections after SCI (Frigon et al. 2011).

It has been hypothesized that the length- and force-dependent reflexes have integrated functions. A rapid ramp-and-hold stretch elicits a fast muscle force response with an initial overshoot that

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subsides into a maintained steady-state phase. The overshoot is probably due to excitation of group Ia afferent fibers, shortly afterwards complemented by excitation of group II afferents and group Ib afferents from GTOs during the length and force hold phases. The composite reflex response is thus a complex response elicited by the different afferents filtered by the distributed spinal IN network possibly including recurrent pathways and integrated premotor INs with distributed convergence (Bonasera and Nichols 1994; Nichols 1989, 1994, 2018).

Inhibitory force feedback is predominantly inter-muscular and distributed. It may promote proportional coordination of the knee and ankle during locomotion and manage inertial interactions between joints, particularly at higher forces and velocities. Together with length feedback, it may manage limb mechanics at a higher, more global level. Collectively, all sources of force feedback as well as length feedback determine the mechanical properties of the limb as a whole (Lyle and Nichols 2018; Nichols 2018).

4.2 Changes in α–Motoneuron Excitabiliy

α-MNs receive multifarious direct or indirect inputs from themselves via excitatory recurrent axon collaterals (recurrent facilitation), recurrent inhibition via Renshaw cells (Sect 4.4), reciprocal Ia inhibitory interneurons (sect 4.3), a plethora of other spinal interneurons, proprio-spinal neurons, sensory afferents of all sorts, and several supraspinal structures. The distribution patterns depend on the animal species, the muscles innervated (e.g., extensors vs. flexors), and their roles in posture and movement. The supraspinal structures include the cerebral cortex, cerebellum, vestibular nuclei, nucleus ruber, reticular formation, and neuromodulatory structures such as the locus coeruleus and raphé nuclei (Baldissera et al. 1981; Windhorst 2021). Brain lesions may damage different combinations of descending tracts and thus create different pathological pictures.

In human spasticity, α-MNs are hyper-excitable. This is indicated by various measures. For example, the latency of the reflex response of single motor unit discharge in the biceps brachii of stroke patients was systematically shorter in the spastic muscle compared with the contralateral muscle (Hu et al. 2015). Also, motor units in the resting spastic-paretic biceps brachii muscle showed sustained spontaneous discharges which increased after voluntary activation only on the impaired side (Chang et al. 2013). It was suggested to be attributable, at least in part, to low-level excitatory synaptic inputs to the resting α-MN pool, possibly from regional or supraspinal centers, while less likely to an increase in PIC activation (Mottram et al. 2010). Nonetheless, in spastic-paretic biceps brachii muscles, the firing rates of motor units during voluntary contractions were abnormally low and their rate modulation was impaired by running into saturation despite increasing force (Mottram et al. 2014).

Such changes may in part have anatomical causes. For example, after SCI, the α-MN somata and dendritic arbors are reduced, which may explain increases in cell input resistance and decreases in rheobase current, alterations in the input/output relationship and hyper-reflexia. Resting membrane potential and spike threshold may or may not depolarize. Voltage-gated ion channels dramatically change and so does α-MN firing after SCI (Jean-Xavier et al. 2018). In part, these changes result from the reduction or complete loss of descending neuromodulation.

4.2.1 Changes in Neuromodulation

As mentioned before, persistent inward currents (PICs) in α-MNs are greatly facilitated by serotonin and noradrenaline released by axons descending from monoaminergic brainstem

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nuclei (Binder et al. 2020). Damage to serotonergic descending axons by SCI changes spinal neuronal activity and has been implicated in paralysis, spasticity, sensory disturbances and pain. Moreover, loss of 5-HT innervation leads to a disinhibition of sensory transmission. Serotonin denervation supersensitivity is one of the key mechanisms underlying the increased α-MN excitability (Nardone et al. 2015).

After SCI, PICs increase in amplitude, which restores α-MN excitability. This recovery may be mediated by hypersensitivity to monoamines in α-MN populations; serotonin (5-HT) receptors become constitutively active following SCI (Nardone et al. 2015). The increased PIC strength thus enables synaptic inputs to evoke prolonged firing activity in α-MNs. These prolonged excitatory postsynaptic potentials can re-activate the PICs and trigger long-lasting reflexes and muscle spasms (Sect 4.7). Long-lasting reflexes and self-sustained firing during muscle spasms are associated with the activation of the Ca^{2+} PICs, whereas the slow and regular firing of motor units after muscle spasms is associated with Na^{+} PIC activation (ElBasiouny et al. 2010; Jean-Xavier et al. 2018).

4.2.2 Changes in Repetitive Discharge

A characteristic feature of α-MNs is the ability to fire repetitively during sustained current injection. After SCI, changes in repetitive firing appear to be modest, with some reductions in the frequency-current (F-I) relationship, which can be partially reversed if the SCI group is exposed to daily exercise. Spike-frequency adaptation (SFA) is particularly prominent in α-MNs that innervate fast-twitch muscle fibers. After SCI, muscle-fiber types and the α-MNs that innervate them revert from diverse slow and fast phenotypes to a more homogeneous fast type (Jean-Xavier et al. 2018).

4.2.3 Synaptic Plasticity and Axonal Sprouting

Spinal cord injury (SCI) interrupts at least some descending motor and neuromodulatory pathway connections and causes a loss of down-stream activity-dependent processes. This activity loss produces spinal interneuron degeneration and several activity-dependent maladaptive changes that underlie hyperreflexia, spasticity, and spasms (Martin 2022).

LTD, LTP and Sprouting. In complete SCI, the loss of long descending connections makes volitional control of movement impossible. Depending on the type and location of incomplete injury, damaged and undamaged neurons show some spontaneous plasticity of the spared axons by sprouting, new synapse formation, and changes in electrophysiological properties. (i) Synaptic connections become stronger and more efficient following short high-frequency bursts and repetitive input (short-term facilitation or LTP, respectively). On a molecular level, single bouts of high-frequency input result in increased neurotransmitter release, while repetitive bouts increases synaptogenesis and synaptic efficiency by modulating post-synaptic AMPA. (ii) Conversely, synaptic connections can become weaker and less efficient after low-frequency input. A burst of low-frequency input results in short-term depression and is associated with decreased presynaptic neurotransmitter release and desensitization of AMPA receptors. Repetitive low-frequency input results in LTD, which results in weakened, less efficient synapses, changes in NMDA receptor composition, and pruning of unused synapses. In contrast to LTP, LTD diminishes and prunes unnecessary, redundant, and inefficient connections Hence, LTP involves receptor-mediated plasticity and synaptogenesis of either intact sprouting axons

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or the regeneration of damaged axons, and LTD does the opposite. Thus, synaptic sprouting and pruning result from LTP and LTD, both may promote recovery and functional improvement. On the other hand, the injury-induced plasticity can also be maladaptive, by aberrant sprouting and synaptogenesis as neurons try either to compensate for lost connections or to regenerate through the injury site as they respond to inflammation. Hyperexcitability and inefficiency result from these new connections, making restoration of normal function nearly impossible (Walker and Ryan-Detloff 2021).

In rats, lesions of the cortico-spinal tract at high cervical level led to significant sprouting of the contra-lateral ventral CST across the midline into the ipsilesional medial MN column of lamina IX, which anatomical plasticity was critical to post-injury gains in function (Weidner et al. 2001). As in rats, non-human primates with unilateral cervical SCI showed some improvement in reaching and grasping over time that corresponded with changes in the distribution of CST terminals in the spinal gray matter compared to intact macaques (Nakagawa et al. 2015). These CST axons rostral and caudal to the injury site terminate in lamina VII, whereas the sprouting fibers synapse near MN pools in lamina IX (Walker and Ryan-Detloff 2021)..

Brain-derived Neutrophic Factor (BDNF) is an important regulator of neuronal development, axon growth, synaptic transmission, and cellular and synaptic plasticity and functions in the formation and maintenance of certain forms of memory. BDNF is intricately involved in spinal plasticity, also after SCI, but BDNF actions are multifaceted because it can mediate both adaptive plasticity and maladaptive plasticity. BDNF effects relate to nociceptive processes (Grau 2014; Grau et al. 2017, 2020). While BDNF is pro-nociceptive in the healthy state, it is not after injury, at least acutely. Increases in BDNF after SCI promote adaptive plasticity and functional recovery (Garraway and Huie 2016).

EPSP Changes. One potential mechanism for the hyperexcitability of α-MNs in spastic muscles of stroke patients may be the prolongation of excitatory postsynaptic potentials (EPSPs) produced by group Ia afferents, which would facilitate the temporal summation of successive group Ia EPSPs and make action-potential initiation easier (Son et al. 2019).

Plasticity of Postsynaptic Membrane Properties occurs, in part, by altering receptor densities and respective ionic concentration gradients across the cell membrane. Intracellular recordings of α-MNs in the adult rodent sacral spinal cord are sensitive to N-methyl-D-aspartate (NMDA), causing spontaneous bursts of rhythmic activity. After SCI, postsynaptic receptor expression favors excitation over inhibition with increased gene expression for NMDA and down-regulation of GABA receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Both NMDA and non-NMDA receptor blockades probably prevent excitotoxicity following SCI. – Since intracellular Cl- increases following spinal cord trauma, postsynaptic inhibitory drive onto α-MNs is reduced, leading to a hyperexcitable state (Jean-Xavier et al. 2018).

Plasticity of Primary Sensory Afferents. Dorsal root injury caused collateral sprouting of adjacent dorsal root axons into the dorsal horn of the cat (Liu and Chambers 1958). Later studies showed that collateral sprouting of primary afferent fibers resulted in recovery of motor function after either dorsal root or spinal cord injury. Sprouting of intact propriospinal interneurons following spinal hemisection occurred as a neural mechanism of locomotor recovery. Altered primary afferent input may be transmitted to MNs through deep DH interneurons, and membrane properties of these interneurons rostral and caudal to SCI demonstrated decreased input resistance and rheobase, indicating a hyperexcitable state (Walker and Ryan-Detloff 2021).

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Plasticity of Nociceptive Afferents exert widespread influences on many types of spinal interneurons (Windhorst 2021), and their dysfunction could therefore play various, in part unknown, roles in pain sensation and motor control. After experimental SCI, nociceptive fibers display maladaptive increases in their terminal arborizations in the DH and exhibit hyperexcitability and increased spontaneous activity. In SCI individuals, findings suggest that morphological and intrinsic changes in these sensory afferents could, in part, mediate the return of functional sensation, as well as maladaptive allodynia and hyperalgesia, and the development of neuropathic pain. But nociceptive signals are also supplied for tissue and joint protection via reflex arcs to modulate normal motor circuit function and motor output. Therefore, aberrant plasticity of nociceptive afferents may be detrimental to functional recovery following SCI (Walker and Ryan-Detloff 2021).

4.2.4 Changes in Muscle Spindle Afferent Inputs?

Decades ago, it was suggested that the increased excitability of the muscle stretch reflex were due to an increased activity of muscle spindle afferents caused by an increased fusimotor bias by γ-MNs which are under influence of inhibitory and facilitatory descending pathways. However, augmented spindle afferent discharge and stretch sensitivity and hence γ-MN activity has not been confirmed in stroke (Hagbarth et al. 1973; Wilson et al. 1999) or SCI patients (Macefield 2013). It is also worth remembering that muscle spindles issue two types of sensory afferents, group Ia and group II, and these types have some shared monosynaptic connections to α-MNs, but otherwise different effects on spinal neurons (Windhorst 2021).

4.3 Changes in Reciprocal Inhibition

It has been shown extensively that spinal networks like reciprocal inhibition, recurrent inhibition (Sect 4.4) and presynaptic inhibition (Sect 4.5) are modulated by many descending and sensory inputs (Baldissera et al. 1981; Katz and Pierrot-Deseilligny 1998; Windhorst 2021). It is self-evident, therefore, that the operation of these networks are bound to change after the disruption of descending inputs following SCI and probably also by the modification of sensory inputs, for which again there is much evidence.

Reciprocal inhibition is important for regulating the actions of antagonist muscles at a joint. It is mediated by reciprocal Ia inhibitory interneurons which inhibit antagonist α-MNs and receive their (partial) proprioceptive inputs from group Ia fibers whose inputs they share with agonist α-MNs. Moreover, with their corresponding α-MNs, these interneurons share many inputs from descending tracts and sensory afferents of various sorts (Baldissera et al. 1981).

Inhibition of hindlimb α-MNs from the cortico-spinal (CST), rubro-spinal (RuST), reticulo-spinal (ReST) and vestibulo-spinal (VeST) tracts is largely mediated via reciprocal Ia inhibitory interneurons (Baldissera et al. 1981; Jankowska 1992; Hultborn 2001; Lundberg et al. 1987; Schomburg 1990). For example, activation of an extensor α-MN pool by the VeST coincides with inhibition of the antagonist flexor α-MNs by collaterals of extensor-activating tracts.

Reciprocal inhibition may contribute to adjust ankle-joint stiffness. For instance, when the soleus muscle is stretched, its autogenetic stretch reflex increases its stiffness. At the same time, the antagonist tibialis anterior (TA) α-MNs receive increased reciprocal inhibition and their

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muscle shortens, which reduces the reciprocal inhibition onto soleus and further increases its stiffness, and vice versa (Nichols 1989, 1994, 2018; Nichols and Koffler-Smulevitz 1991; Windhorst 2021). Things may be somewhat more complicated for co-contractions of antagonists. During co-contractions of TA and soleus, reciprocal Ia inhibition is modulated depending on the soleus/TA activity ratio (Hirabayashi et al. 2019).

Changes in reciprocal inhibition after SCI, mostly tested from tibialis anterior (TA) α-MNs to soleus α-MNs, have been determined many times, and results depend on the site (caudal to rostral), kind (contusion, rupture, tumor, section) and extent (complete, incomplete, to what degree?) of the lesion. They have been reported as depression or elimination (Boorman et al. 1996; Nielsen et al. 2007; Sheean and McGuire 2009) or replacement with facilitation (Crone et al. 2003; Mirbagheri et al. 2014; Xia and Rymer 2005).

But if, after incomplete SCI, reciprocal inhibition is replaced with facilitation (Lon Fok et al. 2021; Mirbagheri et al. 2014), how then does it change to precisely tune co-contraction for ankle stiffness? In other words: What are the mechanisms to adapt it to the new conditions?

During voluntary ankle dorsi-flexion movements by multiple-sclerosis patients, reciprocal inhibition and presynaptic inhibition do not increase at movement onset as is the case in healthy subjects, which may be responsible for the tendency to elicitation of unwanted stretch reflex activity and co-contraction of antagonistic muscles (Morita et al. 2001).

In healthy subjects, the stretch reflex is increased during voluntary muscle contraction, which is attributed in part to the depression of the inhibitory mechanisms. In spastic patients, these inhibitory mechanisms are already depressed at rest and cannot be depressed any further. This depression may in part explain the occurrence of co-contraction in antagonist muscles. In most normal movements, antagonist muscles should remain silent and maximally relaxed. This is ensured by increasing transmission in several spinal inhibitory pathways. In spastic patients, this control is inadequate, and therefore stretch reflexes in antagonist muscles are easily evoked at the beginning of voluntary movements or in the transition from flexor to extensor muscle activity (Nielsen et al. 2005).

In normal human subjects, the strength of reciprocal Ia inhibition between ankle flexor and extensor muscles could be temporarily increased by electrically stimulating, for 30 min, the common peroneal (CP) nerve with a patterned input (10 pulses at 100 pulses/s every 1.5 s; mimicking Ia afferent discharge during stepping), but not regular pattern at the same average rate (1 pulse every 150 ms), but the effect is short-lived. Thus, the patterned stimulation induced but did not maintain plasticity. It has been suggested that various mechanisms could underlie these effects. The glutamatergic group Ia afferent synapses on the reciprocal Ia inhibitory interneurons might be potentiated. Or the inhibitory synapses on α-MNs could be potentiated. Or greater excitability of the reciprocal Ia inhibitory interneuron pool could recruit subliminal interneurons or `latent´ inhibitory connections (Perez et al. 2003).

4.4 Changes in Recurrent Inhibition

In cats, spinal recurrent inhibition is mediated by Renshaw cells (RCs), which receive their most important excitatory input from α-MNs (and some rarer and weaker effects from γ-MNs) and in turn inhibit α-MNs, reciprocal Ia inhibitory interneurons, γ-MNs (weaker and rarer effects), other Renshaw cells and cells of origin of the ventral spino-cerebellar tract (VSCT) (Appelberg et al. 1983; Baldissera et al. 1981; Ellaway 1971; Ellaway and Murphy 1981; Haase et al. 1975; Lindström and Schomburg 1973; Noth 1971; Windhorst 1990, 1996, 2007).

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Recurrent inhibition is further influenced by sensory afferents (not well investigated; Windhorst 2021) and signals descending from supraspinal sources. In cats, Renshaw cells receive modulating inputs from the motor cortex, cerebellum, nucleus ruber, reticular formation and vestibular nuclei, in part independently of inputs of the same origin to α-MNs (Windhorst 2021).

Descending influences have also been investigated in humans. In healthy subjects, recurrent inhibition is modulated in various conditions, i.e., stance, locomotion, voluntary movements. For example, as compared to upright stance supported by a wall, recurrent inhibition is enhanced in soleus muscle during unsupported free stance. This has been interpreted as a mechanism to diminish the reciprocal inhibition between antagonistic α-MN pools to insure rapid alternating contractions of flexors and extensors for fast stance corrections. Recurrent inhibition is decreased during isolated voluntary plantar ankle flexion (by ankle extensor muscles), probably by descending inhibition of Renshaw cells. By contrast, recurrent inhibition is strongly increased during co-contraction of plantar- and dorsi-flexors, which might help diminish the gain of the stretch reflex and prevent it from falling into oscillations and clonus (Katz and Pierrot-Deseilligny 1998).

Recurrent Inhibition in Spasticity. In about half of spastic patients, recurrent inhibition is not abnormal, irrespective of lesion site and origin, while in the rest, these factors influence changes in recurrent inhibition. In hemiplegic patients, recurrent inhibition at rest, if abnormal, was increased compared to the unaffected side and to healthy subjects. In patients with progressive paraparesis (hereditary spastic paraparesis, ALS), recurrent inhibition was decreased when abnormal. In SCI patients, recurrent inhibition was often increased (Katz and Pierrot-Deseilligny 1998; Mazzocchio and Rossi 1997). In other studies, recurrent inhibition has been reported to change after SCI, but in different ways: increase (Shefner et al. 1992), or normal or reduced or absent (Mazzocchio and Rossi 1997).

So, changes of recurrent inhibition in spasticity are complicated, probably reflecting the different kinds of lesions. If the above results somewhat represent the operations of recurrent inhibition under natural conditions, their effects would yet not be simply mirrored by changes in reciprocal inhibition because the latter would be additionally determined by inputs other than recurrent inhibition.

Competition between α-MN Axon Synapses and Group Ia afferent synapses. Siembab et al. (2016) argue that the competition of α-MN axon synapses and group Ia afferent synapses on Renshaw cells is subtle and specific to VGLUT1 synapses (at central group Ia afferent terminals) and cholinergic VAChT synapses (at α-MN axon terminals), and not to VGLUT2 synapses (at other glutamatergic afferents). “One intriguing possibility is that the synaptic formation and maintenance of VGLUT1 and motor synapses involve competition for some critical, limited, RC-derived factor (that could be related to electrical activity or not) on which VGLUT2 synapses do not depend“, for example neuregulin-1, neuroligin-1 or gephyrin (Siembab et al. 2016). The functional rationale of these maturation processes and their underlying mechanisms need to be more fully explored, but they suggest that Renshaw cells might play a strong role in ontogenetic plasticity and possibly other forms.

Competition between Sensory and Descending Inputs. In the neonatal mouse, Renshaw cells receive monosynaptic proprioceptive (probably group Ia) inputs, which subsequently lose weight because of increasing Renshaw cell dendritic growth (Alvarez et al. 2013; Jean-Xavier et al. 2018; Mentis et al. 2006, 2010; Siembab et al. 2016). One reason could be that different synaptic inputs on Renshaw cells compete with each other. In mutant mice, strengthening of the proprioceptive inputs reduces α-MN axon synaptic density on Renshaw cells and, conversely,

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absent or diminished sensory afferent inputs correlate with increased densities of α-MN axon synapses. In contrast, the normal developmental retraction of afferent inputs to Renshaw cells (and α-MNs) does not occur after complete SCI, which leaves Renshaw cells with abnormally few collateral fibers from α-MNs (Smith et al. 2017). Also, increasing sensory activity by electrical stimulation induces axonal withdrawal and decreased connections of the cortico-spinal tract (CST) onto α-MNs and interneurons. Conversely, a decrease of sensory afferent activity by rhizotomy increases CST connections (Jiang et al. 2016). Hence, afferent stimulation affects the CST development, and CST stimulation affects the development of sensory afferent inputs (Chakrabarty and Martin 2011), indicating that proprioceptive afferents and descending fibers compete with each other in contributing to normal spinal circuitry formation (Jean-Xavier et al. 2018; Martin 2022).

Recurrent Inhibition in Motor Learning. A hypothesis about the potential role of α-MNs, their proprioceptive inputs and interneurons including Renshaw cells (RCs) in spinal motor learning has recently been put forward by Brownstone et al. (2015). In this scheme, α-MNs are controllers effecting muscle contractions and thus posture and movement. Group Ia afferents originating in muscle spindles and contacting α-MNs monosynaptically provide `instructive´ feedback about the ongoing motor actions. Renshaw cells, fed by an efference copy of the α-MNs´ outputs, generate a `predictive´ feedforward signal reflecting the expected sensory consequences. The instructive and predictive feedback signals are then compared at the level of α-MNs that have a hybrid role in being the controllers as well as the comparators which compute a `sensory prediction error´ used to adapt system parameters. This arrangement could be regarded as a `fundamental learning module´, which "offer(s) the flexibility for both short-term adjustments, and a circuit in which plasticity can lead to long-term changes" (Brownstone et al. 2015). An important point is the balance between the two types of α-MN input, group Ia afferents and Renshaw cells. If this balance is disturbed, plastic processes should set in to restore it as far as possible. The model suggested by Brownstone et al. (2015) employs supervised learning, as proposed by the authors in reference to cerebellar learning. This hypothesis is important in that it defines an instructive signal initiating the learning process, but detailed mechanisms are as yet unknown.

Important progress has been made by targeting Renshaw cells by genetic modification. In mice, Enjin et al. (2017) used the selective expression of the nicotinic cholinergic receptor2 (Chrna2) to genetically target the vesicular inhibitory amino acid transporter (VIAAT) in Renshaw cells. Loss of VIAAT from Chrna2Cre-expressing Renshaw cells had the following consequences. In adult mice, the loss of VIAAT had no effect on grip strength, the change of gait and on motor coordination. In the neonatal mouse, the loss of VIAAT did not alter drug-induced fictive locomotion. However, α-MNs developed a lower input resistance, had an increased number of proprioceptive glutamatergic and calbindin-labeled putative Renshaw cell synapses on their soma and proximal dendrites, and received spontaneous inhibitory synaptic input at a reduced frequency, Renshaw cells exhibited increased excitability although they received a normal number of cholinergic α-MN synapses (Enjin et al. 2017).

All in all, the above results suggest plastic compensation within the proprioceptive-α-MN-Renshaw cell circuit. It is surprising that the mere elimination of Renshaw cells output elicits distributed plastic changes in proprioceptive-α-MN-Renshaw cell function. The precise mechanisms leading to the coordinated plastic changes have still to be elucidated.

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4.5 Changes in Presynaptic Inhibition

Spinal presynaptic inhibition provides a powerful mechanism by which signal flow from segmental sensory afferents into the CNS may be modulated and regulated at the first central synapse. Presynaptic inhibition is produced predominantly by GABAergic interneurons acting on $GABA_A$ receptors on primary sensory terminals (Quevedo 2009; Rudomin 2009; Rudomin and Schmidt 1999). GABAergic interneurons depolarize primary sensory afferents of all classes, which can be recorded in the dorsal root as primary afferent depolarizeation (PAD). Presynaptic inhibition shows complicated input-output patterns with a fair degree of functional differentiation that suggests the existence of several interneuronal sub-populations, in part located at different places. Presynaptic inhibition is modulated by a variety of descending and sensory systems. Proprioceptive afferents also regulate the level of their presynaptic GABAergic inhibitory input in an activity-dependent manner. This retrograde influence thus constitutes a feedback mechanism by which excitatory sensory activity drives GABAergic inhibition to maintain circuit homeostasis (Mende et al. 2016).

Animal and human studies have shown that presynaptic inhibition can be set to different mean levels and modulated dynamically during rest, locomotion and voluntary movements (McCrea 2001; Rossignol et al. 2006). For example, the inhibition becomes weaker during voluntary contraction (Iles and Roberts 1987). Also, synaptic transmission from group Ia muscle spindle afferents to α-MNs is presynaptically inhibited more strongly during stance than rest (lying), more strongly during locomotion than rest, and more strongly during running than walking (Gosgnach et al. 2000; Katz et al. 1988; Stein 1995). In humans, presynaptic inhibition of group Ia afferent terminals on α-MNs of voluntarily contracting muscles is decreased, while presynaptic inhibition of group Ia fibers to α-MNs of muscles not involved in the contraction is increased. Hence, the control of presynaptic inhibition of group la fibers at the onset of movement may be organized so as to help achieve selectivity of muscle activation (Hultborn et al. 1987).

The disruption of descending tracts should change the operation of presynaptic inhibition. [It should be noted that, in humans, presynaptic inhibition suppresses different reflexes differently: H-reflexes are suppressed strongly, stretch reflexes much less if at all (Morita et al. 1998). For possible reasons, see Enriquez-Denton et al. 2002.] Spinal cord injury has been suggested to lead to hyporeflexia during the 'spinal shock' because of an initial increase in the efficacy of presynaptic inhibition. Afterwards, over the time of chronification, presynaptic inhibition of ankle extensor group Ia input declines to levels less than those of control subjects, thereby contributing to enhance spinal reflexes, consistent with the clinical state of 'spasticity' (Calancie et al. 1993). Confirming results were obtained in paraplegics with bilateral spinal cord lesion sugesting that presynaptic inhibition of soleus group Ia terminals was decreased (Christensen et al. 2017; Faist et al. 1994). More direct evidence for decreased presynaptic inhibition was adduced in decerebrate rats, in which chronic SCI decreased presynaptic inhibition of the plantar H-reflex through a reduction in primary afferent depolarization (PAD) evoked by stimulation of the posterior biceps-semitendinosus (PBSt) muscle group I afferents (Caron et al. 2020). Thus, after SCI, the supraspinal control of interneurons mediating PAD is disengaged, which suggests an augmented role for sensory afferents.

4.6 Changes in Other Spinal Interneuronal Networks?

All of the above-mentioned interneurons as well as α-MNs and γ-MNs receive abundant inputs from sensory afferents and descending fiber systems, mostly mediated via interneurons with the exception of a few monosynaptic connections. SCI triggers interneuron degeneration and

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several activity-dependent adaptive and maladaptive changes underlying spasticity, hyperreflexia and spasms, which can be counteracted by various regimes of electrical stimulation (Martin 2022).

An important characteristic is the wide and often semi-random connectivity between several descending systems, sensory inputs from many and diverse muscles, joints and cutaneous sources to α-MNs innervating multiple and diverse muscles, and among interneurons themselves. Contributors to this extended network may also be the diffuse but fairly weak or modest effects of group Ia muscle spindle afferents, reciprocal inhibition and recurrent inhibition, in distinction to the more concentrated and stronger effects at individual joints (Windhorst 2021). The convergence of group Ia, group II and group Ib muscle afferents in conjunction with other mechano-receptor afferents onto common neurons and the wide distribution of related reflex effects from many muscles to many muscles throughout the limb would enable the handling of the complex peripheral biomechanics, regulating both more local and individual muscle properties such as stiffness and non-linearities as well as transjoint limb mechanics (Nichols 2018; Windhorst 2021).

The spinal reflex system shows a rich anatomical and functional diversity of spinal interneurons, but as a site of convergence, divergence, and processing of multiple types of information also offers a great potential for plasticity. The use of transgenic mice has enabled to define `cardinal classes´ of spinal neurons, to visualize their migration and connectivity, and to define their specific roles in motor and sensory networks. Genetic tools in combination with other approaches, including morphology, electrophysiology, and connectivity, have unravelled a huge diversity of interneurons, particularly within the ventrally (V0-V3) and dorsally (dIs) derived classes. Thus, interneurons comprise a vast range of neuronal types with unique properties and connectivities, and include long and short propriospinal neurons (Flynn et al. 2011, Sect 4.11.4), with ascending and descending projections, as well as local interneurons with projections on the same side (ipsilateral) and/or interneurons with connections crossing the midline (commissural). The behavioral result of `silencing´ or excitation of specific interneurons yields clues as to their function. These methods have also revealed neuroplastic changes within the interneuronal connectivity and identified phenotypic subsets that may contribute to plasticity after traumatic spinal cord injury (SCI) or neurodegenerative diseases. For example, large cholinergic synapses on α-MNs (most likely from $V0_c$ interneurons) could contribute to aberrant excitation during ALS progression. Moreover, in the SOD1-G93A mouse model of ALS, the α-MN innervation by V1-subtype interneurons is susceptible to degeneration over time. A model showed progressive up-regulation (e.g., compensatory plasticity) in V1 synaptic connectivity before breakdown of interneuronal circuits. V2a interneurons contribute to plasticity in mouse models of SCI and ALS (review: Zholudeva et al. 2021).

A computer simulation has recently shown that spinal interneuron networks can self-organize themselves so as to provide proper activity patterns during movement (Enander et al. 2022).

4.7 Potential Sources of Spasms

Spinal cord injury promotes muscle spasms, which often involve complex muscle activation patterns across multiple joints, reciprocal muscle timing, and rhythmic clonus. Evidence has been forwarded that PICs could contribute to spasm generation (Gorassini et al. 2004). It has also been hypothesized that spasms are a manifestation of partially recovered function in spinal CPGs. A sub-group of integrated neurons are the commissural propriospinal V3 neurons that coordinate interlimb movements during locomotion. In mice with a chronic spinal transection,

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V3 neurons were optogenetically activated with a light pulse, which generated a complex coordinated pattern of α-MN activity with reciprocal, crossed, and intersegmental activity. In these same mice, brief sensory stimulation evoked spasms with a complex pattern of activity very similar to that evoked by light. This suggests that sensory activation of V3 neurons suffices to generate spasms. Thus, spasms are generated in part by sensory activation of V3 neurons and associated CPG circuits (Lin et al. 2019).

4.8 Changes in Spastic Muscles

Muscle hypertonia in spastic patients has two components: reflex hypertonia (above) and non-reflex or intrinsic hypertonia. With proper instrumentation, reflex and non-reflex contributions to spasticity can be distinguished and quantified. For example, as compared to normally developing children, children with cerebral palsy showed increased phasic and tonic stretch reflex torque, tendon reflex gain, muscle contraction and half-relaxation rates, as well as non-reflex increased elastic stiffness and viscous damping (Xu et al. 2020). Also, in adult stroke, SCI and multiple sclerosis patients, changes occur in both active and passive properties of ankle plantar-flexor muscles (Lorentzen et al. 2010).

Spastic muscles show variable macroscopic and microscopic changes, including reduced muscle volumes, fascicle lengths and pennation angles, stretched tendons, and fewer sarcomeres in series that are stretched out (Handsfield et al. 2022). In part these changes are caused by reduced neural innervation, in part by accompanying circumstances. Muscle immobilization at short lengths early on reduces the number of serial sarcomeres and increases connective tissue in the muscle, which enhances muscle resistance to passive lengthening without being velocity-dependent. It is also likely that muscle contractures in spastic patients contribute significantly to hypertonia (Trompetto et al. 2014). Muscle contractures might result from disturbances of homeostasis in the neuromuscular–tendon–connective tissue complex and from the interaction of neural, mechanical and metabolic factors, as well as genetic and epigenetic factors (Pingel et al. 2017). Such changes typically lead to a limited range of joint motion, which at the muscle level must originate from a limited muscle-length range of force exertion (Yucesoy and Huijing 2007).

Fibrosis and similar structural changes may influence the myofascial force transmission which is anything but simple. The force generated by sarcomeres of a particular muscle does not only reach the insertion of this muscle´s tendon, but in addition to this intramuscular force transmission, there are extramuscular and intermuscular force-transmission pathways. Collagenous fibers establish direct intermuscular connections, and structures such as the neuro-vascular tracts provide indirect intermuscular connections. Moreover, compartmental boundaries (e.g., intermuscular septa, interosseal membranes, periost and compartmental fascia) are continuous with neuro-vascular tracts and connect muscular and non-muscular tissues. Force can even be transmitted between antagonistic muscles across the interosseal membrane, such as the one between the tibia and fibula of the lower limb. More generally, myofascial force transmission occurs between all muscles within a limb segment. A stiffened system of intra- and epimuscular myofascial force transmission are likely to affect the properties of spastic muscle (Huijing 2007; Yucevoy and Huijing 2007), whereas the extramuscular myofascial pathways may play a limited role in intact muscles (Maas and Sandercock 2010).

These peripheral changes in spasticity are supported by further experiments. For example, by comparing the passive mechanical properties of the biceps brachii on the affected and contralateral non-affected side of chronic hemispheric stroke patients and control subjects, the affected musculo-tendon unit did not strain measurably in response to tendon indentations.

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The mechanisms responsible for altered passive mechanics may lie within extracellular matrix fibrosis (Chardon et al. 2020).

Another change occurs in the contractile muscle properties of patients with chronic complete SCI. In patients with low degrees of spasticity (as determined by clinical evaluation), the contractile dynamics presented the largest changes, in which the speed of contraction increased significantly while there were no statistical differences in the gains between the patient and control groups. By contrast, patients with high degrees of spasticity had slower contractile speeds than the controls, but significantly lower gains. This indicates that in patients with chronic SCI, the severity of spasticity can significantly influence the degree of change in muscle contractile properties. It appears that high degrees of spasticity tend to preserve contractile dynamics, while in less spastic subjects, muscle contractile properties may display faster response characteristics (Hidler et al. 2002).

4.9 Movement Disorders

Spastic movement disorders are characterized by stiff gait, co-activation of antagonist muscles, aberrant muscle activities, reduced movement range and velocity, and insufficiently coordinated movements, It has been argued that the main functional probems of patients with spastic movement disorders are founded in weak muscles, paresis, contractures and inappropriate central motor commands rather than in hyperexcitable reflexes. Stiff posture and gait based on co-activation of antagonist muscles might rather be adaptations that ensure joint and postural stability. To facilitate antagonist co-activation, the reduction of reciprocal inhibition would make sense (Nielsen et al. 2020).

Interestingly, some premotor interneurons in the mouse diverge to synergistic α-MN pools, whereas others diverge to antagonistic α-MN pools. The latter interneurons have been interpreted as modulating joint stiffness or relaxation, depending on whether they are excitatory or inhibitory (Ronzano et al. 2021). Inhibitory processes appear be widely suppressed in spasticity. So, if the divergent inhibitory interneurons were suppressed in spastic mice, they might contribute to co-activation of antagonists by disinhibition. – Furthermore, aberrant muscle activity and impairment of muscle coordination could be related to difficulties in selectively activating muscles due to an inadequate prediction of the sensory consequences of movement. Functional muscle strength and muscle coordination following central motor lesions might be improved by optimizing integration of somato-sensory signals into central feedforward motor programs (Nielsen et al. 2020).

In a study in which patients with hemiparesis had to perform rapid horizontal multi-joint arm movements into different directions from a central starting point, the patients were still able to modulate, in response to target direction, the initial direction of movements performed with the paretic limb. However, compared with the non-paretic limb or control subjects, movements of the paretic limb were misdirected systematically. An inverse-dynamics analysis revealed an abnormal spatial tuning of the muscle torque at the elbow used to initiate movements of the paretic limb. EMG recordings showed similar spatial abnormalities in the initial activations of elbow muscles. It was suggested that these spatial abnormalities could not be attributed to weakness, spasticity-mediated restraints or stereotypic muscle synergies. Instead, the spatial abnormalities would be consistent with an impaired feedforward control of the passive interaction torques which arise during multi-joint movements. This impaired control was hypothesized to reflect a degradation of the internal representation of limb dynamics that occurs either as a primary consequence of brain injury or secondary to disuse (Beer et al. 2000).

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4.10 Recovery in Spinalized Rodents and Humans

A plethora of attempts have been made in humans and animal models, particularly rodents (Kjell and Olson 2016), to improve or restore motor performance after brain and/or spinal cord lesions. A problem in translating results from rodents to humans is that these species differ in various respects (Filipp et al. 2019; Guérout 2021). Some spontaneous recovery of sensory-motor capabilities may occur after SCI, but they can be substantially improved by various means. These include physical training, application of rehabilitation robots, various regimes of electrical of magnetic stimulation to induce neuro-regeneration and neural repair, and – still in the experimental stage – by promotion of axon regrowth and sprouting, transplantation of various cell types, medication (e.g. of neurotrophins), neuroprotection, immunomodulation, neuronal relay formation and myelin regeneration and more sophisticated methods that, e.g., stimulate neurogenesis, overcome axon-growth inibition at glial scars etc. (Assinck et al. 2017; Darian-Smith 2009; Dietz and Fouad 2014; Dimitrijevic et al. 2015; Edgerton et al. 2004; Fong et al. 2009; Gassert and Dietz 2018; Grau et al. 2020; Guérout 2021; Harkema 2008; Hofer and Schwab 2019; Hutson and Di Giovanni 2019; Keefe et al. 2017; Martin 2022; Smith and Knikou 2016; Knikou and Murray 2019; Leech et al. 2018; Liu et al. 2012; Rossignol and Frigon 2011; Roy et al. 2012; Taccola et al. 2018; Takeoka 2020; Zheng et al. 2020; Zholudeva et al. 2018, 2021). Beyond these spinal alterations, plasticity in sub-cortical networks and sensory-motor cortices are also associated with changes in motor function after injury (Leech et al. 2018).

Spinal cord injury has been suggested to enable plasticity by altering the neural context caudal to injury. One more general means appears to be the removal or reduction of a GABAergic inhibition of neural excitation and plasticity. While this plasticity allows neuro-rehabilitation and physical therapy to exert a lasting effect, the system is set in a vulnerable state, wherein noxious stimulation can fuel an over-excitation that can drive pain and spasticity (Grau et al. 2020).

Recovery may be counteracted by noxious stimuli and pain. SCI frees the way for nociceptive sensitization of spinal neurons by disrupting serotonergic (5-HT) fibers that reduce overexcitation. The loss of 5-HT can enhance neural excitability by various cellular mechanisms. Nociceptive stimulation is more effective if experienced soon after SCI. This adverse effect has been linked to a down-regulation in brain-derived neurotrophic factor (BDNF) and an up-regulation in the cytokine, tumor necrosis factor (TNF) (Grau et al. 2017, 2020).

4.10.1 Humans

In human subjects suffering from incomplete SCI, locomotor training induces plastic changes of flexor and extensor reflexes, presynaptic inhibition (Sect 4.5) of soleus group Ia afferents, and soleus H-reflex habituation at rest and during stepping. Most notable is the re-emergence of the soleus H-reflex phase-dependent modulation. More specifically, locomotor training changes actions of group Ia and group Ib inhibitory interneurons on soleus α-MNs at rest resembling that seen in neurologically intact humans and their modulatory reflex actions are adjusted in a phase-dependent pattern during assisted stepping in both the motor complete and incomplete SCI conditions (Knikou et al. 2015).

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4.10.2 Rodents

Spinal cord injury disturbs the inputs to MNs, but can be normalized by locomotor training. For example, in neonatal rats, spinal cord transection at mid-thoracic level induced significant re-organization of synaptic inputs to tibialis anterior (TA) MNs caudal to the site of injury, as studied ultrastructurally in the adult rats. The total number of synaptic boutons apposing γ-MNs, but not α-MNs, was reduced. The proportion of inhibitory to excitatory boutons, however, was increased significantly in both α-MNs and γ-MNs. Hence, a neonatal spinal cord transection increased inhibitory influences, which was associated with poor stepping. SCI followed by successful locomotor training improved bipedal stepping and normalized the proportion of inhibitory and excitatory inputs to the MNs to that observed in intact rats (Ichiyama et al. 2011).

Locomotor training is assumed to exert its beneficial effects by activating proprioceptive inputs in a somewhat natural pattern that stimulates and adapts the operation of spinal neuronal netwotks. Neural circuits processing sensory feedback from the legs play important roles in the generation and regulation of leg movements and, in healthy subjects, are adjusted by descending supraspinal commands that continuously tune the dynamics of these circuits. After SCI, the descending signals of modulation are severely distorted. Hence, sensory signals become the primary source of control to produce and regulate leg movements. After complete SCI in cats, spinal networks controlling standing and locomotion and their interactions with sensory feedback from the limbs remain largely intact (Harnie et al. 2019).

The significance of proprioceptive afferents is also evidenced by the fact that genetically modified mice lacking muscle spindle feedback failed to display the activity-dependent re-organization of neuronal circuits that support recovery after SCI (Takeoka 2020; Takeoka et al. 2014). Furthermore, in mice, complete or spatially restricted proprioceptive ablation affected locomotor performance differentially. After incomplete SCI, proprioceptive ablation below but not above the lesion severely restricted locomotor recovery and descending circuit re-organization. But ablation of proprioceptive afferents after behavioral recovery permanently led to an immediate deterioration of regained locomotor performance, which demonstrates the essential role of proprioceptive afferents for maintaining the gains, despite the re-organized descending circuits. In parallel to recovery, proprioceptive afferents underwent re-organization of activity-dependent synaptic connectivity to specific local spinal targets, in part based on competition. For example, lateral hemisection at low thoracic level induced group Ia afferents to increase their monosynaptic connections specifically to ipsi-lesional hindlimb homo-and heteronynomous S-type α-MNs and to also selectively increase their contacts with interneuronal populations that would normally receive little proprioceptive afferent inputs (Takeoka and Arber 2019).

The beneficial effects of exercise can be supported by BDNF. In rats with hemisected spinal cord at thoracic level, BDNF showed increased spinal concentrations. Synaptic pathways under the regulatory role of BDNF induced by exercise could thus play a role in facilitating recovery of locomotion following spinal cord injury (Ying et al. 2005).

Spared descending fibers in SCI spontaneously re-organize their connections to neurons caudal to the lesion (detour or relay circuit formation), and this re-arrangement is steered by proprioceptive afferent activity. Moreover, after SCI, proprioceptive afferents increase unconventional connections with local interneurons and MNs. While such re-arrangements may be enough to re-establish basic forms of unperturbed locomotion, they are not when it comes to more sophisticated forms such as ladder locomotion which requires precise foot placement (Takeoka 2020).

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Proprioceptive feedback from the trunk should also be important because trunk stability balances gait by actively assisting in the coordination of inter-limb movements and the maintenance of equilibrium. The loss of trunk control leads to impairments of leg control and strongly reduces the ability to generate stable, coordinated gait patterns. Rats with spinal-cord contusion at T8 were trained to stand and step on a treadmill with body-weight support under electrical and pharmacological spinal-cord neuromodulation. A real-time robotic system was designed to study the relationships between medio-lateral trunk orientation and the bilateral modulation of leg motor patterns during bipedal locomotion. It was shown that real-time control of trunk posture re-established dynamic balance among bilateral proprioceptive feedback circuits, and thereby restored left-right symmetry, loading and stepping consistency. A computational model of muscle-spindle feedback circuits showed that optimal locomotor performance emerged when medio-lateral trunk orientation helped preserve the balance between muscle-spindle feedback circuits associated with extensor and flexor muscles for both limbs (Moraud et al. 2018).

4.10.3 Role of Spinal Interneurons

What the normal roles of spinal interneurons are in movement control and how they might change after SCI is as yet little known. But early indications suggest that these interneurons are important for plasticity and function after SCI, by contributing to neural circuit re-modeling and modulation of MN excitability (review: Zholudeva et al. 2021).

Mouse dI3 Interneurons. In adult animals, even following the complete loss of descending inputs after spinal transection, multi-modal sensory afferents (cutaneous, proprioceptive) retain access to spinal locomotor circuits in that stimulation of sensory afferents in *in vitro* isolated spinal cords can suffice to activate spinal locomotor circuits. Stimulation of such afferents (e.g., during locomotor training) promotes locomotor recovery. So-called dI3 interneurons in the mouse dorsal horn are an important link between multi-modal sensory inputs and locomotor circuits (α-MNs and as yet unidentified neurons in the intermediate laminae of the cervical and lumbar spinal cord). Although dI3 interneurons receive rhythmical inhibition from the locomotor circuits and can in turn activate these circuits, dI3 interneurons are not necessary for normal locomotor activity, but are a necessary cellular substrate for motor-system plasticity following spinal transection. Genetically removing dI3 interneurons by eliminating their synaptic transmission left locomotion more or less unchanged, but abolished functional recovery, suggesting that dI3 interneurons play an important role in plastic processes. This has been interpreted as follows. The inhibitory input from the locomotor circuits to dI3 interneurons mirrors the motor output and represents the negative image of the expected excitatory multi-modal input indicative of a predictive forward model. The dI3 interneurons thus serve as comparators between actual and predicted movement and produce a sensory prediction error, which then induces plastic changes in locomotor circuits, mediating long-term learning such as that necessary for locomotor recovery after spinal-cord transection. The underlying mechanisms could include changes in connectivity, synaptic strength, and/or morphology of spinal neurons (Bui et al. 2016). But how exactly the prediction error accomplishes these plastic changes is not known.

4.10.4 Role of Propriospinal Neurons

Propriospinal neurons link structures along the spinal cord over short and long distances (spanning at least one segment) and play a great role in coordinating fore- and hindlimb, trunk and neck muscle activities during posture, locomotion and other movements. Following

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incomplete SCI or stroke, lesion-induced structural and functional plasticity occurs in the cortico-spinal (CST) system, but also in the reticulo-spinal (ReST), rubro-spinal (RuST) or propriospinal projections. Propriospinal neurons may be of importance for (1) the formation or strengthening of spinal detour pathways that bypass supraspinal commands around the lesion site and bridge intermediate SCI gaps, as well as for (2) the activation and coordination of locomotor CPGs (Filli and Schwab 2015; Flynn et al. 2011; Laliberte et al. 2019; Martin 2022; Zholudeva et al. 2018).

5 Changes in Proprioceptive Feedback

A prominent means of promoting locomotor recovery after SCI is locomotor training which is supposed to stimulate and possibly re-organize interneuronal and motoneuronal networks in an activity-dependent way that simulates normal proprioceptive inputs. Since these inputs are diverse and impinge on diverse types of cells, the precise mechanisms of action are not well understood. The simplest connection from group Ia muscle spindle afferents to α-MNs has been well studied because of its easy accessibility. But the many connections to interneurons are difficult to evaluate, and most probably play an important role in recovery (Takeoka 2020; Sects 4.11.3, 6).

Spinal damage to the sensory-motor pathways cause synaptic changes in neuronal circuits, over the post-injury weeks and months. Synaptic plasticity occurs as changes in functional maps in the CNS, structural changes to neurons, and altered firing properties of spared neurons. Dorsal-root sections that interrupt afferent inputs are permanent and do not result in regeneration, but spared axons sprout and make new connections. For example, during the first few months after a cervical dorsal-root lesion in the monkey, adjacent spared nerve fibers sprout locally within the deprived region, presumably to form new connections with second-order neurons. The spared fibers were few in number (<5%) and initially functionally silent. Also in the cat, in which the dorsal roots supplying the hindlimb were cut, initially de-afferented dorsal-horn neurons altered their response properties and developed novel receptive fields. The underlying mechanisms were not identified (Darian-Smith 2009).

De-afferentation injuries alter the normal balance of excitatory and inhibitory circuits within the dorsal horn. Following a dorsal rhizotomy in the monkey spinal cord, there was a significant increase in the GABAergic circuits in the dorsal horn on the side of the lesion compared with the normal side. In rats and monkeys, dorsal-root section also induced neurogenesis within the dorsal horn. In contrast, neurogenesis did not occur in rats with central dorsal-column lesions. If even a small number of these newly born neurons survive and integrate into the local circuitry, the numbers would be sufficient to influence local circuitry re-organization (Darian-Smith 2009).

In the mouse, peripheral muscle nerve injury entails permanent motor deficits without functional recovery, which is partially caused by the withdrawal of group Ia axons and synapses in the ventral horn without restitution. Underlying mechanisms include the activation of microglia around terminal group Ia afferents and the invasion into the ventral spinal cord of blood-derived myeloid cells (Rotterman et al. 2019). Another important factor demonstrated in mutant postnatal mice may be the central absence or diminution of muscle spindle-derived neurotrophin 3 (NT3) (Chen et al. 2002). Activity-dependent effects have been studied in the mouse by genetically abolishing the central monosynaptic neurotransmission between proprioceptive afferents and α-MNs. This increased the fraction of heteronymous α-MNs contacted and the density of sensory bouton contacts on each α-MN while no change occurred

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in the density of synaptic connections with homonymous or antagonistic α-MN pools (Mendelsohn et al. 2015).

In the neonatal mouse, Renshaw cells receive monosynaptic proprioceptive (probably group Ia) inputs, which subsequently lose weight because of increasing Renshaw cell dendritic growth (Alvarez et al. 2013; Mentis et al. 2006, 2010; Siembab et al. 2016). One reason could be that different synaptic inputs on Renshaw cells compete with each other. In mutant mice, strengthening of the proprioceptive inputs reduces α-MN axon synaptic density on Renshaw cells and conversely absent or diminished sensory afferent inputs correlate with increased densities of α-MN axon synapses. Position (place) has been suggested to play an important role so that α-MN axons target Renshaw cells preferentially because Renshaw cells are positioned ventro-medially along the trajectory of α-MN axons towards the ventral root. In contrast, reciprocal Ia inhibitory interneurons receive strong projections from group Ia afferents because they are located along the trajectory of Ia axons projecting to their respective α-MN pools (Siembab et al. 2016).

Proprioceptive feedback can be altered more specifically in genetically modified mice.

Genetically modified mice that lack muscle spindles exhibited gait ataxia, scoliosis, resting tremors, and ptosis, and showed reduced monosynaptic transmission of retained group Ia afferents to α-MNs (Chen et al. 2002). Furthermore, studying locomotor patterns in genetically and biomechanically impaired mice, in which proprioceptive feedback from muscle spindles and Golgi tendon organs (GTOs) was eliminated, showed that these afferents are crucial for regulating the temporal variables of rhythmic movements during walking and swimming, for appropriate alternation in the phasing of selected antagonistic muscles at individual joints, as well as for the cross-joint coordination of limb muscle activity. The absence of muscle spindle (group Ia and II) feedback delayed tibialis anterior (TA) activity during swing phase beyond the onset of gastrocnemius (GS) muscle activation, thus eliciting a co-contraction of TA and GS muscles and possibly stiffening the ankle joint at the end of the swing. The feedback from spindles is therefore necessary for the generation of an alternating pattern of flexor and extensor muscle activity and for ensuring accurate timing of TA offset to achieve accurate foot placement. Additional absence of GTO feedback showed that the combined activities of group Ia/II and group Ib afferents determined the pattern of extensor muscle activity and disrupted the coordination of muscle activations during stepping movements. Thus, group Ia/II and group Ib feedback may collectively control the stance phase (Akay et al. 2014).

6 Changes after Disuse and Increased Chronic Muscle Activity

Immobilization of a limb or part thereof causes changes that resemble those in developing spasticity after the initial spinal shock: increases in H-reflex amplitudes, decreases of presynaptic inhibition of group Ia afferents, changes in cortico-spinal (CST) transmission (Christensen et al. 2017). For example, following two weeks of ankle-joint immobilization in healthy humans, maximal voluntary plantar- and dorsi-flexion torque (MVC) was significantly reduced and the maximal soleus H-reflex amplitude increased with no changes in the maximal compound motor response (Mmax). The depression of the soleus H-reflex, when evoked at intervals shorter than 10 s (homosynaptic post-activation depression), was decreased, suggesting that the activity-dependent regulation of transmitter release from the group Ia afferents was affected by immobilization. Moreover, GABAergic presynaptic inhibition of the soleus group Ia afferents was decreased, while no significant changes in disynaptic reciprocal Ia inhibition were seen. These changes disappeared two weeks after immobilization. Hence, muscle disuse causes plastic changes in spinal interneuron circuits

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responsible for presynaptic inhibition, which appear to at least partially account for H-reflex changes. The underlying mechanisms are not well understood and may only be speculated on. Reduced presynaptic inhibition might be due to changes in sensory input to the PAD interneurons during immobilization. The changes in presynaptic inhibition may result from reduced voluntary motor activity. Or immobilization is accompanied by decreased proprioceptive input inducing the CNS to reduce the amount of presynaptic inhibition of group Ia afferents in order to increase the gain of the actual incoming afferent input (Lundbye-Jensen and Nielsen 2008).

If immobility causes plastic changes in the spinal cord, so does physical training. Soleus H-reflexes are suppressed for 10-15 minutes after acquisition of a task requiring visual guidance. Ballet dancers must perform many strictly controlled movements involving antagonist co-contractions around the ankle for joint stabilization. Co-contractions of antagonist muscles are accompanied by reduced stretch reflexes, H-reflexes and reciprocal inhibition, all of which are down-regulated after long training of ballet dancers, the underying mechanisms possibly including increased presynaptic inhibition of group Ia afferents (Christensen et al.. 2017).

Prolonged increases and decreases in physical activity cause changes in the biophysical properties of α-MNs. These changes include alterations in resting membrane potential, spike threshold, afterhyperpolarization amplitude, and rate of depolarization during spike generation, suggesting the involvement of density, type, location, and/or metabolic modulation of ion conductance channels. Endurance-type exercise reduces the excitatory current required to initiate and maintain rhythmic firing. The mechanisms underlying these adaptations are currently unknown, but may involve alterations in the expression of genes that code for membrane receptors including ion conductances (Gardiner et al. 2005; MacDonell and Gardiner 2018).

Such effects may also follow reduced proprioceptive feedback. In rats, Krutki et al. (2015) cut the tendons of the medial gastrocnemius (MG) synergists (lateral gastrocnemius, soleus, and plantaris) whereby only the MG was able to evoke the foot plantar-flexion. To insure regular MG activation, rats were trained to a low-level treadmill exercise. As soon as after 5 weeks, intracellular recordings from MG α-MNs showed considerable alterations in fast-type α-MNs, including a shortening of the spike duration and the spike rise time, an increase of the afterhyperpolarization amplitude, an increase of the input resistance, a decrease of the rheobase, and a decrease of the minimum current necessary to evoke steady-state firing. Thus, the properties of fast-type α-MNs innervating the overloaded MG muscle had shifted towards electrophysiological properties of slow-type α-MNs.

7 Operant Conditioning of Spinal Stretch and H-reflexes

7.1 Healthy Subjects

Insights into where in the central nervous system (CNS) plastic processes underlying motor learning may occur have been gleaned from the use of a particular experimental paradigm, namely operant conditioning of stretch and H-reflexes in humans, non-human primates and rodents. Operantly conditioned increases or decreases of the size of these reflexes induces complex plasticity at many sites within the CNS. Some of the changes occurring after H-reflex conditioning underlie the new skill, while others are likely to be compensatory changes that prevent the plasticity responsible for the new skill from interfering with pre-existing behaviors. Unlike the H-reflex, the stretch reflex is affected by fusimotor control, comprises several bursts of activity resulting from temporally dispersed afferent inputs, and may activate spinal α-MNs

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via several different spinal and supraspinal pathways (Mrachacz-Kersting et al. 2019; Thompson and Wolpaw 2014a,b).

All in all, there is ample evidence that neuronal circuits undergo long-lasting activity-induced plastic changes. To determine whether the long-term changes occur at the spinal or supraspinal levels, Wolpaw and his colleagues examined the effect of operant conditioning on the stretch or the H-reflex in monkeys and human subjects (Wolpaw et al. 1983; Wolpaw and O´Keefe 1984). They showed that plasticity occurred in two phases: an immediate (acute) phase on the day of training (approximately 8–10% change) and a long-lasting (approximately 1-2%/day for many days) phase. The acute phase occurred in the spinal stretch reflex, but not the long-loop reflexes which probably involve supraspinal centers such as the cerebral cortices. This immediate phase was temporary and diminished within a few hours after the training session. By continuing the training for 4–6 months, the plasticity became more permanent and the modulation persisted for months after termination of the training. Section of the spinal cord after the reflexes had been up- or down-regulated (in two different groups of monkeys) did not diminish the up- or down-regulated reflex, suggesting that the plasticity resided within the spinal circuits (Wolpaw and O´Keefe 1984).

In monkey triceps surae α-MNs, intracellular recordings showed that down-conditioning of triceps surae H-reflexes induced a positive (depolarized) shift in α-MN firing threshold and a reduced motor-axon conduction velocity, which likely were due to depolarized activation threshold for voltage-dependent sodium channels, and a slight decrease in the primary afferent EPSP (Carp and Wolpaw 1994, 1995). Down-conditioning of triceps surae H-reflexes in rats resulted in a significant increase in the fatigue index of fast-twitch motor units, and in a significant decrease in the percentage of F_{int} motor units and a significant increase in that of FR motor units. Up-conditioning had no effect on fatigue index. Neither up- nor down-conditioning affected maximum tetanic force or twitch contraction time (Carp et al. 2001).

In addition, several different synaptic terminals on the α-MNs were changed. Changes occurred in monosynaptic group Ia-α-MN connections, and probably in di- or trisynaptic pathways from groups Ia, II and Ib contributing to the H-reflex, particularly in up-conditioning. Also, the number of identifiable GABAergic terminals was increased, explained by an increase in the number of identifiable GABAergic interneurons in the ventral horn (Thompson and Wolpaw 2014a,b). Incidentically, Renshaw cells are both GABAergic and glycinergic (Cullheim and Kellerth 1981; Schneider and Fyffe 1992). Down-conditioning and up-conditioning are not symmetrical and possibly have different mechanisms. Up-conditioning may result from plasticity in spinal interneurons (Thompson and Wolpaw 2014a,b). Changes also occur in the cerebellum, basal ganglia and cerebral cortex, and the CST is essential for H-reflex conditioning (Thompson and Wolpaw 2014 a; Wolpaw 2018).

In neurologically normal subjects, operantly conditioning the initial component (M1) of the soleus stretch reflex (which is generated mainly by group Ia afferents) to increase (M1up) or to decrease (M1down) led to within-session task-dependent adaptation and across-session long-term change, with different time courses. Task-dependent adaptation was greater with M1up than with the previous H-reflex up-conditioning. This may reflect adaptive changes in muscle spindle sensitivity, which affects the stretch reflex but not the H reflex, and by altered presynaptic inhibition (Mrachacz-Kersting et al. 2019).

In addition to stretch and H-reflexes, another short-latency pathway with group Ia input can be operantly conditioned: reciprocal Ia inhibition. In rats chronically implanted with electromyographic (EMG) electrodes in right soleus (SOL) and tibialis anterior (TA) muscles and a stimulating cuff on the common peroneal (CP) nerve, CP stimulation elicited the TA H-

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reflex and soleus reciprocal Ia inhibition (RI). The latter was operantly up-conditioned (RIup mode) or down-conditioned (RIdown mode) while the TA and soleus background EMG and the TA M-response remained stable. Final soleus RI and TA H-reflex sizes were significantly correlated (Chen et al. 2006a).

7.2 Subjects with Spinal Cord Lesions

In chronic SCI patients, the excitability of spinal stretch reflexes and H-reflexes is often increased, which impairs locomotion. Hyperreflexia in the late swing phase probably contributes to impaired gait, e.g., by exacerbating foot drop and/or clonus. The soleus H-reflex elicited during the late swing-phase is absent or very small in healthy individuals, but abnormally large in SCI patients in whom it impairs locomotion. Its down-conditioning should hypothetically improve locomotion. Indeed, down-conditioning the swing-phase soleus H-reflex decreased the reflex much faster and farther than did the steady-state protocol in people or animals with or without SCI. This effect persisted for at least 6 months after conditioning ended. Down-conditioning the swing-phase H-reflex improved walking speed, reduced step asymmetry and modulation of locomotor electromyograph activity in proximal and distal muscles of both legs (Thompson and Wolpaw 2021).

In patients with ankle clonus and impaired walking ability due to chronic motor-incomplete SCI, two operant conditioning programs were used to test whether they could improve walking, one increased tibialis anterior (TA↑) EMG activity and the other suppressed the soleus H-reflex (SOL↓). TA↑ decreased plantar-flexor spasticity, increased ankle motor control and was associated with increased walking foot clearance and walking distance. Intensive, repetitive TA EMG activation during TA↑ may have unmasked dormant cortico-spinal pathways that preferentially increased recruitment of TA and leg flexor α-MNs, step initiation, and walking function. – SOL↓ decreased the co-activation of soleus and TA muscles during clonus and increased walking distance. It has been suggested that intensive training to inhibit soleus H-reflexes during weak voluntary TA contractions enhanced CST activation of soleus group Ib interneurons, and that the combined effects of decreased co-activation of soleus and TA muscles and increased soleus stretch reflex inhibition improved ankle motor control and walking function (Manella et al. 2013).

Up-conditioning of the soleus H-reflex may improve locomotion in rats with SCI. Rats with mid-thoracic transection of the spinal right lateral column produced a persistent asymmetry in muscle activity during treadmill locomotion. Up-conditioning of the soleus H-reflex increased the right soleus burst and corrected the locomotor asymmetry, in contrast to the locomotor asymmetry in control rats (Chen et al. 2006b).

7.3 Mechanisms

H-reflex conditioning makes use of a complex mixture of underlying mechanisms, morphological and physiological. In monkeys, in whom the triceps-surae H-reflex in one leg had been up-conditioned (HRup mode) or down-conditioned (HRdown mode), significant differences in synaptic coverage on α-MNs appeared between HRup and HRdown monkeys and between HRup and naive (i.e., unconditioned) monkeys. F terminals (i.e., putative inhibitory terminals) were smaller and their active zone coverage on the cell body was lower on α-MNs from the conditioned side of HRup monkeys than on α-MNs from the conditioned side of HRdown monkeys (i.e., terminals associated with postsynaptic cisterns and rough endoplasmic reticulum) were smaller and the number of C terminals in each C complex (i.e., a group of

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contiguous C terminals) was larger on α-MNs from the side of HRup monkeys than on α-MNs either from the conditioned side of HRdown monkeys or from naive monkeys (Feng-Chen and Wolpaw 1996).

Soleus H-reflex down-conditioning is associated wth a positive shift in α-MN firing threshold (possibly resulting from a change in the activation voltage of Na^+ channels). Down-conditioning also goes along with marked increases in GABAergic interneurons in the ventral horn and in GABAergic terminals on the soleus α-MNs. Changes occur in several other synaptic populations on the α-MNs, in other spinal interneurons, even on the contralateral side of the spinal cord. There are also changes in motor-unit properties. Up-conditioning and down-conditioning appear to have different mechanisms. Up-conditioning may result from plasticity in spinal interneurons. Among the descending tracts, solely the cortico-spinal tract (CST) is essential for H-reflex conditioning. This (or related) CST activity is probably responsible for gradually inducing the plasticity underlying long-term change in the H-reflex. In addition, plasticity occurs in sensory-motor cortex or related brain areas as well as the cerebellum and the basal ganglia (Thompson and Wolpaw 2014b).

Under the dynamic conditions of locomotion, the swing-phase H-reflex down-conditioning can access mechanisms such as changes in reciprocal inhibition from the antagonist muscle, autogenic Ib inhibition, recurrent inhibition, and cutaneous and joint afferent inputs. These additional mechanisms could help explain the unprecedently rapid and large decrease in the swing-phase H-reflex (Thompson and Wolpaw 2021). Presynaptic inhibition should also be added to the list. All mechanisms are normally subject to modulation thorughout the step cycle, which may be impaired by SCI. The above down-conditioning paradigm might then contribute to normalize their functions, which should be investigated to reveal the underlying mechanisms.

A recent model based on principles of cerebellar learning suggests that spinal motor learning involves circuits built of group Ia afferents, α-MNs and Renhaw cells (Brownstone et al. 2015; Windhorst 2007). These neuronal elements interact in regulating the properties of spinal circuits. For example, in genetically modified mice, deficient Renshaw cells increased their excitability, while α-MNs showed lower input resistance, received spontaneous inhibitory synaptic inputs and had an increased number of proprioceptive glutamatergic synapses on their soma and proximal dendrites. These changes probably acted as compensatory adaptations so as to prevent alterations of drug-induced fictive locomotion in neonatal mice or changes in gait, motor coordination or grip force in adult mice (Enjin et al. 2017). The precise mechanisms underlying these adaptations remain to be elucidated.

8 Classical and Instrumental Learning

After initial problems, it has been possible to develop appropriate paradigms that allowed to study classical and instrumental learning in the spinal cord (Brumley et al. 2018; Grau et al. 2020).

8.1 Classical Conditioning

Classical conditioning (Pavlovian conditioning) changes the relation of the effects of two stimuli on a response. It is typically studied by pairing a cue [the conditioned stimulus (CS)] with a stimulus [the unconditioned stimulus (US)] that innately elicits an unconditioned (unlearned) response (UR). As a consequence of this training, the paired CS (the CS+) acquires the capacity to produce a stronger response [the conditioned response (CR)], relative

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to an unpaired CS (the CS−) (Grau et al. 2020). It has been possible to identify sensory stimuli that the isolated spinal cord can detect (i.e., tactile, thermal, nociceptive) (Brumley et al. 2018; Grau et al. 2020).

For example, in cats spinalized at high thoracic or low thoracic level, electrical stimulation of the thigh or saphenous nerve (conditioned stimulus [CS]) was paired with stimulation of the superficial peroneal nerve or the paw (unconditioned stimulus [US]). Electrical stimulation of the US produced a leg flexion, whereas stimulation of the CS did not. During training, the CS and US were applied together. Learning was measured by the strength of the flexion response produced by the pairing of stimuli, i.e., the conditioned response [CR]. Pairing of the CS and US increased the strength of the CR. In the control group that received both the CS and US stimulation in an explicitly unpaired fashion, CR magnitude did not increase. In addition, the order of presentation of the CS and US was important, with retention of the CR during extinction trials only being seen when the CS preceded the US (forward conditioning). No retention of the CR was seen when the US preceded the CS (backward conditioning) (Brumley et al. 2018).

In rats, paired stimulation via epidural electrodes of the motor cortex and the dorsal cervical spinal cord strengthened motor responses through their convergence. Motor-evoked potentials (MEPs) were measured from the biceps femoris muscle. MEPs evoked from the motor cortex were robustly augmented with spinal epidural stimulation delivered at an intensity below the threshold for provoking an MEP. Augmentation was critically dependent on the timing and position of spinal stimulation. When the spinal stimulation was timed to coincide with the descending volley from motor-cortex stimulation, MEPs were more than doubled. Repetitive pairing caused strong augmentation of cortical MEPs and spinal excitability that lasted up to an hour after just 5 min of pairing. This supported the hypothesis that paired stimulation is mediated by convergence of descending motor circuits and large-diameter afferents in the spinal cord (Mishra et al. 2017).

Similar results were obtained in humans with incomplete SCI. A cortico-spinal (CST) pathway was activated by transcranial magnetic stimulation (TMS) over the cortical region that innervates a leg and elicits MEPs. This stimulation was paired with antidromic potentials evoked in α-MNs elicited by electrical stimulation of the common peroneal nerve. Repeated pairings of 200 trials increased the MEP elicited by cortical stimulation. This effect outlasted the period of nerve stimulation by 30 min (Urbin et al. 2017). The development of this effect appears to depend upon a form of NMDAR-mediated plasticity (Dongés et al. 2018).

8.2 Instrumental Conditioning

Evidence that the isolated spinal cord is capable of exhibiting instrumental learning when isolated from brain circuits has been adduced in mice, rats and cats. For example, adult cats spinalized at T12-13 showed short-term (milliseconds to minutes) adaptations to repetitively imposed mechanical perturbation on the hindlimb dorsal paw by a rod placed in the path of the leg during the swing phase to trigger a tripping response. The kinematics and EMG were recorded during control (10 steps), trip (1-60 steps with various patterns), and then release (without any tripping stimulus, 10-20 steps) sequences. The muscle activation patterns (EMGs) and kinematics of the hindlimb in the step cycle immediately following the initial trip was modified so as to increase the probability of avoiding the obstacle in the subsequent step. Hence, the lumbo-sacral locomotor circuitry can learn to modulate the activation patterns of the hindlimb α-MNs within the time frame of a single step in order to minimize repeated perturbations (Zhong et al. 2012).

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Similarly, rats spinalized at mid-thoracic level were trained to avoid a shock to the hindleg by maintaining a flexed hindleg position. During training, an electrode was placed in the tibialis anterior (TA) muscle. Whenever the leg extended below a set level, the animal received a shock to the TA muscle, which caused the leg to flex. Without brain input, these animals easily learned over a 30-min training period to maintain their hindleg in a flexed position (response) in order to minimize shock exposure (Brumley et al. 2018; Takeoka 2020).

Underlying Mechanisms. The instrumental response in rats relies on neural circuits within the lower lumbar and upper sacral spinal cord, between the L4 and S2 segments. Instrumental learning depends on the induction of long-term potentiation (LTP). This process is regulated by glutamatergic receptors (i.e., NMDA and AMPA receptors) and can lead to long-term changes in gene expression. When AMPA or NMDA receptors are blocked before instrumental training of the leg flexion response, subjects show a dose-dependent reduction of the acquisition of the learned response. Further, blocking both AMPA and NMDA receptors eliminates maintenance of the learned response (hindleg flexion) (Brumley et al. 2018; Grau et al. 2020).

These examples show that the mechanisms underlying motor adaptation lasting from seconds to hours are intrinsic properties of spinal networks. These networks harbor motor representations activateed by somato-sensory inputs (unwanted noxious stimuli or mechanical perturbations) and select adapted motor outputs appropriately sculpted to the somato-sensory inputs (Takeoka 2020).

9 Final Comments

The musculo-skeletal system is multi-variate, non-linear, time-varying and annoyingly complex, and it is difficult to "understand how these structures define the control problems that are solved by the nervous system" (Tsianos and Loeb 2017; see also Windhorst 2007). Definitely the upper CNS echelons are heavily involved in solving these problems, but "the spinal cord circuitry is in fact capable of solving some of the most complex problems in motor control and, in that sense, spinal mechanisms are much more sophisticated than many neuroscientists give them credit for" (Poppele and Bosco 2003). Specifically, the vertebrate spinal cord is able to solve, at least to some degree, e.g., the degrees-of-freedom problem, the problem of complex spatial sensory-motor transformations, and the inverse-dynamics problem (Poppele and Bosco 2003).

Among the many challenges that organisms face and have to cope with are perturbations, originating externally or internally, harmless or deleterious in nature. We have here dealt with damages to the nervous system to which mammals must react. These reactions may be direct or indirect consequences of the original lesions or attempts to adapt to the circumstances so as to make the best of the situation and potentially come up with a solution to keep going.

Despite the variability of symptoms and anatomical/functional alterations depending on species and lesion sites, one symptom appears to be ubiquitous: spasticity. It may be speculated, therefore, that spasticity has developed trans-individually as a common adaptation with a beneficial effect, namely stabilization of stance and locomotion against weakening muscles. It may be regarded as a learning result of trying to find a solution to changed circumstances. Other learning processes may be taylored to provide individual solutions for particular problems.

"There is a third solution that is based on trial-and-error learning, recall and interpolation of sensorimotor programs that are good-enough rather than limited or optimal. The solution set

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acquired by an individual during the protracted development of motor skills starting in infancy forms the basis of motor habits, which are inherently low-dimensional“ (Loeb 2021).

Thus, after lesions and the loss of substantial descending inputs, the CNS has to learn new sensory-motor programs that are good enough to restore some motor capacities. Since favorable programs depend on the precise site and extent of the lesions, they must be taylored to individual circumstances, using trial-and-error learning supported by inputs that mirror the sensory feedback occurring during natural movements such as locomotion. In so doing, the re-designed spinal circuits must be able to cope with old problems. Important roles in doing so are played by interneuronal networks.

“Engineers use neural networks to control systems too complex for conventional engineering solutions. To examine the behavior of individual hidden units would defeat the purpose of this approach because it would be largely uninterpretable. Yet neurophysiologists spend their careers doing just that! Hidden units contain bits and scraps of signals that yield only arcane hints about network function and no information about how its individual units process signals. Most literature on single-unit recordings attests to this grim fact” (Robinson 1992).

The workings of spinal neuronal networks on the backstage will never be penetrated. An important characteristic of these networks is the wide and often semi-random connectivity between several descending systems, sensory inputs from many and diverse muscles, joints and cutaneous sources to α-MNs innervating multiple and diverse muscles, and among interneurons themselves. Contributors to these extended networks may also be the diffuse but fairly weak or modest effects of group Ia afferent fibers, reciprocal inhibition and recurrent inhibition, in distinction to the more concentrated and stronger effects at individual joints. The convergence of group Ia, group II and group Ib afferents in conjunction with other mechano-receptor afferents onto common neurons and the wide distribution of related reflex effects from many muscles to many muscles throughout the limb would enable the handling of the complex peripheral biomechanics, regulating both more local and individual muscle properties such as stiffness and non-linearities as well as transjoint limb mechanics (Windhorst 2021).

The impenetrability of the backstage network has advanced experimentally more accesible networks like reciprocal Ia inhibition, recurrent inhibition and presynaptic inhibition onto the frontstage. But it should not be forgotten that the latter are complex networks in their own right (Windhorst 2021).

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Conflicts of Interest: None

Abbreviations:

ALS: amyotrophic lateral sclerosis
α-MN: α-motoneuron
AMPA: α-amino-3-hydroxy-5-methylisoxazol-4-propionic acid
BDNF: brain-derived neutrophic factor
5HT: 5-hydroxytryptamine, serotonin
C1-C8: cervical spinal segments
Chrna2: nicotinic cholinergic receptor2

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CIN: commissural interneuron
CNS: central nervous system
COM: center of mass
COP: center of pressure
CP: common peroneal
CPG: central pattern generator
CST: cortico-spinal tract
DOF: degree of freedom
DSCT: dorsal spino-cerebellar tract
EMG: electromyogram, electromyography
EPSP: excitatory post-synaptic potential
GABA: gamma-aminobutyric acid
H-reflex: Hoffmann reflex, elicited by electrical stimulation of group Ia fibers from muscle spindles in a muscle nerve and measured as short EMG wave in the related muscle
γ-MN: γ-motoneuron
IN: interneuron
IPSP: inhibitory post-synaptic potential
L1-L7: lumbar spinal segments
LMC: lateral motoneuron column
LPN: long proprio-spinal neurons
MAG: myelin-associated glycoprotein
MG: medial gastrocnemius
MLR: medium-latency reflex, also M2
MMC: medial motoneuron column
MN: motoneuron
MS: multiple sclerosis
mSOD1-G93A: mouse model of ALS
MVC: maximal voluntary contraction
NMDA: N-methyl-D-aspartate
NMDAR: N-methyl-D-aspartate receptor
OMgp or Omg: oligodendrocyte myelin glycoprotein
pTDP-43: phosphorylated protein TDP-43
PIC: persistent inward current
PSI: presynaptic inhibition
PLR: postural limb reflex
PSP: post-synaptic potential
RC: Renshaw cell
recIaIN - reciprocal Ia inhibitory interneuron
RF: brainstem reticular formation
ReST: reticulo-spinal tract
RuST: rubro-spinal tract
SC: spinal cord
SCI: spinal cord injury
SLR: short-latency reflex, also M1
SMA: spinal muscular atrophy
SMN1: motor neuron 1 gene
SMN2: motor neuron 2 gene
SMNΔ7: mouse model of spinal muscular atrophy
SOD1: mouse model of ALS
SOD-93: mouse model of ALS
TA: tibial anterior
TNF: tumor necrosis factor

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VAChT: vesicular acetylcholine transporter
VGAT: vesicular GABA transporter
VGLUT: vesicular glutamate transporter
VIAAT: vesicular inhibitory amino acid transporter
VOR: vestibulo-ocular reflex
VSCT: ventral spino-cerebellar tract
VST: vestibulo-spinal tract

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