Invited review

Spinal cord pattern generators for locomotion

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Accepted 2 April 2003

Abstract

It is generally accepted that locomotion in mammals, including humans, is based on the activity of neuronal circuits within the spinal cord (the central pattern generator, CPG). Afferent information from the periphery (i.e. the limbs) influences the central pattern and, conversely, the CPG selects appropriate afferent information according to the external requirement. Both the CPG and the reflexes that mediate afferent input to the spinal cord are under the control of the brainstem. There is increasing evidence that in central motor diseases, a defective utilization of afferent input, in combination with secondary compensatory processes, is involved in typical movement disorders, such as spasticity and Parkinson’s disease. Recent studies indicate a plastic behavior of the spinal neuronal circuits following a central motor lesion. This has implications for any rehabilitative therapy that should be directed to take advantage of the plasticity of the central nervous system. The significance of this research is in a better understanding of the pathophysiology underlying movement disorders and the consequences for an appropriate treatment.

Keywords: Locomotion; Pattern generator; Spinal cord; Movement disorder; Parkinson’s disease; Spasticity

1. Introduction

Locomotion in mammals is largely dependent upon the central pattern generator (CPG); that is to say, neuronal circuits (networks of interneurons) within the spinal cord. The CPG is defined as a neural circuit that can produce self-sustained patterns of behavior, independent of sensory input (Grillner, 1986). The understanding of basic principles of CPG function is based on research in invertebrates and primitive fish like the lamprey (Grillner et al., 2001; for reviews, see Grillner, 1981, 1985; Marder, 1998). There is nothing comparable to mammals, especially human beings, where our understanding is only based on indirect evidence.

According to observations made during the last years, bipedal and quadrupedal locomotion share some common spinal neuronal control mechanisms. As in quadrupeds, long projecting proprio spinal neurons couple the cervical and lumbar enlargements in humans (Nathan et al., 1996). Furthermore, the co-ordination of limb movements during walking is similar in human infants (Yang et al., 1998; Pang and Yang, 2000) and adults (Dietz, 1992, 1997) as described for quadrupeds (Grillner, 1981, 1986). Nevertheless, there are also distinct differences because the upper limbs in primates have become specialised to perform skilled hand movements. The evolution of upright stance and gait, in association with a differentiation of hand movements, represent a basic requirement for human cultural development (Herder, 1785).

Pattern generation is basically innate. In humans, step-like movements are present at birth; they are spontaneously initiated or triggered by peripheral stimuli. A central origin of these movements is implied, as an electromyographic (EMG) burst preceding the actual mechanical events (Forssberg, 1986). Infant stepping also occurs in unencephalic children (Forssberg, 1986), which suggests that a spinal mechanism coordinates these movements. Central programming can be influenced by sensory input (Brooks, 1979). This again is illustrated by infant-stepping. Although rhythmic alternating leg movements are coordinated by a CPG, the infant is unable to maintain body equilibrium. These children lack an integration of the appropriate afferent input into the programmed leg muscle electromyographic (EMG) pattern, which is needed to achieve modulation and adaptation to the actual needs.

Afferent information influences the central (spinal)
pattern and, conversely, the CPG selects the appropriate afferent information according to the external requirements (Grillner, 1986; McCrea, 2001; Van de Crommert et al., 1998). Both the spinal locomotor center and the reflexes that mediate afferent input to the spinal cord are under the control of the brainstem (Jankowska and Lundberg, 1981).

In addition, there is a cortico-spinal control of locomotion in humans (Capaday et al., 1999; Schubert et al., 1996) and in the cat (Drew, 1996; Leblond et al., 2001). Voluntary commands have to interact with the spinal locomotor generator in order to change, for example, the direction of gait (Bosco and Poppele, 2001; for review, see Dietz, 1997). In fact, cortico-spinal input during human locomotion is phase-linked (Schubert et al., 1997), similar to that seen in the cat (Drew, 1996). This enables the subject to voluntarily circumvent obstacles without losing postural stability.

For most other rhythmic elementary motor behavior, such as hopping or swimming, CPGs have also been assumed to exist (Grillner, 1986). Any disturbance of the finely coordinated interaction between afferent input and the pattern generation following a central lesion, such as stroke or spinal cord injury (SCI), leads to a movement disorder.

This review deals with the behavior of central pattern generation as the basis of locomotion. It will focus on the neuronal control of walking in humans and the plasticity within this system. Novel rehabilitation strategies use this plasticity after a spinal or supraspinal lesion to improve locomotor function. Only important relationships to observations made in animals will be discussed.

2. Physiological basis – animal models

For an understanding of the possible significance of pattern generation in human locomotion, a short outline about our present understanding of pattern generation in animals is required.

2.1. The spinal pattern generator

For most quadrupedal mammals, it is assumed that the neural control of locomotion is based on CPGs within the spinal cord (for review, see Duysens and Van de Crommert, 1998). This network generates the rhythm and shape the pattern of bursts of motoneurons (Grillner et al., 1995; Grillner, 1985). For the cat, it is assumed that there is at least one such CPG for each limb and that these CPGs are mainly located within the thoraco-lumbar region (for review, see Duysens and Van de Crommert, 1998). The rhythmicogenic capacity of the hindlimb innervating segments of the spinal cord decreases substantially in the rostro-caudal direction so that the caudal lumbar segments are incapable of producing the rhythm (Lev-Tov and Delvoye, 2000).

Primarily, the concept of spinal locomotor centers was based on experiments of Brown (1911, 1912) showing that cats with a transected spinal cord and with cut dorsal roots still produce rhythmic alternating contractions in ankle flexors and extensors. One half of this center induces activity in flexors, the other in extensors. It is thought that monoaminergic transmitters, normally released by descending pathways, facilitate interneurons that are thought to be part of these ‘spinal half centers’ (Forssberg and Grillner, 1973; Lundberg, 1981; Gossard et al., 1994).

Further evidence that neuronal networks in the spinal cord are able to produce rhythmic output was obtained by experiments in which such output was generated, although movement related afferent input was eliminated through pharmacological blocking of the movements (Perret and Cabelguyen, 1980). By recording the output at muscle nerves, rhythmic periods of activity, which are reciprocally organized between agonist and antagonists (‘fictive locomotion’), were demonstrated in hindlimbs (Chandler et al., 1984; Floeter et al., 1993) and forelimbs (Amemiya and Yamaguchi, 1984; Yamaguchi, 1992) of the spinal cat.

The CPG model is not restricted to the cat, since fictive locomotion has also been demonstrated in a wide variety of invertebrates and vertebrates (for reviews, see Grillner, 1985; Rossignol and Dubuc, 1994, Rossignol, 1996).

2.2. Bipedal versus quadrupedal pattern generation

For human pattern generation, only indirect evidence exists. Nevertheless, new treatments in neuro-rehabilitation are frequently founded on basic research in quadrupeds (for review, see Taub et al., 2002). For example, research on walking in cats has led to locomotor training applied in spinal cord injured patients (Barbeau and Fung, 2001; Dietz et al., 1994a, 1995a).

It is not to be expected that the nervous system in various species changes rapidly in evolution. Therefore, it is no surprise that for most of the basic mechanisms underlying locomotion, no fundamental difference seems to exist between bipeds and quadrupeds (Duysens, 2002; Nicol et al., 1995; Macpherson et al., 1989; Nilsson et al., 1985; Pearson, 2000a,b). Essential spinal neuronal mechanisms, such as the convergence of afferent input determining the locomotor pattern are most probably similar for quadrupedal and bipedal locomotion (for review, see Dietz, 2002a).

Nevertheless, there are also differences in some aspects, concerning the relationship between central mechanisms and peripheral input. For example, the regulation of bipedal gait requires specific neuronal mechanisms to maintain the body in an upright position (Dietz et al., 1986). Furthermore, the autonomy of the isolated spinal cord to generate locomotor movements is considerably greater in the spinalized cat or rat (Grillner, 1986) than in monkey (Eidelberg, 1981; Vilensky, 1987) or in humans (Dietz et al., 1995).

The difference between cats and primates may be related to the increased importance of the cortico-spinal tract in primates (see Vilensky and O’Connor, 1998). It is most probable that primate gait relies more on a supraspinal drive.
for the expression of spinal locomotor activities (cf. Armstrong, 1988). The spinal circuitry for locomotion might be suppressed by supraspinal input. The aim of this suppression could be to free the movements of hands and arms from locomotor movements.

3. Locomotor pattern in humans – physiological basis

In contrast to the abundance of data gained from invertebrates, rats and cats, leading to the general assumption of a CPG underlying the central control of locomotion, there is relatively little known about spinal networks acting like CPGs in humans. The most convincing evidence for CPGs, i.e. fictive locomotion, has no direct equivalent in humans. Therefore, the evidence and the implications of CPG activity in human gait are less well defined and have to remain vague to some extent. Nevertheless, there are observations which indicate the neural control of human locomotion is based on the activity of spinal CPGs (for review, see Duysens and Van de Crommert, 1998).

3.1. Basic mechanisms of locomotor control

For the control of human locomotion, afferent information from a variety of sources within the visual, vestibular and proprioceptive systems is utilised by the CPG. The convergence of spinal reflex pathways and descending pathways on common spinal interneurons seem to play an integrative role (for review, see Dietz, 2002) similar as in the cat (Schomburg, 1990). The selection of an appropriate locomotor pattern depends on a combination of central programming and afferent inputs as well as the instruction for a respective motor condition. This information determines the mode of organization of muscle synergies (Horak and Nashner, 1986) which are designed to meet multiple conditions of stance and gait (Dietz, 1992, for review, see Mackay-Lyons, 2002).

For example, for backward walking in humans, a program reversal concept is assumed. This means that during backward walking, the EMG-timing of hip muscles resembles that, reversed in time, for forward walking (Duysens et al., 1996). Furthermore, it is argued that the modulation of cutaneous reflexes observed during backward walking is likely to be determined by the same program as during forward walking, but working in reverse (for review, see Duysens and Van de Crommert, 1998).

Central mechanisms and afferent inputs interact in such a way that the strength of a reflex in a muscle or a synergistic group of muscles follows a program that is dependent on an actual task. The actual weighting of proprioceptive, vestibular and visual inputs to the equilibrium control is context-dependent and can profoundly modify the central program. Through this weighting, inappropriate responses are largely eliminated (for review, see Mackay-Lyons, 2002). In any event, simplistic theories of linear servo-control by proprioceptive reflexes, and any generalizations about reflex function in the context of complex automatic motor control, such as locomotion, are misleading. Any evaluation of reflex function has to be assessed in connection with the actual motor program, the biomechanical events, including their needs and their restraints.

3.2. Developmental aspects

The innate pattern of locomotion, the so-called ‘newborn stepping’, is characterized as in most of our mammalian ancestors by digitigrade stepping (i.e. the toes reach the ground first). This initial pattern of locomotion usually disappears after some weeks. But around 9 months of age, the child starts to adapt the innate locomotor program to the external conditions. These changes in leg muscle activation can be interpreted as a shift away from a low level of motor control towards patterns of leg muscle activation modulated by polysynaptic spinal reflexes (Berger et al., 1984a). This shift is bio-mechanically reflected in a stick-like usage of the legs in the early stage of stepping to a rolling off the body over the standing leg (Sutherland et al., 1980).

Already, during infant stepping, inputs from load receptors in combination with that from receptors reflecting hip joint position represent major sources of afferent input for an appropriate leg muscle activation, i.e. it facilitates the activity of the locomotor pattern generator (Pang and Yang, 2000; Yang et al., 1998).

3.3. Differential control of leg flexor and extensor muscles

During human locomotion, a differential control of leg flexor and extensor muscles seems to exist with a more centrally determined dominance in the control of leg flexor activity, while proprioceptive input determines the extensor activation (for review, see Dietz, 2002b). This assumption is based on the following observations:

1. In humans, powerful presynaptic inhibitory effects from flexor group I afferents onto extensor group I afferents exist, while these effects are weak from extensors to flexors (Iles and Roberts, 1987).
2. Cortico-spinal projections to lower limb motoneurons in humans are stronger to the flexor than to the extensor muscles (Brower and Ashby, 1992). In line with this observation, the effect of transcranial magnetic brain stimulation during locomotion mainly affects the flexor muscles at distinct phases of the swing phase (Schubert et al., 1997).
3. In recent models of locomotor control (Hiebert et al., 1996), the neuronal circuits controlling leg flexor activity of both sides reciprocally inhibit each other during walking, whereas the extensor half centers (the spinal neuronal circuits responsible for the activation of leg extensor muscles during gait) seem only be weakly coupled with each other.
3.4. Interlimb coordination

The regulation of human walking requires a close coordination of muscle activation between the two legs which seems to be achieved by a flexible neuronal coupling at a spinal level (for reviews, see Dietz, 1992, 2002a). For example, during gait, a perturbation of one leg evokes a purposeful, bilateral response pattern which is thought to be mediated at a spinal level (Berger et al., 1984b; Dietz et al., 1986), similar as described for the cat (Forssberg et al., 1976; Gorassini et al., 1994; Orsal et al., 1990). During stepping on a split-belt treadmill, with a belt running at different speeds, the legs act in a co-operative manner in human infants (Thelen et al., 1987) and adults (Prokop et al., 1995; Erni and Dietz, 2001; Dietz et al., 1994b), with each limb affecting the time–space behavior of the other. In general, initiation of the swing phase on one side is contingent on the contra-lateral limb being in the stance phase in both human adults (for review, see Dietz, 1997) and infants (Yang et al., 1998; Pang and Yang, 2001).

3.5. Coordination of arm and leg movements

There is some evidence that during cyclic movements, interlimb coordination in humans is similar in the lower and upper limbs (Zehr and Kido, 2001; Zehr et al., 2001) corresponding to the cat (Drew and Rossignol, 1987), i.e. the neuronal coordination and patterns of reflex modulation seem to be conserved within the human lumbar and cervical spinal cord.

Recent work shows that there are also similarities in the coordination between upper and lower limb muscles in humans and that of fore- and hindlimbs in quadrupeds (cf. Jones, 2002). For example, a neuronal coupling of upper and lower limb muscles during various locomotor activities seem to exist (Wannier et al., 2001). Arm and leg muscle activity is well coordinated during walking, crawling on all fours, or swimming. In these conditions, arm and leg movements are locked with a fixed frequency relationship. Even if the leg movements are slowed by flippers or if the mechanical interactions between the limbs are minimised, this coordination is preserved (Wannier et al., 2001). The frequency relationship characterizing this coordination corresponds to that observed in well-defined biological systems consisting of coupled oscillators (Bartos et al., 1999; Zacksenhouse, 2001).

A linkage between the cervical and lumbar enlargement of spinal cord by propriospinal neuronal circuits with long axons can also be inferred on the basis of H-reflex studies (Baldissera et al., 1998; Delwaide and Crenna, 1984). During rhythmic movements of one foot, a cyclic H-reflex modulation is observed in the upper limbs.

Furthermore, a task-dependency of neuronal coupling between arm and leg movements seems to exist (Dietz, 2002a). When mechanical or electrical impulses are applied to one leg, distinct bilateral arm muscle EMG responses are only evoked during walking (Dietz et al., 2001). The EMG responses in proximal arm muscles are absent when stimuli are applied during either standing with voluntary arm swing or sitting while writing (with comparable background EMG activity). These observations indicate a flexible, task-dependent neuronal coupling between upper and lower limbs (Fig. 1). The pathway that couples upper and lower limb movements seems to become gated by the activity of the CPG during walking, similar, as suggested for the rat (Cazalets and Bertrand, 2000). According to recent studies using functional magnetic resonance imaging (Debaere et al., 2001), the supplementary motor area might be involved in the supraspinal control of this coupling of upper and lower limb movements.

3.6. Locomotor pattern of the isolated spinal cord

The notion that ‘locomotor-like patterns’ can be released also in humans and that there is a basic similarity in spinal locomotor circuitry in cat and man is supported by observations made in patients with complete spinal cord transection. In these patients, electrical stimulation of flexor reflex afferents (FRA) shows characteristics of the neuronal networks similar to those seen in the cat (Robi-Bramy and Bussel, 1987, 1990). Early descriptions of involuntary stepping movements generated by the spinal cord in human subjects with complete paraplegia date back to the work of Lhermite (1919) and Kuhn (1950). Later on, in a patient with a complete spinal cord lesion, rhythmic contractions of the trunk and lower limb extensor muscles were described (Bussel et al., 1988, 1996). This rhythmic activity could be stopped, induced and modulated by peripheral stimulation.
of flexor reflex afferents (Bussel et al., 1989). In line with this, in a patient with spinal cord injury to the cervical spinal cord, involuntary step-like movements were observed (Calancie et al., 1994). Furthermore, in persons with complete spinal lesion, spinal cord stimulation is followed by ‘stepping movements’ with reciprocally organized EMG activity of symmetric muscles of both sides (Rosenfeld et al., 1995).

Further indirect evidence for a spinal pattern generator for locomotion has been suggested from recordings of locomotor activity induced in patients with complete paraplegia standing on a moving treadmill with body weight support (Dietz et al., 1995a; Dobkin et al., 1995; Harkema et al., 1997; for review, see Barbeau and Fung, 2001). According to such experiments, it appears that the strength of the locomotor pattern depends on the level of lesion, i.e. the higher the lesion the more ‘normal’ is the pattern (Dietz et al., 1999). This would imply that neuronal circuits up to a cervical level contribute to the locomotor activity, as it was suggested for the mudpuppy (Cheng et al., 1998).

Recently, locomotor movements were induced by a driven gait orthosis (DGO) that allows to induce leg movements even with 100% body unloading (Dietz et al., 2002). In such a condition, physiological locomotor-like movements alone do not lead to leg muscle activation. Stepping movements only in combination with loading of the legs are associated with a patterned leg muscle activation in both persons with complete para/tetraplegia and healthy subjects. This indicates that stretch reflexes play only a minor role in the generation of leg muscle activity in these patients (Dietz, 1995; Dietz et al., 2002). According to these studies, the appearance of a locomotor pattern seems to depend on afferent input from ‘load receptors’ in combination with hip joint position-related afferent input.

4. Impaired pattern generation – movement disorders

Any damage within the central or peripheral nervous system can be followed by an impairment of pattern generation that leads to a movement disorder. Furthermore, we have to be aware that a movement disorder is the consequence not only of the primary motor lesion but also of secondary processes that can be compensatory and can be supported during rehabilitation.

4.1. Spasticity

A central motor, i.e. cerebral or spinal lesion is associated with an impairment of spinal reflex activity. This leads to a defective processing of peripheral input by central mechanisms. The impaired central control of spinal reflexes results in a loss of inhibition of short-latency reflexes with the consequence of the well-known hyperexcitability of the short-latency stretch reflexes. This is combined with a reduced facilitation of the functionally more important polysynaptic or long-latency reflexes (Berger et al., 1988) that leads to a reduced proprioceptive contribution to the leg muscle activation during gait (for reviews, see Dietz, 2001, 2002b). Therefore, spastic gait is associated with an overall reduced and less well modulated leg muscle activity. At present, it has to remain open, in how far the impaired reflex behavior is mediated by the CPG or, alternatively, is directly due to altered descending signals bypassing the CPG.

In spastic paresis, the basic spinal locomotor programs seem to be intact. Both the timing and reciprocal mode of leg muscle activation during gait and the tri-phasic movement pattern following stance perturbation are preserved (Berger et al., 1988). However, leg muscle activation is impaired in spastic paresis due to an impaired functioning of spinal reflexes with the consequence of a defective utilization of afferent input from various, still undefined, sources. Furthermore, following a central motor lesion the modulation of both cutaneous (Jones and Yang, 1994) and short-latency stretch (Sinkjaer and Magnussen, 1994) reflexes during the step cycle is impaired.

The impaired utilization of afferent input by spinal neuronal circuits leads to changes in leg muscle activation with reduced adaptation of muscle activity to the actual ground conditions (for review, see Dietz, 2000b) and, consequently, contributes to the spastic movements disorder (see Fig. 2). Furthermore, secondary to the primary lesions, there are not only changes in reflex functioning but also compensatory adaptations of the locomotor system. The loss of supraspinal drive has also an effect on muscle function (O’Dwyer et al., 1996; for review, see Dietz, 1997). Motor units become transformed in such a way that regulation of

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**Fig. 2.** Schematic diagram of the mechanisms that contribute to spastic paresis and spastic movement disorder. A central motor lesion leads to an impaired reflex control by the CPG and to a loss of supraspinal drive. The consequence is a hyperexcitability of short-latency reflexes and a loss of long-latency reflexes, as well as changes in muscle properties. The combination of all sequelae of the primary lesion leads to spastic movement disorder, CNS, central nervous system; CPG, central pattern generator (adapted from Dietz, 2002b).
muscle tone is achieved at a lower level of neuronal organization, which also contributes to movement disorder (see Fig. 2). In turn, these changes also enable the patient to walk, as spastic muscle tone is required to support the body during the stance phase of locomotion (for reviews, see Dietz, 2001, 2002b). Therefore, the altered regulation of spastic gait can be considered as compensatory for the loss of central motor system function (cf. Latash and Anson, 1996).

4.2. Parkinson’s disease

Gait analysis shows a characteristic pattern in Parkinson’s disease that allows the separation from other movement disorders, such as seen, for example, in patients with normal pressure hydrocephalus (Stolze et al., 2001). Several reports have suggested that force control in Parkinson’s disease is impaired during both voluntary movements (Delwaide et al., 1991; Stelmach, 1991) and locomotion (Dietz et al., 1995b). Reduced load sensitivity seems to develop with age and becomes exaggerated in Parkinson’s disease (Dietz and Colombo, 1998). The consequence of an impaired processing of load related input by central mechanisms is a reduced leg extensor activation that is suggested to contribute to the gait disorder (Dietz et al., 1995b; Dietz and Colombo, 1998). The reduced and little modulated leg extensor activation is associated with an enhanced tibialis anterior activity during the swing phase of gait in persons with Parkinson’s disease (Fig. 3). This may reflect the defective extensor suppression of the flexor burst generating circuitry (Dietz and Duysens, 2000). In addition, the enhanced tibialis anterior activity may reflect the stronger control of stance and gait in these patients by the visual system.

The control of gait in patients with Parkinson’s disease relies more on visual information, which seems to be exerted through modulation of leg flexor EMG activity (Dietz et al., 1995b). This is in line with the more general observation that visual information can substitute to some extent for the reduced proprioception (for review, see Pearson, 1995, 2000a). A strong dependency of persons with Parkinson’s disease on visual cues during walking becomes evident when an optical flow pattern is imposed during stepping on a treadmill. While the walking velocity of healthy subjects is affected only for a short time by the pattern (Dietz et al., 1992), people with Parkinson’s disease continuously change their speed with the movements of the optical flow (Prokop and Berger, 1996). In conclusion, several aspects of characteristically impaired postural adjustments during gait indicate a defective utilization of load related afferent input in Parkinson’s disease leading to a reduced activation of leg extensor muscles. This may be due to an impaired supraspinal control of spinal interneuronal circuits mediating this input. For compensation, patients automatically rely more on visual feedback which is associated with enhanced tibialis anterior activation.

5. Plasticity of spinal neuronal circuits – rehabilitation issue

There is increasing evidence that a defective utilization of afferent input in central motor diseases, in combination with secondary compensatory processes is involved in typical movement disorders, such as spasticity and Parkinson’s disease. Furthermore, it became evident from cat experiments that neuronal networks underlying the generation of motor patterns are quite flexible after central or peripheral neural lesions (Pearson, 2000b). This has implications for therapy. The aim of rehabilitation should be concentrated on the improvement of function by taking advantage of the plasticity of neuronal centers, and less directed to the correction of isolated clinical signs, such as the reflex excitability. For the monitoring of outcome and for the assessment of the effectiveness of any interventional therapy, standardized functional tests should be established.

5.1. Spinal reflex plasticity

There is increasing evidence that the isolated spinal cord exhibit some neuronal plasticity. Evidence for such a plasticity at the spinal level has been obtained for the relatively simple monosynaptic reflex arc (Wolpaw et al., 1983). Monkeys could either be trained to voluntarily increase or decrease the amplitude of the monosynaptic stretch reflex in response to an imposed muscle lengthening (Wolpaw et al., 1983), as well as of its analogue, the H-reflex (Wolpaw, 1987). The fact that the training effects persist after spinal cord transection (Wolpaw and Lee, 1989) indicates that some kind of learning by neuronal circuits within the spinal cord is possible. Similarly, humans can be
trained to change the gain of the monosynaptic stretch reflex (Wolf and Segal, 1996; for review, see Van de Crommert et al., 1998).

The idea that the spinal cord can learn is also supported by studies of spinal reflex conditioning. Simple hindlimb motor responses to cutaneous or electrical stimulation are enhanced in animals with transected spinal cords via classical reflex conditioning (i.e. pairing the stimulus with another stimulus that evokes a stronger motor response) (Durkovic, 1986). These reflex responses are enhanced within minutes of conditioning indicating that synaptic efficacy along the reflex arc has changed, perhaps through long-term potentiation (Durkovic, 1986).

5.2. Use-dependent plasticity – rehabilitative approaches

There is convincing evidence in spinal animals that a use-dependent phenomenon exists that can be attributed to some form of learning (Edgerton et al., 1997; Pearson, 2000b). When stepping is practiced in spinal cat, this task can be performed more successfully than when it is not practiced (Lovely et al., 1986, 1990), indicating a use-dependent plasticity of the spinal cord. The training of any motor task provides sufficient stimulation to initiate a reorganization of neural networks within the spinal cord and, for example, to generate locomotion. Consequently, the loss of motor capacity following neural injury can become enhanced when locomotor networks are no longer used, for example following a stroke (Edgerton et al., 1997). In contrast, a much greater level of functional recovery might be possible if the concept of use-dependence is applied in both the clinical and rehabilitative settings (Edgerton et al., 1997).

A considerable degree of locomotor recovery in mammals with a spinal cord injury can be attributed to a reorganization of spared neural pathways (Curt and Dietz, 1997; Curt et al., 1998; for review, see Curt and Dietz, 1999). It has been estimated that if as little as 10% of the descending spinal tracts are spared, some locomotor function can recover (Basso, 2000; Metz et al., 2000). If the loss of supraspinal input to the spinal cord is complete, these neuronal networks that exist below the level of the lesion adapt to generate locomotor activity even in the absence of supraspinal input (De Leon et al., 1998a,b; Wirz et al., 2001).

5.3. Task-specific plasticity

It is becoming clear that the plasticity of the sensory-motor networks of the adult mammalian lumbo-sacral spinal cord is greater than has been previously assumed (Edgerton et al., 1992; for review, see Edgerton et al., 1997; Pearson, 2000b). Subsequently, the most prominent aspect of research on CPGs has been the detailed assessment of the modifiability of neuronal network function (Harris-Warrick and Marder, 1991; Dickinson, 1995; Katz, 1995; Pearson, 2000a). The lumbo-sacral spinal cord obviously can execute stepping or standing more successfully if that specific task is practiced. Observations in spinal cats indicate that if the training of a motor task is discontinued and no other task is subsequently trained, then the performance of the task previously trained is degraded (Edgerton et al., 1997). Consequently, plasticity can be exploited by rehabilitative purposes using specific training approaches following a neural injury.

In the cat, recovery of locomotor function following spinal cord transection can be improved using regular training, even in adult animals (Barbeau and Rossignol, 1987, 1994). The provision of an adequate sensory input during such treadmill training is of great importance to achieve an optimal locomotor output of the spinal neuronal circuitry. Correspondingly, in association with hindlimb exercise, reflex activity becomes normalized in adult rats following spinal cord transection (Skinner et al., 1996). Exercise obviously helps to normalize the excitability of spinal reflexes.

Several neurotransmitter systems within the spinal cord (glicnergic and GABA-ergic systems) are suggested to be involved in the adaptation to repetitive use (Edgerton et al., 1997). In animals with a spinal cord transection, stepping can be induced by the administration of the nor-adrenergic agonist clonidine, which enhances the activity in the locomotor generative spinal circuits (Chau et al., 1998; for review, see De Leon et al., 1998a,b). Furthermore, serotonin seems to be involved in the production of locomotor rhythm (Schmidt and Jordan, 2000).

Training paradigms of stepping and standing can modify the efficacy of the inhibitory neurotransmitter, glycine (Edgerton et al., 1997). For example, when strychnine is administered to a chronic spinal cat that has acquired the ability to step successfully, there is little change in its locomotor capability. If it is administered to a stand-trained cat, it becomes able to successfully step with body support (Edgerton et al., 1992, 1997). These findings suggest that the effect of strychnine is in so far specific in its action as it enables spinal networks to integrate sensory input by reducing inhibition (De Leon et al., 1998a,b).

5.4. Effects of locomotor training in persons with a spinal cord injury

As established in preceding paragraphs, the coordination of human gait seems to be controlled in much the same way as in other mammals (for reviews, see Duysens, 2002; Dietz, 2002b). Therefore, it is not surprising that in persons with a complete or incomplete paraplegia, due to a spinal cord injury locomotor EMG activity and movements can be both elicited and trained similar as in the cat. This is achieved by partially unloading (up to 60%) the patients who are standing on a moving treadmill (Dietz et al., 1994a, 1995a, 1998a; for review, see Dietz, 1997). In severely affected patients, the leg movements usually have to be assisted externally, especially during the transmission from stance to swing. The approach is based on findings made in cats and
rats and is directed to train functional movements. It is supposed that by moving the limbs through trajectories under close physiological conditions, sensory inputs, and therefore central neuronal circuits become activated. The timing of the pattern of leg muscle EMG activity recorded in such a condition is similar to that seen in healthy subjects. However, the amplitude of leg muscle EMG is considerably reduced and is less well modulated. This makes the body unloading necessary for the locomotor training.

The analysis of the locomotor pattern in complete paraplegic patients indicates that it is unlikely to be due to rhythmic stretches of the leg muscle because leg muscle EMG activity is, as in healthy subjects, equally distributed during muscle lengthening and shortening (Dietz, 1995). In addition, recent observations indicate that locomotor movements induced in patients who are completely unloaded do not lead to leg muscle activation (Dietz et al., 2002). This implies that the generation of the leg muscle EMG pattern in these patients is programmed at a spinal level rather than generated by stretch reflexes.

During the course of daily locomotor training, the amplitude of the EMG in the leg extensor muscles increases during the stance phase and inappropriate leg flexor activity decreases. Such training effects are seen both in complete and incomplete paraplegic patients (Dietz et al., 1994a, 1995a). These training effects lead to a greater weight bearing function of the extensors, i.e. body unloading during treadmill locomotion can be reduced during the course of training. This indicates that the isolated human spinal cord has the capacity not only to generate a locomotor pattern but also to show some plasticity. However, only persons with incomplete paraplegia benefit from the training program in so far as they can learn to perform unsupported stepping movements on solid ground (Dietz et al., 1994a, 1995a). In complete paraplegic patients, the training effects on leg muscle activation become lost after the training has been stopped (Wirz et al., 2001).

There are several reports about the beneficial effect of locomotor training in incomplete paraplegic patients (Fung et al., 1990; Wernig and Müller, 1992; for review, see Barbeau and Rossignol, 1994) and patients who undergo locomotor training have a greater mobility compared to a control group without training (Wernig et al., 1995). Afferent input from receptors signaling contact forces during the stance phase of gait is essential for the activation of spinal locomotor centers (cf. Harkema et al., 1997; Dietz et al., 2002b) and is important to achieve training effects in paraplegic patients (Dietz et al., 1994a, 1995a). Furthermore, hip joint-related afferent input seems to be essential to generate a locomotor pattern (Dietz et al., 2002).

The improvement of locomotor activity could also be attributed to spontaneous recovery of spinal cord function that can occur over several months following a spinal cord injury (Curt et al., 1998). However, recent observations indicate in both incomplete and complete paraplegic patients, that the increase of leg extensor EMG activity also occurs independently of the spontaneous recovery of spinal cord function, as assessed by clinical and electrophysiological means (Curt et al., 1998; Dietz et al., 1998a,b). Therefore, one might conclude that in persons suffering a spinal cord injury specific training effects on spinal locomotor centers lead to an improvement of locomotor function similar as described for the spinal cat (Dietz et al., 1998a,b). However, part of the recovery in locomotion might also be attributed to changes that occur in the muscles during the training period (Dietz et al., 1998a), similar as observed in the rat (Edgerton et al., 1997).

Unfortunately, patients with complete or almost complete paraplegia do not, as yet, profit from locomotor training for their mobility. In the future, these patients may profit from a combination of regeneration and exploitation of neuronal plasticity, as the research in spinal cord regeneration appears to be quite encouraging (for review, see Schwab and Bartholdi, 1996).

Acknowledgements

I thank R. Jurd for correcting the English. This work was supported by the Swiss National Science Foundation (NCCR Neuro) and the International Research Institute for Paraplegia.

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