Re-expression of Locomotor Function After Partial Spinal Cord Injury

After a complete spinal section, quadruped mammals (cats, rats, and mice) can generally regain hindlimb locomotion on a treadmill because the spinal cord below the lesion can express locomotion through a neural circuitry termed the central pattern generator (CPG). In this review, we propose that the spinal CPG also plays a crucial role in the locomotor recovery after incomplete spinal cord injury.

The consequences of spinal lesions are well known, namely paralysis, sensory and motor impairments, as well as autonomic dysfunctions (37). However, basic mechanisms leading to such deficits remain elusive, and a better understanding is required to design more effective treatments to promote partial or full recovery of these functions. Because of space limitations, we review here only some of the basic mechanisms that may underlie locomotor recovery after incomplete spinal cord injury (SCI) in quadruped mammals, particularly cats, rats, and mice, since this type of lesion is the most frequent in humans.

FIGURE 1 illustrates schematically our current understanding of the control mechanisms of locomotion. Fundamental to the understanding of locomotion is the concept of a spinal central pattern generator (CPG) (60, 107). The CPG is defined as a spinal network of neurons capable of generating a rhythm pattern consisting of alternating activity between flexor and extensor motoneurons on the same side with reciprocal activation of homonymous motoneurons in the other limb of the same girdle. In general, during walking or trotting, this network ensures that flexor motoneurons on one side are active with contralateral extensors and vice versa for extensor motoneurons. However, this pattern is not a simple alternation between flexors and extensors because each muscle has, more or less, its own bursting pattern. The CPG allows an alternating activity between flexor and extensor motoneurons on the same side with reciprocal activation of homonymous motoneurons in the other limb of the same girdle. Additional factors such as cutaneous afferents, are involved in the coordination of the movement.

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obstacles in their paths. The importance of sensory inputs in the expression of locomotion cannot be overstated and has been the subject of a few previous reviews (50, 51, 113).

Although this review mainly deals with partial spinal lesions, it is important to know that, after a complete spinal transection, most quadruped mammals will recover some degree of locomotor function in the limbs below the lesion (33, 108, 110, 111). Cats (112), rats (52), and mice (63) can re-express hindlimb locomotion provided the spinal cord below the complete lesion is properly stimulated, either pharmacologically or through locomotor training. After a complete spinalization, the recovery of hindlimb locomotion evidently results from the re-expression of the spinal CPG, which is facilitated by afferent inputs. In well trained chronic spinal animals, it is possible to record a fictive locomotor pattern with a tonic perineal stimulation without drug application (102), again showing the prominence of a central spinal CPG that has been rendered autonomous by previous locomotor training.

Therefore, locomotion is controlled at multiple levels of the central nervous system, and a subtle and intricate balance is established between these levels of control. This then leads to the question of how an optimal equilibrium is re-established when this exquisite balance is perturbed following lesions of the spinal cord. After partial lesions, both supraspinal and spinal mechanisms could participate in the recovery of locomotion. Traditionally, although the role played by remnant descending inputs has been emphasized, the intrinsic spinal neural network is now receiving more attention (8). Theoretically, remnant descending pathways could take over functions of the damaged spinal cord, reestablishing spinal mechanisms to a secondary role. An alternative is that remnant descending pathways promote reorganization of the spinal circuitry so that the spinal CPG plays a primary role in the recovery of locomotion after partial lesions. Although both supraspinal and spinal mechanisms are most likely involved, it is important to dissociate their respective contributions to promote different rehabilitation strategies.

In this review, we will first discuss various means of producing and evaluating partial spinal lesions in animal models as well as some of the methodology used to assess locomotion and its recovery. We will discuss different types of partial spinal lesions, focusing on remnant locomotor capacities and deficits specific to abolishing certain pathways. Finally, we will discuss recent studies that highlight some of the important spinal mechanisms putatively involved in locomotor recovery and their clinical implications.

**Partial Spinal Lesions**

**General methodological approaches**

Producing partial spinal lesions. Multiple methods for producing partial spinal lesions exist, which can cause problems in interpretation because different pathways can be severed to varying extents. One can distinguish between three large classes of methods: surgical, compressive, or neurotoxic.

With surgical approaches, a laminectomy is made, and after opening the dura matter a section of the spinal cord is made in the transverse plane at the desired vertebral level. This approach is particularly useful for lesioning tracts located dorsally (e.g., dorsal columns, corticospinal, rubrospinal) (67) or for unilateral hemisections (8, 63, 65, 78). Ventral pathways can be severed without eviscerating dorsal pathways through pediclectomy on either side of the vertebrae (18) or through a laminectomy with a lateral approach (55). For compressions, several devices can be used to impact the cord from the dorsal aspect by dropping calibrated weights from different heights or with impactors (see later). Other approaches use a clip with two semi-circular arms to compress the cord for a desired length of time with a calibrated force. Contusions can be more reproducible than surgical transactions because the mechanical devices used (impactors, weight drops, clips) can be precisely calibrated (17, 48, 69, 70, 132).

Other methods to produce partial lesions of the cord include Rose Bengali toxicity (129) or denervation using immunological methods (85, 86). Although these methods may produce more focused lesions, valuable in assessing the role of specific pathways, they do not produce the mechanical damages typical of compression or surgical injuries in which the initial lesion may progress significantly as a result of various secondary mechanisms such as neurotoxicity (125).

It is important to document the extent of the lesion as thoroughly as possible (18). Although lesions are generally assessed using histological methods (35, 59), new approaches using magnetic resonance imaging (MRI) can also evaluate damages to the spinal cord noninvasively in vivo. This is a great asset when dealing with chronic spinal lesions because one can get a fairly good approximation of lesion extent before the terminal histological evaluation. Diffusion weighted imaging (DWI), best known as diffusion tensor imaging (DTI), evaluates diffusion of water molecules through the spinal cord and the isotropy/anisotropy of diffusion along white matter tracts. By connecting the main eigenvectors of successive voxels, the tensors delineate the white matter continuity in various parts of the spinal cord from various seed points in different quadrants, a process called tractography (25). The problem with DTI is that it represents the main vector of diffusion. Other related methods (HARDI for high angular resolution diffusion imaging) such as Q-ball imaging could identify the course of fiber tracts in different directions (26), a potentially very useful feature to detect reconfiguration of pathways around the SCI. Functional MRI (fMRI) could also be used eventually to detect functional changes in the spinal cord following injury. However, the BOLD (blood oxygenation level detection) response is often too delayed, which is why magnetic resonance spectroscopy (MRS) may be more valuable in assessing the role of specific pathways, even though one cannot use this technique noninvasively (18). Other neurological methods such as foot printing and coordination (Rotarod) may also be useful to evaluate the role of specific pathways. Although most of the lesion parameters can be evaluated using these methods, the degree and site of injury can be difficult to quantify. Methionine and dopamine transporters, for example, could be used to detect functional changes in the spinal cord following injury.

**Evaluating locomotor activity**

Evaluating locomotor activity can be a complex problem with respect to the degree and specificity of the lesion. Some methods to evaluate locomotor behavior (trotting, running, foot printing, or footfalling) assume a linearity that is sometimes not realistic in animals with spinal cord injuries. Other locomotor methods such as the rotarod, the beam walk, or the grid walk, which are used to determine the degree and site of injury, do not evaluate the role of specific pathways, which are important in the evaluation of locomotor activity. Other methods to evaluate loss of function include electromyographic (EMG) and chronically implanted electronic stimulators. Some methods to produce partial lesions of the spinal cord are summarized in FIGURE 3.
Different pathways can distinguish surgical, com-pressing, and ischemic lesions, depending on the lesion, as well as its evolution over time (123).

Evaluating Locomotor Performance

Evaluating locomotor performance is crucial to assess the degree and quality of locomotor recovery after SCI. Scoring systems are used to give an overall assessment of locomotor behavior, such as the BBB score (21 points scoring). The BBB assesses various aspects of locomotion such as foot placement, weight bearing, and interlimb coordination (11). This method, however, more or less assumes a linear recovery of locomotion, which might not be realistic. For instance, depending on lesion extent, forelimb-hindlimb coordination can be permanently lost, resulting in a maximal score of 12 that will not reflect further improvements of hindlimb locomotor capacities (3, 108). However, there is a correlation between the size of the lesion produced by a contusion and sensorimotor deficits that may follow a high-order polynomial (77). Other methods evaluate some skilled aspects of locomotion, such as the ability to place the foot on a horizontal ground or treadmill locomotion (46, 57), more detailed analyses demonstrated that, even during “simple” locomotion, persistent deficits arise (67, 73, 96). In cats, early after a bilateral dorsal/dorsolateral lesion at T13, the most consistent deficits are dragging of the hindpaw along the treadmill belt at swing onset due to impaired intralimb coupling between hip and knee joints at the stance-to-swing transition (67). In cats and rats, dorsal/dorsolateral spinal lesions

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deficit the coordination between the fore- and hindlimbs (i.e., interlimb coordination) but not the coupling between homologous limb pairs (47, 56, 67). The main component of the CST does not appear to be critical for the control of locomotion in cats or rats because unilateral or bilateral lesions of the CST at the pyramidal level do not produce long-lasting deficits in overground or treadmill locomotion (46, 97). On the other hand, sectioning other dorsal/dorsolateral pathways, such as the BST and ascending sensory pathways (ASPs), produces persistent deficits during overground and skilled locomotion in the rat. For example, a unilateral dorsolateral funiculus (DLF), dorsal funiculus (DF), or combined DLF/DF lesion at C3 produces clear persistent ipsilateral (i.e., ipsilateral to lesion) forelimb and hindlimb deficits during overground locomotion, mainly in the ability to generate ground reaction forces (130). Skilled locomotion, assessed by a horizontal ladder walking test, is also impaired with increased paw placement errors in the fore- and hindlimbs. Deficits are similar to those observed following unilateral ablation of the red nucleus (98), indicating an important role of the BST in regulating flexor and extensor activity during overground and skilled locomotion. Large lesions of the dorsal spinal cord in rats will even abolish the capacity for skilled locomotion (73).

Deficits stems not solely stem from pathways involved in muscle activation but also from descending pathways that control activity in ascending sensory pathways (ASPs), producing an impairment in interlimb coordination. Therefore, some deficits during skilled locomotion persist for many days or weeks after CST lesions (97, 130). Some deficits persist even after removal of the CST (98), indicating the presence of other pathways that may also contribute to interlimb coordination.

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**FIGURE 2. General methodology for the study of locomotion in cats with spinal lesions**

Initially, the animal is placed with its forelimbs standing on a stationary platform while its hindlimbs walk on the treadmill (arrows within the belt indicate the direction of movement). Later on, cats can walk freely on the treadmill with all four limbs. Pairs of EMG wires are implanted into various muscles (only 1 pair is represented here), and an intrathecal cannula is inserted through the atlanto-occipital ligament down to ~L4. The multi-pin EMG connector, as well as the cannula inlet, are cemented to the skull. Reflective markers are placed at various points on the limb, and the angle measurements are taken in the indicated orientations. For each video field (16.7 ms between fields), the coordinates of the reflective markers are obtained, and the hindlimb movement is reconstructed as indicated in the kinematic model (MTP = metatarsophalangeal joint). From such data, the swing and stance phases of each cycle can be reconstructed as shown below. Note that, to prevent overlap of the stick figures, each one is displaced by an amount equal to the displacement of the foot along the horizontal axis. The foot contact and foot lift are also measured to determine cycle length and duration and also to synchronize EMG events when needed. The digital (SMPTE) time code (top right) is used to synchronize video and EMG recordings. The spinal lesions are made at T13, unless otherwise specified.
Deficits stemming from DLF and/or DF lesions do not solely stem from RST damage. Ascending sensory pathways in the DF are important in regulating muscle activity during locomotion because selective DF lesions that spare the main CST and RST produce deficits similar to DLF lesions (73). Moreover, ascending sensory pathways appear particularly important for functional recovery after RST damage because abolishing these pathways in the DF after bilateral DLF lesions severely impaired recovered skilled locomotion (73).

Whereas in these studies is that descending and ascending pathways in the dorsal/dorsolateral spinal cord are normally involved in overground locomotion and become increasingly important during skilled locomotion. The BST appears relatively more important for hindlimb locomotion in quadruped mammals than the CST because BST lesions produce long-lasting deficits, whereas, following selective lesions of the main component of the CST in cats (46) and rats (97), animals make a full recovery. Although there is no direct evidence, locomotor recovery following BST lesions could be due to "functional substitution" by the BST (67), whereas the CST appears limited in substituting for the BST.

Therefore, lesions of the dorsal/dorsolateral produce initial deficits that gradually recover, particularly during treadmill or overground locomotion, and some deficits that persist, which are more apparent during skilled locomotion. Birth descending and ascending pathways appear to participate in locomotor recovery.

**Ventral-ventrolateral.** Ventral spinal lesions have attracted considerable interest because some of the main descending pathways, such as reticulospinal and vestibulospinal pathways are located ventrally. Given that stimulation of the MLR activates reticulospinal pathways (100, 101, 119), it is natural to presume that lesions of these pathways through ventral spinal lesions will result in severe paralysis. Several lesion studies were performed in rats and cats (1, 54, 55). In the rat, locomotion can be re-instated, provided that part of the ventral pathways remains. However, in the cat, although complete ventral lesions (performed through a pedicleectomy) result in the abolition of voluntary hindlimb locomotion for 3–4 wk, locomotion does return, albeit with some deficits, such as fore-/hindlimb coordination and some weight-support deficits leading to occasional stumbling (18, 19). However, the intralimb locomotor pattern of the hindlimbs is well preserved. Cats also develop a strategy whereby weight support is largely shifted toward the forelimbs, contrary to the case in normal cats. The development of such compensatory strategies involving cervical segments are also found in humans with SCI (59).

Besides its role in triggering locomotion, the reticulospinal pathways are also implicated in the step-by-step control of locomotion. Given their widespread projections, these cells may participate in the coordination between limbs as well as in weight support directly or as an integrative relay between the cortext and spinal cord (39, 42, 71, 72, 103, 104, 116). Similarly, vestibulospinal pathways affected by these lesions normally have an important role in postural control during locomotion (92, 93).

**Hemisections.** In contrast to bilateral lesions of the dorsal/dorsolateral or ventral/ventrolateral spinal cord, unilateral hemisections completely damage ventral and dorsal tracts on one side only, with primarily incomplete damage on the other side. Following such lesions in rodents, cats, and monkeys, treadmill and overground locomotion resumes within days or weeks, depending on the extent and level of the lesion (8, 15, 30, 31, 62, 63, 74, 75, 78, 115, 124). Lesion extent and the amount of locomotor training are the most important factors governing locomotor recovery and performance (e.g., maximal walking speed and endurance) (77). For instance, we recently showed in cats hemisected at the thoracic level that the smaller the lesion the faster the locomotor recovery (8). In the same study, we showed that untrained cats eventually re-expressed a quadruped locomotion but with lesser capacities compared with trained animals with similar lesions.

In cats, during the first few days after hemisection, the hindlimb ipsilateral to the lesion exhibits flaccid paralysis and drags on the treadmill. At this stage, animals walk tripedally and need assistance for hindquarter support and body equilibrium during locomotion (8, 63). Within 2 wk, cats recover...
hindquarter support, and use of the affected hindlimb progresses from a passive crutch with minimal limb excursion to an active locomotor pattern (63, 78). The hindlimb on the lesioned side exhibits an increased swing phase duration and reduced support time that is not observed on the contralateral side. Increased swing duration is, however, marked by a limited limb excursion that results in foot contact behind or just below the hip joint. During swing, an important paw drag is commonly observed and stance is performed on the dorsum of the hindpaw. The swing-to-stance transition on the lesioned side is marked by excessive abduction of the hindlimb and is initiated with a more extended hip position compared with the intact side (8, 63, 78). Interlimb coordination between fore- and hindlimbs is also affected (8, 15, 63, 78). With large lesions, an uncoupling of the fore- and hindlimbs is observed and the cycle frequency is respectively increased and decreased in the fore- and hindlimbs. With smaller lesions, coupling is preserved, but a

**FIGURE 4**

Recovery of quadrupedal locomotion following a unilateral dorsal/dorsolateral low thoracic lesion in a cat

**Left:** a sequence of treadmill locomotion before spinalization (i.e., in the intact state) at 0.8 m/s. Top: the EMGs were recorded in both hindlimbs and are presented with stance phase duty cycles (black bars) in the four limbs. Middle: mean angular excursions of the hip, knee, ankle and metatarsophalangeal (MTP) joints of the left hindlimb. Bottom: stick diagrams represent stance and swing phase extracted from the same sequence as the EMGs. Right: EMGs, mean angular excursion, and stick diagrams obtained in the same cat at the same treadmill speed, 18 days following a unilateral dorsal/dorsolateral lesion of the spinal cord at a low thoracic level (T11). It is worth noting that this cat was trained daily following the lesion, which resulted in a similar pattern of locomotor activity compared with the intact state. l, Left; r, right; St, semitendinosus; GM, medial gastrocnemius; TA, tibialis anterior; HL, hindlimb; FL, forelimb.
During-to-stance pacing activity, in which locomotor movements of homolateral limbs are synchronized, is often observed. This is often seen with spinal lesions and might correspond to a tripod gait, providing a more stable pattern of locomotion (18).

Over time and/or with training, the affected hindlimb exhibits less paw drag during swing, plantar paw placement during stance develops, and the animal can adapt its locomotor pattern to increasing treadmill speed. As a result, a symmetrical gait with proper left/right alternation is restored. However, forelimb movement remains coordinated with hindlimb movements. With large lesions, a 1:1 coupling is most often preserved, but homolateral limbs tend to walk in phase (pacing pattern), whereas in cats with larger lesions a complete uncoupling is maintained over time, the step cycle frequency being different at both girdles. Moreover, skilled locomotion, such as ladder or grid walking is also impaired following spinal hemisection (62, 63, 124). For instance, precise placement of the hindpaw on the rungs of a ladder is dually altered on the side of the lesion, and during overground locomotion the affected hindlimb cannot anticipate encountered obstacles (40).

Therefore, substantial recovery of hindlimb locomotion is observed following lateral hemisection of the spinal cord. Initial and persistent deficits are mostly observed on the side of the lesion and reflect deficits associated with ventral (transiently impaired body equilibrium) and dorsal lesions (impaired skilled locomotion).

**FIGURE 4** illustrates the pattern of EMG discharge and the kinematics before and 18 days after a spinal hemisection on the left side. The similarity of the locomotor pattern is striking, although the post-lesional pattern is somewhat more variable (see standard deviation in angular joint displacements).

**Spinal contusions.** The majority of SCIs in humans results from an impact to the vertebral column, which produces contusions of the spinal cord. In animals, contusion models have helped our understanding of biological mechanisms involved in the secondary injury that follows the initial SCI (121, 132). Contrary to transaction models, contusive lesions are diffuse (24) and generally result in a central cavitation rimed by spared white matter (94, 106). Generally, locomotor recovery correlates with the cavitation volume and lesion severity (106). The extent of spinal white matter damage, depending on the intensity of the injury, is strongly related to the number, localization, and amount of damaged spinal tracts and thus with locomotor deficits (84, 90, 117). On the other hand, the quantity of gray matter lost after contusion poorly correlates with locomotor deficits (88).

The contusion level has a direct bearing on locomotor recovery. For instance, in rats, a contusion at T3-L2 results in greater loss of locomotor function, as assessed by the BBB scale (i.e., absence of coordination and occasional weight support during stepping), compared with the same injury at L3-L4 (88). Contusion at T3-L2 could damage key elements of the spinal CPG for hindlimb locomotion thought to be localized at L1-L2 in the rat (16, 22, 89). In a recent study, the effects of training on electrophysiological properties were studied in different groups of rats 1 mo after compression of the thoracic spinal cord (12). Stimulation of the ventrolateral funiculus at C3 generated extracellular field potentials at L3, and it was shown that neuronal conductivity was severely impaired in untrained rats compared with trained rats, although in both injured groups it remained much below that of uninjured controls. These data indicate that training can restore some of the connectivity between cervical and lumbar levels. The authors attributed a role of brain-derived neurotrophic factor (BDNF) because trained injured rats showed elevated levels of BDNF compared with the untrained group (12). Others have also demonstrated increased levels of BDNF in monkeys after partial spinal lesions (134). Electrophysiological changes were associated with a decreased capability to lift and advance the hindlimbs (28), producing an increased stance phase duration (12). Forelimb stance duration was also increased after contusion at L2 (29), which suggests a strategy to adapt forelimb velocity with impaired hindlimb movements.

With contusion injuries, lesion severity and consequently locomotor deficits can be graded according to the distance travelled by the impact device (77, 87). For example, in mice, forelimb-hindlimb coordination deficits appear after low-intensity contusion (i.e., 0.3-mm distance of impact over 23-msec period), mice show flaccid paralysis during the first week post-injury and gradually recover plantar stepping, although poor forelimb-hindlimb coordination remains. Moreover, mice with moderate contusions exhibit persistent paw drag, paw rotation, and loss of coordination between fore- and hindlimbs. With severe contusion (i.e., 0.8-mm distance of impact over 23-msec period), mice show flaccid paralysis during the first week post-injury and gradually recover small joint movements, but voluntary locomotion with full weight support does not recover (87). A moderate thoracic contusion (i.e., 0.5-mm distance of impact over 23-msec period) produces immediate hindlimb paralysis followed by gradual recovery of plantar stepping, although poor forelimb-hindlimb coordination remains. Moreover, mice with moderate contusions exhibit persistent paw drag, paw rotation, and loss of coordination between fore- and hindlimbs. With severe contusion (i.e., 0.8-mm distance of impact over 23-msec period), mice show flaccid paralysis during the first week post-injury and gradually recover small joint movements, but voluntary locomotion with full weight support does not recover (87). After contusion injury, locomotor training (99, 127, 128) and afferent inputs from the periphery appear to play an important role in the recovery process (122).

Therefore, locomotor capabilities after spinal contusion depend on lesion severity and activity-dependent processes, such as locomotor training (99, 122).

**Compensatory Mechanisms Leading to the Re-expression of Locomotion**

The above summary on partial spinal lesions emphasizes how lesions of various pathways can induce...
variable deficits that affect step length, step frequency, interlimb or intralimb joint coupling, foot drag, or deficits in weight support. What is remarkable is how the CNS’s optimizes locomotion through the action of remnant structures.

Following partial spinal lesions, the voluntary recovery of locomotion undoubtedly reflects changes in sensorimotor interactions within and between the spinal CPG, descending supraspinal and propriospinal inputs, as well as peripheral sensory feedback (109). In cats, after partial or complete spinal lesions, the re-expression of locomotion in the spinal cord is facilitated with like activity in the spinal cord and by stimulating the skin of the peroneal region (5, 8). Whereas perineal stimulation provides a more or less tonic cutaneous input, locomotor training provides phasic cutaneous and proprioceptive feedback that is consistent with normal locomotion. These sensory cues are thought to promote reorganization of the spinal locomotor CPG so that it can operate more efficiently with diminished influences from supraspinal structures (44, 113). Descending motor pathways are also altered following incomplete SCI and, through activity-dependent processes, can induce changes within spinal sensorimotor pathways (23, 126). Compensatory changes within the central nervous system after incomplete SCI no doubt involve several mechanisms, such as sprouting, regeneration, and functional synaptic modifications.

Thus, although there are some specific deficits due to the inactivation of specific functional pathways, animals can in most instances eventually regain a functional locomotor pattern, enabling them to move around even in the open field. Several mechanisms probably participate in the functional recovery of locomotion, and none are mutually exclusive. We will review some of these mechanisms and propose that physiological, and most likely anatomical, plasticity at the spinal level below the injury participates in an important manner in the re-expression of locomotion after partial SCI.

Sprouting and regeneration

Work aimed at blocking molecules (e.g., anti-NOGO, anti-Rho) that hinder regeneration shows fiber growth through or around the spinal lesion. However, these fibers, which may partly originate from regenerating damaged or sprouting undamaged fibers, only reach a few millimeters below the lesion (7). On the other hand, 5-HT fibers can grow for longer distances and as such, change the local excitability of the spinal circuitry below the lesion. Moreover, what is unclear is whether increased sprouting and/or regeneration leads to improved functional outcomes or maladaptive changes within the spinal cord.

It was shown that, following lesions of descending pathways, new circuits could be formed by sprouting of remaining descending fibers that eventually reach the spinal cord via new routes, including propriospinal neurons (7). This is the case after lesioning the CST, in which collaterals reach cell bodies at the origin of other descending pathways (rubrospinal, reticulospinal, propriospinal). This raises the important issue as to whether this represents a new circuitry or the strengthening of an existing circuitry. Recent work in the in vitro neonatal rat preparation (32, 133) has shown, using a combination of serial hemisections and pharmacological stimulation, that propriospinal neurons can not only transmit command signals from the brain stem to segments exert a powerful effect on the lumbar circuitry. In the neonatal rat, it was suggested that low thoracic and upper lumbar segments are critical for locomotion (74). These regions also correspond to regions of higher excitability for rhythmogenesis in the rat (76). Furthermore, excitotoxic destruction of interneurons at L2 in the rat abolishes locomotion. Inactivation of L3-L4 segments using the noradrenergic blocker yohimbine completely blocks locomotion in completely spinal cats (91). Similarly, electrical microstimulation of the spinal cord can induce locomotion in completely spinal cats, provided the integrity of these midlumbar spinal segments is preserved (9, 10). Chronic spinal cats that recovered locomotion after a first complete section at T13 will be unable to walk after a second section at caudal L3-L4 even after weeks of trying to train the animals to walk. This is not a consequence of abolishing all motoneuronal activity since other rhythmic patterns can be evoked such as fast paw shakes (82). Very recent data also suggest, using injections along the spinal cord, that spontaneous deacrebrate locomotion in the cat is abolished by inactivating L3-L4 segments specifically (34). None of the other segments rostral to L3-L4 could block locomotion, although the simultaneous inactivation of several segments eventually abolished locomotion. These data suggest that propriospinal interneurons mainly located above L4 (the segmental circuits or by pharmacological blockade of the CST, in which collaterals reach cell bodies of other descending pathways) are necessary for the re-expression of locomotion after partial SCI. How spinal cord circuits are reconfigured in these plastic modifications remains a matter of considerable debate.

The role of feedback

In experiments using hindlimb locomotors (8), it was shown that treadmill for the quadrupedal hindlimbs could be maintained after the hemisegments at T13. Proprioceptive experiments. These results suggest that the role of feedback during the recovery of locomotion is not limited to the hindlimb locomotor system.

Our interpretation of these findings is that there is a critical period after the partial SCI in which the remaining de....
above L4 (thus mainly hindlimb pretomoneuronal segments) are essential for locomotion. The interest here is of course that, if some segments of the spinal cord play an important role in rhythmogenesis, then targeting these regions with various types of stimulation may prove to be a useful strategy because it would limit the problem to a more circumscribed area of the cord (see also Ref. 52).

How spinal locomotor circuits are activated by descending commands is of course at the heart of the problem with regard to the re-expression of locomotion after partial spinal cord lesion. Several studies reported above suggest that, whatever the lesion, animals can usually re-express locomotion with time, albeit with some specific motor deficits. Therefore, it is important to distinguish clearly how the spinal locomotor rhythm is generated from how it is controlled. Indeed, animals may walk with some interlimb coordination deficits, weight support weakness, or lost drag, but they will walk. The bulk of the evidence suggests that multiple pathways can access the spinal network necessary for expressing locomotion. This is also the conclusion of studies indicating that the relationship between the amount of spared white matter and locomotor recovery is not linear but follows some higher harmonic function (77).

How should one envisage the role of these new or reconfigured pathways? One tacit hypothesis is that these plastic neuroanatomical changes lead to a “take-over” by descending pathways of lost spinal function. This could be achieved either by new anatomical circuits or by physiological alteration of synaptic strength and circuitry. For instance, changes in neuronal properties may occur with chronic exposure to serotonergic stimulation (2).

What is the clinical implication of these concepts? First of all, the evidence is that, in several vertebrates, including mammals such as the cat, the rat, and the mouse, an elaborate circuitry exists in the spinal cord capable of generating the basic locomotor pattern. Some aspects of these basic mechanisms should be conserved in humans and integrated with evolutionary bipedality and greater cortical reorganization. Studies in humans indeed suggest the existence of such a basic spinal circuitry (20, 21, 95, 114, 131). This work shows that involuntary rhythmic activity can be generated at the spinal level in patients with complete or incomplete SCI either spontaneously or through spinal stimulation. According to the preceding indirect definition of a CPG, more evidence is required to irrefutably prove the concept of central pattern generation in humans (complete spinalization and neurochemical paralysis). If the basic control design of locomotion in humans is consistent with millions of years of evolutionary biology, then our attitude toward management of humans with SCI should somehow reflect this understanding.
Locomotor control mechanisms at various levels of the CNS are plastic, as shown by lesions studies, and they are probably amenable to some degree of modifications that could be induced by appropriate interventions. Ongoing clinical trials in humans, using anti-NOGO and anti-Rho, offer tremendous potential to facilitate fiber regrowth. Newly formed or regenerated pathways can, in turn, reach the spinal cord and re-establish contact through short or long propriospinal pathways. Moreover, specific training, such as treadmill locomotor training, maintains optimal function within local spinal circuits capable of generating locomotion and should be viewed as a prerequisite for new connections to function appropriately. Work in various laboratories has indicated beneficial effects of locomotor training in humans or of locomotor activity in general (4, 13, 36, 38, 45), either through the dedication of therapists, through the use of robotic devices, or by spontaneous self locomotor training. In that context, pharmacological stimulation (6) could be helpful, at least initially, in activating and maintaining remnant spinal locomotor functions. These methods, by removing some initial balance and weight support constraints, may altogether improve and maintain spinal locomotor functions so that any new contacts by reorganized descending pathways may find an optimally functioning spinal cord. It should also be expected, as has been clearly shown (66), that new strategies can be added to compensate for specific deficits, which reflect specific spinal lesions, and that locomotor recovery, after incomplete SCI, may result from activating the basic spinal circuitry together with more specific compensatory mechanisms.

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