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Spasticity: Spastic Movement Disorder

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Abstract

Antispastic medications that are directed to reduce clinical signs of spasticity, such as exaggerated reflexes and muscle tone, do not improve the movement disorder. Medication can even increase weakness which might interfere with functional movements, such as walking. In clinical practice, signs of exaggerated tendon tap reflexes associated with muscle hypertonia are the consequence of spinal cord injury (SCI). They are generally thought to be responsible for spastic movement disorders. Most antispastic treatments are, therefore, directed at the reduction of reflex activity. In recent years, a discrepancy between spasticity as measured in the clinic and functional spastic movement disorder was noticed, which is primarily due to the different roles of reflexes in passive and active states, respectively. We now know that central motor lesions are associated with loss of supraspinal drive and defective use of afferent input with impaired behaviour of short-latency and long-latency reflexes. These changes lead to paresis and maladaptation of the movement pattern. Secondary changes in mechanical muscle fibre, collagen tissue, and tendon properties (eg, loss of sarcomeres, subclinical contractures) result in spastic muscle tone, which in part compensates for paresis and allows functional movements on a simpler level of organisation. Antispastic drugs should primarily be applied in complete SCI. In mobile patients they can accentuate paresis and therefore should be applied with caution.

Introduction

Spasticity is a well known syndrome, most commonly arising after stroke, multiple sclerosis, spinal cord injury (SCI), some traumatic brain injuries, and other CNS lesions. Many patients with a spinal lesion have a spastic movement disorder, with slowing of stepping and of voluntary limb movements. Clinical diagnosis of spasticity is based on the combination of physical signs in passive patients—ie, exaggerated tendon reflexes and muscle hypertonia defined as a velocity-dependent resistance of a muscle to stretching (Lance, 1980). In this chapter, we relate the above definition of spasticity to the knowledge of the mechanisms underlying the associated movement disorder. In the passive patient descending overactivity causing exaggerated reflexes might be responsible for muscle hypertonia, which then leads to spastic movement disorder (Abbruzzese, 2002; Denny-Brown, 1980; Gracies, 2001; Sheean, 2002; Wiesendanger, 1989). This view is supported by experiments on decerebrate cats (Lidell and Sherrington, 1924): muscle tone during stretching is substantially reduced after severing the nerves involved in the stretch-reflex loop. Therefore, the intention of most treatment approaches is to attenuate or abolish reflex activity and thereby to reduce muscle tone (Abbruzzese, 2002; Dietz and Young 2003). However, this dominant view does not take into account four important points. First, exaggerated tendon reflexes are only a small part of the reflex mechanisms involved in the control of functional movement, such as

walking. Second, most studies on the effect of antispastic drugs are focused on isolated clinical signs, such as reflex activity, and not on the spastic movement disorder that hampers patients. Third, without the development of spastic muscle tone (eg, after SCI), some patients would be unable to walk because of the paresis. Fourth, rigid muscle tone occurs immediately after decerebration of cats, whereas human spasticity develops over weeks after acute lesions; and last, clinical examination of spasticity is done in the relaxed/passive patient and doesn't reflect the state of CNS in use such as during e.g. walking.

Any changes in the neuronal or biomechanical systems, for example differences in the site and duration of a central lesion, are of importance in determining which neural control mechanisms are deficient and contribute to the movement disorder (Nielsen et al., 2005). Furthermore, such deviations might already be secondary and compensatory to the primary dysfunction of the motor system. There are differences in the appearance of spasticity between spinal and supraspinal lesions and lesions of different origin (e.g., inflammatory or traumatic). However, these factors have little influence on the impairment of function.

Research on functional movement in recent years indicates that the clinical signs of spasticity are little related to the functional spastic movement disorder, which hampers patients and should be the focus of any treatment. For example, exaggerated reflexes, a dominant sign in clinical assessment, have little effect on the movement disorder. In this review, the state of reflex behaviour and muscle mechanics in patients with spasticity and the resulting muscle tone during three conditions (cf. Dietz and Sinkjaer, 2007) becomes described: passive (clinical), active non-functional (laboratory setting), and functional (walking). This can serve as a basis for an appropriate treatment. Lastly specific treatment approaches will be presented and discussed. This review is based on a chapter in the Handbook of Clinical Neurology (Dietz and Sinkjaer 2010).

Clinical signs: passive condition

In a clinical setting, muscle tone and tendon tap reflexes are routinely examined in relaxed patients. Exaggerated tendon tap reflexes and an increased resistance of a muscle to stretching indicate the presence of spasticity caused by a central motor lesion.

Short-latency stretch reflex

The nature and mechanisms underlying exaggerated tendon reflex activity (monosynaptic or oligosynaptic segmental reflexes) have been the focus of many studies in patients with spasticity. The short-latency reflex activity is mediated by fast conducting group Ia nerve fibres from the muscle spindles to the spinal cord. A severe acute central lesion is associated with a loss of tendon tap reflexes followed by hyperreflexia due to neuronal reorganisation in both cats (Mendell, 1984) and human beings (Carr et al., 1993). New connections can cause changes in the strength of reflex excitability and denervation can cause hypersensitivity.

Exaggerated reflexes might result from hyperactivity of fusimotoneurons (Dietrichson, 1973; Rushworth, 1960) (also called gamma motoneurons), which correspond to the

alpha motoneurons innervating normal muscle fibres, although only indirect approaches have been applied, and this has not been proven convincingly (Hagbarth et al., 1973; Vallbo et al., 1979; Wilson et al., 1999). Furthermore, after a central lesion, increased electromyographic activity is not likely to be caused by either reduced recurrent inhibition of motoneurons via Renshaw cell activity (Mazzocchio and Rossi, 1997; Shefner et al., 1992) or intraspinal nerve sprouting (Nacimiento et al., 1993).

However, there is evidence for reduced presynaptic inhibition of Ia afferent fibres in the legs of paraplegic SCI patient but not hemiplegic human stroke subjects (Burke and Ashby, 1972; Faist et al., 1994). There is no association between decreased presynaptic inhibition of Ia afferents and the degree of muscle hypertonia as assessed by the clinical Ashworth scale (Faist et al., 1994). In addition, deficient disynaptic reciprocal inhibition (Crone et al., 1994), increased excitability of reciprocal Ia inhibitory (Crone et al., 1994) pathways (Boorman et al., 1991; Knutsson et al., 1997; Okuma and Lee, 1996), changed postactivation depression (Nielsen et al., 1995) and disinhibition of group II pathways (Marque et al., 2001; Nardone and Schieppati, 2005; Remy-Neris et al., 2003) might lead to hyperreflexia in spasticity after SCI. Other mechanisms are probably also involved (Faist et al., 1994; Nielsen et al., 2007).

A severe central motor lesion can be followed by flaccid paresis with loss of tendon tap reflexes. The H-reflex (an electrically elicited short-latency reflex excluding muscle spindles) is already present during spinal shock when tendon reflexes cannot be elicited (Hiersemenzel et al., 2000). After 1–2 weeks, tendon reflexes and muscle tone reappear. At later stages (4–6 weeks) clinical signs of spasticity (i.e., exaggerated reflexes and increased muscle tone) become established. The loss of reflexes is attributed to reduced excitability of alpha- and gamma motoneurons due to the sudden loss of input from supraspinal centres. When spasticity has developed, the threshold of the soleus stretch reflex is decreased in patients with spasticity (Levin and Feldman, 1994; Nielsen and Sinkjaer, 1996), possibly due to an increase in motoneuron excitability (Powers et al., 1988). However, repetitive, clonic muscle contractions are more likely to be associated with impaired interaction of central and peripheral mechanisms than with a recurrent stretch reflex activity only (Beres-Jones et al., 2003).

Flexor-/ withdrawal reflex

The flexor reflex is a polysynaptic spinal reflex that might be connected with spinal locomotor centres (Bussel et al., 1988). The dominant view is that flexor reflexes are exaggerated after a central nervous lesion and cause muscle spasms after severe spinal cord injury (Ditunno et al., 2004). Also, a spontaneous firing of motoneurons during rest might lead to muscle spasms (Bennett et al., 2004; Gorassini et al., 2004), initially caused by receptor upregulation and later by neuronal sprouting (Goldberger and Murray, 1988; Little et al., 1999).

The increase of flexor reflexes in patients with chronic SCI might represent a marker for neuronal plateau potentials (Hornby et al., 2003; Nielsen et al., 2007). Furthermore, it seems that the sites where flexor reflexes can be elicited become expanded in patients with a spinal or supraspinal lesion as compared to healthy humans (Andersen et al., 2004;

Schmit et al., 2000). Otherwise, a great variability of flexion reflex responses exists in patients with a SCI (Muller and Dietz, 2006).

After an acute, complete SCI, flexor reflex excitability and spastic muscle tone develop in parallel (Hiersemenzel et al., 2000). However, after a few months, there is a divergent course in which the severity and occurrence of muscle spasms increase, whereas flexor reflex amplitude decreases (Hiersemenzel et al., 2000). In line with this, patients with complete chronic SCI have a low incidence of the early component of the flexor reflex (Knikou and Conway, 2005; Muller and Dietz, 2006) and flexion reflexes produce smaller leg joint torques than those in healthy people (Deutsch et al., 2005). These observations suggest that the activity of flexor reflexes is little related to the occurrence of muscle spasms in spasticity of spinal origin.

Muscle tone

Muscle hypertonia is clinically assessed using the Ashworth scale, and is defined as a velocity-dependent resistance to stretch. This is particularly true for the leg extensor (Sinkjaer et al., 1988; Toft et al., 1991) and arm flexor muscles (Condliffe et al., 2005; Powers et al., 1988) (ie, the antigravity muscles). In patients with spastic muscle hypertonia (clinically defined as an increased resistance of a muscle to stretch) is associated with muscle activity measured by electromyography, which largely exceeds that seen in healthy subjects (Dietz et al., 1991; Hufschmidt and Mauritz, 1985). Thus, muscle hypertonia in clinical testing reflects a combination of intrinsic and reflex mediated muscle stiffness.

Despite the extra-electromyographic activity (EMG), which exceeds that observed in healthy subjects after muscle stretch, passive stiffness (eg, muscle contracture) at the ankle joint is also increased and contributes to clinically defined spastic muscle hypertonia (Malouin et al., 1997; Sinkjaer and Magnussen, 1994; Thilmann et al., 1991). In studies that have used a more complete analysis looking at all contributing factors, it becomes evident that the abnormal stretch reflex activity is insufficient to explain increased muscle tone in people with spasticity (Galiana et al., 2005; Hufschmidt and Mauritz, 1985; O'Dwyer and Ada, 1996; Sinkjaer et al., 1993). Reflex-mediated stiffness in the active ankle plantar flexors (Sinkjaer et al., 1993) and elbow flexor muscles (Dietz et al., 1991; Ibrahim et al., 1993; Powers et al., 1988) in patients with spasticity is within the range of healthy controls and seems to be only slightly increased in patients with spinal cord injury (Mirbagheri et al., 2001).

More recent studies indicate a combination with an increase in passive stiffness of a muscle to stretch in patients with spasticity due to changes in collagen tissue and tendons (Hufschmidt and Mauritz, 1985; Sinkjaer and Magnussen, 1994; Sinkjaer et al., 1993), an enhancement of intrinsic stiffness of muscle fibres (Gracies, 2005), and a loss of sarcomeres (O'Dwyer et al., 1996), leading to subclinical contractures (for review see Chung et al., 2008). In addition, morphometric and histochemical investigations show changes in mechanical muscle-fibre properties (Dietz et al., 1986; Edstrom, 1970; Lieber et al., 2004) that might contribute to spastic muscle tone. Consequently, clinical muscle hypertonia seems to be associated with subclinical muscle contracture rather than with

reflex hyperexcitability (O'Dwyer and Ada, 1996; O'Dwyer et al., 1996; Vattanasilp et al., 2000). Changes in biomechanical conditions of a muscle (i.e. loss of sarcomers) might also have an important effect on the stretch reflex behaviour (possibly via group III/IV muscle afferents) in people with spasticity (Kamper et al., 2001; Schmit et al., 2002).

Exaggerated stretch or flexor reflexes elicited in passive muscles, as seen in clinical bedside examinations, are not solely responsible for the increased resistance of a spastic muscle to stretch. Secondary changes in intrinsic and extrinsic muscle properties contribute to spastic muscle tone (Chung et al., 2008). This interpretation is based on observations made in patients with central motor lesions of different origin (eg, traumatic SCI, stroke and multiple sclerosis (Dietz and Young 2003)).

Non-functional movement: active muscle

Active muscle function in normal and impaired motor control is commonly investigated in a laboratory setting in which people can exert a controlled level of voluntary contraction. This method allows insight into the neuronal mechanisms underlying muscle tone regulation compared with the passive condition. When background contractions are matched to normal levels in patients with spasticity, little evidence exists for exaggerated reflex activity (Burne et al., 2005; Gracies, 2005; Lum et al., 2004; Sinkjaer et al., 1993). However, during isotonic leg muscle contractions, modulation and inhibition of Ib afferents (innervating the force-sensitive Golgi tendon organs) is reduced (Marita et al., 2006) and some co-contraction of antagonistic arm muscles can occur (Dewald et al., 1995; Kamper et al., 2003).

Studies that apply joint displacements in voluntarily activated limb muscles show different results from those obtained in the passive muscle. These studies show a uniform pattern of compensatory electro-myographic responses to the displacements. In unaffected muscles, the short-latency reflex is followed by longer latencies reflexes (Dietz, 1997; Dietz, 2003b). In the following we separate these reflexes into the terms short- and long- latency reflexes. Only the short-latency reflex appears in a passive muscle. Long-latency reflexes are assumed to be mediated in part by group II fibres on a spinal level (e.g. during locomotion). Compared with the short-latency reflexes they represent flexible, functionally essential reflex mechanisms (for details about the possible mechanisms and pathways underlying the long-latency reflexes, see elsewhere (Dietz, 1992)). In spasticity, this long-latency reflex is reduced or absent (Dietz et al., 1991; Ibrahim et al., 1993; Toft et al., 1993). Nevertheless, the automatic resistance to the joint displacement is of similar amplitude on the affected and unaffected sides.

During muscle contractions in healthy people, different inhibitory mechanisms on short-latency reflexes are removed (Nielsen et al., 2005). By contrast, in spasticity, presynaptic inhibition, postactivation depression, and reciprocal inhibition do not further decrease during contraction (figure 1). Therefore, short-latency stretch reflexes in patients with spasticity are less different in size between the relaxed and active conditions compared with those in healthy subjects (Dietz et al., 1991; Nielsen et al., 2005). These reflexes are

still prominent but show no task-dependent modulation in the spastic paretic condition as seen in healthy subjects.

In the voluntarily contracted (non-functional) muscle of healthy people, reflex behaviour differs from that in the passive (clinical) condition. By contrast, in patients with spasticity the excitability state remains roughly unchanged in the passive and in the weak voluntarily activated muscles.

In general, in the spastic limb little difference in the activity state exists between active and passive condition. In upper limb muscles stretch evoked EMG-activity and the resulting torque is reduced in the active condition but both are increased in the passive, i.e. clinical condition. Thus, modulation of stretch-induced EMG-activity is restricted to a smaller range and spastic subjects have difficulties to switch off limb muscle activity in a passive condition (Ibrahim et al. 1993). However, in a non-functional perturbation task of an active limb muscle, the overall electromyographic response is reduced on the spastic side despite exaggerated short-latency stretch reflexes due to the loss of functionally important longer-latency reflex component.

Functional movement: walking

After central motor lesions, patients suffer a movement disorder. To achieve adequate treatment, it is crucial to address the mechanisms underlying the impaired function. Several studies indicate that the clinical signs of spasticity are not related to the movement disorder. In this section, we discuss some of the mechanisms underlying the impaired movement.

Pattern of leg muscle activation

During a functional movement, such as locomotion, patients with spastic paraparesis have typical patterns of leg muscle activation recorded with electromyography. Spastic gait is associated with a low level of leg muscle activity compared with that in healthy people (Berger et al., 1984; Dietz, 2003b; Dietz and Berger, 1983). The reduction depends on the severity of paresis. The timing of the pattern (ie, the reciprocal activation of antagonistic leg muscles) is largely preserved (Dietz, 2003b; Kautz et al., 2006; Maegele et al., 2002). Only rarely does some coactivation of antagonistic leg muscles occur during the stance phase of walking (Dietz et al., 1981; Knutsson and Richards, 1979; Levin et al., 2000). Premature leg extensor activation during the stance phase of gait (Dietz et al., 1981; Knutsson and Richards, 1979; Levin et al., 2000) depends on the plantar-flexed position of the spastic-paretic foot. Premature leg extensor activation in the early stance phase, or even before impact, also occurs when healthy people walk by voluntarily tip-toeing (i.e., the extensor activation depends on the foot position before impact (Dietz V., unpublished observation)). Furthermore, coactivation of antagonistic leg muscles can be recorded in healthy people when they are walking with slightly flexed knees (Dietz V, unpublished). In a few patients with spasticity, the impact of the forefoot is associated with the appearance of stretch-reflex potentials (Dietz et al., 1981; Knutsson and Richards, 1979; Levin et al., 2000).

The leg extensor EMG amplitude modulation, which in healthy people typically occurs during the stance phase, is reduced or lacking (figure 2). In line with this, the contribution of afferent feedback to the ongoing locomotor soleus activity is reduced in people with spasticity (Mazzaro et al., 2007).

Overall, evidence gained from studies on functional movements shows that our clinical spasticity measures do not relate to problems in walking, i.e. they are little affected by monosynaptic reflex hyperexcitability, but more by reduced medium and long-latency reflex component (Nardone et al., 2001).

Reflex behaviour

In healthy people, group Ia afferent input to the spinal cord becomes suppressed during the stance phase of gait (Dietz, 1997; Dietz, 2002). Because of reduced Ia suppression in spasticity, short-latency stretch reflexes commonly appear in the leg extensor muscles during the transition from the swing to the stance phase of gait, which is rarely the case in healthy people. Furthermore, the inability to suppress reflex excitability during the swing phase of gait might contribute to impaired walking (Dietz, 2002; Faist et al., 1996; Faist et al., 1999; Fung and Barbeau, 1994; Jones and Yang, 1994; Sinkjaer et al., 1996; Sinkjaer et al., 1995).

During walking in healthy subjects, the H reflex and short-latency stretch reflex (both mediated by group Ia afferents) in leg muscles become modulated in a specific way (Faist et al., 1996; Faist et al., 1999). In subjects suffering spastic paresis, this physiological reflex modulation is impaired (Faist et al., 1999; Fung and Barbeau, 1994; Jones and Yang, 1994; Sinkjaer et al., 1996; Sinkjaer et al., 1995). Also, the modulation of cutaneous reflexes is reduced during gait (Jones and Yang, 1994). In line with this, the fast regulation of motoneuron discharge, which characterises functional muscle activation, is absent in spasticity (Dietz et al., 1986; Rosenfalck and Andreassen, 1980). The quadriceps-tendon jerk-reflex depression, which is present in healthy people, is absent in patients with spinal lesions and is associated with a loss of modulation during the step cycle (Faist et al., 1999). In general there are no qualitative differences in reflex behaviour between spasticity of cerebral origin and that of spinal origin (Faist et al., 1999), although direct comparisons are rare.

During perturbations of gait (eg, short acceleration impulses of the treadmill during the stance phase of stepping) in the unaffected leg, short-latency stretch reflex components are followed by large compensatory long-latency reflexes in extensor (Dietz, 1992; Dietz, 2002; Dietz, 2003a) and dorsiflexor muscles (Christensen et al., 2001). By contrast, in the spastic leg, short-latency reflexes are isolated without a significant long-latency electromyographic (EMG) component (Berger et al., 1984; Sinkjaer et al., 1999). Hence, there is similar reflex behaviour during displacements applied to activated limb muscles in both non-functional and functional conditions. These findings might result from impaired use of afferent input by spinal neuronal circuits after central lesions. The consequence is reduced adaptation of muscle activity to the ground conditions (Mazzaro et al., 2007), which, together with the reduced capacity to modulate reflex activity over

the normal range, might contribute to the spastic movement disorder (Burne et al., 2005; Dietz, 2002).

Tension development

Muscle tone, as defined clinically, cannot be examined during movement. However, tension development at the Achilles tendon, resulting from a combination of muscle stiffness and EMG activity, can be recorded. Tension development differs between the affected and unaffected legs in patients with spastic hemiparesis (Berger et al., 1984). On the unaffected side, changes in tension at the Achilles tendon parallel the amplitude of triceps surae electromyographic activity. On the spastic side, the tension development is associated with a stretching of the triceps surae during the stance phase of gait. During this period, the leg extensor muscles are tonically activated with low electromyographic amplitude (Berger et al., 1984). This is interpreted as tension development on a simpler level of organisation on the spastic side due to changes in mechanical properties of the leg extensor muscles. The possible mechanisms underlying these changes are outlined above. Thus, secondary to a spinal/cerebral lesion, there is a major alteration in the normal muscle–joint relationships (Foran et al., 2005; Lieber and Friden, 2002; O'Dwyer et al., 1996) that allow for support of the body during stepping movements.

In subjects suffering a spinal damage at the cauda level, the flaccid leg muscle paresis does usually not allow to perform stepping without prostheses to stabilize knee and ankle joints. Also functional electrical stimulation of muscles and nerves to compensate for the paresis can usually not be applied after damage of the peripheral cauda nerves. With regard to these aspects, spastic muscle tone can be beneficial to regain the capacity to perform functional movements.

Cerebral versus spinal spasticity

In this review, manifestations of spasticity of cerebral and spinal origin were discussed. Although spasticity due to spinal or cerebral lesions were rarely compared, no qualitative difference in the clinical appearance seems to exist. Differences, for example in the degree of presynaptic inhibition which was greater in spinal cord injured subjects (Faist et al. 1994), were not reflected in any clinical or functional difference. Nevertheless, there are some quantitative differences in the clinical manifestation of spinal and cerebral spasticity. First, compared to a spinal lesion, complete plegia of a limb does rarely occur in e.g. stroke patients and, second, the recovery of function is usually more pronounced in cerebral compared to spinal lesions. Consequently also spastic signs, which are related to the degree of paresis are usually less pronounced in cerebral compared to spinal lesions. This is suggested to be due to the fact that in an unilateral brain damage a small amount of non-crossing cortico-spinal tract fibres supply the affected side.

Conclusion

Recent studies on spastic movement disorder provide evidence that the central pattern of leg muscle activation is largely preserved after a central lesion and the clinically dominant hyperreflexia is little involved in spastic movement disorder. Impaired function and attenuation of long-latency reflexes hamper walking. Secondary to a central lesion, changes in muscle, ligament, and tendon properties occur. No qualitative difference exists

between spasticity of cerebral and spinal origin. The obvious consequence is the regulation of muscle tone on a simpler level. This behaviour of the spastic muscle allows for the support of the body during walking. Therefore, such changes should not be considered as pathological, but rather as adaptive to a primary disorder. They may even be viewed as optimum for a given state of the system of movement production (Latash and Anson, 1996). Knowledge about the nature of these changes in muscle mechanics is still rudimentary.

Therapeutic consequences

Any treatment of spasticity should focus on the specific movement disorders of individual patients. In most cases, the physical signs obtained during the clinical examination are an epiphenomenon rather than the cause of the functional condition. Recent studies have shown that functional movements involve essential reflex mechanisms that are not assessed with clinical tests (figure 3). Nevertheless, site, origin, and severity of a central motor lesion can influence the clinical appearance of spasticity and have to be taken into account for the appropriate treatment of individual patients. The dominant view is that treatment of spasticity should be directed towards a reduction of stretch reflex activity. This treatment approach is primarily based on studies of muscle tone and reflex activity under passive conditions (although treatment with Botulinum toxin type A is commonly based on electromyographic recordings made during muscle contractions).

Investigations of functional leg and arm movements show no causal relationship between exaggerated reflexes and movement disorder following a spinal lesion. Impaired walking might be mainly caused by disabling paresis and impaired use of afferent input by spinal neuronal circuits. As a result, antispastic medications that are directed to reduce clinical signs of spasticity, such as exaggerated reflexes and muscle tone, do not improve the movement disorder (Bass et al., 1988; Bes et al., 1988; Hoogstraten et al., 1988; Lapierre et al., 1987; Stien et al., 1987). Medication can even increase weakness (Hoogstraten et al., 1988; Latash and Penn, 1996; Thach and Montgomery, 1990), which might interfere with functional movements, such as walking.

Similarly, Botulinum toxin type A is assumed to result in a largely cosmetic effect on spastic signs without functional improvement (Corry et al., 1997; Thach and Montgomery, 1990), although this toxin might reduce the activity of the intrafusal fibres (Miscio et al., 2004; Trompetto et al., 2006). Intrathecal baclofen might also reduce hyperactive reflexes without producing significant weakness (Boviatsis et al., 2005; Meythaler et al., 1999; Sadiq and Wang, 2006).

In conclusion, therapeutic interventions in patients with spastic paresis due to an incomplete SCI should be focused on the training, relearning and activation of residual motor function (Centonze et al., 2007; Diserens et al., 2007), and the prevention of secondary complications, such as muscle contractures (Pin et al., 2006).

Antispastic drug therapy might predominantly benefit immobilised patients by reducing muscle tone and relieving muscle spasms (Barnes et al., 2003), which might in turn improve nursing care for these patients.

Specific treatment approaches

Practical Management

Pharmacological management of spasticity is to a large extent empirically determined. Most studies in the literature have focused on reflex activity under artificial conditions. In fact, the few reports of the effects of antispastic drugs on functional movement failed to show any significant change. Similar conclusions can also be drawn for other nondrug treatments of spasticity. Adequately controlled trials have rarely been done, and several studies were empirically, not objectively, conducted (Dietz and Young 2003). For an overview of methods for treating spasticity, see the following reviews: (Davidoff, 1985; Dietz and Young 2003; Glenn and Whyte, 1990).

Nonspecific Procedures

Painful flexor spasms and increased muscle tone frequently result from increased cutaneous reflexes induced by noxious or potentially painful afferent activity such as is associated with infections of the urinary tract, other infections combined with fever, and skin ulcerations, as well as by clothes irritating the skin. Consequently, worsening of spastic symptoms can frequently be alleviated by appropriate treatment of bladder function and skin care in paraplegic patients, as well as by early detection and management of the responsible factors (e.g., appropriate shoes or clothes).

Physiotherapy

Although this statement is not based on hard data, physiotherapy represents a most definitive mode of treatment for mobile and immobilized spastic patients. Active and passive manipulative forms of physiotherapeutic treatment are of great importance for both groups of patients. On the one hand, residual motor functions can be improved by training. On the other hand, contractures of muscles and joints that are difficult to treat when established must be prevented at an early stage by frequent muscle stretching. Physiotherapy within a water-filled pool (i.e., underwater therapy) seems to be promising, because most movements are easier to perform during immersion. Exercise therapy should be directed toward treatment of those defined functions for which training is specifically indicated and for which benefits have been shown to depend on the intensity of training (Kwakkel et al., 1999).

Based on divergent empirical evidence, different physiotherapeutic procedures are being applied. Proprioceptive neuromuscular facilitation (PNF) and myofeedback techniques are meant to activate spinal motoneurons reflexively. The techniques of Bobath and Vojta are primarily used to treat children with cerebral palsy (Dietz, 1997). Stereotyped movements become activated by such stimulation techniques when they are applied to specific dermatomes and joints. The Vojta method tries to activate complex movements that are believed to be programmed in the central nervous System. In contrast, the Bobath

method tries to inhibit spastic symptoms in flexor muscles of the upper extremity and extensors of the lower extremity.

All these techniques hope to achieve the following benefits and goals:

1. Avoidance of secondary complications (i.e., pneumonia, skin ulcerations and deep vein thrombosis)
2. Prevention and treatment of muscle contractures
3. Reduction of muscle hypertonia
4. Training of posture and automatically performed movements by-the induction of voluntarily initiated and controlled complex movements.
5. Learning and training of coordinated movements by the involvement of tactile, auditory, vestibular and visual cues.
6. Appropriate application of supportive aids, such as rollator, wheelchair, crutches, orthoses, and technical equipment (e.g., special shoes).

Each of these techniques is based on questionable theories. Controlled studies documenting positive effects of the treatment exist for none of them. Therefore, it is not yet possible to perform an appropriate evaluation and arrive at a recommendation based on the objective superiority of one of these techniques compared with another in the treatment of a given spastic patient. Nevertheless, physiotherapy must be part of a multidisciplinary integrated approach to patients. It also includes occupational therapy and nursing assistance. These all are means to achieve greater mobility and, as far as possible, independence for the patient.

Locomotor Training

The locomotor training that can ameliorate spasticity is based on observations made in cats with complete spinal lesions (Barbeau and Fung, 1992). Interactive locomotor training is performed on a treadmill with various percentages of the subjects' body weight (about 20%-50%) mechanically supported by an overhead harness using a strain-gauge transducer. As the subjects walk on the treadmill with a reduced load on their lower extremities, coordinated stepping movements and proper muscle activation can be facilitated by the moving treadmill. Recent developments of driven gait orthoses can compensate for this drawback (e.g. Lam et al., 2008).

During the course of training, a progressively "normal" locomotor pattern is developed (Dietz et al., 1994; Visintin and Barbeau, 1989) and patients profit functionally from such training. Improvement of spastic symptoms and of locomotor function by the activation of spinal locomotor centers may also be influenced by the repetitive elements of the therapeutic program; animal experiments have shown that repetitive afferent input is essential for motor learning (Sakamoto et al., 1989). Even in chronic incomplete paraplegic patients, this training can successfully be applied (Wernig et al., 1995; Wirz et al., 2006).

Drug therapy of spasticity

The presumed actions of the best established antispastic drugs are illustrated in figure 4. As a rule, the use of only one substance of these substances at a time is recommended, at least to begin with. There are patients who do best with modest doses of two medications that have different target of action (baclofen and tizanidine, for example), so combination therapy may eventually be necessary. Because relief of spasms and muscle hypertonia may only be achieved at the cost of reduced muscle power, doses should be kept to minimum effective levels, especially in mobile patients. Almost all antispastic drugs may induce side effects, often consisting of drowsiness and nausea (cf. Dietz and Young 2003).

Best antispastic effects are reported for baclofen, tizanidine, and benzodiazepines (e.g., clonazepam). Therefore, these are the drugs of first choice for spastic patients. They are most effective in spasticity of spinal origin such as with multiple sclerosis and traumatic or neoplastic spinal cord lesions (Glenn and Whyte, 1990).

Baclofen acts as a gamma-aminobutyric acid (GABA)-B agonist on a spinal level presynaptically and (less) postsynaptically. Monosynaptic stretch reflexes are depressed more effectively than polysynaptic reflexes, but flexor spasms are particularly reduced. Baclofen can alleviate spasms and muscle hypertonia in patients with spasticity (Duncan et al., 1976; Hattab, 1980).

Gabapentin, a GABA-related drug, is effective particularly for the treatment of painful muscle spasms (Cutter et al., 2000). Tizanidine is an imidazoline derivative closely related to clonidine. Both are thought to act on alpha-2- adrenergic receptors in spasticity of supraspinal origin. It is suggested that these substances reduce the activity of polysynaptic reflexes, in many ways similar to the action of baclofen (Bes et al., 1988; Stien et al., 1987).

Clonidine and tizanidine also have effects on the cord that are generally inhibitory; in part at least, they reduce the release of glutamate. Clonidine and presumably tizanidine produce marked inhibition of spinal reflex responses in alpha motoneurons to group II activity in the spinal cat (Schomburg and Steffens, 1988). Tizanidine also results in non-opiate analgesia by action on alpha-2-receptors in the spinal dorsal horn, which inhibit release of substance P. This would diminish flexor reflex afferent (FRA)—mediated actions. Thus clonidine reduces the frequency and severity of spasms in patients with spinal cord injury (Shefner et al., 1992).

Benzodiazepines (e.g., clonazepam) amplify the inhibitory action of GABA-A at a presynaptic and postsynaptic level. Thereby, excitatory actions become dampened with a negative rebound. It is believed that increasing presynaptic inhibition in the spinal cord of patients with spasticity should reduce the release of excitatory transmitters from afferent fibers and thereby reduce the gain of spinal stretch and flexor reflexes. One can assume that these compounds work directly on the spinal cord (Davidoff, 1985). For diazepam, serious side effects such as development of tolerance, dependency, and drowsiness are reported (Glenn and Whyte, 1990).

Intrathecal infusion of Baclofen

In immobilized patients with severe spastic symptoms, oral antispastic drugs are frequently not well tolerated in the long term because of their adverse effects. In these cases intrathecal baclofen can efficiently reduce painful symptoms and has tolerable side effects (Latash et al., 1989; Ochs et al., 1989; Penn et al., 1989).

The intrathecal dose is minute (100-400 µg/day), but the antispastic effects, especially on muscle tone and spasms, are powerful. Severe spasticity can be transformed into flaccid paresis, which usually makes nursing easier. During the first month, some tolerance develops, which often makes an increase in dosage necessary (Coffey et al., 1993). It is now clear that, in patients with severe spasticity caused by lesions at any level of the CNS, continuous intrathecal baclofen infusion is a safe and effective adjunct to physical therapy (Stewart-Wynne et al., 1991). After termination of chronic treatment with intrathecal baclofen, lasting reduction in spasticity has been reported (Dressnandt and Conrad, 1996).

The main side effects of intrathecal baclofen consist of drowsiness and somnolence, perhaps associated with depression of respiration. These side effects are usually due to an overdose of baclofen reaching the lower brainstem. The catheter system must eventually be repaired; its failure is the main cause of interruption of drug delivery (Schurch, 1993).

Local antispastic therapy

For the treatment of circumscribed muscle hypertonia, local injection of botulinum toxin, which acts to reduce release of acetylcholine from motor nerve endings, has become an established therapy (Al-Khodairy et al., 1998; Davis and Jabbari, 1993). Injections of Botulinum toxin A were reported to reduce moderate spasticity (for review see Hecht et al., 2008; Ozcaker and Sivrioglu, 2007; Simpson et al., 2008) and especially focal spasticity (Marciniak et al., 2008) by the reversible induction of peripheral paresis (chemical denervation). This usually lasts 3 to 4 months (Corry et al., 1997).

It also represents an elegant technique for the improvement of bladder function in patients with incomplete voiding caused by hypertonia of the sphincter externus muscle. (Schurch et al., 1996).

Treatments less frequently recommended

There is a long history of neurosurgical alleviation of spasticity, specifically concerning localized treatment of spastic symptoms by interruption of the peripheral reflex arc. Selective dorsal rhizotomy (Laitinen et al., 1983; Peacock and Staudt, 1991) or dorsal longitudinal myelotomy (Putty and Shapiro, 1991) is most commonly used in children with spasticity. These procedures reduce afferent input responsible for increased muscle tone. Abnormal movement patterns, however, persist after spasticity is reduced (Giuliani, 1991; McLaughlin et al., 1998; Wright et al., 1998). Furthermore, although clinical signs are improved, impairment of functional movements is little changed (Corry et al., 1997). Similarly, infiltration of ventral roots or Muscle and Nerves by phenol or alcohol can transform a spastic into a flaccid paresis (Scott et al., 1985). These treatments should rarely be used, because spasticity usually reappears after some months, and unwelcome

sequels, such as skin ulcerations caused by sensory loss in the corresponding dermatomes, are not uncommon.

Beneficial effects on spasticity are reported with functional electrical stimulation (FES) (Pease, 1998; Weingarden et al., 1998) and by transcutaneous electrical stimulation of several muscles (Seib et al., 1994). More recent controlled studies have shown that the combined use of intensive voluntary exercise and electrical stimulation of the spastic arm have a beneficial effect on arm function in post-stroke hemiplegic patients (Popovic et al., 2001). Also repetitive transcranial magnetic stimulation was reported to ameliorate spasticity (Centonze et al., 2007).

For most patients with moderate spasticity, this treatment is too awkward to be used regularly and may induce increased flexor spasms; negative results have also been reported (Sonde et al., 2000).

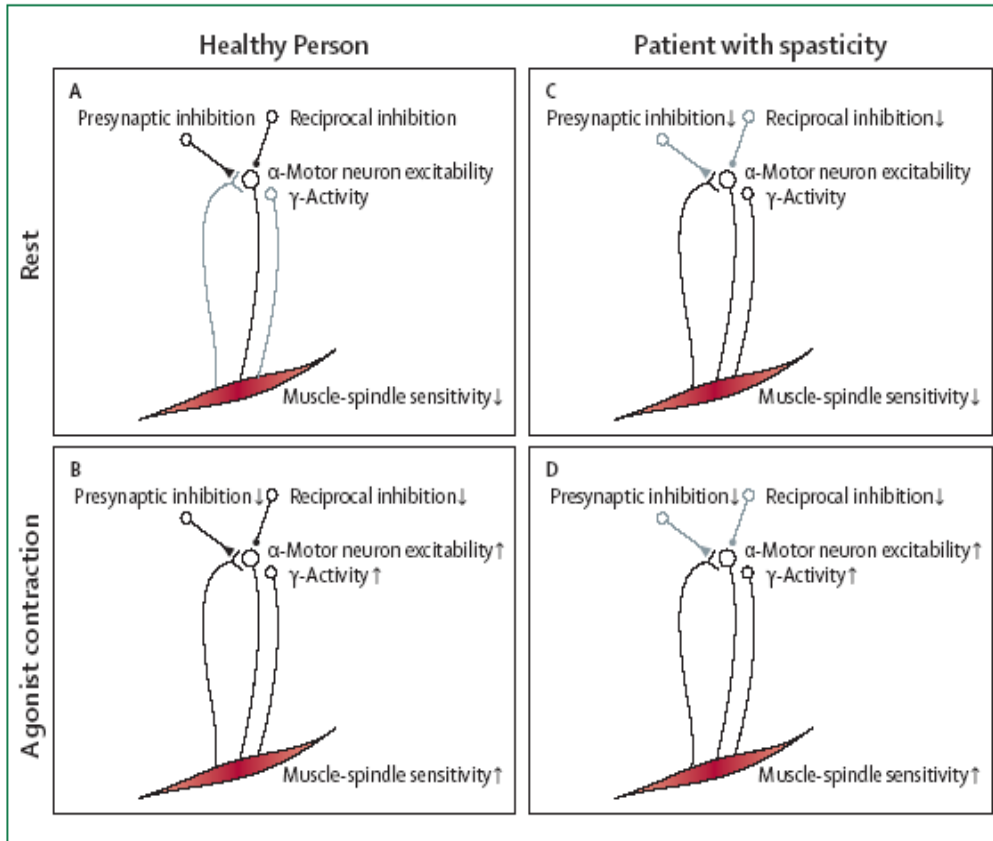
Improvement of spastic symptoms is also reported after chronic stimulation of lobus anterior of the cerebellum (Penn et al., 1978) and of the dorsal columns of the spinal cord (Wiesendanger et al., 1985).

Conclusions

This review describes the differential roles of background and reflex activity as well as muscle fibre function in passive, active, and functional movement disorders after a SCI. In functional movements, changes in muscle fibre properties leading to spastic muscle tone occur and compensate for the loss of neuronal drive. Further studies are needed to understand the regulation and importance of spinal and descending control mechanisms during movement and to detail the intracellular and extracellular modifications of skeletal muscle that occur secondary to a spinal or supraspinal lesion. This might help in the development of novel therapeutic interventions to improve antispastic treatments in patients with overshooting spasticity.

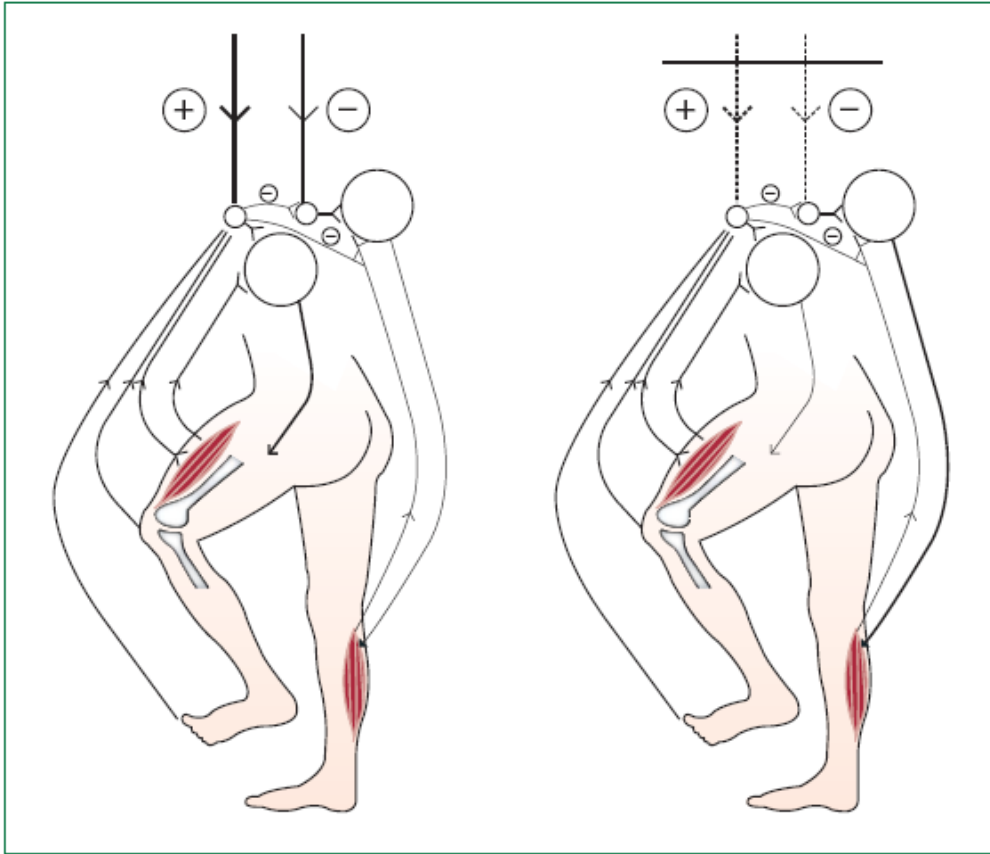
Figures

Figure 1: Short-latency reflex behaviour in passive and active muscle



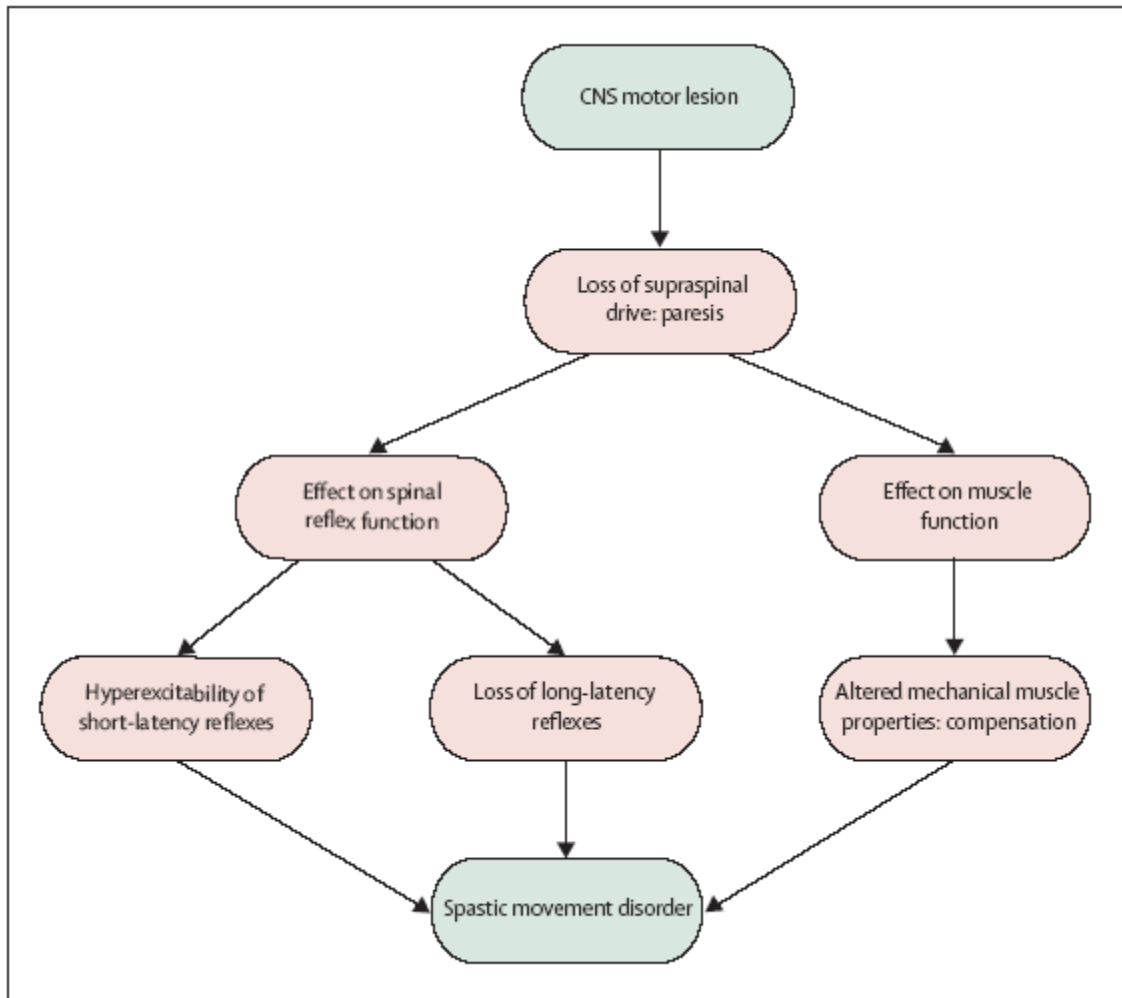
In healthy people, the stretch reflex activity is low at rest (A), which is explained by low excitability of spinal motor neurons, low muscle-spindle sensitivity, low discharge rate of Ia afferents, and pronounced presynaptic inhibition (Ib and Ia afferent discharge increase, whereas p/resynaptic inhibition (Ib inhibition and Ia inhibition) decreases. Stretch reflex activity is consequently high. In spasticity, presynaptic Ib and Ia inhibition is already decreased at rest (C) and stretch reflex activity is high already. During voluntary contraction (D) there is little change in these parameters and the stretch reflex activity is not very different from that at rest. The arrows designate whether the mechanism is decreased or increased during contraction compared with rest (modified from (Nielsen et al., 2005)).

Figure 2: Reflex behaviour during human gait



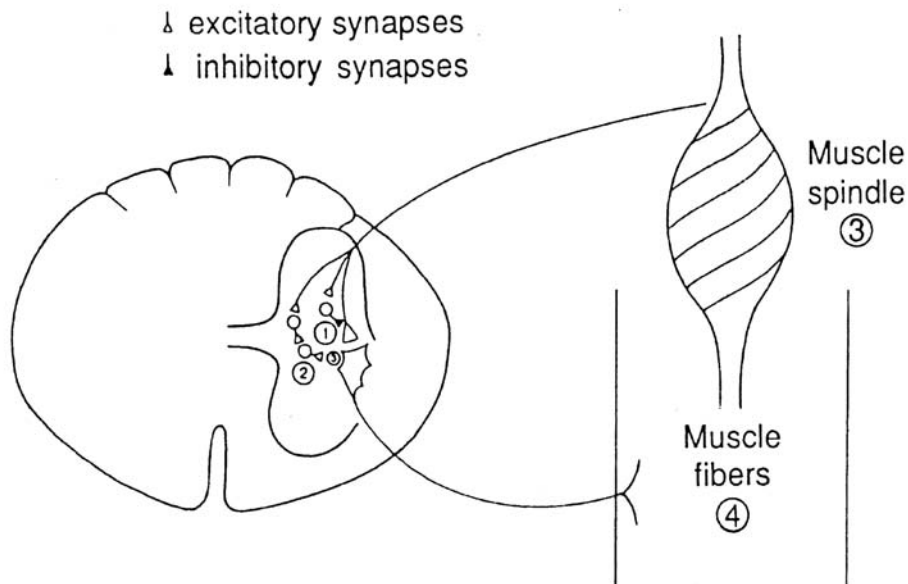
Left: In the healthy physiological condition, long-latency reflex activity is facilitated by supraspinal drive and becomes significantly involved in leg muscle activation to adapt the locomotor pattern to the ground conditions. Ia afferent-mediated inputs are inhibited. Right: after a spinal or supraspinal lesion, the functionally essential activity of long-latency reflexes is impaired owing to the loss of supraspinal input (from Dietz and Sinkjaer, 2007).

Figure 3: Mechanisms involved in spastic movement disorder



A central motor lesion leads to changes in the excitability of spinal reflexes and a loss of supraspinal drive. As a consequence, changes in muscle function occur and lead to altered mechanical muscle properties. The combination of all sequels of the primary lesion leads to the spastic movement disorder (from (Dietz and Sinkjaer, 2007)).

Figure 4: Presumed site of action of drugs with antispastic effects



(1) clonazepam/diazepam facilitate GABA-A mediated presynaptic inhibition; (2) baclofen inhibits activity of polysynaptic reflexes by GABA-B-receptor activation; (3) tizanidine acts on α_2 -adrenergic receptors; (4) dantrolene reduces the sensitivity of peripheral intra-muscular receptors and reduces release of calcium ions from the sarcoplasmic reticulum, which thus weakens muscle contraction. (from Dietz and Young, 2003)

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