

Review Paper

# Neural control of locomotion; Part 1: The central pattern generator from cats to humans

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## Abstract

In the last years it has become possible to regain some locomotor activity in patients suffering from an incomplete spinal cord injury (SCI) through intense training on a treadmill. The ideas behind this approach owe much to insights derived from animal studies. Many studies showed that cats with complete spinal cord transection can recover locomotor function. These observations were at the basis of the concept of the central pattern generator (CPG) located at spinal level. The evidence for such a spinal CPG in cats and primates (including man) is reviewed in part 1, with special emphasis on some very recent developments which support the view that there is a human spinal CPG for locomotion. © 1998 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

Understanding how such seemingly ‘simple’ and automated movements, such as walking and running, are controlled forms a main challenge for modern neuroscience. Somehow the central nervous system (CNS) is able to coordinate which joint has to be moved, how far and at what time. Such movements can only be made properly if a set of biomechanical requirements are met using a pattern of electrical signals sent along the nerves to activate the appropriate set of muscles. Furthermore, the locomotor movements are continuously adapted when obstacles are encountered, thereby ensuring the smooth progression of the ongoing movement. Hence, out of a large flow of sensory input from the periphery the system is able to select the most optimal context-specific information and to incorporate this information into the executed movements.

This task is simplified by the remarkable organization of neural networks, specialized in repeating partic-

ular actions over and over again. For many species the cyclical patterns needed for walking, respiration, mastication or other rhythmical activities, are generated by such neural networks. For locomotion one usually refers to the term central pattern generator (CPG) to indicate a set of neurons responsible for creating a motor pattern, “regardless of whether all aspects of the motor pattern of the intact animal are produced or some part is missing” [1]. It should be emphasized indeed that ‘pattern’ is used here in a broad sense to indicate alternating activity in groups of flexors and extensors. Hence it is not implied that an overground walking animal would use exactly the same pattern of muscle activation as the one seen, for example, in ‘fictive locomotion’. In the latter case the animal is motionless but shows an activation pattern which resembles the one seen in ‘normal’ gait. During normal overground walking one can assume that parts of the muscle activation patterns are not centrally generated but are reflexly induced, e.g. through stretch reflexes [2–5,116].

The term CPG refers to a functional network, which could consist of neurons located in different parts of

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the CNS. This network generates the rhythm and shapes the pattern of the motor bursts of motoneurons [1,6]. For the cat it is assumed that there is at least one such CPG for each limb and that these CPGs are located in the spinal cord.

It is generally thought that the commands for initiation and termination of these rhythm generators are coming from supraspinal levels. After gait initiation, afferents deliver movement-related information to spinal and supraspinal levels. Some of this feedback acts directly on the CPG to aid the phase transitions during the step cycle thus providing the possible induction of variations to meet the environmental demands. On the other hand, afferent feedback is more directly connected to motor neurones through various reflex pathways and these pathways themselves are largely under the control of the CPG. In this way it is ensured that reflex activations of given muscles occurs only at the appropriate times in the step cycle (phase-dependent modulation [111]).

This very general model for locomotion, as described above briefly, is mainly based on data obtained from experimental animals. The extrapolation of the 'animal'-model of locomotion to humans finds its basis in the implicit assumption that no fundamental differences exist between the neural networks of humans and other vertebrates. In the present review it will be shown that there are indeed striking similarities between cat and human with respect to the neural control of locomotion.

This is not to say that there are no important differences as well. The basic pattern may be similar but amplitudes and functions of bursts of activity may differ. For example, the cats hip extensors are propulsion muscles during stance whereas in humans they are dominant for balance control of the upper body (pelvis to head). In humans the plantarflexors are by far the dominant propulsion muscles but in cats they may be less important. The paraspinal muscles in humans are balance control muscles but in cats they are not. During swing the similarities for hip and knee muscles are quite good.

The practical implication of the similarity in neural control between cat and human is that novel approaches towards the restoration of locomotor abilities in spinal cord injured (SCI) patients can be based on findings in cats (see Part 2 of this review). Furthermore, the possible demonstration of a CPG in humans opens the way to entirely new approaches for experiments on humans. In particular, attention will be given to some very recent data, obtained both on SCI patients and intact humans, which strongly support the view that there exists a human CPG for locomotion. The results of experiments on cats, which have given rise to the present existing models of locomotion, will be used as a guide and will be compared with results obtained on humans.

## 2. Evidence for CPG in cat

Gait in intact animals relies on the activation and appropriate coordination of a large variety of muscles in a given phase-dependent pattern. This pattern is to a large extent stereotypic and, once developed, very difficult to change. For example, experiments in newts have shown that transplantations of flexors and extensors, or the implantation of inverted supernumerary limbs do not alter the pattern, even if this pattern is entirely contra productive [7]. Similar experiments with transplantation of antagonist muscles in cats [8,9] and rats [10,114,115], have confirmed this lack of adaptability of the locomotor pattern. Why is it that the system here seems so rigidly captured in a certain pattern and how is this pattern generated?

The classical experiments of Brown (1911) [11] and Brown (1912) [12], showed that cats with a transected spinal cord and with cut dorsal roots still showed rhythmic alternating contractions in ankle flexors and extensors. This was the basis of the concept of a spinal locomotor center which Brown termed the 'half-center' model. One half of this center induced activity in flexors, the other in extensors. Since then there have been many replications of these early experiments (recently reviewed by Rossignol (1996) [13]). Some authors used the same approach as Brown and they showed that, after transection of the dorsal roots seemingly normal locomotor outputs could be observed in spinal cats [14]. However, transection of the dorsal roots does not eliminate all afferent input to the spinal cord because afferent information can reach the spinal cord by means of unmyelinated [15] and myelinated [16] sensory fibers in the ventral (motor) roots. As pointed out by Grillner and Zangger (1984), many of these afferents come from visceral regions [17]. Furthermore, no apparent sensation is evoked after ventral root stimulation [18]. Overall it seems quite unlikely that these afferent ventral root fibers play a role in locomotion.

A potentially important afferent source for the generation of locomotor output at one girdle may be the rhythmic activity generated at another girdle. Forelimb movements may induce hindlimb stepping in forward gait. Grillner and Zangger (1984) claimed that interlimb coordination during hindlimb walking deteriorated following deafferentation in the 'mesencephalic' cat [17]. This is a decerebrated cat (obtained after intercollicular transection at the level of the brain stem) in which complete quadrupedal stepping can be evoked by electrical stimulation of a specific brainstem site below the transection (the mesencephalic locomotor region (MLR), [19]). Depending on the strength of the stimulus, different gait patterns could be produced (walking, trotting, galloping). Termination of locomotion could be achieved by simply removing the excitatory input to this region [20–22]. Further support for the importance

of interlimb coordination was obtained by Cruse and Warnecke (1992) [23], in the intact cat and by Giuliani and Smith (1987) [24], in the chronic spinal cat. The latter authors found that the coupling between hind leg movements during stepping in the air was weaker following deafferentation of a hindlimb. They showed that during the majority of locomotor movements, the bilateral stepping was characterized by irregular phasing, with the intact hindlimb stepping at a faster frequency than the deafferented leg.

That this interlimb coordination is not absolutely essential for the generation of the rhythm is demonstrated by the observation that low spinal cats are able to walk with their hindlimbs on a treadmill despite the lack of input from the forelimbs [25,26]. This spinal stepping of the hindlimbs was adjusted to the belt speed both in kittens [25,26] and in adult cats [27]. In such cases of spinal locomotion, the activity cannot be explained by simple stretch reflexes since activity is generated in periods when the muscles are not stretched [27].

In contrast, flexor reflexes have a much tighter relationship with the locomotor output of spinal cats. Indeed, Brown and Sherrington (1912), emphasized long ago the similarities between the motor output produced during the flexion phase of stepping and the flexor reflex [28]. In both cases there is an activation of all physiological flexors of the leg in one single synergy. In spinal cats, after injection with L-DOPA, Jankowska et al. (1967) showed that stimulation of the so-called flexor reflex afferents (FRA) depressed the classical short-latency flexion responses and instead elicited typical late long-lasting reflexes [29]. The ipsilateral long-latency flexor responses were coupled to the crossed extensor discharges. It is thought that L-DOPA mimics the monoaminergic transmitters, which are normally released by descending pathways during periods of locomotion and facilitate the interneurons involved in the late discharges. The latter neurones were thought to be part of the 'spinal half-centers', which Brown had introduced to explain the generation of rhythmic locomotor patterns [30,31], see above.

### 2.1. Fictive locomotion

The most convincing evidence that neural networks in the spinal cord are able to produce rhythmic output was obtained by experiments in which such output is generated although movement related afferent input is completely eliminated through blocking of the movement. This can be achieved by either injection of neuromuscular relaxants [3], or transection of the efferent nerves at the ventral root or at the muscle nerve level. By recording the output of efferent nerves at the ventral root, rhythmic periods of activity which were reciprocally organized between agonists and antagonists ('fictive locomotion') were demonstrated in both cats'

hindlimb [32–34,112] and forelimb [35–37]. Under these conditions, rhythmic sensory input is absent but static afferent information (e.g. related to hip position) remains and can influence the CPG. This can only be eliminated by combining the curarization with extensive denervation [1].

The demonstration of fictive locomotion is evidence that neural networks in the isolated spinal cord are capable of generating rhythmic output (reciprocally organized between agonists and antagonists) in absence of any signals from efferent descending as well as movement related afferent sources. The networks producing the locomotor pattern are referred to as CPGs.

Despite the impressive capability of the isolated cat spinal cord to generate rhythmic output, very similar to that seen in intact animals, one should keep in mind that this output is always the reflection of a severed spinal cord in which the circuits involved receive abnormal input. Apart from the clear observations of rhythmic output also other features, not present in the intact cat, were seen. For example, the locomotor pattern elicited under above mentioned conditions had in common that the locomotor pattern could be maintained but became much more fragile and could break down [1]. In addition, it was questioned whether some of the patterns described in the literature could be related to forward locomotion, since the fictive pattern often more closely resembled backward locomotion [38]. Furthermore, Pearson and Rossignol (1991) showed that other patterns, for example related to paw shake or to rhythmic leg flexion, could occur during fictive locomotion of chronic spinal cats [39].

The similarities between fictive and real locomotion patterns does not exclude the possibility that, in intact animals, some of the locomotor output is not centrally generated but is derived from reflexes. For example, some of the muscle activity during normal locomotion could originate to a certain extent through stretch reflexes. In the cat several authors have suggested that the activity of hamstrings at end swing could originate from stretch reflexes [2–4]. To shed light on this type of question, transection of the dorsal roots was used and it was shown that a seemingly normal locomotor outputs could remain in acute spinal cats [14,17,40]. Although indeed, a striking similarity exists with the normal pattern it has been argued that the stability of the pattern and some of the details of the activation pattern requires the presence of intact afferents [41]. Especially the central versus peripheral origin of the two-burst pattern in bifunctional muscles such as semitendinosus (ST) is still a subject for debate [4,42].

The CPG model is not only restricted to the cat, since fictive locomotion is also demonstrated in a wide variety of invertebrates and vertebrates (reviewed in [1,43,44]). In fact, in view of this very extensive evidence for locomotor CPGs in these various species, it

would be very surprising if primates would completely lack a CPG-like structure. However, it is possible that primate gait relies less on spinal automatisms and more on supraspinal control for the expression of the locomotor activities (for review on the supraspinal control of gait, see [45]).

### 3. CPG in primates, including man

In contrast to the abundance of data in animals leading to the general assumption of a CPG underlying the central control of locomotion, there is very little known about spinal networks acting like CPGs in primates in general and in humans in particular. Hence, in the context of human locomotion, the important question arises: is there a CPG in primates?

In non-human primates, several attempts have been made to find evidence for the existence of a CPG for locomotion. Phillipson (1905) reported that a monkey with transected spinal cord showed alternating movements of the hindlimbs about 1 month after the lesion [46]. In contrast, Eidelberg (1981a) found no evidence for hindlimb stepping in their macaque monkeys with a complete spinal transection [47]. However, after a partial lesion (T8) hindlimb stepping could be elicited using tail pinches, provided the monkeys were well-trained, as soon as possible after the lesioning (treadmill training 5 days/week). These authors claimed that sparing of the ventrolateral quadrant (including vestibulospinal and reticulospinal tracts) was most essential for the stepping to occur. A later reinvestigation of these same animals emphasized that, initially, monkeys showed much less bilateral hindlimb stepping than cats with similar partial lesions of the spinal cord [48]. The difference between cats and primates may be related to the increased importance of the corticospinal tract in primates (for review, see [49]). It is thought that, in primates, the spinal circuitry for locomotion is suppressed by input from the cortex ('cortical dominance'). The aim of this suppression could be to free the movements of hands and arms from locomotor movements of the hindlimb (interlimb coordination automatisms).

Consistent with these ideas is that the best illustrations for primate spinal stepping generators come from studies of the more 'primitive' New World monkeys with a less-developed corticospinal tract. Until now there is only a single report that delivered detailed and convincing evidence for a primate CPG for locomotion and this study on fictive locomotion was made on decerebrated and spinalized marmoset (New World monkey; [50]). In addition, Vilensky and O'Connor (1997) report that they observed stepping movements in a squirrel monkey (New World) some 39 days after complete transection of the spinal cord (T8) [49]. For Old World monkey and higher primates the evidence is much less convincing.

### 3.1. Evidence for the human CPG

#### 3.1.1. Flexor reflex afferents

The notion that there is a basic similarity in spinal locomotor circuitry in cat and man is supported by experiments performed in patients with clinically complete spinal cord section. In these patients, electrical stimulation of FRA revealed similar characteristics of the L-DOPA networks, as seen in cat [51–53] (for review, see [54,55]).

The main features are the following:

(1) In both cat and man the appearance of long-latency flexor discharges is accompanied by presynaptic inhibition of Ia afferents [52].

(2) Late flexor discharges on one side are accompanied by inhibition of contralateral late flexor discharges in both species [53]. This inhibition acts at the level of interneurons which are specifically involved in these late discharges since there is no concomitant inhibition of early flexion reflexes or of flexor H-reflexes.

(3) One of the characteristics of the late discharges in cats is that they only appear after the termination of a sural nerve stimulus train, whatever its duration. Exactly the same was observed in spinal man [51–53]. A functional interpretation of this type of result in the cat was given by Duysens (1977) using premammillary cats (cats with a high decerebration above the MLR) [56]. In these cats, which can walk spontaneously on a treadmill, it was found that distal tibial and sural nerve stimulation of low intensity was effective in inducing a switch from the flexion to the extension phase. Since these nerves innervate the foot, it was suggested that low threshold afferents from this area are able to detect footfall and can reflexly induce the transition from flexion to foot placement by exerting direct inhibition on the flexor half-center of the CPG. It was argued that the post-stimulation discharges described above were due to disinhibition, and that the late flexor discharges are basically rebound excitation, due to the release of the flexor half-center from inhibitory influence from the stimulated cutaneous afferents (rebound hypothesis, [56]).

#### 3.1.2. Rhythmic movements and contractions in SCI patients

Rhythmic activity is very rare after complete but not after incomplete transection of the spinal cord. Early descriptions of rhythmic involuntary movements generated by the spinal cord lacking supraspinal input, date back from the work of Lhermite (1919) [57] and Kuhn (1950) [58]. The latter author even claimed that a patient with completely transected spinal cord could produce 'self-propagating' stepping movements at times. More recently, the group of Bussel reported the presence of rhythmic contractions of the trunk and

lower limb extensor muscles [59] (see also [60]), in a patient with a complete spinal cord lesion. This rhythmic myoclonic activity (frequency <1 Hz) could be stopped, induced and modulated by peripheral stimulation of FRA. However, the rhythmic contractions never occurred spontaneously and had only one 'step cycle' duration. Alternating flexion and extension of the lower extremities were rarely present in response to stimulation. In contrast, in patients with incomplete lesions the presence of alternating flexor and extensor activity is more common [61]. Calancie et al. (1994) described a patient with a 17-year history of neurologically incomplete injury to the cervical spinal cord [62]. This patient displayed involuntary lower limb stepping-like movements which were evoked when lying supine with extended hips. The movements were rhythmic, alternating and forceful and involved all muscles of both lower extremities. It is interesting to mention that these movements started about 1 week after beginning an intensive locomotor training and were never observed before. This can mean that the rhythmic alternating contraction, as seen in this man, is elicited in some way by the extensive locomotor training. This has also been reported, but less extensively, by Dobkin et al. (1995), in a person with an incomplete spinal cord injury (SCI) [63]. When lying supine, this subject developed alternating left and right lower extremity flexion and extension movements in response to extension of the hips. He could only terminate these movements by placing the hips in a flexed position. Remarkably, this involuntary cyclical activity declined soon after ending his locomotor training.

Finally, in some patients the appearance of automatic stepping movements is linked to loss of supraspinal control. For example, Hanna and Frank (1995) reported alternating leg movements with a frequency of 0.2–0.5 Hz in patients in the period preceding or following brain death [64]. This may be equivalent to much older observations by Landry and by Robin (described by Luys (1893), [65]), who reported that after decapitation of animals and humans (death executions) some rhythmic flexor reflexes or movements could be elicited, for example following skin contact.

While all this evidence points to the existence of human spinal CPGs it should be pointed out that as yet it is not proven that these CPGs are the same as those used during normal walking. Furthermore, in the cases of incomplete spinal cord lesions, it is still unclear whether higher centres are needed to interact with the spinal CPG to generate locomotion or whether locomotion is controlled from these higher levels.

### 3.1.3. Sleep-related periodic leg movements (SRPLM)

Another example of involuntary stepping movements is given by sleep-related periodic leg movements (SR-

PLM). SRPLM are stereotyped, periodic, repetitive movements involving one or both lower limbs. These movements consist of dorsiflexion of the ankle and toes and flexion of the hip and knee and occur in clusters while the subject is lying down or asleep [66,67]. Such SRPLM are not disease-specific and can also appear in healthy subjects over 30 years old [68]. The finding of SRPLMs in SCI patients [69], suggests that a SCI injury may permit the expression of a spinal generator [70]. This generator could be activated through the combination of the interruption of descending inhibitory spinal pathways and the sleep related periodic somatic and vegetative phenomena ('disinhibited generator'; [70,71]). The spinal origin of such generator is supported by the presence of such SRPLM in persons with a complete spinal lesion. Furthermore, the triple flexion of the ankle, knee and hip during these SRPLM periods is very similar to the flexor reflex which all patients exhibit. Therefore, it was suggested that PLM is related to spinal automatisms [69].

Other related phenomena ('periodic nocturnal myoclonus') have been described in patients with hyperekplexia (startle disease; [72,73]). In the latter disease there is a mutation in the gene encoding the  $\alpha$ 1 subunit of the glycine receptor. Since glycine is important for recurrent and reciprocal inhibition, it is possible that the release from inhibition is an element in the generation of the locomotor-like activity. To this we can add an alternative explanation in terms of a spinal CPG released from control from reticular nuclei from the lower brainstem. Whether this CPG is the one used for the production of normal gait remains an open question.

### 3.1.4. Spinal cord stimulation

Another evidence that neural networks, responsible for generating rhythmic locomotor activity can be located in the spinal cord is delivered by experiments in which specific sites of the spinal cord were electrical stimulated. As already shown, the method of electrical stimulation of brain stem sites proved to be an effective method to elicit locomotion in the decerebrated cat. Recently, it appeared that this method was also effective when applied to lower levels of the CNS. It was shown that tonic electrical stimulation of the dorsal side of the spinal cord could induce locomotor activity in intact, decerebrated and low spinalized cats. Stimulation of the L3-L4 segments was effective in eliciting alternating reciprocal activity of both hindlimbs (or one hindlimb). It was found that rhythmic activity could be present also in the forelimbs as well. In the intact cat (under chloralose anesthesia), reciprocal interlimb activity in the hindlimb muscle group could be best obtained when the electrodes were placed over the L3-L4 segments [74].

The same method of spinal cord stimulation was applied to persons with a complete spinal lesion at thoracic level [75–80]. It was shown that continuous stimulation of the spinal cord, most effectively at L2-L3 level, elicited myoclonic stepping with reciprocal organized EMG activity of symmetric muscles. These results suggest that a comparable neural network (CPG) to that seen in the cat, lies at the basis of these evoked locomotor phenomena. Compatible with this explanation is the observation that during the induced rhythmic activity there is a reduction in the soleus H-reflexes [81]. Indeed, as mentioned above, late flexor discharges are accompanied by presynaptic inhibition of Ia afferents.

### 3.1.5. *Vibration induced air-stepping*

A new way to activate the CPG in intact humans was recently explored by a Russian group [82,83]. In healthy subjects one leg was horizontally suspended in a weightless simulator. They were instructed to relax and not to intervene with the induced movements. It was shown that vibration of a muscle of the suspended leg could elicit cyclical hip and knee movements in both legs with rhythmic EMG activity, reciprocally organized in the muscles around the hip joint. These locomotor like-movements could be elicited by vibration of single muscles or of antagonistic muscles (which made the movement smoother and better coordinated). When successful, the movements can mimic either forward or backward locomotion or can switch between these two modes. In order to investigate whether these movements were critically dependent on periodic afferent signal from moving joints of both legs, some of the joints were fixed. Under these conditions, the movements of the free leg still persisted if muscles were vibrated. Interestingly, these movements could be facilitated if ground contact was simulated by delivering pressure by a small platform beneath the sole of the suspended leg. It was suggested that the constant inflow of proprioceptive afferents, due to the vibration, initiated and sustained the CPG activity. This evoked activity was certainly not strong enough for body support and propulsion, but at least it supports the view that the basic rhythm underlying locomotion can be generated involuntarily in humans.

### 3.1.6. *Neonate walking*

As will be described later (Part 2) more extensively, it is possible to evoke hindlimb walking in spinalized cats by applying a special training regime on a treadmill to restore locomotion. Based on this strategy it was shown that a walking pattern can be elicited in young spinal cats. These kittens were spinalized at thoracic level, 1–2 days after birth before any locomotor pattern was expressed. Even before a normal kitten showed any walking ability, these kittens could readily generate a

locomotor pattern [84]. These data reveal the strong innate ‘hard-wired’ character of the spinal control of locomotor patterns.

The possible existence of innate networks in humans is shown by the presence of primitive step-like movements in the newborn infant when externally supported (for review, see [85]). These movements reveal complex inter- and intra-limb coordinated muscle activity but lack some specific functions that are unique for human plantigrade locomotion [86]. Remarkably, these primitive characteristics of newborn stepping remain with the onset of real walking (including ankle hyperextension at the end of the step, hyper flexion of the hip and knee and excessive muscle activation), thus suggesting that mature walking may evolve from the newborn stereotyped movement pattern [87].

The innate character of the CPG is further supported by the well-known presence of coordinated movements during the prenatal phase. Monitoring such fetal movements showed that the coordination of the whole-body movements was very similar to the one seen in the newborn infant [88].

### 3.1.7. *Backward walking*

For several species, including crayfish and cat, it was proposed that the same neural mechanism (‘motor program’) is used for both forward and backward walking (FW and BW, respectively; for review see [89,90]). Several studies on BW in the cat [38,91,92], indicated that FW and BW could both be controlled by the same pattern generator.

It is well known that the CPG for FW controls various reflex pathways to ensure that reflex activations of given muscles occurs only at the appropriate times in the step cycle (phase-dependent modulation). Since BW is not an every day activity (i.e. not as overlearned as FW), one might expect that the phase-dependent modulation would reverse in case the CPG works in reverse if both FW and BW are controlled by the same pattern generator. Buford and Smith (1993) investigated responses to mechanical or electrical stimulation of the hind paw of the cat during different phases of BW [38]. They found that there were no major differences between the phase-dependent modulation of responses during FW and BW and that most of the differences could simply be explained by differences in muscle activation between the two forms of locomotion. Hence, at first sight these results did not confirm the hypothesis that FW and BW could both be controlled by the same pattern generator. However, it is possible that an insufficient number of phases was investigated to reveal the details of the phase-dependent modulation.

In humans, this ‘program reversal’ concept for BW was investigated based on the kinematics, biomechanics and EMG patterns during both FW and BW [93–95].

## ALL SUBJECTS

## ST

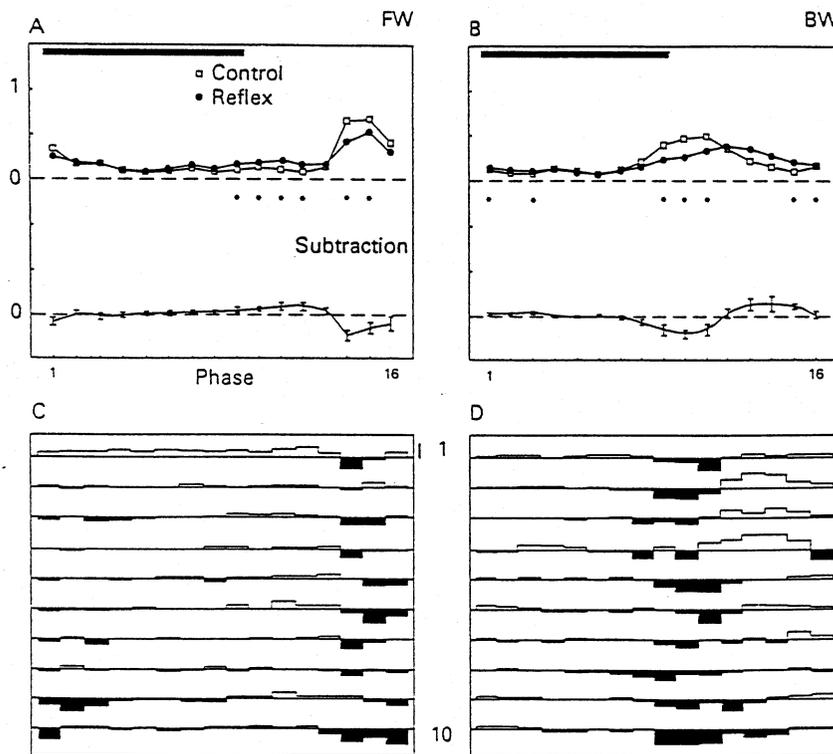


Fig. 1. Phase-dependent modulation of semitendinosus responses of 10 subjects for FW (left) and BW (right). Top (A,B): Average responses for all subjects ( $n = 10$ ). Data were first normalized for each subject individually. The significance (indicated by asterix) was tested on the basis of the subtracted responses (lower part of A and B). Horizontal bar: stance phase. Bottom (C,D): subtracted averaged ( $N = 10$ ) responses at 16 phases for the 10 subjects individually. Order of phases in C and D is the same as in A and B, respectively. Subjects were ranked according to the sum of the subtracted values of 16 phases, with subject 1 having the highest amount of facilitatory responses. Open bars (above zero) represent facilitatory and black bars (below zero) represent suppressive responses. Cal: in C and D the small dark vertical bars indicate the maximum level of background activity in the step cycle. From [96].

The leg trajectories and the EMG timing of hip muscles during BW resembled those of 'reversed-in-time' FW. Winter et al. (1989) suggested that "backward walking is almost a simple reversal of forward walking" [95]. Duysens et al. (1996) studied the regulation of the gain of cutaneous reflex pathways during BW [96]. The hypothesis was that if BW walking in humans is produced by a forward motor program, reversed in sequence, then the phase-dependent modulation pattern of cutaneous reflexes should be reversed in sequence during BW. At one of the 16 different phases of the step cycle an electrical stimulus train was applied over the sural nerve at two perception threshold (PT) both during FW and BW and unpredictable for the subject.

The responses following this kind of stimulation occurred with a latency between 70 and 80 ms (P2-responses) and had a clear phase-dependent modulation (see Fig. 1). To obtain the 'pure' responses (such as described in Fig. 1C,D), the background EMG activity was subtracted from the reflex responses. This made it

possible to study both facilitatory and suppressive responses. During FW, the subjects showed significant facilitatory responses in ST at end stance, and during the beginning of swing. At the maximum of spontaneous activity near the end of swing (phase 14), there was a reversal to a significant suppressive response (Fig. 1A). During BW a different modulation pattern than during FW was seen (Fig. 1B). Small facilitatory responses were present during the beginning of the stance phase. At the end of the stance phase a reversal towards suppressive responses could be observed, lasting throughout the beginning of swing and reaching a maximum when the control activity was at its peak. During the middle of swing there was a second reversal point, with the response sign changing from suppressive to facilitatory. Hence a phase-dependent reflex reversal is present both in FW and BW but the reversal had a different sign and occurred at a different time in the step cycle for these two forms of locomotion. Assuming that the phase-dependent modulation of reflexes during

FW is caused centrally through the intervention of a CPG-like structure it was argued that the modulation of cutaneous reflexes observed during BW is likely to be determined by the same motor program, but working in reverse. Based on the half-center idea of Brown, one may think of the CPG as controlling the two main parts of the step cycle, namely stance as well as swing. If one assumes that each of these centers works in reverse during BW as compared to FW then one expects suppressive responses to occur in early swing in BW, as was indeed observed in this study (Fig. 1A,B).

#### 4. Supraspinal activation of CPG

After transection of their spinal cord, most cats are not able to generate locomotor movements. This suggests that commands for the initiation of locomotor activity must be given at some level in the CNS above the lesion. By varying the level of transection of the neural axis, it was shown that the regions for initiation of locomotion are located in the brain stem, at supraspinal level (reviewed most recently by Rossignol (1996) [75] and Whelan (1996) [97]). In paralysed decerebrated cat, electrical stimulation of the MLR region can be used for the initiation of so-called 'fictive' locomotion (i.e. in absence of movement related afferent feedback; [98]). The existence of such MLR regions has also been described in different vertebrate species, including primates [50,99]. There are also clinical studies suggesting the existence of similar areas in adult man [64,100].

Another type of evidence for supraspinal control of the initiation of locomotion, is provided by the effects of substances mimicking the action of descending pathways (noradrenergic agonists and/or precursors; L-DOPA + nialamide or clonidine). It was shown that a walking pattern can be elicited in acute spinalized cats put on a treadmill (i.e. spinal cord disconnected from the so-called 'locomotor regions') after intravenous injection of such substances [27,33,39,101–104]. Furthermore, intravenous injection of clonidine (noradrenogenic agonist) in the chronic low spinalized adult cat, at a time when stable locomotion performance was achieved, could increase the step cycle duration and step length [102,113]. This was reflected in the increased duration of flexor and extensor activity bursts and increased angular excursions of joints [27]. Clonidine was also effective in triggering full weight bearing hindlimb walking on a treadmill in the low spinalized adult cat within the first week after spinalization, which was not seen if no drugs were used [102,105]. The noradrenaline precursor L-DOPA had comparable influences on the locomotor pattern but seemed especially efficient in increasing the amplitude of flexor activity [106].

In addition to a role in the initiation and termination of locomotion, the brain stem contains centers which are important for the modulation of locomotor activity. Reticulospinal, rubrospinal and vestibulospinal pathways are capable of influencing locomotor related neural circuits in the spinal cord [110]. Both amplitude modulation of EMG activity in different phases of the step cycle and shifts in timing of rhythm are seen as a result of stimulation of the descending tracts in the decerebrated cat [19,107] (for review see [13]).

#### 5. Conclusions

In the cat, there is good evidence for a spinal rhythm generating system, which most researchers in this field refer to as a locomotor CPG. This rhythm generating structure normally receives supraspinal and afferent input, yet in its absence it can still generate a pattern which often closely mimics the one seen in normal locomotion.

In contrast to the abundance of data in 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 a CPG, i.e. fictive locomotion, has no direct equivalent in humans. Nevertheless, several recent lines of research have provided observations which support the notion of a human CPG. This is of particular interest in view of recent advances made in the rehabilitation of patients with spinal cord lesions [108,109]. Treadmill training is thought by many to rely on the adequate afferent activation of a human CPG. In the next part of this review, the role of afferent activity in such rhythmic locomotor patterns will be dealt with.

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