ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2007, 67: 235–257

Locomotor recovery after thoracic spinal cord lesions in cats, rats and humans

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Review

Abstract. More than a hundred years of extensive studies have led to the development of clinically valid animal models of spinal cord injury (SCI) used to investigate neurophysiological mechanisms, pathology and potential therapies. The cat and rat models of SCI were found particularly useful due to several behavioral responses that correspond to clinical symptoms seen in patients. This review concentrates on recovery of motor behavior in the rat and cat models of thoracic spinal cord injury. At the beginning an outline of the general concept of neural control of locomotion: the existence of a spinal network producing the locomotor activity and the supraspinal and sensory inputs that influence this network is presented. Next, the severity of functional impairment in relation to the extent and precise location of lesions at the thoracic level in cats and rats is described. Finally, the impact of animal studies on the treatment of SCI patients and the possibility that a spinal network producing the locomotor activity also exists in humans is discussed.

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Key words: spinal cord injury, central pattern generator, cat, rat, human

INTRODUCTION

Spinal cord injury (SCI) interrupts sensory, motor and autonomic fibers. Within the central nervous system, brain structures are no longer able to communicate with spinal structures (and *vice versa*), so the function of the various parts of the body controlled by spinal cord is altered. The effect of SCI is mainly determined by the topographical organization of the spinal cord, the site of the impact and the extent of the damage (lesion). In patients, SCI may cause severe functional impairments among which locomotor disability (difficulty in walking) is one of the most important. This can have a devastating social and economic impact on those affected. In the United States alone there are more than 10 000 cases of SCI every year. In European countries an annual incidence of 15 to 40 traumatic SCI cases per million population are reported (data from SCI centers). Due to the seriousness of this condition, considerable effort has been directed at enhancing the recovery of locomotion and to develop effective therapies for reducing the debilitating results of spinal cord injury. Animal models of SCI have been extremely helpful in (1) understanding the mechanisms responsible for producing the locomotor pattern which evokes rhythmic limb movements associated with locomotion, and (2) in developing effective treatments of spinal cord injury that have been successfully applied to human patients. Nevertheless it is still unclear how close animal models of spinal cord injury come to reproducing SCI in humans. In this review we will discuss how the location and extent of spinal cord damage influence locomotion in the cat, rat and humans.

NEURAL CONTROL OF LOCOMOTION

Spinal network

It has been shown that the neural control of locomotion in most mammals is based on a central pattern generator (CPG). This corresponds to a network of spinal cord neurons producing phasic signals evoking alternating activity in groups of flexor and extensor muscles, which results in leg movements and locomotion. The understanding of the basic functional principles of neural circuits (networks of interneurons) within the spinal cord that are responsible for locomotion and interact with specific sensory information is based on many years research performed in invertebrates and primitive fish (lamprey). Although the contribution of this spinal cord neuronal network to the control of locomotor movements has been investigated for many decades, little is known about the organization of the CPG in higher vertebrates. Our understanding of stereotyped motor responses to external stimuli produced by these neural structures is mainly based on observations of locomotion in cats. The pioneering studies of Sherrington (1910) and Brown (1911, 1912) indicated a great degree of complexity in the spinal cord circuitry regulating limb movements. Brown showed that in cats after total transection of the spinal cord and with additional dorsal roots cut, the rhythmic alternating contraction of ankle flexor and extensor muscles could be observed (Brown 1911, 1912). These observations led to the idea that rhythmic motor activity is generated by the reciprocal inhibition of two "half-centers". One half-center produces activity in the flexor and the other in the extensor muscles. Thus, in addition to mono- and polysynaptic reflexes (Sherrington 1910), the spinal cord circuitry can generate motion of several joints that leads to limb movements. Experiments carried out over the last century have confirmed these ideas (for review see Dietz 2003, Duysens and van de Crommert 1998, Grillner 1975, 1981, 1985, Jankowska 1967a,b, MacKay-Lyons 2002, Marder and Bucher 2001, Pearson 2004, Rossignol 1996, Whelan 1996, Wetzel and Stuart 1976). Now, it is well documented that locomotor movements are generated by neuronal circuitry located in the spinal cord and the group of neurons responsible are referred to as the CPG (Grillner 1975, Grillner and Zangger 1975, Lundberg 1979, Shik and Orlovsky 1976). The activity of this spinal neural circuitry (see Fig. 1) can be modulated by many afferent inputs (descending supraspinal pathways, propriospinal and ascending afferents from the periphery). However, limb movements do not depend entirely on sensory inputs, because rhythmic activity can be generated by the CPG even when the descending pathways have been disrupted by total spinal cord transection and dorsal roots have also been cut (deafferentation). Total transection of the spinal cord completely disrupts the influence of supraspinal structures on the part of the spinal cord below the lesion containing the network responsible for generating the locomotor pattern. However, cutting the dorsal roots does not complete-

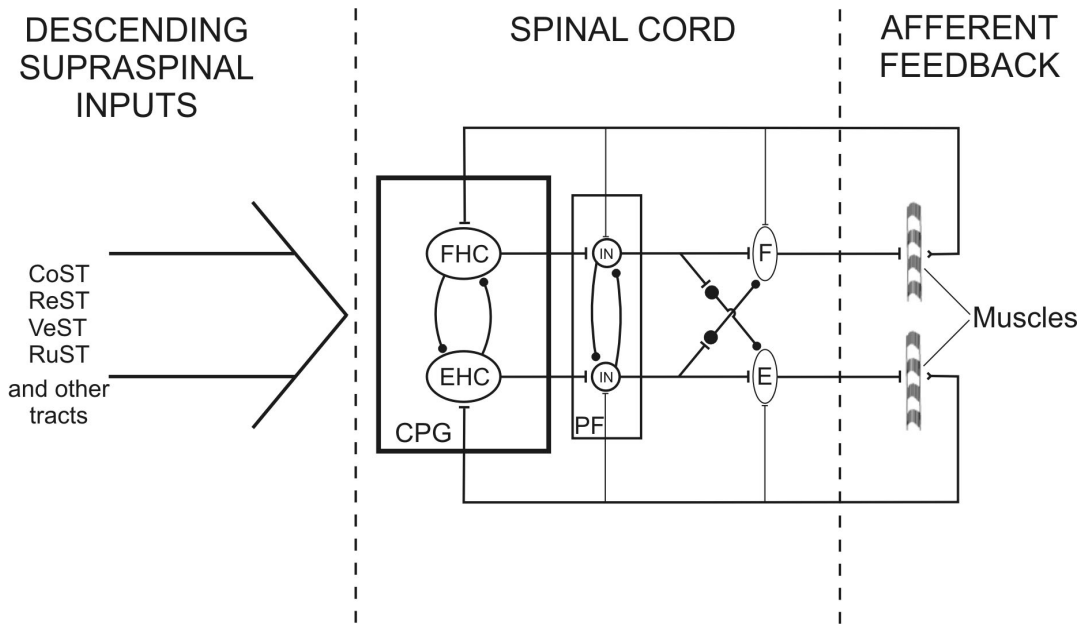

Fig. 1. Simplified schematic diagram of spinal circuitry involved in producing locomotor pattern and peripheral and supraspinal inputs which can modify locomotor activity at various levels (based on Dietz and Harkema 2004, Frigon and Rossignol 2006, Hultborn et al. 1998, McCrea 2001, Rybak et al. 2006a, 2006b, Stecina et al. 2005, Wolpaw 2006). Spinal cord circuitry consists of separate network for rhythm generation and a network for pattern formation that distributes excitation and inhibition to motoneurons. This circuitry is under influence of descending supraspinal inputs and intraspinal connections as well as of muscle, joint and skin afferents. Abbreviations: (CPG) central pattern generator; (FHC) flexor half center; (EHC) extensor half centre; (PF) pattern formation; (IN) interneuron; (E) extensor motoneurons; (F) flexor motoneurons; (CoSt) corticospinal; (ReST) reticulospinal; (RuST) rubrospinal; (VeST) – vestibulospinal.

ly abolish afferent inputs since some afferent information reaches the spinal cord through the ventral roots (Coggeshall et al. 1997, Loeb 1976). Nevertheless, it is rather unlikely that ventral root afferents play any role in locomotion because most of them come from the visceral region (Grillner and Zangger 1984) and stimulation of ventral roots does not evoke any obvious sensation (Duysens and van de Crommert 1998).

The most convincing evidence that the CPG exists in cats was the recording of a rhythmic locomotor pattern in ventral roots of animals in which the limb movement (and therefore the feedback of movement) was eliminated by application of muscle relaxant (e.g., curare) or by cutting the nerves at the ventral roots or muscle nerves. Since these rhythmic patterns occurred in the absence of any movement, such neural activity was called "fictive locomotion" (for review see MacKay-Lyons 2002). Further investigation using the fictive locomotion preparation led to better understanding reflex pathway organization and to identification of the spinal interneurons involved in locomotor-dependent reflexes and the organization of the mammalian CPG (for review see McCrea 2001). McCrea with his colleagues (Angel et al. 2005, Lafreniere-Roula and McCrea 2005, Rybak et al. 2006a, 2006b, Stecina et al. 2005, Yakovenko et al. 2005) proposed a model of the spinal circuitry for locomotion with a layer of interneurons between the CPG and the motoneurons. Thus, the CPG acting within a limb can be divided into two networks: one for rhythm generation (i.e. cycle period and phase) and the other for distributing excitation and inhibition to motoneurons, or pattern formation (see Fig. 1).

Supraspinal control

All of these findings do not diminish the importance of supraspinal and sensory inputs in regulating locomotion under normal conditions. Supraspinal structures have several functions in the control of locomotion (Orlovsky 1991): initiating and terminating the

spinal locomotor CPGs, controlling the level of their activity, maintaining equilibrium in locomotion, adapting paw movements to external circumstances and coordinating other motor performance with locomotion. The spinal circuitry is reserved only to generate the complex pattern of muscle activity needed for locomotion.

It is well documented that the spinal network not only has the capacity to generate basic locomotor rhythmicity in the absence of any supraspinal or sensory input to the spinal cord in chronic spinal animals, but that this can also be activated in decerebrated animals by tonic descending activation from centers in the brain stem: mesencephalic and subthalamic locomotor regions (Orlovsky 1969, Shik and Orlovsky 1976). Stimulation of these locomotor regions initiates and controls the locomotor movements. To maintain locomotion, many other supraspinal structures are engaged, including the sensorimotor cortex, the cerebellum and the basal ganglia. There is now good evidence that neurons originating from several areas of the brainstem are important for initiating and maintaining locomotion (for review see Fouad and Pearson 2004). The brainstem structures that are the sources of the reticulo- and vestibulospinal pathways play an important role in producing the muscle tonus necessary to support the body weight, for ensuring the lateral stability of the animal and for producing step-by-step regulation of muscle activity during locomotion. In addition, the reticulospinal pathways can modulate the body posture to ensure stability under dynamic conditions. In comparison, the rubrospinal pathway, that is well developed in lower mammals and less so in humans, exerts excitatory effects on flexor muscles and inhibits extensor muscles. Whereas, removing the sensorimotor cortex or cutting the corticospinal tract does not influence stereotypical locomotion including walking uphill, downhill and running at different speeds (Orlovsky 1991). However, more demanding locomotor tasks like walking over barriers produced increased bursting activity in pyramidal tract neurons in an intact cat. Thus, it seems that the corticospinal pathway provides a crucial contribution to the control of basic locomotor movements required to negotiate obstacles in the environment.

The role of the cerebellum in locomotion is not completely clear. Mori and coauthors (1999) observed that stimulation of the hook bundle of Russell in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. It is also known that the cerebellar cortex integrates proprioceptive, exteroceptive, visual, and vestibular afferent information originating from a wide variety of sources (Armstrong 1978, Armstrong et al. 1997, Arshavsky et al. 1986). The cerebellum receives information about state of the CPG via ventral spinocerebellar and spinoreticulocerebellar tracts and afferent information from the peripheral motor apparatus via the dorsal spinocerebellar tract. The cerebellum indirectly influences motoneurons through the vestibulospinal, rubrospinal, reticulospinal and corticospinal tracts. Furthermore, removal of the cerebellum results in the deterioration of locomotor movements characterized by poor interlimb coordination, inaccurate foot placement and impairment of balance. The basal ganglia are now also recognized as part of a larger motor system involving the cerebral cortex and thalamus, which is responsible for planning, initiation, execution and termination of motor tasks as well as motor learning (Graybiel 1995, Martin and Obeso 1994). Both cerebellum and basal ganglia are thought to maintain the timing of sequential muscle activation, with the basal ganglia working over a long time scale (Lansner and Ekerberg 1994, MacKay-Lyons 2002, Wichmann and deLong 1996).

CPG activity is modulated by a number of different neurotransmitters, employed by several pathways that originate from separate brainstem structures: the raphe nucleus containing serotonergic cells, the locus coeruleus containing noradrenergic cells, plus the nucleus reticularis gigantocellularis and the pontine reticular nucleus, both containing glutamatergic cells. Clonidine, an agonist of noradrenergic Alpha 2 receptor can initiate locomotion in acute spinal cats (Barbeau et al. 1993, Forssberg and Grillner 1973). The glutamatergic system may also play a substantial role in the initiation of locomotor movements in cats (Chau et al. 2002, Douglas et al. 1993) and rats (Cazalets et al. 1992, 1995, Cowley and Schmidt 1995, Kiehn et al. 1992, Kjaerulff and Kiehn 1996). Serotonin is a potent neurotransmitter influencing the network generating locomotor pattern, since intrathecal application of serotonin itself improves locomotor movements in spinal adult rats (Feraboli-Lohnherr et al. 1999). Moreover, the implantation of embryonic tissue from the raphe nucleus containing serotonergic neurons improves hindlimb stepping in spinal rats (Feraboli-Lohnherr et al. 1997, Gimenez-Ribota et al.

2000, Majczyński et al. 2005b, Sławińska et al. 2000). Interestingly, data from rats and cats indicate that the same drugs may act differently in separate species and in different animal models. Clonidine can initiate locomotion in acute spinal cats and improve ongoing locomotor movements in chronic spinal cats (Barbeau and Rossignol 1991), but is ineffective in acute and chronic rats (Fouad and Pearson 2004). In contrast, serotonin is effective in initiating locomotor activity in spinal rats (Feraboli-Lohnherr et al. 1999) but ineffective in spinal cats (Barbeau and Rossignol 1991). Recent data indicate that at least in rats, both serotonergic and noradrenergic systems play an important role in locomotion since blocking of receptors with specific antagonists abolishes locomotion in intact animals (Majczyński et al. 2005a, 2006). All of the supraspinal structures mentioned above influence motor activity through descending pathways that can be grouped into two principal systems according to their medial or lateral location in the spinal cord (Drew et al. 2002). A medial system includes the reticulo- and vestibulospinal pathways while the lateral system comprises the cortico- and rubrospinal pathways (Fig. 2). The former has a relatively diffuse action on flexor and extensor muscles (Mori 1987, Mori et al. 1992), while the latter is responsible for fine control and voluntary modification of locomotion (Beloozerova and Sirota 1993, Kuypers 1963).

Afferent influence

Although, limb movements do not depend entirely on sensory inputs it is well known that the afferent feedback influences the neural network responsible for producing the locomotor pattern in order to adapt movements to changes in the internal and external environments (MacKay-Lyons 2002). According to Pearson (1993) there are 3 main functions of afferent influences on the CPG: (1) to augment CPG activity especially during the excitation of weight-bearing muscles, like limb extensor muscles active in the stance phase, (2) to control the timing of the motor output to ensure that the muscle drive is appropriate for the biomechanical state of the moving body with regard to the position, direction of movement and force, and (3) to control the phase transition to avoid the switching of gait phases until a suitable biomechanical state of the limbs and body has been achieved.

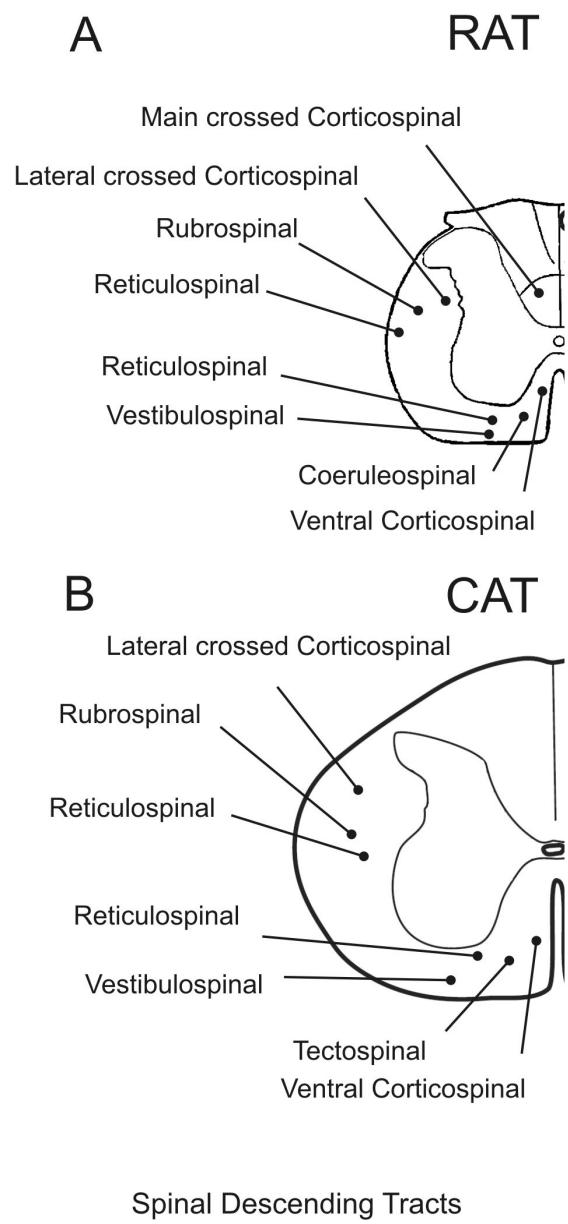

Fig. 2. Pictorial depiction of various descending tracts location in the spinal cord of (A) rat (Schucht et al. 2002, Webb and Muir 2004) and (B) cat (Holstege and Kuypers 1982, 1987, Kuypers 1981). It has to be pointed that an approximate area within the spinal cord varies slightly along the length of the spinal cord in rats and cats as well. Note that in rat, unlike in cat, the corticospinal tract runs mainly in the dorsal spinal cord with only a small number of fibers located in the ventral part of the spinal cord.

Augmentation of the CPG activity was demonstrated in experiments in which stretching the Achilles tendon increased both the amplitude and duration of EMG bursts in the ankle extensor and decreased EMG bursts in flexor muscles in a pre-mammillary cat (cat with

a brain transection made rostrally to the superior colliculus and continued rostroventrally to the rostral tip of the mammillary bodies; for review of preparation see Whelan 1996) walking on a treadmill (Duysens and Pearson 1980). Also electrical stimulation of extensor group I afferents in the same preparation prolonged the extensor EMG burst (Whelan et al. 1995). It is not clear which afferents are responsible for this reinforcement of the EMG burst: group Ib from the Golgi tendon organs or group Ia from muscle spindles. However, most experiments support the hypothesis that during the stance phase the signal from group Ib afferents inhibits the flexor half-center of the CPG (Duysens and Pearson 1980). A second function of the influence of afferents on the CPG is related to low threshold cutaneous afferents innervating the foot. Stimulation of the cutaneous nerve supplying the dorsum of the foot enhances extensor activity during the stance phase and flexor activity during the swing phase (Guertin et al. 1995, LaBella et al. 1992). This input to the CPG can inhibit motor centers producing flexion during the stance phase, so in this phase they act in a manner similar to group I afferents. Several experiments demonstrated that afferent signals from the hip influence the termination of the stance and initiation of the swing phase of that limb (for review see Grillner 1985). This phase transition is associated with the angle of the leg extension at the hip joint (Grillner and Rossignol 1978). Two categories of receptors might be involved: those from the hip joint and those from hip muscles. The results of experiments studying fictive locomotion (Kriellars et al. 1994) and decerebrate cat walking on a treadmill indicate that signals from position-related Ia afferents of flexor muscles influence the transition from stance to swing phase. Thus, feedback from muscle and skin afferents as well as from other senses influences the timing of major phase transitions in the motor pattern, contributes to the production of burst activity and is required for the adaptation of the motor pattern in response to alterations in leg abilities to move (for detailed review see: Pearson 2004, Rossignol et al. 2006).

Pattern generation for human walking

With respect to the neural control of locomotion, the extrapolation of the "animal" model to humans is based on the assumption that no fundamental differences exist between the neural networks of humans and other vertebrates (Duysens and Van de Crommert 1998). However, it is well known that in contrast to the descending brain stem pathways the descending cortical pathways to spinal cord vary in different species with respect to both their trajectories and their terminal distribution (for comparison of location of various descending pathways in the spinal cord of cat and rat see Fig. 2). Moreover, although there are certainly striking similarities between cat and human locomotor performance, important differences exist as well.

The concept of the existence of spinal circuitry for locomotion within the lumbosacral spinal cord in humans and adult primates remains an open question (Bussel et al. 1988, Calancie et al. 1994, Dietz et al. 1994, 1995, Dimitrijevic et al. 1998, Eidelberg et al. 1981b, Rémy-Néris et al. 1999, Stewart et al. 1991, Vilensky et al. 1992, Wernig and Muller 1992, Wernig et al. 1995). Confirmatory evidence exists for a CPG in adult lower mammals (cat, rat, rabbit and dog) (Cazalets et al. 1995, Grillner 1981), but there is only indirect evidence for stepping movements in spinal primates (Eidelberg et al. 1981b, Fedirchuk et al. 1998). In 1905, Philippson reported that a monkey with a transected spinal cord showed alternating movements of the legs about 1 month after the lesion (Philippson 1905). In contrast, Eidelberg (Eidelberg et al. 1981b) demonstrated that in macaque monkeys, hindlimb stepping movements could be elicited by tail pinches only after partial lesions (T8). Undoubtedly, monkeys with spinal cord injury could be trained (5 days per week) using a treadmill to perform a correct walking pattern. A subsequent investigation confirmed that initially, monkeys showed much less bilateral hindlimb stepping than cats with similar partial lesions of the spinal cord (Vilensky et al. 1992).

Further evidence for the existence of a spinal network controlling locomotion in primates was provided by an investigation of electromyographic activity that was pharmacologically induced in the isolated spinal cords of marmoset monkeys. However, these patterns seem to be less complete and more difficult to obtain compared with lower mammals (Fedirchuk et al. 1998).

The bipedal human gait is unique with respect to its set of stereotyped features and foot movement patterns (Forssberg 1985). It is obvious that the major differences in human locomotion in comparison to other mammals are related to the upright position of

the human body, which induces several adaptations in the functional organization of movements in the skeletal and muscle systems. The attribute of bipedal walking is the leaning body positioned above the unstable support of two legs. The most important difference compared to animals is related to the heel strike at the start of the stance phase, followed by the lengthening contraction time of the ankle dorsiflexor muscles in the early stance phase and the lengthening contraction time of the ankle plantar flexors throughout most of the stance phase, with the controlled forward shift of the center of body weight by propulsive power supplied mainly by the ankle plantar flexor muscles. The subsequent controlled fall of the body is only stopped by initiation of the next stance phase (Nielsen 2003). Thus, the most significant difference between bipedal and quadrupedal gait is the nature of the foot-ankle movement control; i.e. plantigrade for bipedal (humans) and digitigrade for quadrupedal (animals).

According to muscle activity recordings it seems that the operation of hip and knee muscles during bipedal and quadrupedal locomotion is quite similar during the swing phase, while during the stance phase the basic pattern may be similar but amplitudes and functions of bursts of activity may differ. For example, during the stance phase the cat hip extensors are propulsion muscles whereas in humans they are dominant in balance control of the upper body (pelvis to head). Additionally, in humans the plantar flexors are by far the most dominant propulsion muscles but in the cat they may be less important. Lastly, the paraspinal muscles in humans are balance control muscles but in cats they are not (Duysens and Van de Crommert 1998).

The question of whether human locomotion is controlled by a spinal neural circuitry similar to that of other mammals may only be answered based on indirect evidence, the most important of which comes from observations of the development of walking in infants. It is well known that step-like movements are present at birth (Andre-Thomas and Autgarden 1966) and even before birth according to ultrasound recordings (deVries et al. 1982). Forssberg (1985), who was the first to describe in detail the maturation of infant stepping into independent walking, found that the kinematic pattern of joint movement gradually develops from asynchronous motion of the ankle, knee and hip, to the more segmental pattern seen in adults. In babies the limb joints (hip, knee and ankle) move in phase during most of the step cycle and antagonist muscles at all joints are co-activated with only a minor time delay between flexor and extensor muscle activation. It is important to note that although rhythmic alternating leg movements are coordinated, the infant is unable to maintain body equilibrium. Moreover, children lack integration of the appropriate afferent input into the leg muscle activity pattern, which is needed to achieve modulation and adaptation to the environmental circumstances. The pattern of locomotion in children differs markedly from the adult plantigrade locomotor pattern. At approximately one year of age there is a progressive transformation to a plantigrade gait, which takes about four years. The slow and gradual maturation of the gait pattern suggests program modification rather than a change of programs. This means that the original circuits are still generating the rhythm but, due to adaptive mechanisms, another pattern is developed (Forssberg 1985).

The locomotor-like steps of fetuses and newborn infants suggest that locomotion is an innate behavior that is controlled in a manner similar to that in other mammals. Although maturation of stepping into independent walking incorporates some new features, many of the features of infant stepping remain in adult walking. For example, the legs take steps alternately, the flexors and extensors are activated alternately, and the duration of the stance phase varies much more than the swing phase as walking speed changes (Yang and Gorassini 2006, Yang et al. 1998). Analysis of muscle activity demonstrates that dorsiflexors and plantarflexors at the ankle joint are alternately recruited, whereas flexors and extensors at the knee show greater coactivation. However, there are also some notable differences in comparison with the adult pattern of walking. First, babies present digitigrade stepping. Second, unlike in adults, babies show a short burst of activity in many muscles at the time the foot makes contact with the ground (Berger et al. 1984, Forssberg 1985, Yang et al. 1998). It is possible that this activity is associated with segmental reflexes because it happens immediately after foot-floor contact. Moreover, young children show an absence of dorsiflexor activity at the end of the swing and beginning of the stance phase that corresponds to the toe drag. The activity of dorsiflexor muscles at this transition between swing and stance in adults is responsible for lowering the foot to the ground (Yang

et al. 2004). The lack of dorsiflexor muscle activity at foot contact confirms the essential role of the motor cortex in controlling distal flexor muscles in adult walking.

The findings described above imply that humans possess a network in the spinal cord that is capable of generating basic rhythmic walking activity. However, the activity of this network depends much more on supraspinal influences than in other animals. Moreover, due to the functional requirements of bipedal locomotion this network and its reliance on supraspinal structures have important modifications. The reasons for the switch to habitual bipedalism in the early history of humans remain unknown. The most widely accepted theory is related to idea of uncoupling hand and arm movements from locomotor movements of the legs to permit the hands to be free to carry food and children, to develop tools, or to manipulate the environment in other ways (Duysens and Van de Crommert 1998, Nielsen 2003). The development of a bipedal pattern of walking was probably associated with the increased importance of the corticospinal tract in primates (for review see Duysens and Van de Crommert 1998, Vilensky and O'Connor 1997). Furthermore, a very considerable adaptation and modification of the motor control networks occurred, because human locomotion is not simply equivalent to a cat or monkey walking on its hind legs. First of all, it is well known that the autonomy of the isolated spinal cord to generate locomotor movements is considerably greater in the cat or rat (Cazalets et al. 1995, Grillner 1981) than in monkeys (Eidelberg 1981, Eidelberg et al. 1981b, Vilensky et al. 1992) or humans (Dietz 2003, Dimitrijevic et al. 1998, Roby-Brami and Bussel 1987). Second, in primates, the spinal circuitry for locomotion might be suppressed by dominant input from the cortex (Dietz 2003).

CHANGES IN LOCOMOTION AFTER SPINAL CORD INJURY

In the spinal cord, each descending, ascending or intrinsic neural system is topographically organized and has functional specificity; so injuries to different sites of the cord and of different extents do not imply that sparing a greater amount of white matter causes less severe impairment of locomotion (Collazos-Castro et al. 2006). We will discuss the effect of site and extent of lesions performed at the low thoracic level on the impairment of locomotion in cats, rats and briefly in humans.

Changes in locomotion after spinal cord injury in cats

As mentioned above, a number of investigations dating back to the early part of the previous century demonstrated the substantial contribution of the spinal cord to both the generation and control of vertebrate locomotion (for review see Grillner 1975, 1985, Rossignol et al. 2002). Major efforts have been made to try to understand the particular roles of the spinal cord, supraspinal structures and peripheral afferents in the control of normal locomotion. In awake cats, locomotion has been mainly studied by examining movement overground or on a treadmill. In both conditions intact cats demonstrate well defined patterns of coordination of forelimb-forelimb, hindlimb-hindlimb, and forelimb-hindlimb step cycles of which two forms have been described: alternate and in-phase. Thus, step cycles of the forelimbs and hindlimbs are coordinated via a single trotting mode of coupling or a possible variation of this mode (diagonal couplet coordination), while pacing modes of step cycle coordination are less common (English 1980, Górska et al. 1993a,b,c, 1995, 1996). Walking is a complicated motor act requiring four-limb coordinated movement that is the result of the coordinated activity of many muscles of the trunk and limbs, involving many joints. Such complex behavior is regulated by the integrated activity of descending and peripheral pathways acting upon the neural spinal cord circuitry. Thus, the normal control of locomotion represents an exquisite and dynamic balance between different levels of the nervous system. Although such normal control is very complex, after a large lesion or even after a complete transection of the spinal cord, cats can re-express hindlimb locomotor movements (deLeon et al. 1998a,b, 1999, Edgerton et al. 2001, Rossignol et al. 1996, 2001, 2002). Such a situation is possible due to the remarkable ability of the spinal cord to optimize the locomotor functions within the remaining structures of the CNS, which suggests the occurrence of plasticity in the mechanisms controlling locomotion. Many recent studies have produced strong evidence that after a lesion, the spinal cord network is gradually modified and in this way the ability to express more or less appropriate locomotion is eventually regained.

TOTAL SPINAL CORD TRANSECTION

The cat seems to be particularly privileged in its capacity to regain locomotor movements after spinal cord injury in the low thoracic region. The spontaneous recovery of hindlimb locomotion in cats after total spinal cord transection may occur at any time, from a few days to a few weeks after the lesion (Rossignol and Bouyer 2004). This phenomenon, however, is only observed when the cats' hindlimbs are placed on a treadmill while the forelimbs stand on a stationary platform, but not during spontaneous overground locomotion. In only a few days after injury, when the animal is placed on the treadmill, strong manual stimulation of the perineum or the base of the tail elicits small alternate rhythmic movements of the otherwise flaccid hindlimbs. Such stimulation evokes flexion movements mainly at the hips, while the feet drag on the dorsum and very little knee and ankle flexion is observed. Thus, the hindlimbs move more or less rhythmically and are then being passively extended at the hip joint. At this very early stage, the animals are unable to support the weight of their hindquarters. After more or less quick progression (10 to 21 days), the cats reach a plateau in locomotor pattern with plantar contact of the paw with the belt and adequate muscle force to support the hindquarters (Belanger et al. 1996, Rossignol et al. 2002). Thus, two to three weeks after a complete section of the spinal cord at T13, cats can recover almost authentic hindlimb locomotor movements on a treadmill making plantigrade contact, and can support the weight of their hindquarters (Barbeau and Rossignol 1987, Belanger et al. 1996, Rossignol and Bouyer 2004). Moreover, spinal cats can then adapt their hindlimb locomotor movements to the varying speed of the treadmill and, if the progression of one leg is perturbed by contact with an obstacle, the limb can generate a coordinated hyperflexion to bring the foot up and around the obstacle (Forssberg et al. 1975). However, there are some obvious deficits in hindlimb locomotor movements of spinal cats such as a lack of voluntary control, an absence of sustained coordination between the fore- and the hindlimbs during quadrupedal locomotion and an almost total absence of balance control. In the situation where the animals can support their hindquarters, balance must be supplied by holding the tail. Other defects tend to vary from one cat to another. Typical variations include foot dragging in the initial part of the swing phase, irregularities in the stepping frequency, exaggerated adduction of the hindlimbs and sometimes incomplete weight support (Belanger et al. 1996). After a few weeks of locomotor training, spinal cats can walk on a treadmill but are unable to perform any hindlimb overground locomotor movements in their home cages – they move around using forelimbs only. It seems that the specific defects observed in cats after total spinal cord transection can be attributed to the loss of normal control provided by the descending pathways from the cortex, brainstem and propriospinal system (Brustein and Rossignol 1998, Jiang and Drew 1996, Rossignol et al. 1999).

PARTIAL TRANSECTION OF THE SPINAL CORD

Investigations carried out using animal models with total spinal cord transections indicate the existence of spinal mechanisms controlling hindlimb locomotor movement, related to the interneuronal circuitry that can produce a basic pattern of rhythmic activity. As described in detail above, the activity of these mechanisms is under the control of many descending pathways that can be divided into two principal spinal systems: medial, including the reticulo- and vestibulospinal pathways and lateral, including the cortico- and reticulospinal pathways. A number of investigations on the recovery of cat overground quadrupedal locomotion after partial spinal cord lesions of different extent have provided information concerning the role of supraspinal control, via both the medial and lateral systems, in the regulation of hindlimb locomotion (e.g., Afelt 1974, Eidelberg et al. 1981a, English 1980, Górska et al. 1990, 1993a,b,c, 1996, Rossignol et al. 1999). In contrast to the results of investigations of cats with total spinal cord transection, the findings concerning animals with partial lesions are less consistent. For example, Górska and co-workers (Bem et al. 1995, Górska et al. 1990, 1993b,c) reported that in general there are three different forms of impairment of fore-hindlimb coordination after partial spinal cord lesions of different extent: (1) lesions sparing the dorsolateral or the ventral funiculus on one side preserve the equality of the fore-hindlimb locomotor rhythms but change the coupling between the movements of both girdles compared to intact animals, so a tendency toward pacing-like locomotion is obtained; (2) more extensive lesions involving the ventral quadrants of the spinal cord and major parts of the dorsolateral funiculi as well

as lesions sparing ventrolateral and ventral funiculi result in episodes of rhythmic oscillations in both girdles, with small changes in these rhythms; (3) lesions destroying almost the whole spinal cord sparing only small parts of the dorsolateral funiculus and/or parts of dorsal columns as well as lesions sparing ventral funiculus result in permanent impairment of intergirdle coordination, i.e., a permanent change in the rhythm of the step cycle durations of the fore- and hindlimbs is observed. The main conclusion on the base of these results was that not only the ventral but also the dorsolateral funiculi play an important role in preservation of the rhythm equality in both girdles.

The results of earlier studies based on lesions sparing small patches of spinal cord tissue (Afelt 1974, Eidelberg 1981, Eidelberg et al. 1981a) imply that the ventral and ventrolateral pathways are crucial for quadrupedal locomotion. Signals conveying information about the body balance in particular appear to play an important role. The additional synchronization between girdles might be a consequence of possible deficits in equilibrium control in animals in which lumbar enlargement neurons were deprived of the vestibulospinal pathway (Bem et al. 1995, Brustein and Rossignol 1998). However, in contrast to the findings of the aforementioned studies, there is now growing evidence that despite extensive lesions in the ventral and lateral quadrants that eliminate the vestibulo- and severely damage the reticulospinal pathways, recovery of voluntary locomotion is possible in the long-term (Bem et al. 1995, Brustein and Rossignol 1998, Górska et al. 1993a, 1996). It may be concluded that even after a massive lesion to the ventral and ventrolateral quadrants, severing the vestibulospinal pathway, the recovery of quadrupedal locomotion is related to structures in the dorsolateral funiculus such as the corticospinal pathway. Moreover, these results suggest that dorsolateral funiculi play a major role in preserving the equality of rhythms in the fore- and hindlimbs, while lesions to the ventral quadrants influence the coupling between limbs. Other investigators (Jiang and Drew 1996) have reported that lesions of the dorsolateral funiculi at the low thoracic level that completely interrupt both the cortico- and rubrospinal pathways produce long-term deficits in overground locomotion including paw-dragging, while smaller lesions only initially produced similar deficits from which the cats recovered relatively quickly (Drew et al. 2002). Even 3 to 5 months after injury, cats with the largest lesions affecting the dorsolateral funiculi were unable to modify their gait over obstacles attached to a treadmill belt. The massive lesions of the dorsolateral funiculi sparing ventral and/or partly ventrolateral funiculi in cats evoked shortening of tibialis anterior muscle activity resulted in the lack of coactivation of tibialis anterior and gastrocnemius lateralis muscles during overground locomotion (Fig. 3). These changes in muscle activity timing could cause a foot dropping observed at the end of swing phase occurring in operated animals (Zmysłowski et al. 1993). According to Drew and colleagues (2002), damage to the cortico- and rubrospinal input to motoneurons controlling distal muscles as well as a change in the relative timing of muscles acting around the hip and knee might be responsible for such deficits. In addition, the proprospinal pathways in the dorsal columns may participate in intergirdle coordination (English 1980, 1985, 1989, English and Lennard 1982, English et al. 1985). However, it is also possible that mechanical coupling via the trunk is responsible for this coordination. The trunk muscles are likely to play an important role since any pulling or pushing action from one girdle to another is transmitted via the trunk, resulting in a change in the position of the body in relation to the limb being in contact with the ground

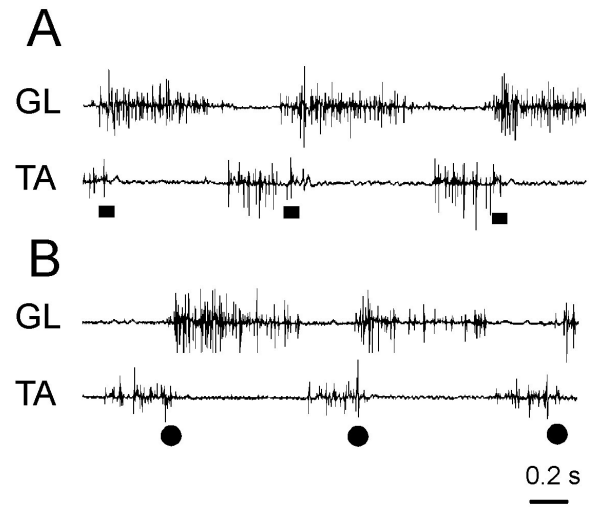

Fig. 3. EMG activity of hindlimb flexor (tibialis anterior – TA) and extensor (gastrocnemius lateralis – GL) muscles during overground locomotion in an intact cat (A) and in a cat with spinal cord lateral funiculi lesion (B). Note the shorter flexor activity observed in an injured cat (indicated by dots) than in intact cat (indicated by rectangles) (modified from Zmysłowski et al. 1993).

(Rossignol et al. 1993). Thus, it is likely that a crucial role in the control of fore-hindlimb coordination is played by long descending and ascending propriospinal pathways interconnecting the spinal enlargements.

The results of numerous studies concerning the role of the lateral system (for review see Drew et al. 2002) imply that although the corticospinal tract is not essential for the production of the basic locomotor rhythm in cats, it does contribute to the regulation of locomotion, particularly in situations where there is a requirement for precise control of paw placement or limb trajectory. This means that the medial, reticulo- and vestibulospinal pathways are unable to fully compensate for damage to the lateral pathways (Drew et al. 2002).

All these results taken together show the great variability in different types of functional impairments that might suggest lack of particular functional specification for various descending or ascending pathways or might be a result of the huge inconsistency in the extent of the spinal lesions and of afferent input destruction. Brustein and Rossignol (1998) suggested that inconsistency in partial spinal lesion studies might be related to limitations in the method of light microscopy used for estimation of the surviving axons. In highly necrotic and deformed tissue, more axons could survive than estimated from the observed lesion size, which could explain recovery.

The results obtained from studies on cats have increased our understanding of the behavioral and pathophysiological effects of spinal cord injury. Although these findings cannot be directly transferred to explain the consequences of SCI in humans, this knowledge is helpful in the development of new treatments (therapeutic interventions) for promoting the recovery of locomotion in patients.

Changes in locomotion after spinal cord injury in rats

Rodents and especially rats are currently the most popular animal model of SCI. Despite physiological and functional differences between rodents and humans, the rat model can assist in understanding the mechanisms of locomotor impairment and processes of recovery after CNS trauma and has been vital in the development of many new techniques for encouraging recovery after spinal cord injury, which may be applied to patients.

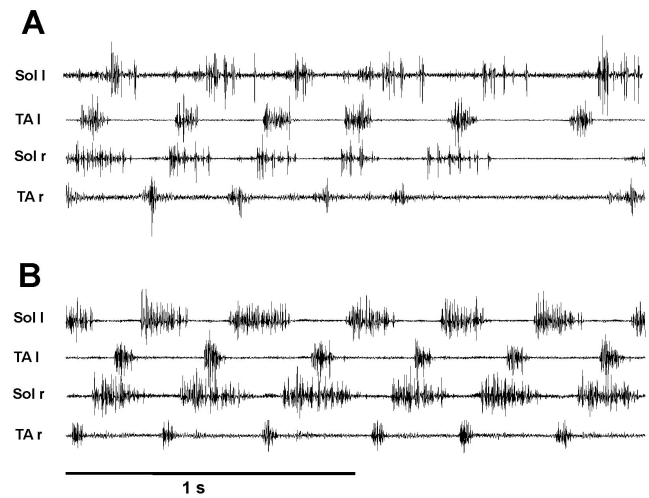

Fig. 4. EMG activity of hindlimb flexor (tibialis anterior – TA) and extensor (soleus – Sol) muscles recorded (A) during locomotor-like movements induced by tail pinching of a spinal rat on a treadmill and (B) during spontaneous overground locomotion of an intact rat (l, r – left, right hindlimb muscle).

TOTAL SPINAL CORD TRANSECTION

In adult rats, complete transection of the spinal cord at the low thoracic level (T8–T10) abolishes hindlimb locomotor movements (Celichowski et al. 2006, Feraboli-Lohnherr et al. 1997, Majczyński et al. 2005b, Sławińska et al. 2000). These spinal rats move around using their forelimbs while the caudal part of the trunk, the hindquarters and the hindlimbs are dragged behind. The EMG activity of two hindlimb muscles, the tibialis anterior and soleus, recorded during hindlimb locomotor-like movement induced by tail pinching in spinal rats suspended over the treadmill indicated substantial abnormalities in burst duration of EMG activity. In spinal rats (Fig. 4A), unlike in intact rats (Fig. 4B), the activity between flexor and extensor muscle very often overlap and coupling between the activities of the muscles in the right and left hindlimbs is obtained. When sitting motionless, spinal rats keep their hindlimbs passively extended behind the body.

PARTIAL SPINAL CORD TRANSECTION

Following partial lesions of the spinal cord at the low thoracic level when a part of the white matter is spared, rats can regain quadrupedal walking after a period of recovery although with obvious deficits

correlated with the number of intact fibers remaining (Górska et al. 2007). The questions of which supraspinal structures are crucial and the amount of spared fibers that is sufficient for the recovery of hindquarters support and maintaining hindlimb locomotor movements have been addressed by numerous studies over the last decade. In general it has been shown that in rats (as in cats; see the previous chapter) the spinal white matter in ventral and ventrolateral parts seems to be more important than that contained in the dorsal part of the spinal cord (Grill et al. 1997, Loy et al. 2002a,b, Schucht et al. 2002). Dorsal hemisection at the low thoracic level (T7), which interrupted several motor pathways including the corticospinal, rubrospinal, coeruleospinal, and some raphespinal, vestibulospinal and propriospinal tracts did not affect overground locomotion when rats were tested 1 month after surgery (Grill et al. 1997). Similar results were obtained in rats after dorsal hemisection when tested 3 months after surgery (Metz et al. 2000a); out of 71 operated rats only 17 recovered partial body weight support [13–14 out of 21 scores in BBB scale that reflect locomotor functions (Basso et al. 1995)], while the rest attained high locomotor ability. More severe impairment of locomotion was observed by Hamers and others (2001) in rats following dorsal hemisection at T9. Soon after surgery, the rats showed only occasional weight-supported plantar stepping by the hindlimbs (BBB score of 10), but they recovered significantly within 28 days, reaching a score 13 on the BBB scale (frequent fore-hindlimb coordination).

Similar experiments were performed on adult rats with a dorsal lesion of different extents at the T8 spinal cord level (Kaegi et al. 2001). The day after surgery, rats with the most severe lesions could not walk while those with mild injury showed hindlimb plantar stepping with body weight support. Despite the fact that some of the rats had less than 30% of the white matter remaining at the site of the lesion, all regained hindlimb locomotor movements within 3 days and a gradual improvement in locomotor performance was observed up to 14 days after surgery when the experiment ended. A strong correlation between the quality of hindlimb locomotor movements and the amount of white matter spared was noted. The EMG activity of two hindlimb muscles, the tibialis anterior and vastus lateralis, recorded during the recovery period indicated substantial abnormalities in parameters such as the amplitude and duration of EMG activity, the activity overlap between flexor and extensor muscle, and coupling between the activities of the muscles in the right and left hindlimbs. Most of these measures returned to control levels after 14 days, but a prolonged flexor burst and an overlap between the activity of the flexor and extensor muscles were still present.

The strong correlation between the locomotor quality and the amount of spared white matter, and the substantial role of the ventrolateral funiculi in the recovery of locomotion in rats with dorsal lesions of different extents at the T9 level were also demonstrated by You and colleagues (2003). They showed that sparing of less than 5% of the white matter in the ventrolateral part of the spinal cord was enough to allow eventual restoration of hindlimb locomotor movements. Moreover, it has been demonstrated that bilateral demyelinating ventrolateral funiculus (VLF) or ventral column (VC) lesions at T9–11 had little impact on spontaneous overground locomotion, while joint lesion of VLF and VC or a lesion of greater extent induced severe locomotor deficits in the hindlimbs (Loy et al. 2002a). The pathways that are likely to be severed by this type of lesion include the reticulospinal, raphespinal, coeruleospinal, vestibulospinal and spinocerebellar tracts. It may be concluded that the pathways crucial for the initiation of locomotion are probably redundant within the ventral part of the spinal cord since the degree of locomotor impairment is proportional to the extent of damage to the ventral white matter. In the same experimental model it was shown that combined lesion of the myelinated fibers in the dorsal column (DC) and in the dorsal corticospinal tract (CST) and in VLF cause mild locomotor deficits, while lesion of these fibers in both the dorsolateral funiculus (DLF) and VLF produce more severe locomotor impairment (Loy et al. 2002b). Descending fibers that are likely to be damaged in part by VLF + DLF lesions include those in the corticospinal, rubrospinal, reticulospinal, vestibulospinal, coeruleospinal, raphespinal and propriospinal tracts. Separate destruction of most of these tracts does not cause deterioration of locomotor movements. These results raise the question of the importance of these individual pathways during locomotion. Nevertheless, since neither dorsal hemisection, VLF lesion nor VC lesion alone produced significant locomotor deficits it was concluded that a tract present in all of these parts of the spinal cord is likely to be responsible for the initiation of locomotion. Loy and coauthors (2002b) proposed that the reticulospinal

tract, which projects in the rat ventral columns, VLF, lateral columns and DLF, fulfils this function.

Similar results supporting a significant role for the reticulospinal tract in locomotion were obtained in experiments with partial spinal transection performed at the low thoracic level (T8) in rats (Schucht et al. 2002). In rats with dorsal or ventral lesions, the relationship between the spared spinal cord white matter and the outcome with respect to locomotion was examined. The results demonstrated the importance of fibers descending in the ventrolateral funiculus and the insignificance of fibers in the dorsal funiculus for overground locomotion. Sparing the entire dorsal funiculus was insufficient for hindlimb locomotion, but if a small amount of white matter in the ventral or lateral funiculus was also left intact this enabled initiation of locomotor movements. In the case of both dorsal and ventral lesions, there was a high level of correlation between the amount of spared white matter and the quality of locomotor movements. However, the correlation for the dorsal lesions was higher than for the ventral, indicating that ventral parts of the spinal cord have a stronger influence on open-field locomotion. In addition, after extensive dorsal lesions, rats recovered to perform rhythmic hindlimb movements without body weight support, while after ventral lesions with a much higher amount of white matter spared (entire dorsal columns) rats did not show any hindlimb movement. These results indicate the substantial role of fibers in dorsolateral, lateral and ventrolateral funiculi. Pathways within these funiculi include descending vestibulospinal fibers, serotonergic fibers from the raphe nucleus, noradrenergic fibers from the locus coeruleus, and glutamatergic fibers mainly from the nucleus reticularis gigantocerularis and the pontine reticular nucleus. These reticulospinal glutamatergic axons seem to be the most important for the initiation of locomotion and a small residual number of reticulospinal fibers reaching the lower spinal cord appear to be sufficient to initiate locomotor movements.

Although the use of the BBB scale indicated functional recovery there is a need for more precise tools to evaluate changes in the locomotor pattern following spinal cord lesion (Ballermann et al. 2006, Majczyński et al. 2007). In experiments in which rats with damage to the dorsal part of the spinal cord at T8 reach a plateau in their locomotor performance within 8 to 22 days depending on the severity of the lesion. The quality of locomotor performance showed strong correlation with the percent of spared white matter (Ballermann et al. 2006). Furthermore, more subtle changes in locomotor movements were observed in EMG activity and trajectory of hindlimbs even in rats that had recovered apparently normal locomotion. The most important changes were an increase in hindlimb extension during the stance phase leading to a more upright position, an increase in the EMG amplitude of the triceps brachii (a forelimb extensor) indicating compensation of the deficit in hindlimb propulsion, and an increase in the temporal separation between activity of the tibialis anterior and vastus lateralis muscles. These finding indicate that following recovery from spinal cord damage, the pattern of locomotor movement does not necessary follow that seen in intact animals.

Small lesions at the T8 level restricted to the corticospinal tract (CST) caused comparable effects to those restricted to the rubrospinal tract (RST). Rats showed plantar walking with weight support and frequent but inconsistent fore-hindlimb coordination corresponding to a BBB score of 13 (Muir and Whishaw 1999, 2000). However, the time-scale of recovery from these two types of lesion was significantly different. Animals with a CST lesion reached a plateau of locomotor recovery within one week, whereas those with an RST lesion recovered to the same level of locomotor performance after 7 weeks. Rats with a dorsal hemisection were most severely impaired and reached a plateau of locomotor performance 2 weeks after surgery with a score of 11 on the BBB scale (plantar stepping with no fore-hindlimb coordination). A unilateral pyramidal tract section evoked less severe locomotor impairment (Metz et al. 1998). On the first day after surgery, toe dragging and external rotation of the hindlimb contralateral to the lesion as well as trunk instability were observed. Rats recovered rapidly during the first postoperative week, but by day 28 some discrete movement impairment like hypermetria and trunk instability persisted.

CONTUSION AND COMPRESSION INJURIES

In addition to surgical methods of spinal cord injury that produce more or less specific lesions of particular ascending and descending connections it is important to use methods that will give lesions that are more comparable to those seen in human SCI patients. For several decades, contusion and compression injuries of

the spinal cord have been studied in rodents. These injuries are more reproducible than transection of the spinal cord and more akin to the majority of SCI seen in humans. The disadvantage of these methods is that selective disruption of particular spinal cord tracts is unlikely. Contusion and compression usually cause a central cavity surrounded by an outer rim of spared white matter (Metz et al. 2000b). Depending on the energy of the impact or the value of the pressure applied, different amounts of white matter are spared. At small contusion severities the pathological changes are mainly confined to the central gray matter and with increasing severity the damage progresses outward (Kloos et al. 2005). In small lesions of this type, dorsal fiber tracts including the corticospinal and propriospinal tracts are usually disrupted, while in larger lesions, the dorsal, lateral and ventral tracts are severely damaged. Dorsal white matter is usually more affected by contusion/compression lesions than the ventral white matter. Moreover, large diameter axons are more vulnerable than small diameter axons.

In most experiments in which the spinal cord was damaged at the low thoracic level (T8–T10) using contusion or compression there is a strong correlation between the percentage of spared white matter and the locomotor performance (Basso et al. 1995, 1996, Bresnahan et al. 1989, Cao et al. 2005, Collazos-Castro et al. 2006, Gruner et al. 1996, Kloos et al. 2005). In general, the relationship between locomotor performance, usually evaluated using the BBB scale, and the amount of spared white was linear (Basso et al. 1996, Cao et al. 2005, Collazos-Castro et al. 2006). Contrary to these results, another study in which locomotion in the open field was rated according to the 15 grade Ohio State motor scale found that the relationship between locomotor ability and the spared white matter area best fitted 2nd order polynominal regression plots (Gruner et al. 1996). Also, a large-scale study revealed that a progressive increase in lesion severity did not produce proportionate changes in the degree of locomotor impairment (Kloos et al. 2005). The best fit for the relationship between the percentage of spared white matter and the locomotor impairment evaluated by the BBB score was a curvilinear, fourth-order polynominal regression. At low levels of locomotor performance, small changes in the percentage of spared white matter were related to large increases in BBB scores; rats with less than 5% of spared fibers were unable to support body weight with their hindlimbs, while rats with 10% tissue spared could not only support weight but could also consistently perform locomotor movements. A gradual increase in the percentage of spared fibers was not related to a parallel improvement in motor performance; the locomotor ability as measured by the BBB scale was not significantly different between rats with 45 or 90% sparing of white matter (Basso et al. 1995). Similar results concerning the percentage of spared white matter and the hindlimb locomotor ability of rats were reported by Kloos and others (2005). Sparing of only 10% of the white matter was sufficient for recovery of consistent plantar stepping. Larger improvements, like fore-hindlimb coordination, normal trunk stability and toe clearance were observed in rats in which 25% of the white matter was saved. However, complete recovery of locomotor performance with precise positioning of the paws was only seen in rats with more than 90% sparing.

The investigation of contusion injuries has also confirmed the importance of ventral, ventrolateral and lateral funiculi in the recovery of locomotion. In the study of Cao and coauthors (2005) the most pronounced changes in locomotor performance were observed when the lateral and ventral funiculi were injured and the degree of locomotor ability as measured by the BBB score was dependent on the degree of white matter sparing. These authors claimed that the most likely candidate for promoting locomotor recovery is the reticulospinal tract diffusely distributed in the ventral and lateral funiculi. Kloos and colleagues (2005) also suggested that the reticulospinal tract is dominant in mediating the recovery of locomotion after spinal cord injury at the low thoracic level, especially when the impairment is more severe. They claimed that in mild lesions, which induce small impairment of locomotor movement like loss of fore-hindlimb coordination, centrally located corticospinal and propriospinal tracts are most likely to be extensively damaged. Moreover, the loss of locomotor abilities, such as precise paw position, after very small injuries may be due to damage to large diameter axons, which are more susceptible to injury than small diameter axons. Among these, the large axons belonging to the reticulospinal pathway seem to play a significant role in the observed rudimental locomotor impairment.

The role of propriospinal tracts, which are involved in information transmission between cervical and lumbar enlargements and from supraspinal locomotor centers to the lumbar CPG, in recovery of motor function

after thoracic spinal cord injury was highlighted by Cao and others (2005). These tracts may not be essential for locomotion in intact rats, but in the injured spinal cord they might at least partly compensate for impaired supraspinal projection to the lumbar spinal cord.

The widely held belief that the survival of a few residual axons is sufficient for the recovery of sustained locomotion is not far from truth. The minimal residual amount of spared white matter sufficient to maintain locomotor movement is relatively low, especially when it comprises the ventrolateral funiculi where the reticulospinal fibers controlling locomotion are located. The minimal sparing of white matter sufficient for stereotyped hindlimb movements was about 5% for rats (You et al. 2003), 10% for cats (Blight and DeCrescito 1986), 10% for humans (Kaelan et al. 1988, Kakulas 1999) and 25% for non-human primates (Eidelberg et al. 1981b). These values suggest that there is a similar relationship between spared white matter and the functional outcome of spinal cord injury in rats and humans. This was confirmed by Metz and others (2000a,b) who compared functional electrophysiological and morphological results of spinal cord injury in rats and humans. Due to these similarities between rats and humans in this respect, the results from studies on spinal injuries in rats may be of great use in understanding and devising treatment strategies for equivalent injuries in humans.

Changes in locomotion after spinal cord injury in humans

The progress in understanding the possibility for stimulation of the adaptive plasticity processes after spinal cord injury, based on research performed on cats and rats, allowed to develop the promising rehabilitative method for patients with spinal cord injury. Although, the existence of the CPG producing locomotor movements in humans is still not proved, the locomotor training is now successfully used in clinics. By definition a spinal pattern generator for walking should be capable of operating without input from the brain or the periphery (Grillner 1981). In 1988, Bussel and co-workers (Bussel et al. 1988) described a rhythmic spinal activity observed in a patient with a clinically complete spinal cord transection. Previously, the same group had produced indirect evidence of a spinal mechanism for the control of stepping movements in humans by demonstrating that flexor reflexes in paraplegic subjects have long-latency, late-flexion reflex responses (Roby-Brami and Bussel 1987). At present the growing body of evidence from patients, indicates the possibility of locomotor-like activity after SCI. For example, locomotor-like EMG activity, as well as complex bilateral muscle activation of the leg could be induced by epidural electrical stimulation of the posterior structures of the lumbar spinal cord in patients with complete paraplegia (Dietz et al. 1995, Dobkin et al. 1995, Dimitrijevic et al. 1998). Moreover, spontaneous involuntary rhythmic leg movements have been reported after both clinically complete (Holmes 1915, Kuhn 1950) and incomplete (Calancie et al. 1994) spinal cord injuries in humans. Finally, during the last two decades, it has been demonstrated that locomotor function in chronic incomplete SCI patients can be improved by manually assisted locomotor training on a treadmill or by a robotic device (Wernig et al. 1995, Wirz et al. 2001). As it was seen in spinal cats after locomotor training also in motor-incomplete SCI patients, daily training with body-weight-support on a treadmill often results in significant improvements in locomotor functions (Barbeau et al. 1999, Dietz et al. 1995, 1998, Dobkin et al. 1995, Wernig et al. 1995). Some forms of retrained walking may become possible not only on a treadmill but even outside the laboratory. However, no beneficial effects of training in chronic complete SCI patients were reported (Dietz and Harkema 2004, Dietz and Muller 2004). Positive effects of this therapy are most likely where the training starts early after SCI, is performed with some continuity over time and provides an appropriate afferent input (Dietz et al. 1995, 2002). Even, in acute SCI patients, positive training effects can usually be seen (Dietz et al. 1995). Such significant progress in the rehabilitation of patients after spinal cord injury raised the further question of whether locomotor skills developed with training on a treadmill depend on reactivation of normal motor patterns or whether they rely on learning new strategies for motor movement (Grasso et al. 2004). The positive effects of locomotor training cannot exclude the possibility that some neuronal plasticity could be achieved by other approaches. As it was suggested on the base of experiments performed on animal models (Wolpaw 2006) the recovery of locomotor functions can be achieved by: (1) plasticity in the spinal cord network itself; (2) supraspinal plasticity e.g. changes in descending connections to the spianal cord; and (3) neuromuscular changes involving alteration of the sensory inputs

and/or of the spinal cord output. There are strong indications that training using a treadmill and body-weight-support influences the motor patterns just by the peripheral sensory inputs (Dobkin et al. 1995, Harkema et al. 1997, Maegele et al. 2002, Wernig et al. 1995). However, there is evidence indicating that lost functions could be replaced in patients with severe lesions and they could be trained to walk by the use of new motor strategies (Grasso et al. 2004). Such new strategies might employ unusual forms of the phase-relationship in the angular motion of the various lower limb segments that are very different from controls. Although the pattern of muscle activity is different from the control, the new motor strategies developed by each individual patient are quite effective and generate foot motion closely resembling normal under laboratory conditions. These findings together with the fact that unsupported walking seldom, if ever, recovers in motor-complete SCI patients, question whether the pattern generator is important for the recovery of walking movements in humans (Yang and Gorassini 2006). Without doubt, the data on infants indicate that the neural networks for pattern generation are present in subcortical structures in humans and they behave in a similar way to the CPG in other mammals. Additionally, the sensory control of walking remains possible following clinically motor-complete SCI in human adults.

As described above, many studies have been carried out over recent decades with the aim of developing new rehabilitation strategies to assist the recovery of walking ability after CNS injury. In contrast to experiments performed on animal models, in most of studies carried out in clinics, subjects are described as motor-incomplete or -complete SCI patients and hardly any information about the site and extent of lesions is given. It is surprising that although anatomical correlation with functional abilities is the foundation of neurology, the necessary investigations have been seldom undertaken. One reason for this situation may be that patients with apparently the same lesion, judged by its site and extent, may show different motor defects (Nathan 1994) or may not recover in the same way. There is very limited data regarding the effect of selective lesions in man. However, there are some data described by Nathan (1994) who investigated motor deficits following selective lesion of the pyramidal tracts (cordotomy) performed for the relief of pain caused by cancer invading the peripheral nerves and nerves roots. The investigation was focused on motility that was assessed before and repeatedly after cordotomy. As noted previously, the pyramidal tract seems to play crucial role in the control of movement in humans, while its role is rather facultative in more primitive mammals during normal walking on a flat surface (see data from cats Armstrong 1988, Drew et al. 1996). The pyramidal tract plays a critical role only in modifications of gait in response to environmental motivational influences (Nielsen 2003). The patients described by Nathan (1994) with very large bilateral incisions dividing many descending tracts caudal to the cervical enlargement were unable to sit without support, stand or walk in an acute state. Recovery of motor functions following such an extensive incision, which divided most of the lateral cortical tract and a great many fibers in the lateral and anterior columns, was minimal. The patients were neither able to sit nor stand, although some movements of the lower limbs and some limited capacity for walking returned after 5 months. At the same time patients with large but unilateral incisions dividing most of the ipsilateral descending tracts demonstrated flaccid paralysis of the ipsilateral limbs, the degree of which was dependent on the extent of damage to the lateral cortical tract immediately after injury. Later, voluntary movements began to appear; thus the recovery from hemiplegia started within hours and by 18–21 days after the operation the patients could walk with a stick but with a typical hemiplegic gait. The most surprising conclusion from the study of Nathan (1994) is that the anterior half of the cord can be divided below the cervical enlargement without any disturbances to the motility of the trunk or lower limbs. However in individuals where the incisions extended further to the posterior, the defects in motility were markedly more severe than in cases in which incisions were larger but more to the anterior. It was concluded that the more posterior to the equatorial plane that the incision was located, the greater were the defects in motility and the more likely were patients to show spasticity and the reflex flexion synergy associated with paraparesis. These observations confirmed that in humans, the pyramidal tract does play a role in the control of walking, but as in the cat, there is redundancy so that other descending pathways may take over some control of locomotor movements in the absence of an intact pyramidal tract to ensure that the same tasks are performed in other ways (Nielsen 2003).

All of the observations described above indicate that the lumbosacral spinal cord in humans, completely deprived of brain motor control, has some capability to

generate locomotor-like activity. However, it seems that in contrast to animal models the pattern generator in humans is either not as important for walking or is not as easy to activate (Yang and Gorassini 2006). Moreover, the activity of this neural network depends much more on supraspinal influences than in lower animals. It is well known that the functional deficits following motor cortical lesion are rather limited in animals such as the cat and rat (Porter and Lemon 1993), while in humans, complete or nearly complete paralysis is regularly observed. This is probably due to the direct monosynaptic corticospinal pathway to spinal motoneurones found in both primates and humans. In addition, some reflexes that in cats are integrated at a spinal level, tend in humans to be mainly integrated at a supraspinal level and in this way become totally dependent on intact cortical transmission (Nielsen 2003). Due to the functional requirements of bipedal locomotion, this network and its reliance on supraspinal structures appear to have been highly modified. Nevertheless, the significant role of the spinal cord network in human locomotion has been confirmed in SCI patients, as has the usefulness of training on a treadmill in promoting the recovery of some locomotor ability in this group (Grasso et al. 2004).

CONCLUSIONS

Most knowledge concerning the mechanisms controlling locomotor movements has been obtained from a variety of animal models. Among the basic principles there is the existence of a spinal neuronal network producing the locomotor pattern (Central Pattern Generator) with considerable role of supraspinal structures and sensory inputs in the modification of CPG activity. This concept was confirmed in the rat, which has recently become a very popular model for studying the effects of spinal cord injury. Besides providing a better understanding of the mechanisms that govern the generation and maintenance of the locomotor pattern, the main goal of these animal experiments was to develop effective rehabilitation strategies for improving motor recovery in humans. Some of these rehabilitation methods such as locomotor training on a treadmill with body weight support appear to have been successful in improving the ability to walk in SCI patients. The over one hundred years of experiments using animal models and the data from SCI patients suggest that to see positive effects of new rehabilitative technique the three categories of plasticity should be employed: primary plasticity that supports the new strategy of walking behavior, compensatory plasticity that restores old behavior, and reactive plasticity that integrate the changes in activity due to primary and compensatory plasticity. It was also established that the spinal cord plasticity responsible for the training-induced functional improvement is critically dependent on afferent, efferent and interneuronal activity that occur during training. Moreover, recent work provided indications that a certain minimum level of appropriately timed sensory input is essential (Rossignol and Bouyer 2004). Hopefully further works in near future will defined which and how the various type of plasticity processes can be initiated and modulated in aim to restore (preserve) the complete repertoire of motor behavior in SCI patients

ACKNOWLEDGEMENTS

The paper was supported from Polish Ministry of Science and Higher Education by grant no. 2 P05A 092 27 and statutory grant to Nencki Institute.

REFERENCES

Afelt Z (1974) Functional significance of ventral descending tracts of the spinal cord in the cat. Acta Neurobiol Exp (Wars) 34: 393–407.

Andre-Thomas, Autgarden S (1966) Locomotion from pre- to postnatal life: how the newborn begins to acquire psychosensory functions. In: Clinics in Developmental Medicine, Vol. 24. Spastics Society Medical Education and Information Unit in association with W. Heinemann Medical Books, Lavenham Press, Lavenham (UK), p. 1–21.

Angel MJ, Jankowska E, McCrea DA (2005) Candidate interneurones mediating group I disynaptic EPSPs in extensor motoneurones during fictive locomotion in the cat. J Physiol 563: 597–610.

Armstrong DM (1978) The mammalian cerebellum and its contribution to movement control. In: International Review of Physiology. Neurophysiology III, Vol. 17 (Porter R, ed.). University Park, Baltimore, MD, p. 239–294.

Armstrong DM (1988) The supraspinal control of mammalian locomotion J Physiol 405: 1–37.

Armstrong DM, Apps R, Marple-Horvat DE (1997) Aspects of cerebellar function in relation to locomotor movements. In: Progress in Brain Research. The Cerebellum: From Structure to Control, Vol. 114 (De Zeeuw CI, Strata P, Voogd J, eds). Elsevier, Amsterdam, p. 401–421.

Arshavsky YI, Gelfand IM, Orlovsky GN (1986) Cerebellum and Rhythmical Movements. Springer-Verlag, Berlin.

Ballermann M, Tse ADY, Misiaszek JE, Fouad K (2006) Adaptation in the walking pattern of spinal cord injured rats. J Neurotrauma 23: 897–907.

Barbeau H, Rossignol S (1987) Recovery of locomotion after chronic spinalization in the adult cat. Brain Res 412: 84–95.

Barbeau H, Rossignol S (1991) Initiation and modulation of the locomotor pattern in the adult chronic spinal cat by noradrenergic, serotonergic and dopaminergic drugs. Brain Res 546: 250–260.

Barbeau H, Chau C, Rossignol S (1993) Noradrenergic agonists and locomotor training affect locomotor recovery after spinal cord transection in adult cats. Brain Res Bull 30: 387–393.

Barbeau H, McCrea DA, O'Donovan MJ, Rossignol S, Grill WM, Lemay MA (1999) Tapping into spinal circuits to restore motor function. Brain Res Rev 30: 27–51.

Basso DM, Beattie MS, Bresnahan JC (1995) A sensitive and reliable locomotor rating scale for open field testing in rats. J Neurotrauma 12: 1–21.

Basso DM, Beattie MS, Bresnahan JC (1996) Graded histological and locomotor outcomes after spinal cord contusion using the NYU weight-drop device versus transection. Exp Neurol 139: 244–256.

Belanger M., Drew T, Provencher J, Rossignol S (1996) A comparison of treadmill locomotion in adult cats before and after spinal transection. J Neurophysiol 76: 471–491.

Beloozerova IN, Sirota MG (1993) The role of the motor cortex in the control of accuracy of locomotor movements in the cat. J Physiol 461: 1–25.

Bem T, Górska T, Majczyński H, Zmysłowski W (1995) Different patterns of fore-hindlimb coordination during overground locomotion in cats with ventral and lateral spinal lesions. Exp Brain Res 104: 70–80.

Berger W, Altenmueller E, Dietz V (1984) Normal and impaired development of children's gait. Hum Neurobiol 3: 163–170.

Blight AR, DeCrescito V (1986) Morphometric analysis of experimental spinal cord injury in the cat: the relation of injury intensity to survival of myelinated axons. Neuroscience 19: 321–341.

Bresnahan JC, Beattie MS, Todd III FD, Noyes DH (1989) A behavioral and anatomical analysis of spinal cord injury produced by a feedback-controlled impaction device. Exp Neurol 95: 548–570.

Brown TG (1911) The intrinsic factors in the act of progression in the mammal. Proc R Soc Lond B Biol Sci 84: 308–319.

Brown TG (1912) The factors in rhythmic activity of the nervous system. Proc R Soc Lond B Biol Sci 85: 278–289.

Brustein E, Rossignol S (1998) Recovery of locomotion after ventral and ventrolateral spinal lesions in the cat. I. Deficits and adaptive mechanisms. J Neurophysiol 80: 1245–1267.

Bussel B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A, Held JP (1988) Myoclonus in a patient with spinal cord transection. Possible involvement of the spinal stepping generator. Brain 111: 1235–1245.

Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zyg G, Green BA (1994) Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. Brain 117: 1143–1149.

Cao Q, Zhang YP, Innoatti C, deVries D, Xu XM, Shields CB, Whittemore SR (2005) Functional and electrophysiological changes after graded traumatic spinal cord injury in adult rats. Exp Neurol 191: S3–S16.

Cazalets JR, Sqalli-Houssaini Y, Clarac F (1992) Activation of the central pattern generators for locomotion by serotonin and excitatory amino acids in neonatal rat. J Physiol 455: 187–204.

Cazalets JR, Borde M, Clarac F (1995) Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. J Neurosci 15: 4943–4951.

Celichowski J, Mrówczyński W, Krutki P, Górska T, Majczyński H, Sławińska U (2006) Changes in contractile properties of motor units of the rat medial gastrocnemius muscle after spinal cord transection. Exp Physiol 91: 887–895.

Chau C, Giroux N, Barbeau H, Jordan L, Rossignol S (2002) Effects of intrathecal glutamatergic drugs on locomotion. Part I. NMDA in short-term spinal cats. J Neurophysiol 88: 3032–3045.

Coggeshall RE, Coulter JD, Willis WD Jr (1997) Unmyelinated fibers in the ventral root. Brain Res 57: 229–233.

Collazos-Castro JE, Lopez-Dolado E, Nieto-Sampedro M (2006) Locomotor deficits and adaptive mechanisms after thoracic spinal cord contusion in the adult rat. J Neurotrauma 23: 1–17.

Cowley KC, Schmidt BJ (1995) Effects of inhibitory amino acid antagonists on reciprocal inhibitory interactions during rhythmic motor activity in the in vitro neonatal rat. J Neurophysiol 74: 1109–1117.

deLeon RD, Hodgson JA, Roy RR, Edgerton VR (1998a) Locomotor capacity attributable to step training versus spontaneous recovery following spinalization in adult cats. J Neurophysiol 79: 1329–1340.

deLeon RD, Hodgson JA, Roy RR, Edgerton VR (1998b) Full weight-bearing hindlimb standing following stand training in the adult spinal cat. J Neurophysiol 80: 83–91.

deLeon RD, Hodgson JA, Roy RR, Edgerton VR (1999) Retention of hindlimb stepping ability in adult spinal cats after the cessation of step training. J Neurophysiol 81: 85–94.

deVries JIP, Visser GHA, Prechtl HFR (1982) The emergence of fetal behavior. I. Qualitative aspects. Early Hum Dev 7: 301–322.

Dietz V (2003) Spinal cord pattern generators for locomotion. Clinical Neurophysiol 114: 1379–1383.

Dietz V, Harkema S (2004) Locomotor activity in spinal cord-injured persons. J Appl Physiol 96: 1954–1960.

Dietz V, Müller R (2004) Degradation of neuronal function following a spinal cord injury: mechanisms and countermeasures. Brain 127: 2221–2231.

Dietz V, Colombo G, Jensen L (1994) Locomotor activity in spinal man. Lancet 344: 1260–1263.

Dietz V, Colombo G, Jensen L, Baumgartner L (1995) Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol 37: 574–582.

Dietz V, Wirz M, Curt A, Colombo G (1998) Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function. Spinal Cord 36: 380–390.

Dietz V, Müller R, Colombo G (2002) Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain 125: 2626–2634.

Dimitrijevic MR, Gerasimenko Y, Pinter MM (1998) Evidence for a spinal central pattern generator in humans. Ann N Y Acad Sci 860: 360–376.

Dobkin BH, Harkema S, Requejo P, Edgerton VR (1995) Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. J Neurol Rehabil 9: 183–190.

Douglas JR, Noga BR, Dai X, Jordan LM (1993) The effects of intrathecal administration of excitatory amino acid agonists and antagonists on the initiation of locomotion in adult cats. J Neurosci 13: 990–1000.

Drew T, Jiang W, Kably B, Lavoie S (1996) Role of the motor cortex in the control of visually triggered gait modifications. Can J Physiol Pharmacol 74: 426–442.

Drew T, Jiang W, Widajewicz W (2002) Contributions of the motor cortex to the control of the hindlimbs during locomotion in the cat. Brain Res Rev 40: 178–191.

Duysens J, Pearson KG (1980) Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. Brain Res 187: 321–332.

Duysens J, Van de Crommert HW (1998) Neural control of locomotion; The central pattern generator from cats to humans. Gait Posture 7: 131–141.

Edgerton VR, deLeon RD, Harkema SJ, Hodgson JA, London N, Reinkensmeyer DJ, Roy RR, Talmadge RJ, Tillakaratne NJ, Timoszyk W, Tobin A (2001) Retraining the injured spinal cord. J Physiol 533: 15–22.

Eidelberg E (1981) Consequences of spinal cord lesions upon motor function with special reference to locomotor activity. Prog Neurobiol 17: 185–202.

Eidelberg E, Story JL, Walden JG, Meyer BL (1981a) Anatomical correlates of return of locomotor function after partial spinal cord lesions in cats. Exp Brain Res 42: 81–88.

Eidelberg E, Walden JG, Nguyen LH (1981b) Locomotor control in macaque monkeys. Brain 104: 647–663.

English AW (1980) Interlimb coordination during stepping in the cat: effects of dorsal column section. J Neurophysiol 44: 270–279.

English AW (1985) Interlimb coordination during stepping in the cat. The role of the dorsal spinocerebellar tract. Exp Neurol 87: 96–108.

English AW (1989) Interlimb coordination during locomotion. Am Zool 29: 255–266.

English AW, Lennard PR (1982) Interlimb coordination during stepping in the cat: in-phase stepping and gait transitions. Brain Res 245: 353–364.

English AW, Tigges J, Lennard PR (1985) Anatomic organization of long ascending propriospinal neurons in the cat spinal cord. J Comp Neurol 240: 349–358.

Fedirchuk B, Nielsen J, Petersen N, Hultborn H (1998) Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset monkey (Callithrix jacchus). Exp Brain Res 122: 351–361.

Feraboli-Lohnherr D, Orsal D, Yakovleff A, Gimenez-Ribota M, Privat A (1997) Recovery of locomotor activity in the adult chronic spinal rat after sublesional transplantation of embryonic nervous cells: specific role of serotonergic neurones. Exp Brain Res 113: 443–454.

Feraboli-Lohnherr D, Barthe JY, Orsal D (1999) Serotonin-induced activation of the network for locomotion in adult spinal rats. J Neurosci Res 55: 87–98.

Forssberg H (1985) Ontogeny of human locomotor control I. Infant stepping, supported locomotion and transition to independent locomotion. Exp Brain Res 57: 480–493.

Forssberg H, Grillner S (1973) The locomotion of the acute spinal cat injected with clonidine i.v. Brain Res 50: 184–186.

Forssberg H, Grillner S, Rossignol S (1975) Phase dependent reflex reversal during walking in chronic spinal cats. Brain Res 85: 103–107.

Fouad K, Pearson K (2004) Restoring walking after spinal cord injury. Prog Neurobiol 73: 107–126.

Frigon A, Rossignol S (2006) Functional plasticity following spinal cord lesions. Prog Brain Res 157: 231–260.

Gimenez-Ribota MG, Provencher J, Feraboli-Lohnherr D, Rossignol S, Privat A, Orsal D (2000) Activation of locomotion in adult chronic spinal rats is achieved by transplantation of embryonic raphe cells reinnervating a precise lumbar level. J Neurosci 20: 5144–5152.

Górska T, Bem T, Majczyński H (1990) Locomotion in cats with ventral spinal lesions: support patterns and duration of support phases during unrestrained walking. Acta Neurobiol Exp (Wars) 50: 191–200.

Górska T, Bem T, Majczyński H, Zmysłowski W (1993a) Unrestrained walking in intact cats. Brain Res Bull 32: 235–240.

Górska T, Bem T, Majczyński H, Zmysłowski W (1993b) Unrestrained walking in cats with partial spinal lesions. Brain Res Bull 32: 241–249.

Górska T, Majczyński H, Bem T, Zmysłowski W (1993c) Hindlimb swing, stance and step relationships during unrestrained walking in cats with lateral funicular lesion. Acta Neurobiol Exp (Wars) 53: 133–142.

Górska T, Ioffe M, Zmysłowski W, Bem T, Majczyński H, Mats VN (1995) Unrestrained walking in cats with medial pontine reticular lesions. Brain Res Bull 38: 297–304.

Górska T, Bem T, Majczyński H, Zmysłowski W (1996) Different forms of impairment of the fore-hindlimb coordination after partial spinal lesions in cats. Acta Neurobiol Exp (Wars) 56: 177–188.

Górska T, Chojnicka-Gittins B, Majczyński H, Zmysłowski W (2007) Overground locomotion after incomplete spinal lesions in the rat: Quantitative gait analysis. J Neurotrauma 24: 1198–1218.

Grasso R., Ivanenko YP Zago M, Molinari M, Scivoletto G, Castellano V, Macellari V, Lacquaniti1 F (2004) Distributed plasticity of locomotor pattern generators in spinal cord injured patients. Brain 127: 1019–1034.

Graybiel AM (1995) Building action repertoires: memory and learning functions of the basal ganglia. Curr Opin Neurobiol 5: 733–741.

Grill R, Murai K, Blesch A, Gage FH, Tuszynski MH (1997) Cellular delivery of Neurotrophin-3 promotes corticospinal axonal growth and partial functional recovery after spinal cord injury. J Neurosci 17: 5560–5572.

Grillner S (1975) Locomotion in vertebrates: Central mechanisms and reflex interaction. Physiol Rev 55: 247–304.

Grillner S (1981) Control of locomotion in bipeds, tetrapods, and fish. In: Handbook of Physiology. The Nervous System II (Brookhart JM, Mountcastle VB, eds). Am Physiol Soc, Bethesda, p. 1179–1236.

Grillner S (1985) Neurobiological bases of rhythmic motor acts in vertebrates. Science 228: 143–149.

Grillner S, Rossignol S (1978) On the initiation of the swing phase of locomotion in chronic spinal cats. Brain Res 146: 269–277.

Grillner S, Zangger P (1975) How detailed is the central pattern generation for locomotion? Brain Res 88: 367–371.

Grillner S, Zangger P (1984) The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. Acta Physiol Scand 120: 393–405.

Gruner JA, Yee AK, Blight AR (1996) Histological and functional evaluation of experimental spinal cord injury: evidence of stepwise response to graded compression. Brain Res 729: 90–101.

Guertin P, Angel MJ, Perreault MC, McCrea DA (1995) Ankle extensor group I afferents excite extensors throughout the hindlimb during fictive locomotion in the cat. J Physiol 487: 197–209.

Hamers FP, Lankhorst AJ, van Laar TJ, Veldhuis WB, Gispen WH (2001) Automated quantitative gait analysis during overground locomotion in the rat: its application to spinal contusion and transection injuries. J Neurotrauma 18: 187–201.

Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR (1997) Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol 77: 797–811.

Holmes G (1915) Spinal injuries of warfare: II. The clinical symptoms of gunshot injuries of the spine. Br Med J 2: 815–821.

Holstege JC, Kuypers HG (1982) The anatomy of brain stem pathways to the spinal cord in cat. A labeled amino acid tracing study. Prog Brain Res 57: 145–175.

Holstege JC, Kuypers HG (1987) Brainstem projections to spinal motoneurons: an update. Neuroscience 23: 809–821.

Hultborn H, Conway BA, Gossard J-P, Brownstone R, Fedirchuk B, Schomburg ED, Enriquez-Denton M, Perreault M-C (1998) How do we approach the locomotor network in the mammalian spinal cord? Ann N Y Acad Sci 860: 70–82.

Jankowska E, Jukes MG, Lund S, Lundberg A (1967a) The effect of DOPA on the spinal cord. 5. Reciprocal organization of pathways transmitting excitatory action to alpha motoneurones of flexors and extensors. Acta Physiol Scand 70: 369–388.

Jankowska E, Jukes MG, Lund S, Lundberg A (1967b) The effect of DOPA on the spinal cord. 6. Half-centre organization of interneurones transmitting effects from the flexor reflex afferents. Acta Physiol Scand 70: 389–402.

Jiang W, Drew T (1996) Effects of bilateral lesions of the dorsolateral funiculi and dorsal columns at the level of the low thoracic spinal cord on the control of locomotion in the adult cat: I. Treadmill walking. J Neurophysiol 76: 849–866.

Kaegi S, Schwab ME, Dietz V, Fouad K (2001) Electromyographic activity associated with spontaneous functional recovery after spinal cord injury in rats. Eur J Neurosci 16: 249–258.

Kaelan C, Jacobsen PF, Kakulas BA (1988) An investigation of possible transynaptic neuronal degeneration in human spinal cord injury. J Neurol Sci 86: 231–237.

Kakulas BA (1999) The applied neuropathology of human spinal cord injury. Spinal Cord 37: 79–88.

Kiehn O, Iizuka M, Kudo N (1992) Resetting from low threshold afferents of N-methyl-D-aspartate-induced locomotor rhythm in the isolated spinal cord-hindlimb preparation from newborn rats. Neurosci Lett 148: 43–46.

Kjaerulff O, Kiehn O (1996) Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. J Neurosci 16: 5777–5794.

Kloos AD, Fisher LC, Detloff MR, Hassenzahl DL, Basso DM (2005) Stepwise motor and all-or-none sensory recovery is associated with nonlinear sparing after incremental spinal cord injury in rats. Exp Neurol 191: 251–265.

Kriellars DJ, Brownstone RM, Noga BR, Jordan LM (1994) Mechanical entrainment of fictive locomotion in the decerebrate cat. J Neurophysiol 71: 2074–2086.

Kuhn RA (1950) Functional capacity of the isolated human spinal cord. Brain 73: 1–51.

Kuypers HGJM (1963) The organization of the 'motor system'. Int J Neurol 4: 78–91.

Kuypers HGJM (1981) Anatomy of descending pathways. In: Handbook of Physiology. The Nervous System II (Brookhart JM, Mountcastle VB, eds). Am Physiol Soc, Bethesda, p. 597–665.

LaBella LA, Niechaj A, Rossignol S (1992) Low-threshold, short-latency cutaneous reflexes during fictive locomotion in the "semi-chronic" spinal cat. Exp Brain Res 91: 236–248.

Lafreniere-Roula M, McCrea DA (2005) Deletions of rhythmic motoneuron activity during fictive locomotion and scratch provide clues to the organization of the mammalian central pattern generator. J Neurophysiol 94: 1120–1132.

Lansner A, Ekeberg O (1994) Neuronal network of motor generations and control. Curr Opin Neurobiol 4: 903–908.

Loeb GE (1976) Ventral root projections of myelinated dorsal root ganglion cells in the cat. Brain Res 106: 159–165.

Loy NL, Magnuson DSK, Zhang YP, Onifer SM, Mills MD, Cao QL, Darnall JB. Fajardo CL Burke DA, Whittemore SR (2002a) Functional redundancy of ventral spinal locomotor pathways. J Neurosci 22: 315–323.

Loy NL, Talbott JF, Onifer SM, Mills MD, Burke DA, Dennison JB, Fajardo CL, Magnuson DSK, Whittemore SR (2002b) Both dorsal and ventral spinal cord pathways contribute to overground locomotion in the adult rat. Exp Neurol 177: 575–580.

Lundberg A (1979) Multisensory control of spinal reflex pathways. In: Reflex Control of Posture and Movement (Granit R, Pompeiano O, eds). Prog Brain Res 50: 11–28.

MacKay-Lyons M (2002) Central pattern generation of locomotion: a review of the evidence. Phys Ther 82: 69–83.

Maegele M, Muller S, Wernig A, Edgerton VR, Harkema SJ (2002) Recruitment of spinal motor pools during voluntary movements versus stepping after human spinal cord injury. J Neurotrauma 19: 1217–1229.

Majczyński H, Cabaj A, Górska T (2005a) Intrathecal application of cyproheptadine impairs locomotion in intact rats. Neurosci Lett 381: 16–20.

Majczyński H, Maleszak K, Cabaj A, Sławińska U (2005b) Serotonin-related enhancement of recovery of hindlimb motor functions in spinal rats after grafting of embryonic raphe nuclei. J Neurotrauma 22: 590–604.

Majczyński H, Cabaj A, Sławińska U, Górska T (2006) Intrathecal administration of yohimbine impairs locomotion in intact rats. Behav Brain Res 175: 315–322.

Majczyński H, Maleszak K, Górska T, Sławińska U (2007) Comparison of two methods used for quantitative assessment of locomotion in the rat. J Neurosci Methods 163: 197–207.

Marder E, Bucher D (2001) Central pattern generators and the control of rhythmic movements Curr Biol 11: 986–996.

Martin CD, Obeso JA (1994) Inaccuracy and instability of sequential movements in Parkinson's disease. Exp Brain Res 102: 131–140.

McCrea DA (2001) Spinal circuitry of sensorimotor control of locomotion. J Physiol 533: 41–50.

Metz GA, Dietz V, Schwab ME, Van de Meent H (1998) The effects of unilateral pyramidal tract section on hindlimb motor performance in the rat. Behav Brain Res 96: 37–46.

Metz GA, Merkel D, Dietz V, Schwab ME, Foaud K (2000a) Efficient testing of motor function in spinal cord injured rats. Brain Res 883: 165–177.

Metz GA, Curt A, van de Meent H, Klusman I, Schwab ME, Dietz V (2000b) Validation of the weight-drop contusion model in rats: a comparative study of human spinal cord injury. J Neurotrauma 17: 1–17.

Mori S (1987) Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. Prog Neurobiol 28: 161–195.

Mori S, Matsuyama K, Kohyama J, Kobayashi Y, Takakusaki K (1992) Neuronal constituents of postural and locomotor control systems and their interactions in cats. Brain Dev 14 (Suppl.) S109–S120.

Mori S, Toshihiro M, Bunya K, Mitsuru A, Katsumi N, Kiyoji M (1999) Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J Neurophysiol 82: 290–300.

Muir GD, Whishaw IQ (1999) Complete locomotor recovery following corticospinal tract lesions: measurement of ground reaction forces during overground locomotion in rats. Behav Brain Res 103: 45-53.

Muir GD, Whishaw IQ (2000) Red nucleus lesions impair overground locomotion in rats: a kinetic analysis. Eur J Neurosci 12: 1113-1122.

Nathan PW (1994) Effects on movement of surgical incisions into the human spinal cord. Brain 117: 337–346.

Nielsen JB (2003) How we walk: central control of muscle activity during human walking. Neuroscientist 9: 195–204.

Orlovsky GN (1969) Spontaneous and induced locomotion of the thalamic cat. Biophysics 14: 1154–1162.

Orlovsky GN (1991) Cerebellum and locomotion. In: Neurobiological Basis of Human Locomotion (Shimamaura M, Grillner S, Edgerton VR, eds). Japan Scientific Societies Press, Tokyo, Japan, p. 187–199.

Pearson KG (1993) Common principles of motor control in vertebrates and invertebrates. Annu Rev Neurosci 16: 265–297.

Pearson KG (2004) Generating the walking gait: role of sensory feedback. Prog Brain Res 143: 123–128.

Philippson M (1905) Autonomy and centralization of nervous system in animals (in French). Trav Lab Physiol Inst Solvay (Brussels) 7: 1–208.

Porter R, Lemon R (1993) Corticospinal Function and Voluntary Movement. Monographs of the Physiological Society, No. 45. Oxford University Press, New York.

Rémy-Néris O, Barbeau H, Daniel O, Boiteau F, Bussel B (1999) Effects of intrathecal clonidine injection on spinal reflexes and human locomotion in incomplete paraplegic subjects. Exp Brain Res 129: 433–440.

Roby-Brami A, Bussel B (1987) Long latency spinal reflex in man after flexor reflex afferent stimulation. Brain 110: 707–725.

Rossignol S (1996) Neural control of stereotypic limb movements. In: Handbook of Physiology, Section 12, Exercise: Regulation and Integration of Multiple Systems (Rowell LB, Sheperd JT, eds). Oxford University Press, New York, p. 173–216.

Rossignol S, Bouyer L (2004) Adaptive mechanisms of spinal locomotion in cats. Integr Comp Biol 44: 71–79.

Rossignol S, Saltiel P, Perreault MC, Drew T, Pearson KG, Belanger M (1993) Intralimb and interlimb coordination in the cat during real and fictive rhythmic motor programs. Semin Neurosci 5: 67–75.

Rossignol S, Chau C, Brustein E, Belanger M, Barbeau H, Drew T (1996) Locomotor capacities after complete and partial lesions of the spinal cord. Acta Neurobiol Exp (Wars) 56: 449–463.

Rossignol S, Drew T, Brustein E, Jiang W (1999) Locomotor performance and adaptation after partial or complete spinal cord lesions in the cat. Prog Brain Res 123: 349–365.

Rossignol S, Giroux N, Chau C, Marcoux J, Brustein E, Reader TA (2001) Pharmacological aids to locomotor training after spinal injury in the cat. J Physiol 533: 65–74.

Rossignol S, Bouyer L, Barthelemy D, Langlet C, Leblond H (2002) Recovery of locomotion in the cat following spinal cord lesions. Brain Res Rev 40: 257–266.

Rossignol S, Dubuc R, Gossard JP (2006) Dynamic sensorimotor interactions in locomotion. Physiol Rev 86: 89-154

Rybak IA, Shevtsova NA, Lafreniere-Roula M, McMcrea DA (2006a) Modelling spinal circuitry involved in locomotor pattern generation: insights from deletions during fictive locomotion. J Physiol 577: 617–639.

Rybak IA, Stecina K, Shevtsova NA, McMcrea DA (2006b) Modelling spinal circuitry involved in locomotor pattern generation: insights from effects of afferent stimulation. J Physiol 577: 641–658.

Schucht P, Raineteau O, Schwab ME, Fouad K (2002) Anatomical correlates of locomotor recovery following dorsal and ventral lesions of the rat spinal cord. Exp Neurol 176: 143–153.

Shik ML, Orlovsky GN (1976) Neurophysiology of locomotor automatism. Physiol Rev 55: 465–501.

Sherrington CS (1910) Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 40: 28–121.

Sławińska U, Majczyński H, Djavadian R (2000) Recovery of hindlimb motor functions after spinal cord transection is enhanced by grafts of the embryonic raphe nuclei. Exp Brain Res 132: 27–38.

Stecina K, Quevedo J, McCrea DA (2005) Parallel reflex pathways from flexor muscle afferents evoking resetting and flexion enhacement during fictive locomotion and scratch in the cat. J Physiol 569: 275–290.

Stewart JE, Barbeau H, Gauthier S (1991) The effects of clonidine in the modulation of the locomotor pattern and spasticity in spinal cord injured patients: a preliminary study. Can J Neurol Sci 18: 321–333.

Vilensky JA, O'Connor BL (1997) Stepping in humans with complete spinal cord transection: a phylogenetic evaluation. Mot Cont 1: 284–292.

Vilensky JA, Moore AM, Eidelberg E, Walden JG (1992) Recovery of locomotion in monkeys with spinal cord lesions. J Mot Behav 24: 288–296.

Webb AA, Muir GD (2004) Course of motor recovery following ventrolateral spinal cord injury in the rat. Behav Brain Res 155: 55–65.

Wernig A, Muller S (1992) Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia 30: 229–238.

Wernig A, Muller S, Nanassy A, Cagol E (1995) Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons. Eur J Neurosci 7: 823–829.

Wetzel MC, Stuart DG (1976) Ensemble characteristics of cat locomotion and its neural control. Prog Neurobiol 7: 1–98.

Whelan PJ (1996) Control of locomotion in the decerebrate cat. Prog Neurobiol 49: 481–515.

Whelan PJ, Hiebert GW, Pearson KG (1995) Stimulation of the group I extensor afferents prolongs the stance phase in walking cats. Exp Brain Res 103: 20–30.

Wichmann T, deLong MR (1996) Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 6: 417–422.

Wirz M, Colombo G, Dietz V (2001) Long term effects of locomotor training in spinal humans. J Neurol Neurosurg Psychiatry 71: 93–96.

Wolpaw JR (2006) The education and re-education of the spinal cord. Prog Brain Res 157: 261–279.

Yakovenko S, McCrea DA, Stecina K, Prochazka A (2005) Control of locomotor cycle durations. J Neurophysiol 94: 1057–1065.

Yang JF, Gorassini M (2006) Spinal and brain control of human walking: implications for retraining of walking. Neuroscientist 12: 379–389.

Yang JF, Stephens MJ, Vishram R (1998) Infant stepping: a method to study the sensory control of human walking. J Physiol 507: 927–937.

Yang JF, Lam T, Pang MYC, Lamont E, Musselman K, Seinen E (2004) Infant stepping: a window to the behaviour of the human pattern generator for walking. Can J Physiol Pharmacol 82: 662–674.

You SW, Chen BY, Liu HL, Lang B, Xia JL, Jiao XY, Ju G (2003) Spontaneous recovery of locomotion induced by remaining fibers after spinal cord transection in adult rats. Restor Neurol Neurosci 21: 38–45.

Zmysłowski W, Górska T, Majczyński H., Bem T (1993) Hindlimb muscle activity during unrestrained walking in cats with lesions of the lateral funiculi. Acta Neurobiol Exp (Wars) 53: 143–153.

Received 17 May 2007, accepted 26 July 2007