CHANGES IN NEURONAL PROPERTIES AND SPINAL REFLEXES DURING DEVELOPMENT OF SPASTICITY FOLLOWING SPINAL CORD LESIONS AND STROKE: STUDIES IN ANIMAL MODELS AND PATIENTS

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It is a well-known fact that spinal reflexes may gradually change and often become enhanced following spinal cord lesions. Although these phenomena are known, the underlying mechanisms are still unknown and under investigation, mainly in animal models. Over the last twenty years, new methods have been developed that can reliably estimate the activity of specific spinal pathways in humans at rest and during voluntary movement. These methods now make it possible to describe components of the spinal pathophysiology in spasticity in humans following spinal lesions or stroke. We now know that spinal networks are capable of generating the basic pattern of locomotion in a large number of vertebrates, including the monkey – and in all likelihood, humans. Although spinal networks are capable of generating locomotor-like activity in the absence of afferent signals, functional gait is not possible without sensory feedback. The results of animal studies on the sensory control of and the transmitter systems involved in the spinal locomotor centers are now being used to improve rehabilitation of walking in persons with spinal cord injury and hemiplegia.

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INTRODUCTION

The aim of this article is to briefly summarize the present trends in investigations of the mechanisms underlying the development of spasticity following spinal cord lesions. This field covers changes in cellular mechanisms and altered reflex transmission, as well as some basic strategies in rehabilitation that may reflect the origin of spasticity. This review will cover some relevant animal models and research in spastic patients, since more refined techniques now make it possible to quantify the function of a large number of specific spinal pathways.

Prior to a discussion on the various neuronal responses and reflex pathways which may be involved in the enhanced spinal reflexes in spasticity, some comments should be made on the possible mechanisms behind the "malfunction" of these spinal neurones and pathways in spasticity. On some occasions an erroneous descending control of a normal spinal cord can explain this malfunction. That is certainly the case in decerebrate rigidity, which has often been used as an animal model of spasticity. Altered reflex transmission may also be due to primary or secondary changes at spinal segmental level, as must be the case with the slowly developing spasticity following a complete spinal transection. Following lesions in the cortex or internal capsule it is reasonable to assume that a combination of erroneous activity in the remaining descending tracts and changes at spinal level (e.g. secondary to degeneration of descending tracts with partial denervation of spinal neurons, as well as a changed activity pattern) are responsible for altered reflex transmission.

Twenty to thirty years ago, headlines like supersensitivity, collateral sprouting, and gamma rigidity/spasticity (via the muscle spindles) dominated reviews and published articles (1, 2). Although these topics are still current, the general development in neurobiology has permitted deeper insight and resulted in a change in focus. The previous "supersensitivity" can now be defined as upward or downward regulation of specific receptor systems (or their secondary intracellular cascades). Collateral sprouting is still a very active field; however, the rapid rearrangement of responses to afferent stimulation due to functional activation of morphologically, already present connections (partly via removal of inhibition) has also gained prominence. Changes in cellular properties may play a key role in the understanding of why specific reflexes are increased or suppressed. Using animal experiments, it is now possible to reliably recognize, in humans, some of the specific reflexes described in physiology textbooks. This phenomenon has not only contributed to a better understanding of their use in normal voluntary movement, but also to their role under pathophysiological conditions. Increased knowledge in the fields referred to above has made it possible to design new rehabilitation strategies. In particular, training of locomotion in spinal animals has proved the extensive capacity of the remaining (isolated, undamaged) parts of the central nervous system. Several of these rehabilitation strategies are now being introduced to human patients as well. In this brief review I will discuss: 1) animal experiments on a transmitter-controlled inward persistent current in motoneurones, which is responsible for an amplifica-

tion of excitatory input and may lead to self-sustained and maintained activity (and muscle contraction); 2) animal models on enhanced reflexes following spinal transection and hemisections; 3) the identification of a number of specific spinal reflexes in humans, and their change following spinal lesions; and finally 4) the new rehabilitation strategies for regaining locomotion in spinal animals.

SPINAL NEURONES AND REFLEX PATHWAYS

In the following section, I will summarize recent work on intrinsic properties in the ∕ -motoneurones, which now appear to be very important for the development of spasticity. The monosynaptic projection from muscle spindles, via Ia afferents with monosynaptic projection to the motoneurones of its own (homonymous) muscle is the pathway underlying the tendon jerk, and this pathway surely contributes to the tonic stretch reflex itself. In addition to this negative feedback (to keep muscle length constant despite external disturbances), other contributions to the modification of the stretch reflexes are group II muscle spindle afferents (not indicated in Fig. 1); autogenetic inhibition from Golgi tendon organs (via Ib afferents); recurrent inhibition (via motor axon collaterals and Renshaw cells); and reciprocal inhibition from muscle spindle Ia afferents from the antagonist muscles. All these factors are likely to be of particular importance when the patient tries to perform voluntary movements.
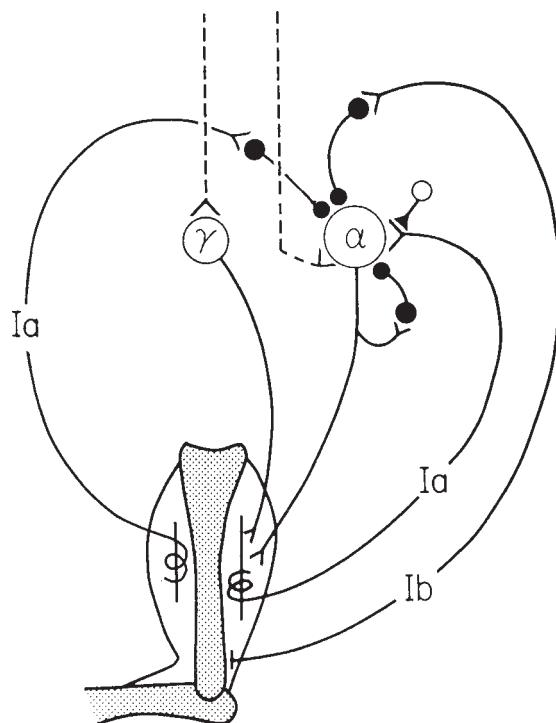

Fig. 1. Schematic drawing of segmental reflex pathways discussed in this article. Further description in the text.

MOTONEURONE PROPERTIES FOLLOWING SPINAL LESIONS, WITH SPECIAL REFERENCE TO PLATEAU POTENTIALS

The classical view of the mammalian spinal motoneurone, which emerged from the laboratories of Eccles and Granit in the 1950s and 1960s, held that the cell membrane was essentially passive in areas of synaptic contact (largely the dendrites), allowing a linear summation of synaptic inputs and passive transmission to the spike-initiating region (i.e., the initial segment/soma). During the last 15 years, research has shown that several active membrane properties, including voltage-dependent, persistent inward Ca^{2+} currents (the Cav 1.3, which expresses the ∕ $_{1D}$ subunit; see 3 for nomenclature), further shape the motoneuronal output (4–8). These inward currents can produce prolonged depolarizations (plateau potentials) when opposing outward currents are reduced or the Ca^{2+} channels facilitated by, e.g. serotonergic and noradrenergic innervation of the motoneurones.

When a graded depolarizing current is injected through an intracellular electrode into a motoneurone of a decerebrate cat, a critical threshold (plateau threshold) is reached. Above this threshold, further depolarization can trigger a regenerative activation of a sustained inward current. With such intracellular current injection into the soma, the plateau threshold is above the recruitment level of the cell (6, 7). With the motoneurone already firing, plateau activation produces a distinct jump to a higher firing rate. Recent experiments have shown that the threshold of the plateau potential (as measured from the soma) can be shifted during tonic synaptic input: it is lowered during synaptic excitation of the dendrites and increased during a corresponding inhibition (9). Most significantly, with synaptic excitation the plateau potential may be activated at, or even below, the spike threshold. One possible explanation for this phenomenon is that the plateau potentials arise primarily from inward currents in dendrites at a significant distance from the soma. Accordingly, synaptic input to the entire soma-dendritic membrane would affect the plateau currents more effectively than would the current injected through the recording micro-electrode in the soma. On the other hand, current injection through the micro-electrode would more easily activate the Na^+ spikes of the initial segment/soma than the plateau currents in the dendrites.

Single motor unit recording from awake, unrestrained rats (10–12) and during voluntary contractions in humans (13–16) has provided strong circumstantial evidence for plateau potentials during normal motor behavior. During quiet standing, rat soleus motor units could display "jumps" between two "stable" firing frequencies (triggered by brief bursts of synaptic excitation and inhibition) (10), which were very similar to those recorded with intracellular electrodes in cat motoneurones. However, results obtained with more dynamic movements in the rat and during voluntary contractions in humans did not demonstrate such "bistable" firing behavior. Rather, the firing pattern at recruitment could be interpreted to mean that the activation of the plateau potential actually contributed to recruitment itself, securing sustained fir-

ing thereafter. Therefore, it is proposed that the plateau potentials of the motoneurones serve as an important mechanism for the regulation of firing under normal motor activities (7).

Large spinal lesions in humans lead to an immediate depression of spinal reflex activity (spinal shock). Subsequently, flexor and tonic stretch reflexes return and become exaggerated several weeks and even months later. A similar spastic syndrome is seen in the cat following a complete spinal transection at the low thoracic level (17, see also review in 18, which describes unpublished results from the Copenhagen group). In few cases, it was possible to demonstrate that plateau potentials can again be induced in the chronic spinal state without adding any neurotransmitter precursors or agonists (18). This suggested that plateau properties, returning long after the spinal injury, can play a role in the pathophysiology of spasticity. Recently, Bennett and colleagues (19, 20) have developed a rat preparation in which a very low chronic spinal lesion causes pronounced spasticity of the tail without interfering with normal hindlimb or bladder function. Results from paired motor unit recording strongly suggested that their activation was supported by plateau potentials (19). Because the sacrocaudal spinal cord is very thin, it was possible to study the tail motoneurones in an in vitro preparation, as illustrated in Fig. 2 and then compare the intrinsic properties of tail motoneurones after an acute transection (control cells; Fig. 2A, C, E) and after chronic lesions (test cells; Fig. 2B, D, F), in which the rats had developed spasticity and hyperreflexia. Plateau properties were regularly seen in the chronic test state, but not in the acute control situation (20). Clearly, these observations have opened new horizons for further investigation of the cellular mechanisms underlying spasticity and other changes following chronic lesions within the central nervous system.

In anesthetized cats, whose plateau potentials and persistent inward Ca^{2+} channels discussed above were inhibited, a chronic spinal transection resulted in an overall increase in amplitude of the monosynaptic Ia excitatory postsynaptic potentials (21). The passive intrinsic properties of the motoneurones were somewhat changed (22, 23) which could only partially explain the increased monosynaptic Ia EPSPs (excitatory postsynaptic potential). Thus, it can be concluded that alterations occur in the synaptic mechanisms underlying Ia EPSPs in chronic spinal preparations.
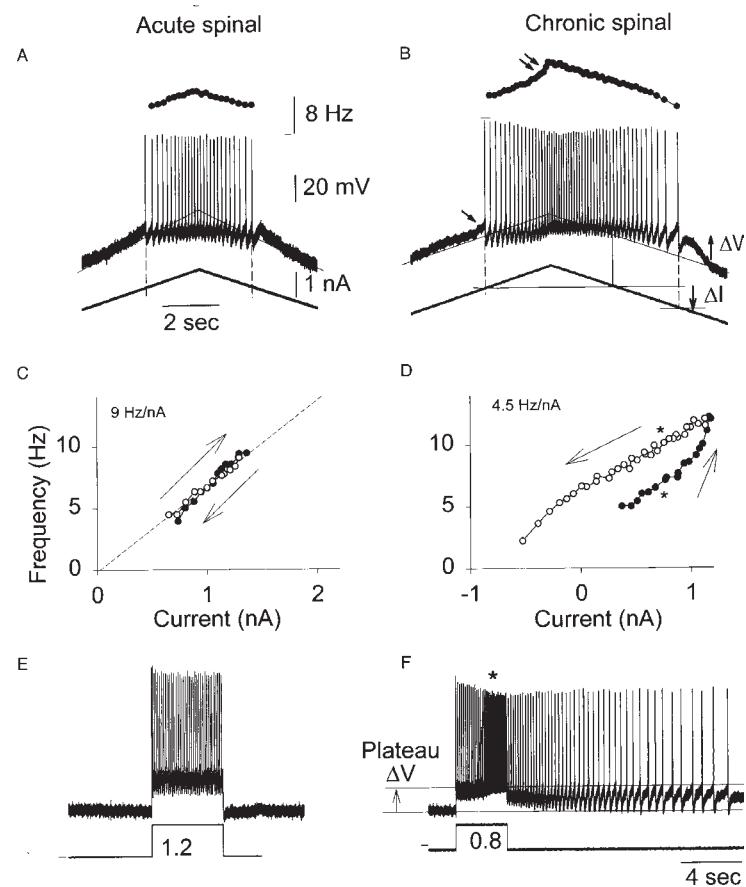

Fig. 2. Plateau in tail motoneurones of acute spinal (control) rats (A, C and E) and a chronic spinal rat (B, D and F). *A:* membrane potential and firing rate response to slow current ramp in low-threshold motoneurone of acute spinal rat. Note symmetry of response in relation to current, and thus lack of plateau. Scaled current (thin line) plotted with potential for reference. Tick marks denote 0 Hz. *B:* response to same current ramp in low-threshold motoneurone of chronic spinal rat. Note acceleration in potential (single arrow) and firing (double arrow), indicating the onset of a plateau (i.e. I_{PIC}). The plateau caused a sustained depolarization (OV) and discharge that continued until the current was reduced by I (= I_{PIC}). *C* and *D:* frequency-current (F-I) plots for A and B. Black symbols, upward ramp; white, downward. Note the late acceleration in firing in D (chronic spinal), although overall lower F-I slope than in acute spinal rat. *E* and *F:* responses to current pulses in acute and chronic spinal rats. The plateau caused self-sustained firing in the chronic spinal rat (F, plateau onset at asterisk). Same scales on A, B, E, and F. (From 20).

CHANGES IN SEGMENTAL REFLEXES FOLLOWING CHRONIC SPINAL HEMISECTIONS IN CATS AND RATS

Several groups of researchers (24, 25) have used an experimental model in which the lesion was a chronic spinal hemisection. The effect on the distal part of the spinal cord was subsequently investigated in a terminal experiment after a complete spinal transection below the chronic lesion, in order to eliminate asymmetric influences from the rostral parts of the nervous system (25, 26).

As seen in Fig. 3, the corresponding reflexes on the left and right sides were compared during the terminal experiment. The same figure demonstrates that monosynaptic, as well as polysynaptic reflexes, were larger on the side of the chronic hemisection. In further experiments, in which a monosynaptic test reflex was conditioned from various sources to test the strength of specific reflexes (e.g. cutaneous excitation and inhibition, reciprocal Ia inhibition, recurrent inhibition and presynaptic inhibition) all effects were larger on the side of chronic lesion. This was the case for both inhibitory excitatory reflex effects. In addition, there were no clinical signs of spasticity on the hemisected side nor any significant paresis lasting longer than a few weeks after the lesion. Actually, these cats were walking, running, and even climbing effectively, even though visually guided avoidance of obstacles was impaired. Taken together, the symptoms are much milder in these animal models than would have been expected from similar lesions in humans.
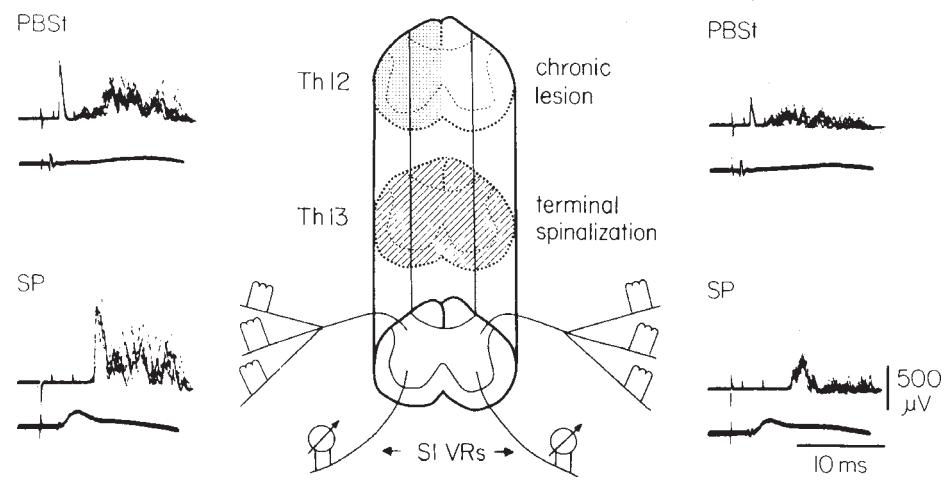
ACUTE DECERBRATION AS AN ANIMAL MODEL OF SPASTICITY

For a long period, the Sherringtonian decerebrate rigidity was regarded as a useful animal model of spasticity. After an intercollicular decerebration, the stretch reflexes are greatly and consistently enhanced, which makes it feasible to investigate underlying changes in spinal reflex transmission. In this preparation there is an increased excitabilitity of motoneurones (in particular extensor motoneurones), which seems to be related to both a high activity in the vestibulospinal tract (27) and the serotonergic raphe-spinal projection (enabling the plateau properties of the motoneurones (see 28 for a discussion). The sensitivity of muscle spindles to static stretch is greatly enhanced in the decerebrate preparation due to an increased activity of static 3-motoneurones (see 29 for a full discussion). Presynaptic inhibition at Ia terminals by volleys I group I afferents is not suppressed in the decerebrate preparation (30). It therefore seems unlikely that a reduced presynaptic inhibition of transmission from Ia afferents would be responsible for the increased response to stretch. The autogenetic Ib inhibition is reduced considerably due to a tonic reticulospinal inhibition of the interposed interneurones (30). This seems to be an important factor, as the tonic stretch reflexes were eliminated after an interruption of this reticulospinal system. Increased stretch reflexes could conceivably be explained by a decrease of recurrent inhibition (inhibition of Renshaw cells), but most reports refute that possibility (31, 32).

To summarize, the limitation of the decerebrate preparation as a model for humans spasticity is obviously related to the fundamental differences in their pathogenesis. Nevertheless, the investigation of the mechanism behind decerebrate rigidity/spasticity has hinted at mechanisms that also proved to be relevant in the slow development of the spastic syndrome following a central lesion. Most notably, the enhanced, voltage-gated, persistent inward current in motoneurones (their plateau properties) seems to play a crucial role following both an acute decerebration and a chronic spinal transection in the rat. The role of this mechanism in human spasticity is still unclear.

Fig. 3. Chronic spinal hemisection and changes in spinal reflexes. Arrangement at terminal experiment. A chronic spinal lesion, in this example, a hemisection, was made at Th 12. The terminal experiment was performed after a selected postlesional survival time. During this experiment a spinal transection was made one segment below the initial lesion. Peripheral nerves were placed on stimulating electrodes. Ventral roots L6, L7 and S1 (only the last is illustrated) were placed on recording electrodes. Dorsal root incoming volleys were recorded from one or more surface electrodes. In each pair of traces the upper trace is the response in the ventral root S1 to stimulation in the peripheral nerves of 50xT. The lower trace, recorded simultaneously, is the dorsal root incoming volley. The peripheral nerves are a flexor nerve (PBSt, posterior biceps and semitendinousus), and a cutaneous nerve (SP, superficial peroneal nerve, muscle branches removed). The reflex discharges illustrated are from a cat with a postlesional survival time of 169 days. (From 26).

SPINAL REFLEX TRANSMISSION IN SPASTIC PATIENTS COMPARED TO THAT OF HEALTHY SUBJECTS

Since published reviews already refer extensively to the original work on spinal reflexes in animals (30, 33), reference will be restricted to major work on human subjects, and in particular to those that focus on changes in spasticity. The most common techniques used in the investigations on humans include the H-reflex to assess motoneuronal excitability, and conditioning stimuli were arranged to activate the specific pathways to be evaluated. In order to keep this review short and concise, the reader is advised to consult the original references for information on the particular methods used in the study.

The monosynaptic excitation by muscle spindle Ia afferents and presynaptic inhibition of Ia afferents

It is well established that both the tendon reflex and the H-reflex (following electrical stimulation of the muscle spindle Ia afferents in the nerve) are enhanced in spasticity. Previously, the larger enhancement of the tendon jerk (natural stimulation) as compared to the H-reflex (electrical stimulation) was taken as an indication of increased sensitivity of the muscle spindles (by hyperactivity of γ-motoneurones); however, this phenomenon can most likely be explained by the different size of the control situation. (Smaller responses are more sensitive to facilitation, (34)). Direct recording from Ia afferents with microneurographical methods has not revealed signs of enhanced muscle spindle sensitivity (35). Presently, there is no positive support for the hypothesis that the stretch reflexes in human spasticity are due to a γ-motoneurone hyperactivity and enhanced sensitivity of the muscle spindles. The increased H-reflexes can more likely be explained by an enhanced transmission from the Ia afferents to the motoneurones (resulting in larger Ia EPSPs) and an increased motoneuronal excitability.

Presynaptic inhibition controls the transmission from Ia afferents. A selective method for evaluating presynaptic inhibition of Ia afferents in humans has been established (36). Under normal conditions, the amount of presynaptic inhibition is regulated during voluntary movement (37). In short, a tonic presynaptic inhibition at rest may prevent unwarranted reflex activation. However, at the start of a voluntary movement presynaptic inhibition decreases substantially, which may ensure the effective use of the afferent information in shaping the movement (37). In spasticity following spinal cord lesions (paraplegia), the amount of presynaptic inhibition decreases (38, 39). In addition, the specific regulation of the presynaptic inhibition at the start of a voluntary movement is lost, even in cases where the patients are still able to achieve a functionally relevant voluntary activation (40). When the amount of presynaptic inhibition was estimated in hemiplegic (unilateral cerebral lesion) patients with a unilateral spasticity there was, surprisingly, no decrease in presynaptic inhibition (38). In the case of the upper arm, however, Aymard et al. (41), with reference to earlier confirmatory studies, also con-

sistently found a decrease in presynaptic inhibition of Ia afferents on the affected side. Presently there thus seems to be a difference between upper and lower limbs. To summarize, the decrease in the amount of presynaptic inhibition of Ia afferents in paraplegic patients may contribute to their increased stretch reflexes.

Post-activation depression of transmission from Ia afferents

For a long time, it has been known that an H-reflex is depressed for several seconds (10–15 s) following previous activation of the reflex arc by a number of different procedures, including an electrical stimulation of the nerve used to evoke the H-reflex, a tap applied to the tendon, or even a passive lengthening of the muscle (42). Analyses of this post-activation depression in parallel human and animal experiments concluded that it was strictly related to the previous activity of the tested fiber (a strictly homosynaptic post-activation depression; (42). It is probably due to a truly intrinsic mechanism, in which paired stimuli facilitate transmitter release at short intervals, but cause a reduced probability of transmitter release with longer intervals, lasting for many seconds (42). In retrospect, much of the long-lasting depression in the "recovery curve" previously observed (42–44) is, in all likelihood, related to this post-activation depression (45). Further, the inhibition of H-reflexes during vibration of the muscle (44) seems to be related to a post-activation depression of the Ia afferents rather than to a classical presynaptic inhibition (45). Even though the post-activation depression seems to be a truly intrinsic mechanism that regulates the transmitter release in the individual afferent, depending on the activation history, it seems to be adaptable and decreases considerably in spastic patients (39, 44, 46, 47). To summarize, the post-activation depression of transmission from Ia afferents is reduced in paraplegia and may thereby contribute to the increased muscle tone in these patients.

Reciprocal inhibition from Ia afferents

Reciprocal inhibition mediated via the muscle spindle Ia afferents from the antagonist muscle was identified and investigated in healthy subjects (48, 49, for a review with extensive references see 50). The reciprocal Ia inhibition is enhanced during voluntary activation of the antagonist, e.g. it prevents stretch reflexes in the antagonist muscle as the muscle is passively stretched. In spastic patients, in hemiplegia as well as paraplegia, the amount of Ia reciprocal inhibition is reduced (51) and its regulation during (the remaining) voluntary movement is more or less eliminated (40). Although a significant decrease of reciprocal inhibition is seen in spastic patients, it has been difficult to correlate the amount of decrease with the clinical severity of spasticity. Nevertheless a few longitudinal studies may suggest the presence of a positive correlation. One group of researchers reported that the Ia inhibition returns with clinical recovery (52, 53). Another longitudinal study of stroke patients found that the development of

spasticity was paralleled not only with a decrease or absence of reciprocal inhibition, but even by the appearance of a "reciprocal facilitation" (54). To summarize, reciprocal Ia inhibition is strongly reduced in spastic patients and may even be substituted by a short latency excitation. The normal regulation of reciprocal inhibition is absent even when the patients can activate their muscles.

Inhibition from Golgi tendon organ Ib afferents

Autogenetic Ib inhibition, or "non-reciprocal group I inhibition," (33) has been identified in humans (55). During voluntary contraction of the muscle group the inhibition seems to be reduced (56). In animal experiments it has been demonstrated that during locomotion, there is not only a reduction of the di-/trisynaptic inhibition, but even the appearance of a "new" locomotor-related Ib excitation (57). It has not been possible to confirm this "reflex reversal" in experiments on human locomotion. The reports on changes in Ib inhibition during spasticity are conflicting. Delwaide & Olivier (58) and Delwaide & Pennisi (59) report that the Ib inhibition is reduced (and can even be reversed into facilitation), and that the reduction is correlated to the degree of spasticity. Furthermore, Delwaide & Pennisi (59) describe that tizanidine both reduces spasticity and enhances the Ib inhibition. Downes et al. (60) could not confirm a reduction in Ib inhibition in spasticity and suggest that the apparent differences may depend on pathophysiological differences in cerebral and spinal spasticity. To summarize, the Ib inhibition has not been investigated as extensively in relation to spasticity as has reciprocal inhibition and presynaptic inhibition, and the results are conflicting. It is clear that further investigations, both on the normal function in motor control and the role in regulating muscle tone following supraspinal and spinal lesions, are warranted.

Recurrent inhibition

Bussel & Pierrot-Deseilligny (61) established an experimental design for investigating recurrent inhibition in humans. Essentially, it estimates the recurrent inhibition evoked by a conditioning H-reflex. The size of the following test H-reflex is actually affected by both the amount of recurrent inhibition and the post-hyperpolarization in the motoneurones. Experiments using this paradigm suggest that the Renshaw cells (mediating the recurrent inhibition to the motoneurones) are facilitated during weak contractions and inhibited during strong ones (62). This may be interpreted as a sign of a "variable gain regulator" at the spinal output stage, somewhat similar to a gear in a car (63). The amount of recurrent inhibition does not seem to change at resting state in hemiplegic (stroke) spastic patients, but normal regulation during voluntary contraction is absent (64). The most common findings in spinal spasticity (traumatic or hereditary spastic paresis) were a substantial reduction of recurrent inhibition, and lack of normal control during voluntary contraction (65). On the other hand, Shefner et al. (66) reached the opposite conclusion by the same method (increased recurrent inhibition in patients with spinal cord lesions), but found a drastically reduced amount of recurrent inhibition in spastic patients with amyotrophic lateral sclerosis (67). An extensive review on recurrent inhibition in health and disease was published recently (68). To summarize, even though the amount of recurrent inhibition at rest seems to be normal in many spastic patients, the control of Renshaw cells is disturbed in these patients, a situation which probably contributes to their motor disability.

RECOVERY OF LOCOMOTION FOLLOWING SPINAL CORD LESION

In almost all species studied to date, neuronal networks, known as central pattern generators (CPGs), can generate locomotor movements, even in the absence of afferent inputs. Intensive research during the last 25 years has elucidated many details of the cellular and network properties of locomotor CPGs in selected invertebrates and a few lower vertebrates. The fact that the spinal cord of numerous vertebrate species contains the necessary circuitry to generate locomotor patterns is well-documented (69–73). The pioneering work by Jankowska and co-workers regarding decerebrate, spinal, and paralyzed preparations and the effect of DOPA on the spinal cord revealed the key elements of a neuronal network that could generate rhythmic activity (74, 75). A few years later, Grillner & Zangger demonstrated that complex locomotor patterns could be generated in the absence of rhythmic peripheral feedback (76) when the locomotor CPGs were activated pharmacologically.

It has been demonstrated that, after spinalization at low thoracic level, kittens (77, 78) or adult cats (79) can, after a few weeks of training (71), walk on a treadmill with a plantar foot contact during the stance phase and adequate weight support of the hindquarters. The fact that the hindlimb locomotion is coordinated in relation to the ground (the treadmill) is due to the afferent information (mainly hip position and load) that is acting on the spinal CPG circuits. Fig. 4 illustrates the localization of the locomotor CPG for the hindlimbs to the lumbosacral region, and the control from the brain stem (the mesencephalic locomotor region), from which organized locomotion can be evoked in decerebrate cats (Fig. 4A). Following chronic spinal lesions, cats can be trained to walk on a treadmill (Fig. 4B). Following an acute spinal transection (in decerebrate unanesthetized cats) pharmacological treatment with DOPA and monoaminoxidase inhibitors can elicit a locomotor pattern, which can be recorded as activity in motor nerves in paralyzed preparations (fictive locomotion; Fig. 4C).

Early knowledge on the importance of monoaminergic drugs for activating the spinal locomotor network in reduced preparations prompted the use of pharmacological tools to trigger or modulate the expression of the locomotor pattern at different periods after spinalization (80–83). When researchers found that
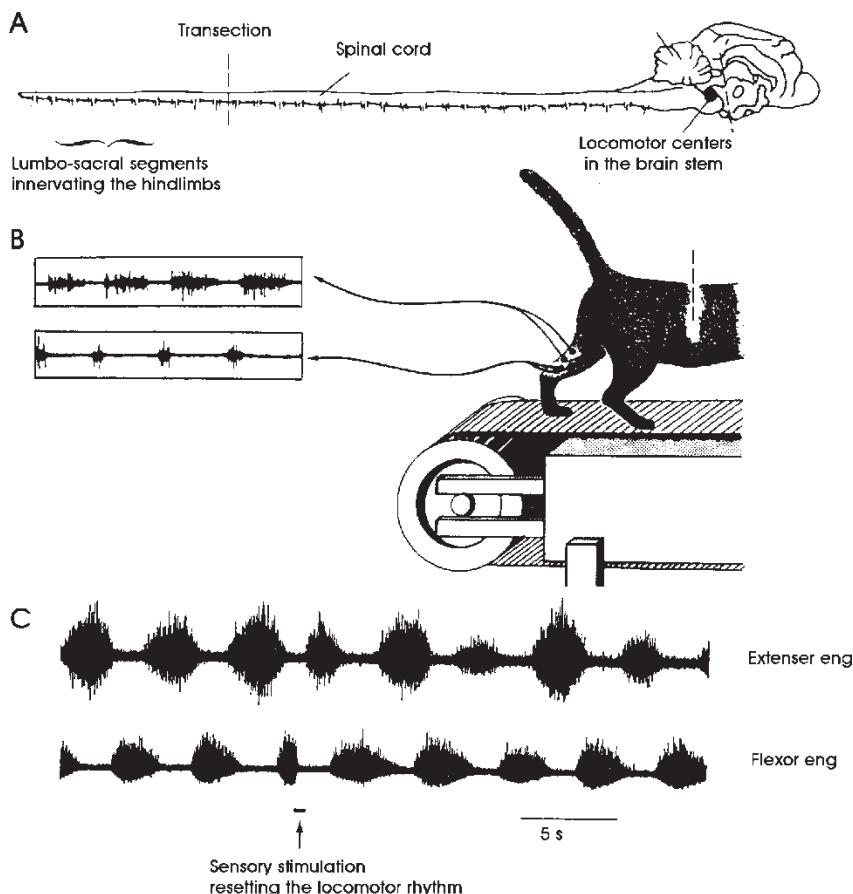
Fig. 4. Locomotor capability in spinal cats. Upper part *(A)* illustrates the localization of the locomotor central pattern generator for the hindlimbs to the lumbosacral region, and the control from the brain stem (the mesencephalic locomotor region) from which organized locomotion can be evoked in decerebrate cats. Following chronic spinal lesions, cats can be trained to walk on a treadmill *(B)*. Following an acute spinal transection (in decerebrate unanesthetized cats) pharmacological treatment with DOPA and mono-aminoxidase inhibitors can elicit a locomotor activity, which can be recorded as activity in motor nerves in paralyzed preparations (fictive locomotion). Note that a brief train of stimuli to extensor group I afferents could reset the spontaneous rhythmi-city; the flexor activity was terminated and a new extensor phase initiated *(C)* (Recordings in C from 96).

intrathecal drug administration can greatly facilitate the locomotor training, they reasoned that transplantation of serotonergic neurones to the spinal cord caudal to the lesion would improve the ability of spinal rats to regain locomotor capability (84). This proved to be the case, and further developments in this research model have been most rewarding (85, 86).

Training improves the functional capability of the remaining circuits caudal to the lesion. It is important to realize that improvement is closely related to the specific movements that are trained, for example, standing or stepping (87, 88). The behavioral and physiological effects of spinal cord transection are reflected in adaptations in most, if not all, neurotransmitter systems in the lumbosacral spinal cord. Thus, it has been demonstrated that both the GABAergic and glycinergic inhibitory systems are up-regulated following complete spinal cord transection. Training to step or stand resulted in regional down-regulation of these transmitter systems toward control levels in different parts of the gray matter (88).

The remarkable capacity of the spinal circuits below the spinal lesion to adapt and be "trained" to generate coordinated locomotor movements certainly triggered considerable interest in introducing similar strategies in patients with spinal cord injuries. Here,

the target was not patients with complete transections, which would make any voluntary control of walking impossible. Rather, the focus has been on patients with partial lesions and some remaining voluntary control, but not enough to produce any useful walking. Several groups of researchers have contributed to the evaluation of gait training on treadmills, often in combination with graded and controled body weight support, functional electrical stimulation, and drug administration, both to reduce spasticity and to facilitate the spinal locomotor network. Recent reviews on progress in this field include references 89–95.

CONCLUDING REMARKS

In this article I have attempted to describe the developments in some research areas related to motor symptoms that arise after spinal and supraspinal lesions. There are a number of reliable animal models, but their validity for the human pathophysiology is often questionable. Many new, more sophisticated tests of specific spinal circuits can now be applied to both healthy human subjects and patients. These tests are now being applied to different forms of spasticity, including cases with well-defined genetic

defects. It is expected that this approach to studying very specific groups of patients will contribute to a deeper understanding of the mechanisms underlying spasticity in patients with more common causes behind their condition, such as stroke and spinal cord lesions. There are also several promising openings in new rehabilitation strategies, originating from animal models, that should be implemented in clinical trials.

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