Chapter 2: Pathophysiology of spasticity

By Jens Bo Nielsen, Maria Willerslev-Olsen and Jakob Lorentzen.

This chapter will argue

- that proper evaluation of spasticity requires biomechanical and electrophysiological techniques
- that spasticity is not caused by pyramidal tract lesion
- that spasticity is caused by plastic adaptation in neural networks
- that spasticity is not caused by a single mechanism but by a multitude of alterations in spinal motoneurones and interneurons
- that clonus, spasms and spastic dystonia are caused by at least partly different pathophysiological mechanisms than spasticity

1.0 How to measure spasticity - from clinical evaluation to biomechanical techniques

The clinical evaluation of spasticity currently rests on the eyes and hands of the clinician. Muscle tone is essentially determined by sensing the resistance to passive movement around a joint with the patient in an as relaxed position as possible. By making movements at different velocities the clinician may get a feeling of whether the resistance is present at all velocities or only with the fastest stretch of the muscles. Sometimes a distinct brief resistance – a catch - may be determined with quick stretches at specific positions of the joint. Backed up by other signs such as large – and especially non-symmetrical - tendon jerks and the presence of clonus, the clinician may decide that the resistance is velocity-dependent and may possibly be related to hyperexcitable stretch reflexes; i.e. that the muscle resistance is caused by spasticity according to Lance´s definition. In many cases the determination of the presence of spasticity is relatively straightforward and unproblematic.

However, if the patient is not fully relaxed, if the changes in reflex excitability are not very large or if other mechanisms also contribute to increased muscle resistance the precise diagnosis may be difficult. The presence of alterations in the elastic properties of the muscle, connective tissue and/or tendons especially makes it difficult to perform the evaluation sufficiently fast and powerfully and it therefore becomes a challenge to determine the presence of spasticity. The presence of involuntary static muscle activity (spastic dystonia) and an associated inability of the patient to fully relax the muscle also make the evaluation difficult. Clinical evaluation of spasticity has consequently been
shown to have variable reproducibility within and between raters (Bhimani et al 2011, Biering-Sorensen et al 2006, Haugh et al 2006, Mutlu et al 2008) and to be very little related to objective biomechanical measures of spasticity (Lorentzen et al 2010, Willerslev-Olsen et al 2013). The Ashworth scale was introduced in 1964 (Ashworth 1964) as a simple 5 point scale ranging from normal muscle tone (0) to rigidity (4) in order to quantify spasticity in multiple sclerosis before and after treatment. The scale does not distinguish stretch reflex mediated muscle resistance from other causes of muscle resistance (in particular contractures) and an additional grade (1+) was therefore introduced in 1987 to designate slight resistance with a clear catch (Bohannon & Smith 1987). This modified Ashworth Scale (MAS) is now the most commonly used clinical scale, although it is confounded by the same limitations as the original scale except for the additional grade.

Furthermore, the introduction of this additional grade seems not to have improved the reliability of the scoring (Bhimani et al 2011, Biering-Sorensen et al 2006) and a conspicuous over-representation of scores 1-2 suggests that what is scored in most patients is ‘some resistance but not too much’ (Biering-Sorensen et al 2006). The scale has consequently shown low validity in studies in which it has been related to biomechanical measures of stiffness (Biering-Sorensen et al 2006, Lorentzen et al 2010, Sehgal & McGuire 1998). It is surprising given these drawbacks that the scale has become the scale of choice in the clinic rather than the older Tardieu scale. The Tardieu scale was introduced originally in 1954 (Tardieu et al 1954) and has later been modified to the scale that is in use today (Haugh et al 2006, Held 1969). The essence of the scale is that the examiner has to move the examined limb at three different velocities (slow, moderate and as fast as possible) in order to determine range of movement, presence of passive resistance and the presence of spasticity. The scoring of spasticity is based on the presence of a catch and clonus. Although the Tardieu scale theoretically should more adequately distinguish passive and active components of muscle resistance than the Ashworth scale, it has not gained an as wide use in the clinic as the Ashworth
scale. Part of the reason for this is that the technique is more demanding for the examiner and is therefore less easy to perform in a similar way for two raters. The scale also lacks sufficient dimensionality to cover patients with very severe spasticity that prevents elicitation of stretch reflexes and clonus. The focus on the presence of clonus is also problematic given the uncertainty regarding the mechanisms of clonus and its relation to spasticity (see below).

Biomechanical evaluation of spasticity was introduced in 1976 (Knutsson & Martensson 1976) and various devices and techniques have been developed and tested since then (Mirbagheri et al 2005, Mirbagheri et al 2009, Mirbagheri et al 2004, Sinkjaer 1997, Sinkjaer et al 1992, Sinkjaer & Magnussen 1994, Sinkjaer et al 1995, Sinkjaer et al 1988, Toft et al 1989b, Toft et al 1989c, Wood et al 2005). The main advantage of these techniques is that they provide an objective and quantitative assessment of muscle resistance. With the addition of EMG measurements from the stretched muscles they may provide an objective and precise way of distinguishing reflex-mediated from passive muscle resistance (Lorentzen et al 2010, Sinkjaer et al 1993, Toft et al 1989b, Willerslev-Olsen et al 2013). From this point of view biomechanical evaluation combined with electrophysiological measures might be considered a ´gold standard´ for spasticity evaluation with which other measures may be compared. However, the expertise and technology involved is too demanding for routine clinical use. Hand-held dynamometers and other simplified biomechanical devices may provide sufficiently reliable and consistent measures, but none of the commercially-available devices have so far shown sufficiently promising results to be used more widely in the clinic for spasticity evaluation (Barden et al 2012, Benard et al 2010, Calota et al 2008, Kim et al 2011, Lee et al 2004, Lorentzen et al 2012, Waldman et al 2013). Only few of the existing devices provide a distinction between reflex-mediated and passive muscle stiffness and there is therefore a clear need of developing more optimal easy-to-use devices that can help the clinician in the routine clinical diagnosis.
2.0 The nature of the muscle response to stretch

In order to understand the pathophysiology of spasticity it is useful initially to consider the responses of a muscle to stretch (Fig. 2). At velocities below the threshold of the stretch reflex the resistance against the movement is caused solely by the passive elastic properties of the muscle, connective tissue, tendon and joint (Lorentzen et al 2010, Mirbagheri et al 2005, Mirbagheri et al 2004, Toft et al 1989a, Toft et al 1989b). This resistance is usually called passive stiffness (Toft et al 1989a, Toft et al 1989b) and appears to be relatively insensitive to the velocity of the stretch (Lorentzen et al 2010). However, it varies with the position of the joint and thus the degree of stretch of the muscle (Mirbagheri et al 2005, Mirbagheri et al 2009, Mirbagheri et al 2004). If the subject is not fully relaxed neural activation of the muscle will result in formation of cross-bridges between myosin and actin filaments that will impede the stretch and add very significantly to the stiffness (Fig. 2). This stiffness is usually called intrinsic stiffness to distinguish it from the passive and reflex-mediated stiffness (Sinkjaer et al 1993), but it should be emphasized that it is caused by an (extrinsic) neural signal and may be very difficult to distinguish in practice from reflex-mediated stiffness given the integration between descending motor commands and reflexes (Nielsen 2004).

When stretches above a certain threshold (which is determined individually by the sensitivity of muscle spindles, transmitter release from central synapses and the excitability of motoneurones) are applied, a stretch reflex response will be evoked and add to the resistance against the movement (Fig. 2). This reflex mediated stiffness is at least in theory equivalent to the catch that is assessed as part of the clinical evaluation of spasticity. The mechanical response evoked by the stretch conceals that there are at least two separate reflex responses in most muscles (Christensen et al 2000). These responses may be demonstrated by EMG measurement from the muscle (Toft et al 1989b, Toft et al 1991). The initial (short-latency or M1) response is mediated by the spinal monosynaptic Ia
pathway and is equivalent to the reflex response elicited by a tendon tap (Morita et al 1998). The response is generally strongly exaggerated in spastic patients (Ibrahim et al 1993, Sinkjaer & Magnussen 1994, Sinkjaer et al 1993). In lower limb muscles the initial response is followed by a second (medium-latency or M2) and sometimes a third (long-latency or M3) response (Christensen et al 2000). The M2 response has been shown in all likelihood to be mediated by gr. II afferents from the muscle spindles (Christensen et al 2000, Grey et al 2001). Similar to the M1 response it is generally exaggerated in spastic patients (Sinkjaer & Magnussen 1994, Sinkjaer et al 1993, Willerslev-Olsen et al 2014). The third response on the other hand is generally reduced or abolished in spastic patients consistent with the idea that it is mediated by a transcortical pathway which is involved in the lesion(Christensen et al 2000). Similar mechanisms probably also contribute to the stretch response observed at longer latency than the M1 response (generally called long-latency or M2 response) in upper limb muscles, but due to the short difference in conduction time for spinal and transcortical responses the responses appear to be difficult to separate (Christensen et al 2000). These later responses in upper limb muscles may therefore be reduced, unchanged or exaggerated in the individual patient.

Since the mechanical resistance sensed either by a clinical examiner or a biomechanical device is the sum of these different reflex responses, transmission in all the involved pathways should be taken into account when considering the cause of an exaggeration of the muscle resistance.

3.0 Is spasticity caused by lesion of the pyramidal tract?

Spasticity is observed following both spinal and cortical lesions and is in the clinic commonly associated to lesion of the corticospinal tract, but studies in animal suggest that this is wrong. Tower (1940) was the first to observe in monkeys that selective lesion of the pyramidal tract produced flaccid paresis without any signs of spasticity (Tower 1940). This was investigated in more detail in
the seminal studies by Lawrence & Kuypers (Lawrence & Kuypers 1968a, Lawrence & Kuypers 1968b). They reported that complete unilateral or bilateral pyramidal tract lesion in monkeys produced severe reduction in muscle tone, whereas lesion of brainstem tracts left the monkeys with increased reflex excitability and high muscle tone (Lawrence & Kuypers 1968a, Lawrence & Kuypers 1968b). These observations have been confirmed in several subsequent studies in both monkeys and other animals (Aoki et al 1976, Metz et al 1998). The evidence that the pyramidal tract is not involved in the development of spasticity in animals is thus convincing.

The most convincing evidence from human subjects is that of Nathan (1994) who reported the effect of surgical incision in the spinal cord to relieve chronic pain. His findings are well in line with the studies in monkey. In subjects in whom lateral incisions severing the corticospinal tract were made, no spasticity was observed, whereas this was the case for more ventral lesions which severed descending tracts from the brain stem (Nathan 1994). Other studies on the topic have only involved observations from single subjects. Sherman et al. (2000) somewhat confusingly reported increased biceps brachii tendon jerk without clinical signs of spasticity in a single patient with selective unilateral lesion of the pyramidal tract (Sherman et al 2000). In all likelihood this finding says more about the clinical examination than anything else. The same may be the case for the study of Paulson et al. (1986), who reported development of spasticity in a single patient with selective lesion of the medullary pyramids (Paulson et al 1986). On balance the human studies thus point in the same direction as the animal studies in suggesting that spasticity is caused by lesion of brain stem pathways or their cortical control rather than lesion of the corticospinal tract. The low occurrence of spasticity in stroke survivors with severe paresis or paralysis as sign of corticospinal lesion is well in line with this (Wissel et al 2013).

These findings suggest that lesion of the corticospinal tract alone is insufficient to start the range of spinal adaptations that result in spasticity. Apparently, additional affection of the vast innervation of
spinal motoneurones and interneurons by reticulospinal pathways and other descending tracts from
the brain stem is required in order to set the adaptive changes in motion, but we have little
understanding why this is.

4.0 Spasticity does not appear immediately after lesion but is caused by adaptive changes in
spinal networks
The excitability of spinal circuitries is depressed during a variable period in both animals and
humans following a spinal lesion due to what is called ´spinal shock´ (Ditunno et al 2004). The
mechanisms responsible for spinal shock are not fully clarified but seem to involve loss of
descending excitation, increased spinal inhibition, reduction of persistent inward currents in the
spinal motoneurones due to loss of serotonergic innervation, reduced neuronal metabolism and
retraction of dendrites and synapses (Ditunno et al 2004). The time course of development of
spasticity following spinal lesion is likely related both to the gradual relief of spinal shock and the
gradual development of a hyperexcitable state leading to spasticity. In the clinic spasticity usually
becomes manifest in spinal cord injured subjects 1-12 month after the lesion whereas reflex
hyperexcitability is observed in animals within 1-2 month (Aoki et al 1976, Ditunno et al 2004).
Spinal shock is not observed following stroke or supraspinal lesions in animals and it is therefore
possible to follow the development of spasticity without the interference from spinal shock in such
cases. In the clinic spasticity develops in some patients already within the first month after stroke,
but in the majority of patients spasticity is not manifest until more than 3 month after stroke (Wissel
et al 2013). The importance of this is that spasticity is not caused by simple release of the spinal
circuitries from a tonic supraspinal inhibition, which was believed some years ago (Burke 1988).
This idea ties into another old belief which has also been proven wrong: That spinal reflexes are
primitive reflexes which in humans are only seen in the first year of life, but are then suppressed as
the corticospinal tract develops and achieves functional connections with the spinal circuitries. With this mindset it follows that in adults reflexes and exaggerated reflexes in particular are seen as abnormal and require treatment because they are thought of as being caused by the release of a normal inhibitory descending influence. However, what really happens during development is that the corticospinal tract and spinal circuitries become functionally integrated and learn to collaborate to mediate voluntary movements (Clowry 2007, Nielsen 2004).

Moreover, the gradual development of spasticity puts emphasis on plastic changes in the spinal circuitries below the lesion as adaptations to the loss of descending supraspinal drive (Burke 1988).

5.0 Pathophysiology of exaggerated stretch reflex activity (or increased muscle tone)

It may seem self-evident to point out that the task of a spinal motoneurone is to activate the muscle fibres that it innervates and thereby contribute to movement. However, this simple notion provides an intuitive way of understanding the adaptive changes that occur in the spinal networks in response to lesion of descending motor fibres: When descending excitation of the motoneurone is lost, regulatory mechanisms that aim to help the motoneurone to restore an efficient output to the muscle set in. This point has been illustrated in a simplified version in Fig. 2. In the normal situation sensory input and descending drive both contribute to the activation of the motoneurones. Following lesion of central motor fibres, the descending drive is reduced and the sensory input is insufficient to maintain a normal output from the spinal cord to the muscles. As spasticity develops compensatory plastic mechanisms set in. These involved increased sensory drive, increased descending drive in surviving motor fibres and alteration of intrinsic mechanisms in the spinal motoneurones. These changes help to increase the output from the spinal cord to the muscles, albeit not necessarily to the level before lesion.
In the motoneurone these plastic changes involves up-regulation of membrane channels and receptors that increase the excitability of the membrane and reduction of the threshold for action potential generation (Fig. 3a). It also involves sprouting of nearby fibres (descending fibres as well as sensory afferents and fibres from local interneurons), growth of motoneuronal dendrites and establishment of new synaptic sites (Fig. 3b). Mechanisms that regulate transmitter release from sensory afferents (and in all likelihood also central motor fibres), such as presynaptic inhibition, ensure that the efficiency of the synapses that contribute to the motoneuronal drive is increased (Fig. 3c). A general up-regulation of excitation and down-regulation of inhibitory influences from various interneuronal populations on the motoneurones is seen (Fig. 3d). All these mechanisms work in concert with the common aim to maintain a functional output from the spinal cord to the muscles. Spasticity thus reflects an adaptive change in the spinal cord aimed at maintaining a functional output when a significant part of the normal descending excitatory drive to the motoneurones is lost. It is difficult to see this as a maladaption. It is essentially a very sensible adaptation.

5.1 Pathophysiological role of motoneuronal changes

The neuronal membrane is packed with receptors and channels that contribute to the regulation of the excitability of the cell. The number, density, type and state of these receptors and channels is regulated by a large number of intracellular messenger systems. These mediate changes in the receptors and channels themselves and regulate gene transcription and production of the proteins necessary for new receptors. The excitability of the cell is thus in essence a dynamic property which is continuously regulated according to the immediate and more distant experience of the cell. Dramatic changes such as loss of a major part of the excitatory drive to the cell therefore have
significant immediate and long-term impact on the trafficking of molecules and molecular signaling within and between the individual cells.

Voltage dependent Ca2+ and Na+ persistent inward currents (PICs) play a central role in this regulation of motoneuron (as well as interneuronal) excitability (Heckman et al 2003, Hultborn et al 2004, Powers & Binder 2001, Rekling et al 2000). Inward currents produce prolonged depolarizations (plateau potentials) when opposing outward currents are reduced or the Ca2+ channels are facilitated by, e.g. serotonergic and noradrenergic innervation of the motoneurons (Heckman et al 2003, Hultborn et al 2004, Powers & Binder 2001, Rekling et al 2000). Under normal circumstances the function of PICs is however much more dynamic and subtle. Although not fully clarified one important functional role of PICs seems to be to enhance the synaptic effect of excitatory inputs to the motoneurons. EPSPs in motoneurons produced by pyramidal tract activation are thus boosted by PICs to an extent that it has been argued that physiological descending drive to the motoneurons would be insufficient to drive the motoneurons at the firing frequencies observed during movement without them (Binder 2002, Hultborn et al 2004, Hultborn et al 2003). It has also been argued that EPSPs generated at dendritic sites distant from the cell soma would be unable to reach the spike initiation zone without the existence of PICs in the membrane to increase the gain of the EPSPs (Binder 2002). As already mentioned PICs cannot be evoked during the period of spinal shock following spinal cord lesions unless specifically increased by monoaminergic agonists (Ditunno et al 2004, Hultborn et al 2004). However, plateau potentials may be induced again at least in some cases in the chronic spinal state without adding any neurotransmitter precursors or agonists (see Hultborn et al. 2004). Bennett et al. (1999, 2001) developed a rat preparation in which a very low chronic spinal lesion causes pronounced hyperreflexia of the tail without interfering with normal hindlimb or bladder function. PICs were regularly seen in the chronic test state, but never in the acute control situation (Bennett et al 1999,
This appears to be linked to upregulation of monoaminergic receptors, in particular 5-HT(2B) and 5-HT(2C) receptors in the motoneuronal membrane (Murray et al 2010, Murray et al 2011a, Rank et al 2011, Ren et al 2013, Wienecke et al 2010). It is likely that similar plastic changes occur also at interneuronal level although this has not been shown.

Little is known about a possible contribution of PICs to the development of spasticity in human subjects because of the difficulty in demonstrating the existence of such intrinsic membrane properties in the intact organism. However, Nickolls et al. (2004) found that muscle stimulation, which provided an excitatory sensory drive to the spinal motoneurones, did not induce plateau-like behaviour of motor unit activity in patients with spinal cord injury as easily as in healthy subjects, but nevertheless argued that plateau potentials might contribute to the clinical manifestations of the patients, such as spasticity (Nickolls et al 2004). It is not immediately clear how this should be the case.

From observations of motor unit behaviour during spasms in spinal cord injured patients, Gorassini et al. (2004) inferred that motor units required significantly less synaptic drive in order to be de-recruited at the end of spasms as compared to the synaptic drive required to recruit them in the beginning of the spasm. From this they argued that persistent inward currents were activated during the spasm and appeared to contribute to the occurrence of the spasms (Gorassini et al 2004). In line with animal experiments this appears to depend on upregulation of serotonergic receptors (D'Amico et al 2013a, D'Amico et al 2013b). These findings from both animal and humans are certainly of relevance for the pathophysiology of spasms, but given the mechanisms involved, upregulation of PICs is unlikely to be a universal explanation of spasticity. Loss of serotonergic innervation and subsequent upregulation of 5-HT receptors likely only occurs to any significant extent following spinal cord injury, but not following supraspinal lesions. This likely also explains
why spasms are rare in spastic patients following stroke. This in turn undermines the idea that PICs should be causally involved in the pathophysiology of spasticity.

5.2 Sprouting, new synapses

Following lesions in the central nervous system several morphological changes are usually seen including outgrowth of dendrites, ‘collateral sprouting’ from remaining/surviving neurons as a result of partial denervation and establishment of new synapses ((Bareyre et al 2004, Fouad et al 2001, Raineteau & Schwab 2001, Raisman 1969, Weidner et al 2001). Such adaptations are well documented for terminations of descending fibres on the spinal motoneurones following especially spinal cord injury (Fouad et al 2001, Raineteau & Schwab 2001). They probably contribute to ‘overactivity’ phenomena such as spastic dystonia (see later) and lack of specificity of voluntary motor control following central lesions. They may thus contribute to the inability of patients in performing precise movement, the tendency to perform involuntary associated movements and the development of ‘spastic’ postures involving involuntary excessive activation of postural muscles during movement. However, to what an extent these mechanisms also contribute to stretch reflex exaggeration is unclear. Muscle afferents likely also sprout and innervate vacant synaptic sites from descending fibres on spinal motoneurones, but there is little direct evidence of this.

5.3 Regulation at presynaptic sites: Increasing the input from surviving fibres

Although the majority of interest has naturally been devoted to alterations in transmitter release from sensory afferents in relation to the development of spasticity it should be emphasized that it is likely that synapses of surviving descending fibres and spinal interneurons are also upregulated in order to facilitate activation of the motoneurones following the lesion as already mentioned above. However, such changes have to the best of our knowledge not been thoroughly investigated.
Presynaptic inhibition elicited by sensory afferents (see below) has been shown not to be distributed to descending motor fibres (Nielsen & Petersen 1994, Rudomin et al 1991). Post-activation depression (see below) also does not seem to affect transmission from descending pathways (Hultborn et al 1996). However, it is unlikely that synapses of the descending fibres as the only synapses in the nervous system would not be subjected to some kind of regulation and thereby amenable to plastic adaptive changes following lesion.

5.3.1. **Presynaptic inhibition**

Presynaptic inhibition of sensory afferent terminals was described originally in the cat spinal cord by Frank & Fuortes in 1957 (Frank 1957) and subsequently investigated in more detail by John Eccles and his co-workers ((Eccles et al 1962a, Eccles et al 1963, Eccles et al 1962b) and see reviews by (Rudomin & Schmidt 1999, Willis 2006). The interneurons responsible for presynaptic inhibition receive considerable input from a range of sensory afferents of different modality throughout the leg as well as descending control from the corticospinal tract and brainstem nuclei (Burke 2012, Jankowska 1992, Rudomin & Schmidt 1999, Willis 2006). The interneurons in turn project widely in the spinal cord to suppress transmitter release from sensory afferent terminals on motoneurones by releasing GABA which binds to receptors located on the presynaptic terminals of the sensory afferents (Burke 2012, Rudomin & Schmidt 1999). Activation of GABA-A receptors result in opening of Cl channels which causes an outward Cl current and thereby a depolarization of the terminals (primary afferent depolarization; PAD – although other mechanisms may also contribute to this phenomenon (Hochman et al 2010). PAD inactivates some of the voltage-sensitive sodium channels and thereby reduces the amplitude of any subsequent action potentials. As a consequence fewer voltage sensitive Ca channels are opened and transmitter release from the terminals is reduced (Burke 2012, Rudomin & Schmidt 1999).
In both human and animal experiments presynaptic inhibition has been found to be strongly regulated by supraspinal control centres (Burke 2012, Meunier 1999, Rudomin et al 2004). During voluntary movement including locomotion presynaptic inhibition is turned into a highly focused modulatory mechanism which shapes the sensory inflow to spinal motoneurones and interneurons according to the needs of the given task and the central command (Dietz et al 1990, Faist et al 1996). Activation of some muscles may thereby be facilitated by removing presynaptic inhibition of the sensory afferents, while ensuring that unwanted activation of other muscles (such as antagonists) does not take place (Crone & Nielsen 1989b, Hultborn et al 1987, Nielsen & Kagamihara 1993). This regulation of presynaptic inhibition in relation to voluntary movement is of significance for the functional relevance of spasticity and will be further described in chapter 4.

Following spinal cord lesion in cats presynaptic inhibition of sensory afferents is reduced and this reduction seems to follow the development of spasticity (Naftchi et al 1979). In humans presynaptic inhibition of Ia afferents on spinal motoneurones supplying leg muscles has been found to be reduced in multiple sclerosis and spinal cord injured subjects with spasticity as compared to a population of able-bodied individuals (Fig. 4; (Faist et al 1994, Nielsen et al 1995b). This is also the case in cerebral palsy individuals with clinical signs of spasticity (Achache et al 2010). Presynaptic inhibition of Ia afferents from upper limb muscles is also reduced in spastic stroke survivors (Aymard et al 2000, Lamy et al 2009), but this is not the case for presynaptic inhibition of Ia afferents from leg muscles (Aymard et al 2000, Faist et al 1994, Lamy et al 2009). It has therefore been argued that reduced presynaptic inhibition is unlikely to be involved in the pathophysiology of spasticity, but is more likely an epiphenomenon (Lamy et al 2009), possibly in relation to the disuse of the limb (Lundbye-Jensen & Nielsen 2008). The observation that there is no correlation between reduced presynaptic inhibition and the degree of spasticity evaluated by the Ashworth scale is in line with this (Aymard et al 2000, Lamy et al 2009, Nielsen et al 1995b).
However, as mentioned above the Ashworth scale has been shown to be a poor measure of the extent of spasticity and this finding may therefore rather be related to short-comings of the clinical evaluation of spasticity.

The success of GABAergic drugs, such as diazepam and baclofen, in reducing reflexes and diminishing spasticity (Abbruzzese 2002, Macdonell et al 1989, Verrier et al 1975) should not be taken as support that presynaptic inhibition plays an important role for the development of spasticity. Any drug that reduces transmitter release from sensory afferent terminals on spinal motoneurones or suppress motoneuronal excitability would have a similar effect and contrary to what is sometimes claimed a specific effect on an important pathophysiological mechanism would make little difference (Murray et al 2011b).

5.3.2 Post-activation depression

It was originally described by Curtis & Eccles (1960) that Ia EPSPs are frequency dependent, with a relative facilitation at short intervals, and a depression with longer intervals (Curtis & Eccles 1960). This naturally influences also the size of stretch reflexes and it is therefore not surprising that a similar pattern of facilitation and suppression of the Soleus H-reflex and stretch reflex may be demonstrated in humans (Crone & Nielsen 1989a, Grey et al 2008, Hultborn et al 1996, Taborikova & Sax 1968). Following a single elicitation of a stretch reflex or an H-reflex subsequent reflexes are strongly depressed for up to 10-15 seconds (Fig. 5). This depression has been called post-activation depression since it is seen following a previous activation of homonymous Ia afferents and is not (or only to a limited extent) seen for afferents that have not been activated (Hultborn et al. 1996). It is therefore assumed that the depression results primarily from mechanisms operating within the presynaptic terminals (Lev-Tov & Pinco 1992, Li & Burke 2001, Pinco & Lev-Tov 1993). It is unclear whether similar mechanisms are involved but post-activation depression shares many
features with the short-term homosynaptic plasticity described for synapses in the hippocampus (Andersson & Hanse 2011).

Post-activation depression is reduced in spastic patients with spinal cord injury (Nielsen et al 1993, Nielsen et al 1995b), multiple sclerosis (Nielsen et al. 1995; Grey et al. 2008), stroke (Aymard et al 2000, Grey et al 2008, Lamy et al 2009, Schindler-Ivens & Shields 2000) and cerebral palsy (Achache et al 2010), thus ensuring that transmitter release is not significantly reduced with discharges of Ia afferents at rates above 0.1 Hz (Fig. 5). This is well within the physiological range of the firing rate of Ia afferents and normal activity of Ia afferents must therefore be expected to be influenced by this. It is also within the range of frequencies used during the neurological examination of spasticity and the reduction in post-activation depression thus directly contributes to the exaggeration of the stretch reflex and the increased reflex mediated muscle tone determined during the examination (Grey et al. 2008). In fact, the data from Grey et al. (2008) indicates that if the neurological examiner made sure to test reflexes and muscle tone at intervals longer than 10 s no significant reflex alteration as compared to healthy subjects would be detected. It is in other words only because the neurological examination usually involves multiple attempts at moving the limb or evoking the reflex, which then causes post-activation depression to be elicited, that reflex exaggeration is determined in spastic patients. This may also explain the close correlation between reduced post-activation depression and the clinical assessment of spasticity (Grey et al. 2008; Lamy et al. 2009; Achache et al. 2010), although the limitations in this assessment should be kept in mind. Post-activation depression is also the only mechanism which has been shown to be affected in both the lower and upper limb in spastic subjects regardless of the ethiology of spasticity (Achache et al 2010, Lamy et al 2009). This may indicate a key role of reduced post-activation depression in the string of events leading to spasticity. The simple regulation of the contribution of sensory inputs to
the activation of the motoneurones that it provides is an attractively simple means of upgrading sensory input when descending drive is lost. However, it should be pointed out that we still have no clear understanding of the functional significance of post-activation depression—as will be further discussed in Chapter 4.

It is not known how a spinal lesion could affect Ia terminals, but an impressive array of mechanisms have been identified that contribute to short-term synaptic plasticity in general (both the initial facilitation and the following depression; recently reviewed by Zucker & Regehr 2002). Although post-activation depression appears to be a mechanism intrinsic to the synapses, several studies have provided evidence that it may be regulated by descending motor commands and is thus a highly regulated mechanism (Nielsen et al 2007, Raoul et al 2012). It is certainly a possibility that loss of this descending regulation leads to alterations in the mechanisms responsible for the depression, possibly secondary to alterations in monoaminergic neurotransmitters and their receptors similar to what has been described for motoneurones (D'Amico et al 2013b, Murray et al 2011b, Rank et al 2011). It has also been suggested that the reduced post-activation depression may be related to lack of sensory activity secondary to disuse of the limb (Lundbye-Jensen & Nielsen 2008).

5.4 Transmission in group II pathways

As already mentioned muscle stretch and passive manipulation of a limb as part of clinical and biomechanical evaluation of spasticity, generates activity also in gr. II pathways that probably contribute to the muscle resistance sensed during the clinical examination. The interneurons mediating these effects appear to be primarily located in Rexed's laminae IV and VIII, whereas another group of interneurons located in Rexed's laminae V-VII integrate input from gr. II afferents and gr. Ib afferents from Golgi tendon organs (Jankowska & Edgley 2010). Some of these interneurons are inhibitory whereas others are excitatory and the effect on a given set of spinal
motoneurons by activation of the afferents thus depends heavily on central regulation of the interneurons (Jankowska 1989, Jankowska & Edgley 2010). Notably, monoaminergic neurotransmitters effectively suppress transmission in group II pathways and may thereby produce a selective suppression of the medium-latency (M2) reflex responses in lower limb muscles (Corna et al 1995, Grey et al 2001). The antispastic effect of Tizanidine (Kamen et al 2008) may be related to this selective depression. Most studies have reported exaggerated group II reflexes in spastic subjects and there is evidence to suggest that transmission in excitatory group II pathways are released from descending monoaminergic suppression in patients with central motor lesions (Nardone & Schieppati 2005). However, it is not clarified to what an extent group II interneurons play a pathophysiological role in spasticity.

5.5 Pathophysiological role of changes in postsynaptic inhibition of motoneurones

Motoneurones are under close inhibitory control from a number of spinal interneuronal populations. The most well studied are the interneurons mediating reciprocal Ia inhibition, Recurrent inhibition, Ib autogenetic inhibition and Non-reciprocal gr. I inhibition (Fig. 3).

5.5.1 Disynaptic reciprocal Ia inhibition

It was Charles Sherrington who provided the first evidence of a spinal pathway that could elicit suppression of antagonist muscles (his reciprocal innervation (Sherrington 1906)), but it was work by John Eccles which demonstrated the disynaptic nature of the reciprocal Ia inhibitory pathway (Hultborn 2006). Work by Hans Hultborn in the late 1960s and 1970s clarified the organization of the interneurons interposed in the pathway and especially the parallel activation of descending fibres and sensory afferents on common motoneurones and Ia inhibitory interneurons (Hultborn 1976, Hultborn et al 1976a, Hultborn et al 1976b, Hultborn et al 1976c, Hultborn et al 1971,

For reciprocal inhibition to be of any pathophysiological relevance for spasticity it is essential that there is evidence that the interneurones interposed at least in the pathway from ankle dorsiflexors to plantarflexors are tonically active in healthy subjects at rest (Nielsen et al 1995a). The pathway thus contributes to maintaining the excitability of soleus motoneurones low in resting subjects. The reduction of reciprocal inhibition between ankle dorsiflexors and plantarflexors which has been observed in spastic patients with multiple sclerosis (Crone et al 1994), stroke (Bhagchandani & Schindler-Ivens 2012, Crone et al 2003, Crone et al 2000, Okuma & Lee 1996, Okuma et al 2002, Okuma et al 1999), spinal cord injury (Crone et al 2003) and hereditary spastic paraparesis (Crone et al 2004) may therefore potentially contribute to hyperreflexia and increased reflex mediated muscle tone in the ankle plantarflexors. Achache et al. (2010) reported that reciprocal inhibition was similar in healthy subjects and adults with CP, but since there was hardly any inhibition in healthy subjects, a possible reduction of reciprocal inhibition in CP subjects may have gone unnoticed.

Reciprocal inhibition from ankle plantarflexors to dorsiflexors is in contrast usually found to be increased in spastic patients (Mailis & Ashby 1990, Yanagisawa et al 1976). As dorsiflexor muscles seldom show any spasticity this may not be too surprising. Reciprocal inhibition has also been found to be deficient in wrist muscles (Artieda et al 1991), but since newer studies have put doubt on the origin and nature of the inhibition observed between wrist muscles, the significance of this finding is unclear (Wargon et al 2006).
It has generally not been possible to find any correlation between reduced reciprocal inhibition and the degree of spasticity evaluated by the Ashworth scale, but given the lack of reliability of the Ashworth scale and the small size of reciprocal inhibition in many subjects, this is not surprising. On the other hand a positive correlation has been found between reduced reciprocal inhibition and functional deficits in stroke patients and regardless of its pathophysiological role in spasticity, reciprocal inhibition thus appears to be of clinical importance for at least gait function in spastic patients (Bhagchandani & Schindler-Ivens 2012, Okuma & Lee 1996).

5.5.2 Recurrent inhibition

Recurrent inhibition is mediated by Renshaw cells, which are located in the ventral horn of the spinal cord, where they receive excitatory collaterals from the motor axons and project back to the motoneurones as well as Ia inhibitory interneurones (Fig. 6). Recurrent inhibition is not easy to study in human subjects, but Pierrot-Deseilligny & Bussel (1975) have developed a complex H-reflex technique by which this is possible (Pierrot-Deseilligny & Bussel 1975). The basis of the technique is to use a previous reflex discharge to activate the Renshaw cells and study the effect of this activation on a subsequently evoked test reflex. With this technique it has been demonstrated that recurrent inhibition at rest appears to be normal in most patients with spasticity (Katz & Pierrot-Deseilligny 1999, Katz et al 1982). Only in patients with progressive paraparesis or ALS is a reduction found at rest and it is doubtful that this reduction contributes to the spasticity observed in these patients (Mazzocchio & Rossi 1989, Raynor & Shefner 1994). Changes in recurrent inhibition thus probably play no major role in the pathophysiology of spasticity.
5.5.3 Autogenetic Ib inhibition

Autogenetic Ib inhibition was described originally in the cat spinal cord in the 1950s (Laporte & Lloyd 1952). The inhibition is caused by activation of Ib afferents coming from Golgi tendon organs and is mediated by segmental inhibitory interneurones projecting to the motoneurones of the same muscle. Ib inhibition may also be demonstrated in human subjects by stimulating the branch from the tibial nerve which innervates the medial gastrocnemius muscle and measuring the subsequent depression of the soleus H-reflex (Pierrot-Deseilligny et al 1979). Whereas this inhibition is easily demonstrated in healthy subjects, Delwaide & Olivier (1988) failed to produce any inhibition on the paretic side in six of six hemiplegic patients, but instead observed a facilitatory effect in many subjects (Delwaide & Oliver 1988). This may relate to the pronounced facilitatory effect on the soleus H-reflex following stimulation of the peroneal nerve, which was observed by Crone et al. (2003) in their study of patients with stroke and spinal cord injury (Crone et al 2003). One possible explanation of the occurrence of this facilitation, which paralleled the development of hyperreflexia, is increased excitability of excitatory Ib afferent pathways, similar to those described in the cat spinal cord (Gossard et al 1994, McCrea et al 1995). Furthermore it has been argued that reciprocal inhibition at wrist level is mediated by Ib inhibitory pathways (Wargon et al 2006). If so, the observation that reciprocal inhibition at the wrist level is reduced in hemiplegic patients (Nakashima et al 1989) may provide further evidence that alteration of Ib inhibition/excitation plays a role in the pathophysiology of spasticity. It thus seems likely that changes in the balance between inhibitory and excitatory Ib pathways play an important role in the development of spasticity and further studies in this area are certainly needed.

5.5.4 Fusimotor drive. Gamma-spasticity
Increased fusimotor drive leading to increased sensitivity of the muscle spindles to muscle stretch was a popular explanation of spasticity some 20–30 years ago (so-called gamma-spasticity). It was found during the 1960s and 1970s that stretch reflexes, which are influenced by the sensitivity of the muscle spindles, tended to be more increased in spastic patients than the H-reflex which is evoked by electrical stimulation of the peripheral nerve and is therefore not influenced by the sensitivity of the muscle spindles (Ashby & Verrier 1976). However, subsequent studies have demonstrated that H-reflexes and stretch reflexes differ in many other ways than their sensitivity to changes in fusimotor drive and a comparison of the two reflexes therefore cannot be used to make any conclusions regarding changes in muscle spindle sensitivity (Burke et al 1983, Burke et al 1984, Morita et al 1998). Microneurography studies have also failed to demonstrate any changes in the discharge of muscle spindle afferents in spastic patients making it unlikely that any significant changes in fusimotor drive exists (Hagbarth et al 1973, Wilson et al 1999a, Wilson et al 1999b).

6.0 How is clonus related to spasticity?
Clonus is characterized by rhythmic alternating oscillation at relatively low frequency (3-8 Hz) at distal joints, in particular the ankle joint, following muscle stretch that is sufficiently fast to elicit a stretch reflex (or catch). Clonus is primarily seen in spastic patients and exaggerated stretch reflexes are usually present when clonus is observed (Mukherjee & Chakravarty 2010). Clonus is therefore also often considered as an integrated part of spasticity as also witnessed by the focus on clonus in the Tardieu scale (Haugh et al 2006). However, many patients with severe spasticity fail to show clonus and especially when muscle tone is very pronounced clonus is seldom seen (Mukherjee & Chakravarty 2010). One possible explanation of this is that at least partly different pathophysiological mechanisms may be involved in the development of spasticity and clonus. Clonus has traditionally been thought to be caused by alternating elicitation of stretch reflexes in
antagonist muscles (Hidler & Rymer 1999). The observation that the frequency of clonus depends on the length of the limb segment in which clonus is observed, is consistent with this idea (Hidler & Rymer 1999). Furthermore, clonus has been observed to be reset by stimulation of peripheral nerves and to disappear when sensory afferent activity is blocked by ischemia (Rossi et al 1990). Modelling studies also show that increased stretch reflex excitability with appropriate conduction delays may adequately explain the occurrence of clonus (Hidler & Rymer 1999). If this is correct, inclusion of clonus in the definition of spasticity and its use in the Tardieu scale would be justified. However, several studies have suggested that other mechanisms may at least contribute to the occurrence of clonus (Beres-Jones et al 2003, Dimitrijevic et al 1980, Walsh & Wright 1987). Dimitrijevic et al. (1980), contrary to Rossi et al. (1990), failed to interfere with clonus by sensory inputs and demonstrated examples where clonus was elicited by cutaneous input rather than muscle stretch. Walsh & Wright (1987) also failed to interfere with clonus by mechanical loading of the limb. Beres-Jones et al (2003) observed that EMG patterns in antagonistic ankle joint muscles during clonus in spinal cord injured subjects were often synchronized and unrelated to mechanical stretch of the muscles (Beres-Jones et al 2003). These studies, thus, suggest that central oscillator networks may at least contribute to the occurrence of clonus. Their central idea is that sensory input to the spinal cord may activate the rhythmic locomotor network in the cord. This network has been shown to be capable of oscillating for prolonged periods of time following sensory input in animals and to some extent also in humans (Calancie et al 1994, Dietz et al 1997, Pinter & Dimitrijevic 1999). Due to the contradictory findings in the various studies it seems at least possible that both mechanisms may be involved, possibly to varying extent in different patients. Regardless of this, caution should be made when relating clonus too closely to spasticity.

7.0 What causes a spasm?
Spasms are involuntary muscle contractions, which last from seconds to minutes and are usually provoked by a sensory stimulus, although in some cases no clear sensory stimulus can be determined. Spasms are differentiated from spasticity by the longer duration and strength of the contraction, which can sometimes be so severe that it becomes painful. Spasms are also differentiated from spasticity by being elicited preferentially by cutaneous rather than muscle afferent inputs. Spasms are mainly seen following spinal cord injury, whereas they are rarely seen in stroke patients even with very significant exaggeration of stretch reflexes and severe muscle tone (Malik et al 2014). Spasms are thus clearly distinct pathophysiologically from spasticity. The occurrence of spasms is closely related to increased withdrawal reflexes following injury and it is generally accepted that spasms are caused by pathologically increased transmission in flexor reflex afferent (FRA) circuitries in the spinal cord (Barolat & Maiman 1987). As already discussed, studies in both animal and human have suggested a significant role of upregulation of 5-HT receptors, secondary to loss of serotonergic innervation and resulting in increased persistent inward currents (PICs) in motoneurones and possibly also in interneurons in the FRA circuitries (Bennett et al 1999, Bennett et al 2001, D'Amico et al 2013b, Gorassini et al 2004, Murray et al 2011a). This would explain why spasms are mainly seen in spinal cord injured subjects and rarely following stroke or in cerebral palsy.

8.0 Spastic dystonia is not caused by increased stretch reflex activity

Spastic dystonia is a term that was introduced by Denny-Brown to designate tonic muscle activity in arm muscles in monkeys following central motor lesion (Denny-Brown 1966). He observed that the activity persisted when dorsal roots were cut and concluded that stretch reflex activity was not involved. In humans it is seen in the upper limb where it contributes to the hemiplegic posture primarily in subjects with stroke or cerebral palsy (Gracies 2005, Sheean 2002, Sheean & McGuire 2009). In humans a dynamic form of spastic dystonia is also seen during standing and gait where
the subject may adopt a posture with plantarflexion at the ankle, pronounced extension at the knee and associated flexion at the elbow (Gracies 2005, Sheean 2002, Sheean & McGuire 2009). These features resemble the overflow phenomena observed in patients with extrapyramidal (basal ganglia) lesions, hence the term dystonia. We have at present no clear indication of what causes spastic dystonia except for the findings in monkey by Denny-Brown (and which need to be confirmed in humans). Plastic changes at a spinal level involving upregulation and sprouting of surviving descending fibres may explain both the tonic and dynamic form, whereas upregulation of PICs in motoneurones may possibly explain the tonic form (Gorassini et al 2004). However, changes at a cortical level may also play a role and it should also be kept in mind that stroke often involves other structures than the descending pathways and that basal ganglia affection is not uncommon in stroke patients. Spastic dystonia may thus be the end-result of reduced voluntary control of muscles due to (partial) corticospinal lesion and increased involuntary activation due to basal ganglia lesion.

**Concluding remarks**

This chapter has emphasized that there is a range of adaptations in spinal circuitries following lesion of central motor fibres. These adaptations should be seen as an attempt to ensure a functional output from the spinal cord following loss of some of the normal supraspinal drive to the spinal motoneurones. We have the possibility of testing part of the circuitries that show adaptation following lesion by imposing muscle stretch and eliciting a sensory input to the spinal cord. The increased muscle resistance that we may sense in this way thus provides information of only some of the adaptations that occur and it is therefore not surprising that spasticity; i.e. hyperactive stretch reflexes only provide a partial insight into the full range of clinical manifestations of the adaptations to central lesions. In a broader sense these adaptations are also responsible for such manifestations as spasms, clonus and spastic dystonia as well as the movement disabilities encountered by patients
following central motor lesions. These may to some extent be related to spasticity but may also be seen separately. Treatment of patients with central motor lesions should take the different underlying pathophysiological mechanisms responsible for the various manifestations of spinal cord adaptations into account. The realization that sensory feedback is closely integrated with descending motor commands as a basis of all movements and that spasticity is a reflection of an upgrading of sensory feedback as a compensation for loss of descending drive, should also warrant caution when prescribing antispastic medication to patients with some functional ability.

**REFERENCES**


Hultborn H, Brownstone RB, Toth TI, Gossard JP. 2004. Key mechanisms for setting the input-output gain across the motoneuron pool. *Progress in brain research* 143: 77-95


Tardieu G, Shentoub S, Delarue R. 1954. [Research on a technic for measurement of spasticity]. *Revue neurologique* 91: 143-4


Toft E, Sinkjaer T, Andreassen S. 1989b. Mechanical and electromyographic responses to stretch of the human anterior tibial muscle at different levels of contraction. *Experimental brain research* 74: 213-9


Tower SS. 1940. Pyramidal lesion in the monkey. *Brain : a journal of neurology* 63: 36-90


Willerslev-Olsen M, Lorentzen J, Sinkjaer T, Nielsen JB. 2013. Passive muscle properties are altered in children with cerebral palsy before the age of 3 years and are difficult to distinguish clinically from spasticity. *Developmental medicine and child neurology* 55: 617-23


FIGURES AND LEGENDS

Fig. 1. Objective biomechanical and electrophysiological evaluation of spasticity
Fig. 2. Theoretical changes in sensory and descending input to spinal motoneurones in the acute and chronic phase following central motor lesion.
Fig. 3. The stretch reflex circuitry and spinal pathophysiological mechanisms in spasticity

Fig. 4 Presynaptic inhibition and spasticity
Fig. 5. Post-activation depression and spasticity
Fig. 6. Disynaptic reciprocal inhibition and spasticity