Neural Basis of Spasticity

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…dissolution is not only a "taking off" of the higher but is at the very same time a "letting go" of the lower.
– John Hughlings Jackson,
Croonian lectures, Royal College of Physicians, London, 1884.

- Spasticity arises after a neurological injury; hence it clearly has a neural basis. However, it has many definitions and manifestations, and the underlying mechanisms are still not clearly understood.
- This chapter reviews the definitions of spasticity, the time course of its development, and the types of neural injury that may cause it by disinhibiting inhibitory brainstem pathways as well as by facilitating excitatory brainstem pathways, that result in an excitatory-inhibitory imbalance in the spinal cord interneuronal network.
- The descending pathways modulate persistent inward currents via serotonin and norepinephrine, which provide a low-level depolarizing synaptic drive to the resting motoneuron pool resulting in increased afferent sensitivity and can account for hyperreflexia.
- However, the abnormal brainstem descending inputs and persistent inward currents cannot fully account for other spasticity-related motor impairments, such as muscle stiffness.

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Definition of Spasticity

It is well-known that damage to the descending motor pathways anywhere from the cerebral cortex to the lower end of the spinal cord can give rise to a set of symptoms called the upper motor neuron syndrome. John Hughlings Jackson observed in the late nineteenth century that neural injury often leads to dual symptomatology. For example in hemiplegia, in addition to loss of movement (negative symptoms), excess activity also develops (positive symptoms) such as increased tendon reflexes and excess muscle tone, which he attributed to the "release" of the lower centers from control by the damaged higher centers that are "taken-off" [1]. The idea of "release" phenomena characterizing the upper motor neuron syndrome continues to inform our understanding of spasticity.

In fact, Lance and colleagues defined spasticity at a consensus symposium in 1980 [2] as:

> a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome.

Subsequently, Pandyan et al. [3] attempted to validate Lance's definition by reviewing the literature since, and concluded that spasticity is not a pure motor disorder and that it does not result exclusively from hyperexcitability of the stretch reflex. The changes in resistance to imposed passive movement were also not found to be uniquely related to increased muscle activity, and the phenomenon of velocity dependence was not exclusive to stretch reflex hyperexcitability. Hence spasticity was redefined as:

> disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles.

This definition suggests that spasticity is a disorder of sensorimotor control, rather than a motor disorder alone. Furthermore, it suggests that spasticity presents as muscle overactivity, rather than solely as stretch reflex hyperexcitability, which had major implications for treatment that was then directed to reducing muscle overactivity.

A more recent definition of spasticity proposed by Li et al. [4] is even broader, and specifies a neuroanatomical substrate for the hyperexcitability, rather than the release of control by the higher centers as alluded to by Hughlings Jackson. By this definition, spasticity is:

> manifested as velocity- and muscle length–dependent increase in resistance to externally imposed muscle stretch. It results from hyperexcitable descending excitatory brainstem pathways and from the resultant exaggerated stretch reflex responses. Other related motor impairments, including abnormal synergies, inappropriate muscle activation, and anomalous muscle coactivation, coexist with spasticity and share similar pathophysiological origins.

Abnormal excitability of the stretch reflex is still the central mechanism as per this latest definition of spasticity. However, it also attributes spasticity-related motor impairments to the excitatory brainstem pathways.

Time Course of the Development of Spasticity

Although hyperreflexia is central to defining spasticity, several studies have shown nonreflex-related resistance to movement in patients with "spasticity" [5–7]. Furthermore, although hyperreflexia is elicited relatively early after injury, the resistance to passive movement measured using the Modified Ashworth Scale (MAS), which is commonly used to assess spasticity clinically, tends to increase in prevalence over the ensuing weeks and months [8–10]. Even mild hyperreflexia early on is an important predictor of severe spasticity and increased resistance to passive movement later [11, 12], suggesting that hyperreflexia may trigger a cascade of events that lead to a build up of the resistance to movement. In a retrospective study of chronic stroke survivors with moderate-to-severe upper limb motor impairment, 97% of subjects demonstrated increased resistance to passive movement which was associated with impaired motor control [13]. Thus, it is important to understand the characteristics of the neurologic injury that lead to the development of spasticity and the ensuing resistance to movement to initiate measures for prevention and early treatment. Untreated, spasticity leads to fatigue, pain, sleep problems, and urinary dysfunction among others, affecting physical health [14], and restricting activities of daily living (ADL) and mobility that contribute to disability and increased health care costs [15, 16].

What Types of Neural Injury Lead to the Development of Spasticity?

Several recent studies have shown a positive correlation between spasticity and the overall degree of injury to the sensorimotor system – the greater the lesion volume and severity of injury, the greater the likelihood of developing spasticity [17]. However, small lesions involving specific regions of the brain such as the putamen, internal (posterior limb) and external capsule, thalamus, and insula, which are involved in sensorimotor processing, have also shown to be correlated with the degree of spasticity [18]. Note that in these studies, the resistance to passive movement on the MAS, which is not specific to the neural component, was used to measure spasticity (see Chaps. 3 and 4). More recently, the velocity-dependent neural component of hand spasticity was shown to be related to lesion load of the corticospinal tract (CST), after controlling for motor impairment and lesion volume [11].

To fully comprehend the effect of neural injury, especially given the strong correlation between motor impairment and spasticity reported recently [13], it is helpful to review the origin and termination of the CST, which modulates brain stem and spinal cord activity. The CST originates from a wide range of cortical areas having different functions, including the primary motor cortex (M1) which is involved in

the execution of movement, the dorsal (PMd) and ventral (PMv) premotor areas involved in the sensory guidance of movement, the supplementary motor area (SMA) involved in planning and coordination of internally generated movement sequences, the cingulate motor areas involved in emotional aspects of voluntary movement, including changes in autonomic function [19], and corticospinal projections from the parietal lobe including the primary somatosensory cortex, posterior parietal cortex, and parietal operculum (SII) [20, 21].

The termination of the corticospinal projections within the spinal gray matter is also varied (Fig. 1.1) [22–24]. Projections from the somatosensory cortex terminate

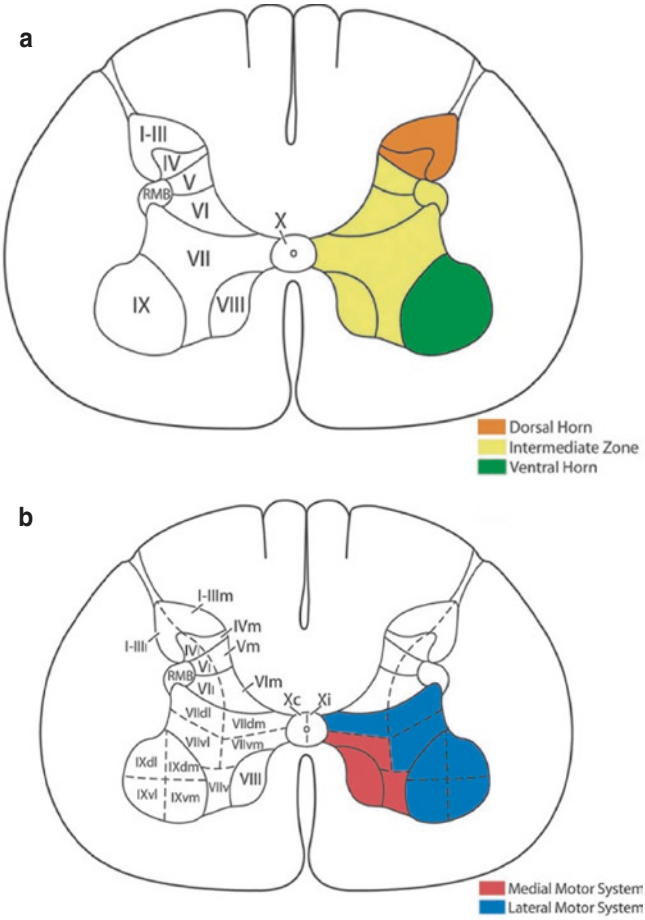

Fig. 1.1 Schematic diagram of the general anatomical organization of the spinal cord adapted from Kuypers [23]. (**a**) The ventral horn consists of lamina IX (green), the intermediate zone laminae V, VI, VII, VIII, and the reticulated marginal border (RMB) (yellow), and the dorsal horn laminae I–III and IV (orange). (**b**) The Rexed laminae are further subdivided into 20 subdivisions in each half of the spinal cord. The blue shaded regions of laminae VII and IX represent spinal components of Kuypers "lateral motor system" [24]. The red shaded region of lamina VII and lamina VIII constitute parts of his "medial motor system". (From Morecraft et al. [22], with permission)

mainly in the more dorsal parts of the spinal gray matter (Rexed laminae I–V) and are involved in the descending control of sensory afferent input. These projections are an important source of presynaptic inhibition of primary sensory afferent fibers [25, 26], and are responsible for sensory reafference or gating of inputs arising from one's own movement [27, 28]. Projections from M1 target most areas of the intermediate zone of the spinal cord gray matter (Rexed lamina VII). These are the indirect oligosynaptic projections that mediate corticospinal input to motor neurons via a premotoneuronal network [22]. Inputs to the premotoneuronal network originate in a variety of descending motor pathways, in ascending and descending propriospinal pathways, in local segmental interneurons, as well as in sensory afferent inputs from the periphery. Integration of information in this network is critical to achieve the precise timing and balance of activity in the motoneuron pool, contributing to highly flexible movement responses in the healthy state [29]. Recent evidence suggests that corticospinal projections from the dorsal and ventral premotor areas terminate in laminae VII and VIII, and govern proximal upper limb musculature involved in postural stabilization and control of the proximal limb during reaching and grasping through the indirect oligosynaptic neural networks [30]. These projections, as well as the corticospinal projections from the leg area of M1 to motoneurons of more proximal leg muscles, are bilateral [30, 31]. Injury to these pathways can account for increased spasticity when standing [32, 33].

In contrast, direct cortico-motoneuronal connections in the ventral horn (Rexed lamina IX) originate from both M1 and SMA, but the corticospinal projections from M1 to the hand muscle motor nuclei are denser than those from the SMA [34]. In humans, fast-conducting direct mono-synaptic cortico-motoneuronal connections have been found to be responsible for precision grasp, but not power grasp [35, 36]. Selective lesions of the CST may therefore only impede individuated finger movements as has been shown in monkeys [37].

Thus, injury to the CST at its origin, especially when it involves both sensory and motor areas [38, 39], along its path, or at the level of the spinal cord, regardless of etiology leads to widespread consequences depending on the corticospinal projections affected and their particular function. The function of the CST reflects its origins and terminations and includes: (1) descending control of afferent inputs, including nociception [25, 26]; (2) selection, gating, and gain control of spinal reflexes [40]; (3) direct and indirect excitation of motoneurons [41, 42]; (4) inhibition of motoneurons [43, 44]; (5) autonomic control [45]; (6) long-term plasticity of spinal cord circuits [46]; and (7) trophic functions during development [47, 48]. Individuals who present with spasticity invariably present with symptoms reflecting additional corticospinal dysfunction depending on the pathways affected.

How Does Injury to the Corticospinal Tract Lead to Spasticity?

In 1946, Magoun and Rhines found an area in the brainstem, the ventromedial medullary reticular formation, which when stimulated could inhibit any type of muscle activity, including stretch reflex activity. This region receives facilitatory influences from the premotor cortex [49]. Extensive lesions involving premotor

and supplementary motor areas, and/or their projections were found to inhibit the medullary reticular formation, leading to release or disinhibition of stretch reflex activity, causing hyperreflexia [50]. The inhibitory influences from the medullary reticular formation are transmitted to the spinal cord by the dorsal reticulospinal tract (RST), which runs very close to the lateral corticospinal tract. Stimulation of the dorsal RST in decerebrate cats was also shown to inhibit excitability in the spinal interneurons [51, 52]. Section of the dorsal half of the lateral funiculus, which contains the dorsal RST in humans, to treat parkinsonism was also followed by spasticity [53]. This lent further support to the idea that the disruption of cortical inputs to the brainstem, specifically injury to cortico-reticulospinal fibers, and/or damage to the dorsal RST, releases the spinal neural network from inhibitory control causing an imbalance between excitatory and inhibitory inputs [54, 55].

While disinhibition can explain hyperreflexia that is seen soon after injury, the question of what leads to the development of increased resistance to passive movement, abnormal synergies, inappropriate muscle activation, and anomalous muscle coactivation remains. One possibility is that the imbalanced neural excitability becomes amplified through increased facilitatory influences involving alternative brainstem control pathways. Magoun and Rhines also found that stimulation of the reticular formation of the dorsal brain stem (pontine reticular formation) can facilitate or exaggerate any type of muscle activity, including the stretch reflexes [49]. The facilitatory influences from the pontine reticular formation are transmitted to the spinal cord by the medial RST, which along with the vestibulospinal tract (VST) provides excitatory input to the spinal neural network. The VST is thought to play a minor role, as section of the anterior funiculus of the cord to relieve hypertonia resulted in only transient reduction in spasticity [56]. In contrast, extensive unilateral or bilateral anterior cordotomy, which is likely to have destroyed both the VST and the medial RST, was followed by a dramatic reduction in spasticity [57].

Recent studies in monkeys demonstrate that the projections from nonprimary motor cortices (PM and SMA) are denser and end mainly ipsilaterally in the pontine reticular formation, whereas the projections from the primary motor cortex (M1) are less dense and end contralaterally [58]. The importance of the denser ipsilateral projections from the uninjured PM and SMA is that these projections are thought to compensate for injury to the contralateral CST and enable at least partial recovery of motor function in monkeys [59–62], and in humans with mild impairment [63–68]. However, severely impaired individuals also show increased activation of the ipsilesional premotor regions [69–71] associated with compensatory movement strategies [72–74]. Hence it is hypothesized that the motor overflow from the ipsilesional to the impaired side contributes to increased spasticity and disordered motor control [75]. Indirect support for this hypothesis was noted in an imaging study which showed strong correlation of synergistic arm movements with the functional reorganization in the reticulospinal pathways suggesting a contributory role in the development of compensatory motor strategies [76]. Hence it is suggested that spasticity and the related motor impairments are exacerbated by the ipsilateral excitatory contribution from the medial RST to the spinal neural network as shown by the dashed line in Fig. 1.2 [77].

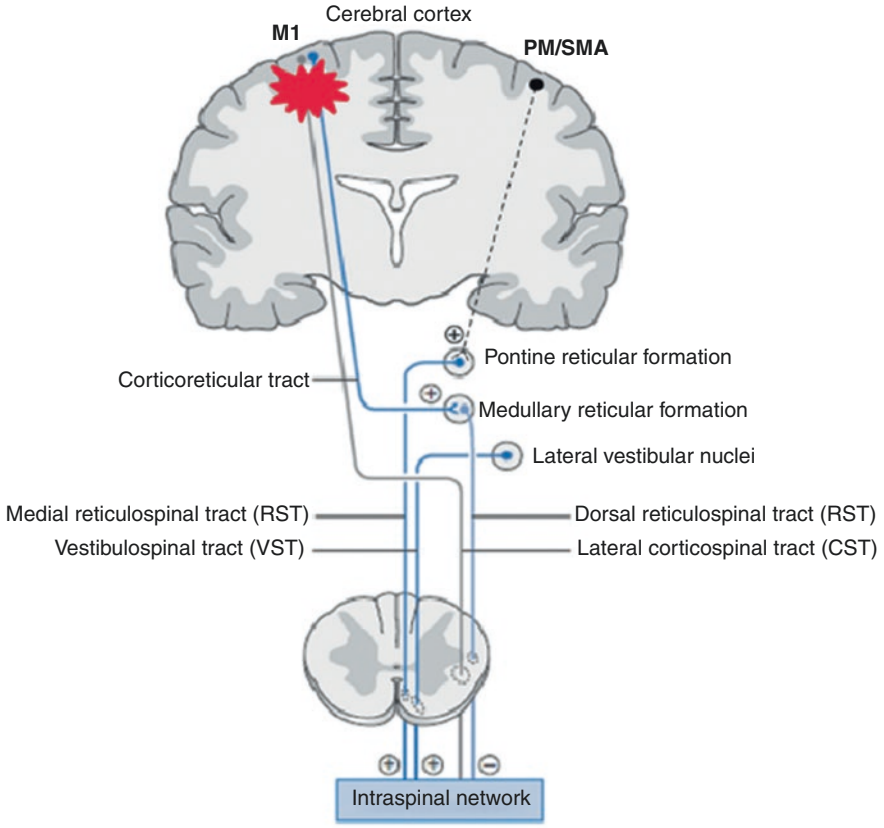

Fig. 1.2 Schematic diagram illustrating the descending pathways contributing to the medial reticulospinal tract in the pathophysiology of spasticity. The pontine reticular formation receives cortical input primarily from the ipsilateral premotor (PM) cortex and supplementary motor area (SMA), and via the medial reticulospinal tract (RST) provides excitatory descending input to the spinal circuitry. The medullary reticular formation receives cortical input primarily from the contralateral primary motor cortex (M1), and via the dorsal RST provides inhibitory descending inputs to the spinal circuitry. Injury to the corticospinal tract (indicated in red) leads to reduced inhibition of the spinal circuitry via the dorsal RST causing an excitatory-inhibitory imbalance. In addition, it is proposed that the contribution of the contralesional hemisphere to the excitatory medial RST becomes gradually upregulated and unopposed further increasing spinal hyperexcitability. (+) excitatory; (–) inhibitory. (From Li et al. [77], with permission (open access))

Consequences of Excitatory-Inhibitory Imbalance in Spinal Circuitry

The descending RST inputs are primarily mediated by the monoamines serotonin (5-HT) and norepinephrine (NE), which have neuromodulatory effects that correlate with the level of behavioral arousal and/or the behavioral state, for example

when awake and in fight or flight situations [78]. These neuromodulatory effects, in turn, have been shown to be mediated via persistent inward currents (PIC). A PIC is a depolarizing current generated by voltage-sensitive channels that stay open as long as the membrane potential remains above the threshold of activation. This persistence stands in marked contrast to the inward currents that generate the action potential, which inactivate within 1–2 ms, even during prolonged membrane depolarization [79]. PICs increase the sensitivity of neurons to both excitation and inhibition – they have strong excitatory actions on motoneurons involved in tonic motor activity, for example in antigravity muscles and other muscle groups associated with gross motor activity. These neuromodulatory inputs have been shown to be critical for the production of high forces and have a major influence on input-output behavior of the whole system [80, 81]. Turning off these sustained outputs also requires considerably large inhibitory inputs [82]. In contrast to their strong excitatory actions on motoneurons, monoamines inhibit many of the synaptic inputs to interneurons [78]. This inhibition is largely presynaptic and focused on sensory afferents that mediate both high- and low-threshold cutaneous inputs [83], and high-threshold muscle afferents [84]. The differential role of monoaminergic actions on motoneurons and interneurons occurs via their action on different receptor subtypes – facilitation of PICs in motoneurons appears to occur via 5HT2 and NE alpha 1 receptors, whereas inhibition occurs via 5HT1b/d and NE alpha 2 receptors [85]. In effect, monoamines increase the sensitivity of motoneurons to both excitation and inhibition in a movement-dependent manner [86]. Accumulating evidence indicates that the movement-related motor excitability is related to coactivation of the sympathetic nervous system and to modulation of afferent inputs [79].

When descending pathways are interrupted following CNS injury, the overall excitability of the spinal motoneuronal pool is initially reduced, producing weakness and flaccidity. However, the acute loss of descending brainstem inhibition of presynaptic afferent inputs, especially cutaneous inputs, is thought to increase intrinsic motoneuron excitability via the development of PICs [87, 88]. At first, these low-threshold polysynaptic inputs do not produce long-lasting reflexes because of lack of motoneuron excitability in a monoamine-deficient state. Over time, the PICs become supersensitive to the residual monoamines below the level of the injury [89], which more than compensate for the monoamine deficiency, leading to the development of large PICs and hyperexcitable motoneurons which trigger sustained motoneuron discharges associated with long-lasting reflexes and muscle spasms to innocuous stimulation, such as gently rubbing the skin or passive movement [88]. In fact, indirect measurements of PIC amplitude from paired motor unit recordings in human subjects suggest that PICs in motor neurons contribute to muscle spasms after spinal cord injury [90]. Pharmacologically blocking the PICs on the motoneurons, without inhibiting the synaptic inputs, can eliminate the long-lasting reflexes [91].

However, in individuals with stroke, PIC estimates have not been found to be larger in spastic-paretic motoneurons, compared with contralateral, and

age-matched healthy control motoneurons. Instead, following voluntary isometric contractions, the majority of the low-threshold motor units in spastic-paretic muscles exhibit spontaneous discharges, suggesting that firing changes are likely due to low-level depolarizing synaptic drive to the resting motoneuron pool [92, 93], which can account for hyperreflexia. However, voluntary activation of the spastic-paretic motoneuron pool results in saturation in firing profiles of the individual motor units, and an inability to modulate firing rates [94], suggesting lack of synaptic drive for voluntary muscle activation or paresis. The contradiction in the PIC estimates of the spastic-paretic motorneurons can be reconciled by considering that the net excitability of the alpha motor neuron is achieved via a complex and poorly quantified afferent pool that influences the central state of the cells, which is influenced by the function of both lesioned and nonlesioned areas contributing to the tracts. This is in contrast to the more simplistic view of hyperreflexia described historically (Fig. 1.3) [95, 96].

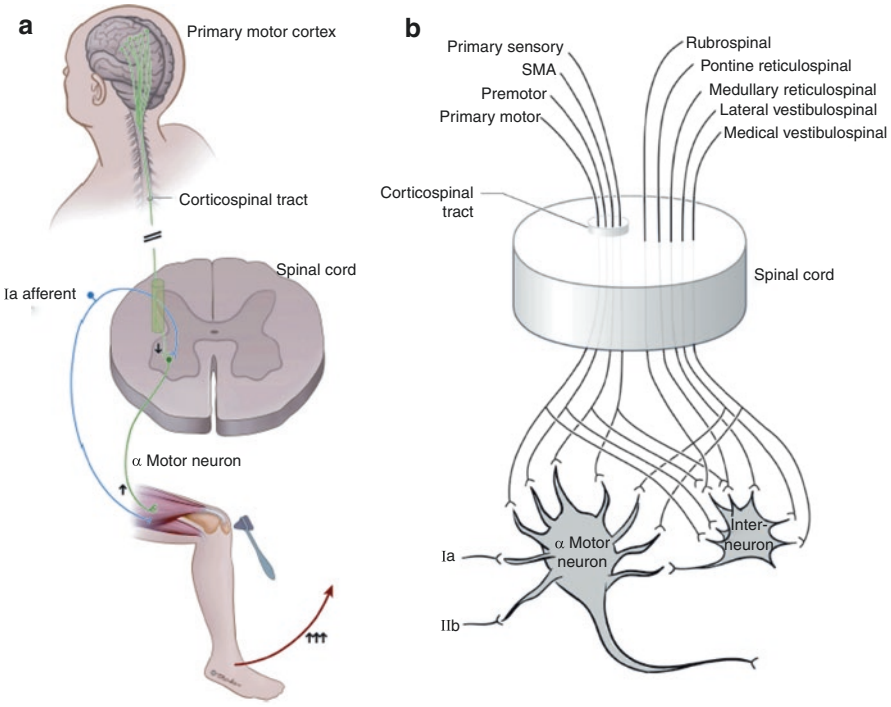

Fig. 1.3 Schematic illustration of the spinal stretch reflex. (**a**) The classically described spinal reflex arc demonstrating hyperreflexia (indicated by the arrows) after corticospinal tract injury. (**b**) Contemporary summary of the afferent pool of the alpha motor neuron showing significant contributions from the spinal interneuron pool whose inputs include projections received from the corticospinal tract. (From Florman et al. [95], with permission (open access))

Conclusion

Injury to the central nervous system results in both negative symptoms such as paresis and positive symptoms such as spasticity. While findings from both animal studies and studies with human subjects support the role of the dorsal reticulospinal tract in producing hyperexcitability of the spinal stretch reflexes, a more contemporary view is that the overall state of excitability of the spinal afferent pool is influenced by cortical input from both lesioned and nonlesioned areas and their descending pathways.

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