Spinal plasticity in the recovery of locomotion

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Abstract: Locomotion is a very robust motor pattern which can be optimized after different types of lesions to the central and/or peripheral nervous system. This implies that several plastic mechanisms are at play to re-express locomotion after such lesions. Here, we review some of the key observations that helped identify some of these plastic mechanisms. At the core of this plasticity is the existence of a spinal central pattern generator (CPG) which is responsible for hindlimb locomotion as observed after a complete spinal cord section. However, normally, the CPG pattern is adapted by sensory inputs to take the environment into account and by supraspinal inputs in the context of goal-directed locomotion. We therefore also review some of the sensory and supraspinal mechanisms involved in the recovery of locomotion after partial spinal injury. We particularly stress a recent development using a dual spinal lesion paradigm in which a first partial spinal lesion is made which is then followed, some weeks later, by a complete spinalization. The results show that the spinal cord below the spinalization has been changed by the initial partial lesion suggesting that, in the recovery of locomotion after partial spinal lesion, plastic mechanisms within the spinal cord itself are very important.

Keywords: locomotion; plasticity; spinal cord injury; reflex; rehabilitation; training.

Introduction

The study of locomotion offers several opportunities to investigate the various levels of

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with the hindlimbs on a small nature trail outside the lab while a research assistant held its tail to partially support the weight of its hindquarters and provide some lateral balance. Even more surprising, the spontaneous forward walking movements of the intact forelimbs were at times strong enough that the hindquarters would rise and the cat would make a few unaided steps with the hindlimbs before losing balance. Although there was a long history of the locomotor capabilities of spinal animals in many species (as well summarized by Grillner, 1981), this provided a model which could be investigated with modern tools of electrophysiology and which obviously provided a scientific framework that also had a great potential impact on spinal cord injured (SCI) patients. These observations were clearly showing that the spinal cord below a complete spinal section was capable of generating the basic pattern of locomotion with even some elaborate timing details. Therefore rehabilitation after SCI should strive to maintain or activate the sub-lesional spinal circuits. The concept of spinal generation of locomotion is robust (Delcomyn, 1980; Rossignol, 1995, 1996; Rossignol et al., 2000) and relevant even for other animal species such as the rat (Courtine et al., 2009; Gimenez y Ribotta et al., 2000), the mouse (Leblond et al., 2003), and humans (Bussel et al., 1988; Calancie, 2006; Dietz and Harkema, 2004; Gerasimenko et al., 2010; Harkema, 2008; Nadeau et al., 2010). The importance of spinal generation of locomotion was strongly revived more recently when we observed that, even after partial SCI (the most common lesion in humans), the recovery of hindlimb locomotion also depends to a great extent on changes that have occurred in the spinal circuits below the SCI (Barrière et al., 2008, 2010; Rossignol et al., 2009). This observation is also of clinical importance since it emphasizes the possibility of profoundly modifying the spinal cord through rehabilitation strategies in humans after SCI. The aim of the present paper is to link various observations made over the years that lead to such conclusions.

Generation of spinal locomotion

Undoubtedly, the original observations on the generation of locomotion in spinal kittens were seminal (Forssberg et al., 1980a,b; Grillner, 1973). They established the very important concept that the spinal circuitry for generating locomotion was inborn (genetically determined) and that kittens could produce walking movements 1–2 days after spinalization without having had to “learn” walking. More detailed studies using electromyographic recordings (EMG) showed that several features of the muscle discharge resembled those seen in the hindlimbs of normal cats walking on the treadmill (Forssberg et al., 1980a). Other detailed features of the EMGs in spinal kittens were of interest. For instance, the recruitment of muscle discharges in extensors was quite similar to that of the intact cat with a gradual build-up of activity in knee extensors and a more abrupt onset of activity in ankle extensors. One important feature was that the discharge of ankle extensors occurred prior to foot contact, as was also seen during walking in intact cats (Engberg and Lundberg, 1969). This suggested that the onset of activity in these muscles was not triggered by foot contact that would subsequently trigger a chain of spinal reflexes but was pre-programmed centrally. A series of papers on the effects of DOPA on the spinal cord suggested that indeed central alternating rhythms in flexor and extensor muscle nerves could be evoked by stimulating peripheral nerves in otherwise curarized animals (Jankowska et al., 1967a,b; Stuart and Hultborn, 2008). The concept of central generation of locomotion was conclusively established in curarized and acutely spinalized adult cats showing that l-DOPA could evoke complex spinal rhythms that had many of the timing characteristics found in cats walking over ground or on a treadmill (Grillner and Zanigger, 1979). Similar findings were made in chronic spinal cats that had been trained to walk on a treadmill for several weeks on a treadmill (Pearson and Rossignol, 1991). A simple perineal
stimulation in these previously trained spinal animals could evoke bilaterally organized rhythms in both hindlimbs even after curarization.

In spinal kittens, the absolute amplitude values of muscle discharge could not be directly compared with those obtained in intact conditions because there was no control period as such and muscles were recorded through acutely inserted electrodes for each session so that variability of electrode position could have affected their discharge profile. In adult chronic spinal cats implanted with EMG electrodes, it was possible to evaluate muscle discharges and compare the activity before and after SCI in the same cat (Belanger et al., 1996; Chau et al., 1998a; Frigon and Rossignol, 2008; Rossignol, 1996). Although some changes in amplitude could be observed such as an overall reduction in limb extensors and an increase in limb flexors, the general pattern was overwhelmingly similar to the intact condition in the same cats taken as their own control. Of interest was the coupling of onset of activity between some muscles, especially flexor muscles. It was observed that, whereas in the intact state the knee flexor Semitendinosus was activated before foot lift and that the hip flexor Sartorius was activated after foot lift, these two muscles often tended to discharge almost synchronously after SCI whereas the ankle flexor Tibialis Anterior was activated earlier. This led in some spinal cats (especially early after spinalization) to a foot drag in the first part of swing (equivalent of foot drop in humans) because the ankle flexed prior to the foot being lifted by the knee flexors.

Altogether these observations confirm that the spinal cord can centrally generate hindlimb locomotion. Much of this conclusion derives from a long history of observations dating back to Sherrington (1910) and that was well-recognized and summarized before (Grillner, 1981; Rossignol, 1996; Rossignol et al., 2006; Stuart and Hultborn, 2008). It is important to remember some of these findings to better understand how other work on spinal locomotion has progressed in later years. Indeed, having clearly established that the lumbosacral spinal cord of adult cats can generate hindlimb locomotion it was important to understand (1) how this spinal pattern could be modulated by various neurotransmitters and sensory inputs; (2) which spinal segments and which descending pathways were important in triggering and/or modulating this spinal rhythm; (3) if lumbosacral circuits are important when the spinal cord is only partially damaged as is often the case in humans, and (4) if all this could really matter for humans with SCI.

Modulation of spinal locomotion

Neurotransmitter modulation

As mentioned above, early work using the noradrenaline precursor L-DOPA in acute spinal cats (Jankowska et al., 1967a,b) led to the concept of a central pattern generator (CPG) for locomotion (Grillner and Zangger, 1979). This seminal work triggered other research to determine which neurotransmitter systems and which receptors on which these can act could trigger and/or modulate the locomotor pattern.

Noradrenergic mechanisms

The noradrenergic system was mostly studied in this respect. First, agonists of different subtypes of adrenergic receptors were used. Clonidine, an alpha-2 noradrenergic agonist can trigger a well-developed bilateral hindlimb walking pattern on a treadmill within minutes after the injection (i.p. or i.v.) in acutely spinalized adult cats demonstrating that specific stimulation of a noradrenergic alpha-2 receptors activates an already extant spinal locomotor circuit (Forssberg and Grillner, 1973). Later, we found that, in adult spinal cats chronically implanted with EMG electrodes, only the alpha-2 adrenergic agonists such as clonidine injected intraperitoneally (Barbeau et al., 1987) or other alpha-2 agonists...
(tizanidine, oxymethazoline) injected intrathecally (Chau et al., 1998b) could induce locomotion in the early days following spinalization. After some weeks, when complete spinal cats had recovered spontaneous locomotion, clonidine still exerted potent effects on the spontaneously generated locomotor pattern by increasing EMG burst duration and overall step length. The effects of clonidine differ whether the cats have an intact spinal cord or whether they have a complete or partial spinal lesion (Rossignol et al., 1998, 2001). In the intact state, intrathecal injection of clonidine exerts little effect but, in the same cat, early after spinal section, it has the striking effect of evoking locomotion as described above (Giroux et al., 2001). Moreover, in cats with a large ventrolateral lesion, clonidine can decrease weight support and in the worst case can stop voluntary quadrupedal locomotion (Brustein and Rossignol, 1999). In conclusion then, the state of pre- and postsynaptic receptors may differ in different preparation and determine the effects of the neurotransmitter agonists. This is important when assessing drugs in humans since the excitability state of the receptors is unknown (Remy-Neris et al., 1999).

Yohimbine, an alpha-2 adrenergic blocker, reverses the effect of clonidine on the initiation of locomotion or on the clonidine-induced change in the step cycle (Barbeau et al., 1987; Giroux et al., 2001). However, yohimbine has no effect in the chronic spinal cat trained to walk on a treadmill. This might appear obvious since the neurotransmitter is no longer present following spinalization but it is important to block these receptors to show that residual noradrenaline and other molecules that could potentially activate these receptors are not responsible for the ability of the cat to walk. However, in the intact cat, yohimbine reduced the correct coordination between the fore- and hindlimbs with the trunk often bending on one side or the other (Giroux et al., 2001) suggesting that in normal locomotion, noradrenergic neurotransmission is important for interlimb coordination (McDearmid et al., 1997).

**Serotonergic mechanisms**

In acute spinal cat, 5-HT2 serotoninergic agonists such as quipazine, 5-O-DMT, or the precursor 5-HTP do not initiate locomotion (Barbeau and Rossignol, 1990). This might be related to the level of the spinal section as suggested by others (Schmidt and Jordan, 2000) on the basis of the segmental distribution of 5-HT receptor subtypes that may be important for locomotion (Noga et al., 2009). Therefore, the level of spinal section should be taken into account in evaluating the effects of stimulation by certain drugs since specific subclasses of receptors may preferentially be distributed above or below the spinal lesion. Although 5-HT agonists do not initiate locomotion in acute spinal cats, they markedly alter the output amplitude of activity of hindlimb muscles (especially extensors) and paraxial muscles (Barbeau and Rossignol, 1990). In cats with bilateral ventrolateral spinal lesions, 5-HT agonists increased weight support as well as the ability of the cats to walk uninterruptedly (Brustein and Rossignol, 1999). The pharmacological effects of 5-HT agonists reinforced the voluntarily generated locomotor pattern. This is important because it shows that “voluntary” locomotion can be improved by increasing spinal excitability provided by the pharmacological stimulation. This obviously is of interest within the context of rehabilitation since one could imagine that a temporary state of enhanced excitability of the spinal cord could be induced to facilitate the expression of locomotion and therefore facilitate or accelerate the beneficial outcome of locomotor training.

Although there have been some differences between the response of cats and rats to 5-HT agonists, as far as initiation of locomotion is concerned, there is no doubt that similarities on the output pattern by the spinal cord predominate. Using grafts of embryonic mesencephalic 5-HT cells below a complete spinal lesion in adult rats, we showed that rats, which cannot usually express a spontaneous locomotor pattern of the hindlimbs after spinalization, could express a full pattern of
hindlimb locomotion (Gimenez y Ribotta et al., 2000). Later studies also showed a beneficial effect on the expression of locomotion with chronic 5-HT injections in adult spinal rats (Antri et al., 2005).

A recurrent question is the mechanism through which 5-HT could act to improve the recovery of spinal excitability and locomotion and even perhaps spasticity. The first mechanism that was described is that of hypersensitivity of 5-HT receptors (Bédard et al., 1979) in which similar doses of 5-HT agonists could exert progressively larger effects. Besides such denervation sensitivity, some remnant 5-HT fibers have been described that may originate from endogenous sources (Takeoka et al., 2009). However, other mechanisms may be at play. It has been shown that some membrane properties of spinal motoneurones such as dendritic persistent inward currents (PICs) may be important in the recovery of spinal cord excitability and its ability to express locomotion (Heckmann et al., 2005; Hultborn et al., 2004). In fact, after acute spinalization, PICs are lost and can be reinstated by 5-HT agonists and also noradrenaline (Conway et al., 1988; Hounsgaard et al., 1988). One could then infer that remnant 5-HT after spinalization could participate in the recovery of spinal excitability and locomotion (Harvey et al., 2006a,b; Li et al., 2007). Even more fascinating is the possibility that constitutive 5-HT receptors may become a key mechanism for recovery of excitability and even spasticity as suggested (Murray et al., 2010). In that context it is of interest that cyproheptadine, a 5-HT blocker, had a potent inhibitory effect on spinal locomotion in spinal cats after injection of quipazine (Barbeau and Rossignol, 1990, 1991).

Other neurotransmitters

Intrathecal injections of NMDA, contrary to in vitro neonatal rats (Cazalets et al., 1992; Kiehn and Kjaerulff, 1996) or lampreys (Grillner et al., 1981) and in contrast to decerebrate cats (Douglas et al., 1993), did not induce locomotion in adult spinal cats even though they markedly increased excitability as evidenced from hindfeet tremor and toe fanning (Chau et al., 2002; Giroux et al., 2003). In cats that just started to generate small steps (around 6–7 days) after spinalization, NMDA could boost the expression of emergent locomotor patterns for several hours (Chau et al., 2002). When the spontaneous recovered locomotor pattern was expressed several weeks after spinalization, NMDA had only little effects. In the intact cat AP-5, an NMDA blocker, was shown to influence locomotion by reducing weight support which was, however, rapidly compensated. The same drug injected in the same cat but after spinalization completely blocked the spontaneously generated locomotion (Giroux et al., 2003). This suggests that NMDA receptors play a critical role in maintaining spinal locomotion perhaps by potentializing the release of glutamate by afferents.

In summary then, agonists or antagonists of various transmitters illustrate how neurotransmitters produced by cells in the brain stem, and more or less absent after spinalization, can induce changes in membrane properties and circuits within the spinal cord and enhance the expression of locomotor circuits that are already present. Recent work illustrating how 5-HT agonists can facilitate the expression of locomotion in chronic spinal rats (Courtine et al., 2009) should be interpreted in this light. The circuits already exist in the cord but because the monoaminergic and indoleaminergic inputs are severed, cell properties of these circuits are deficient. Providing exogenous neurotransmitters or agonists of their receptors could favor the spontaneous regain of function by promoting changes in membrane properties necessary for the behavior. In this context, it is also of great importance to better document changes in receptors, not only in their properties but also their number and localization (Chau et al., 2001; Giroux et al., 1999) as these may vary with time after various types of lesions.
**Sensory modulation**

The field of sensorimotor interactions during locomotion has been reviewed several times and more specifically in Rossignol et al. (2006). The details of the observations will not be reviewed but only broad principles that apply to the modulation of the spinal circuits generating locomotion. The complexity of sensorimotor interactions has been well expressed earlier in clear terms: “Normally there is an interaction between the periphery and the central generator and presumably the former is of great importance although the basic structures of the cycle is laid down centrally” (Grillner, 1973).

*Tonic* sensory stimuli can modify the state of the locomotor circuits. Thus a spinal cat injected with clonidine may appear motionless on a moving treadmill but an unspecific perineal stimulation can trigger a well-coordinated pattern of hindlimb locomotion (Barbeau et al., 1987; Belanger et al., 1996). A pinch of the skin in the dorsal lumbosacral region can immediately stop locomotion in spinal cats much as what was shown for spinal rabbits (Viala et al., 1978). Similarly, unspecific electrical stimulation of the dorsal portion of the cord or the dorsal roots can elicit locomotion in spinal cats and rats (Barthélemy et al., 2006, 2007; Courtine et al., 2009; Gerasimenko et al., 2007; Ichiyama et al., 2005). Tonic stimulation can also define the operating range of operation of the spinal circuits and inhibit their expression. The power of proprioceptive inputs especially at the hip joint was first studied in chronic spinal kittens in which it was demonstrated that hip flexion on one side stopped the walking movements on that side (Rossignol et al., 1975) while the other limb continued walking. When the hip reached a critical angle of hip extension the limb started to walk in alternation with the contralateral hindlimb. Hindlimb fictive locomotion in cats can be blocked completely by flexing the hip (Pearson and Rossignol, 1991) on one side. Similarly, the overall pattern can be biased toward flexor or extensor outputs by various degrees of hip extension. In the forelimbs, protraction or retraction of the shoulder can change the actual structure of the locomotor pattern on the manipulated side and compensatory changes in the other forelimb (Saltiel and Rossignol, 2004).

The study of *phasic* sensory also revealed important principles namely that reflexes are modulated in a phase-dependent manner. Initial observations in spinal kittens showed that a tap to the dorsum of the foot in various phases of the step cycle evoked short latency flexion responses during swing and short latency excitation in extensors when applied during stance (Forssberg et al., 1975). This reflex reversal made sense because the sensory evoked responses assisted the ongoing specific phase of the locomotor pattern. Using a very precise cutaneous nerve stimulation in the same cat, it was possible to essentially confirm the finding that the reflex responses were dramatically changed after spinalization (Frigon and Rossignol, 2008) and that “new” reflex responses could be evoked namely short latency extensor responses.

How are reflexes controlled during dynamic rhythmic processes such as locomotion? Several mechanisms have been proposed (Frigon and Rossignol, 2006a,b; Rossignol et al., 2006). Besides the more obvious rhythmic modulation of interneuronal circuits, presynaptic mechanisms may play a crucial role. Cyclical modulation of afferent excitability has been demonstrated (Gossard et al., 1989; Rudomin et al., 1993) but also cyclical antidromic discharges in primary afferents were found (Beloozerova and Rossignol, 1999, 2004). Such antidromic discharges may also have a role in *tritonia* swimming (Sakurai and Katz, 2009) but also in mastication (Kolta et al., 1995). It is possible that multiple discharge sites in neurones could be implicated in regulation of sensorimotor interactions and participate in the reorganization of circuits after lesions by providing alternative modes of activation of the circuitry.

The experimental approaches described above mainly served to investigate the role of sensory inputs by stimulating nerves or receptive fields.
Since it is known that a fictive locomotor pattern can be evoked centrally in cats being curarized or following a dorsal rhizotomy (Grillner and Zangger, 1974) afferent inputs are not critical for initiating the basic locomotor pattern but for adapting it. This is most probably the reason why locomotor training is so important in spinal cats which has otherwise lost all other inputs (Frigon and Rossignol, 2006b; Rossignol, 2006; Rossignol et al., 2006). Another observation showing the importance of sensory inputs for the correct execution of locomotor movement comes from studies on cutaneous denervation. If the cutaneous innervation of both hindfeet is severed by cutting all cutaneous nerves, the otherwise intact cat can walk rather well on the treadmill with proper foot contact but the same cats will be unable to place the feet correctly after spinalization (Bouyer and Rossignol, 2003a,b). This suggests that other sensory or descending pathways compensated for the cutaneous denervation when the cat was otherwise intact. The reduced spinal preparation which has a limited repertoire of other compensatory mechanisms shows how important the cutaneous inputs are. Other experiments have also shown that severing ankle muscles has minor effects on walking in intact cats (Carrier et al., 1997) but major effects in the same cat after spinalization. Similar findings were made after lesioning extensor nerves of the ankle in which a denervation performed in the intact state hampered significantly the recovery of locomotion after spinalization (Frigon and Rossignol, 2009). Finally, the importance of sensorimotor interactions in locomotion can be evaluated by plastic processes occurring in reflex pathways after locomotor training. It was indeed shown that locomotor training could “normalize” the amplitude of proprioceptive and cutaneous pathways after locomotor training (Côté and Gossard, 2004; Côté et al., 2003). This opens the way to other rehabilitation approaches in which the normalization of reflex pathways could help the recovery of locomotor function (Chen and Wolpaw, 2002; Frigon and Rossignol, 2006b; Wolpaw and Carp, 2006).

Segmental and suprasegmental control of locomotion

The first section introduced the concept of a CPG while, in the second one, I summarized some of the observations on the modulation of this CPG by neurochemical substances or by activation of reflex pathways to mimic how this CPG could adapt to various environmental demands or states. How is this spinal locomotor pattern turned on and off or adapted for purposeful locomotion? Most of this question is outside the range of this review and has been well summarized previously (Armstrong, 1988; Drew et al., 2004; Grillner, 1981; Grillner et al., 2008a,b; Rossignol, 1996; Rossignol et al., 2006; Yakovenko and Drew, 2009). However, recent observations have re-emphasized the role of the CPG in the recovery of function after various types of spinal lesions and only these aspects will be reported here.

Segmental control

Some early work suggested that intrathecal drug injections around rostral lumbar segments of the spinal cord in cats (at around L4) were very effective in triggering or modulating locomotion (Chau et al., 1998a,b; Giroux et al., 2001). Later, in cats spinalized 1 week earlier, an intraspinal injection of clonidine or yohimbine restricted to the L4 segment (i.e., rostral to the main hindlimb motoneuron pools; Vanderhorst and Holstege, 1997) initiated or blocked spinal locomotion (Marcoux and Rossignol, 2000). Experiments with serial complete sections were performed. Cats were spinalized at T13 and trained to recover locomotion of the hindlimbs on the treadmill. Thereafter, each cat was submitted to a second complete spinal section and their locomotor ability re-evaluated for several weeks (Langlet et al., 2005). Whereas a second lesion at L2 or rostral L3 did not prevent the locomotion that had recovered after the initial T13 spinalization, lesions at caudal L3 or L4 completely abolished locomotion.
and the latter could not be reinstated even after 3–4 weeks of locomotor training. However, other rhythmic activities such as fast paw shake were not only present but enhanced showing the preserved rhythmogenic capability of the spinal cord. This also indicated that motoneurones of recorded muscles were undamaged by the lesion (because they were rhythmically active in fast paw shake) and that other neural elements important for triggering locomotion are located at or above L4. Finally, mid-lumbar segments may be important in evoking locomotion by other means. It was shown that intraspinal electrical microstimulation applied at different spinal levels could initiate locomotion in 1-week spinal cats (Barthélemy et al., 2005). After inactivating these mid-lumbar segments by yohimbine or performing a second lesion at caudal L4, locomotion could no longer be evoked by intraspinal electrical microstimulation at other more caudal lumbar levels (Barthélemy et al., 2007). We raised the question as to whether these segments were also important for locomotion in the decerebrate cat. Indeed, inactivation of L3–L4 by intraspinal yohimbine abolishes temporarily spontaneous locomotion (Delivet-Mongrain et al., 2008) and it is likely that these segments play an important role even when locomotion is triggered by brain stem pathways. Propriospinal pathways (Sherrington and Laslett, 1903) are important here as suggested by more recent experiments (Courtine et al., 2008, 2009; Cowley et al., 2008; Zaporozhets et al., 2006).

**Suprasegmental control and the dual spinal lesion paradigm**

In the context of recovery of locomotion after lesions of the spinal cord, it is important to distinguish what part is played by supraspinal structures and by spinal structures respectively. Indeed, after partial spinal lesion, it is clear that regeneration or sprouting occur (Ghosh et al., 2009; Rossignol et al., 2007). One could envisage that such descending inputs re-establish a new state of dynamic interactions between supraspinal structures and the spinal cord. However, we also showed that the spinal locomotor circuitry was very important for the recovery of hindlimb locomotion after a partial lesion of the spinal cord. This conclusion was reached using a double spinal lesion paradigm (Barrière et al., 2008, 2010). Firstly, a left hemisection was performed at thoracic levels (T10–T11) and cats were trained three to five times a week to walk on a treadmill until they reached a stable level of voluntary quadrupedal locomotor performance. The spinal cord was then completely sectioned at T13 (same level as in Barbeau and Rossignol, 1987; Belanger et al., 1996) thus removing all inputs from supraspinal fibers that were left intact by the previous partial lesion, as well as all fibers that may have regenerated or sprouted. Remarkably, within 24 h after spinalization, these cats could walk with the hindlimbs at high speeds and with bilateral plantar foot contact. This is in sharp contrast to the few weeks needed to reach such performance in cats without a prior partial lesion before spinalization, as previously mentioned (Barbeau and Rossignol, 1987). Therefore, during the period of locomotor training following the partial spinal lesion, plastic changes occurred in the lumbosacral spinal cord, creating a configuration of the locomotor circuitry that enabled it to operate without or with limited supraspinal influences. Mechanisms responsible for such plasticity below the lesion are still under study. The first question that may be raised is that of an unspecified priming effect of the first lesion on the subsequent spinalization. However, changes appear to have more specificity than that would imply. A recent paper described changes in cutaneous reflexes, evoked by stimulating cuff electrodes placed bilaterally around the superficial peroneal nerves innervating the dorsum of the foot (Frigon et al., 2009). After a partial spinal lesion at T10–T11, reflexes showed a marked asymmetry between the left and right hindlimbs. More specifically, the changes in short excitatory
(P1) responses could differ between hindlimbs. Remarkably, after complete spinalization, some reflex changes that were identifiable in the late stages of the partial spinal lesion could persist for a few days after complete section but then cutaneous reflexes on both sides increased more or less symmetrically. This provided one objective indication that changes had occurred in simple spinal circuits and that these changes could remain for some time before reflexes adapted again to the new, more symmetrical situation following complete spinal transection.

Detailed analysis of the locomotor kinematics throughout the period of partial lesion and complete lesion showed several compensatory adjustments in footfall patterns, step cycle duration, duration of various sub-phases of the step cycle and interlimb coupling (Barrière et al., 2010). Even more interesting is the observation that some of the compensatory changes seen during the partial lesion period are actually reversed after a complete spinalization, a phenomenon akin to the Bechterew phenomenon seen after serial labyrinthectomy (Galiana et al., 1984). This implies that during the partial lesion period, covert changes occurred in the intrinsic spinal CPG that were revealed by the complete spinalization.

Conclusions

This short review has per force concentrated mainly on some of the work performed in my group over the last 35 years. I cannot even begin to thank the numerous students, postdocs, assistants, and colleagues who have contributed to this work and the still exciting journey. They know and I know. I hope this mini-review conveys the excitement of discovering new things and rediscovering old things, of how concepts evolve and are revived by new observations, how old questions persist and continue to nag us. How is the spinal cord generating locomotion in mammals? How are simple circuits maintained while increasing their capabilities (Grillner and Jessell, 2009)? Can we help patients with spinal cord injury regain useful function through this basic knowledge (Nadeau et al., 2010)?

This symposium was meant to bring together scientists from the diverse fields of the neural control of breathing, chewing, and locomotion. The tradition in the field of motor control consisting in bringing scientists studying different types of movements in different species has been rich and productive and has spanned over several decades. Jim Lund, to whom this book is dedicated, was a firm believer in such an interdisciplinary approach to neuroscience and we will regret his friendly and enthusiastic input. Another nagging and simple question: do we know how mastication is controlled during locomotion while breathing (Lund et al., 1984)?

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