Regulation of Arm and Leg Movement during Human Locomotion

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Walking can be a very automated process, and it is likely that central pattern generators (CPGs) play a role in the coordination of the limbs. Recent evidence suggests that both the arms and legs are regulated by CPGs and that sensory feedback also regulates the CPG activity and assists in mediating interlimb coordination. Although the strength of coupling between the legs is stronger than that between the arms, arm and leg movements are similarly regulated by CPG activity and sensory feedback (e.g., reflex control) during locomotion. NEUROSCIENTIST 10(3):000–000, 2004. DOI: 10.1177/1073858404264680

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> Machine-like regularity and fatality of reaction, although characteristic of spinal reflexes, is yet not exemplified by them to such extent that similar stimuli will always elicit from the spinal animal similar responses. This want of certainty as to response is an interesting difficulty attending the study of spinal reactions. The variation in the responses of the skeletal musculature manifests itself not only in regard to the extent of the movement, but also in regard to the direction of movement.
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> —Sir Charles S. Sherrington (1900) from "On the Innervation of Antagonistic Muscles. Sixth Note." Proc Roy Soc 66:66–67.

The fine regulation of rhythmic human movement typified by locomotion can be understood as the sublime interaction of a tripartite system consisting of supraspinal input, spinal central pattern generating circuits (CPG; see Box 1), and sensory feedback (see Fig. 1). Within this framework, activation of locomotion can be triggered by descending commands originating from the cortex voluntarily and likely mediated by the mesencephalic locomotor region of the brain stem (Whelan 1996). These descending commands delegate the motor command for rhythmic movement to the CPG networks controlling the arms and legs. Locomotor movement ensues, and a flood of peripheral feedback arrives at the spinal cord to inform the CNS of local conditions and to help sculpt CPG output. In this way, CPGs can be seen as basic building blocks on which behavior is predicated. Sensory feedback contributes strongly to the regulation of the basic pattern, and together the whole system results in seamless and smooth locomotor movement.

Generating the Locomotor Pattern

The smooth, coordinated movement between the hands and between the arms and legs are motor outputs that most people take completely for granted while they walk. However, the nature of coordination between the limbs is an area of uncertainty in motor control research. Certainly, both voluntary and involuntary (i.e., reflex) mechanisms are involved in this finely tuned coordination. Sir Charles Sherrington articulated the view that reflexes support and play roles in the generation and control of many kinds of movement when he described the role of reflexes within the "integrative action of the nervous system" (Sherrington 1947). Sherrington (1910) showed that the "crossed extension reflex" involving ipsilateral flexion and contralateral extension was a purposeful integrated reflex. Indeed, during rhythmic lower limb movements such as walking, elaborations of simple crossed extension reflexes could underpin the neural networks controlling locomotion. In his experiments on the quadruped, Brown (1911) provided compelling evidence of neural oscillators resident in the spinal cord. An extension of the "half-center" model suggested that discrete rhythm or pattern generating (i.e., CPG) networks were responsible for producing the basic locomotor rhythm. Interactions within and between flexors and extensors of each hindlimb were

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Box 1. Central Pattern Generator (CPG)

The term *locomotor CPG* refers to a functional network, generating the rhythm and shaping the pattern of the motor bursts of motoneurons (Grillner 1985; Grillner and Wallen 1985). For both the cat and humans, it is assumed that there is at least one such CPG for each limb and that these CPGs are located in the spinal cord (Fig. 2). Brown (Brown 1911, 1914) showed that activity in antagonist muscles in the leg can still be seen after cutting the spinal cord and after deafferentation (cutting the dorsal roots). Later, Anders Lundberg and his colleagues took up the idea of Sherrington that there is a similarity between the flexor reflex and the normal activation pattern of muscles during the swing phase. Injections of L-dopa could induce sustained alternating activity in flexors and extensors, as seen during locomotion (Jankowska and others 1967). Pattern-generating networks are quite flexible and can underlie different motor behaviors (reviewed in Grillner 1975; Clarac 1984; Pearson 1993). In cats, several different forms of walking (walk, trot, gallop, upslope, downslope, forward, and backward) are probably generated by the locomotor CPGs (Miller and others 1975; English and Lennard 1982; Buford and Smith 1990, 1993; Perell and others 1993; Pratt and others 1996). For human legs, the evidence for a control by the CPGs during walking is mostly indirect (Duysens and Van de Crommert 1998; Nielsen 2003). The basic similarity in spinal locomotor circuitry in cats and humans is demonstrated by experiments performed in patients with clinically complete spinal cord section. Electrical stimulation of nerves yielded reflex responses with similar characteristics as seen in the L-dopa networks in cat (Roby-Brami and Bussel 1987). Very rarely, some spontaneous rhythmic activity is seen after complete transection of the spinal cord (Bussel and others 1988). Sleep provides another means of isolating the spinal cord from some descending controls, and it is striking that involuntary stepping movements can indeed be seen under these circumstances (sleep-related periodic leg movements; (Coleman and others 1980). Direct spinal cord stimulation can probably also activate CPGs because it can elicit myoclonic stepping in patients with spinal cord injury (Gerasimenko and others 2002).

presumed to underlie the observed locomotor coordination. The available evidence based on studies of many invertebrate and vertebrate preparations indicates that central rhythm generators can produce coordinated motor patterns in isolation but that exquisite functional regulation of relevant motor patterns requires afferent and supraspinal input (Rossignol 1996; Stein and Smith 1997; Nielsen 2003). Unlike the case of lower animal models, such as the lamprey in which direct cellular measurements can be made, in the human we must rely on indirect evidence and inference. Using observations from other animal preparations as background, we can speculate and hypothesize about what should be observable if CPGs are active to control rhythmic human movement. The preponderance of evidence in spinal cord–injured humans during partial body weight support treadmill walking suggests that CPG mechanisms contribute to the locomotor pattern for walking (Barbeau and Rossignol 1994; Dietz and others 1994; Dietz 1997; Harkema and others 1997; MacKay-Lyons 2002). Furthermore, it has been shown that afferent feedback contributes to the modulation of the CPG output (Duysens 1998; Duysens and Van de Crommert 1998; Van de Crommert and others 1998). Thus, modulation of motor activity due to changes in peripheral feedback during movement can be used to infer CPG activity. In this way, activity in a given feedback pathway can be used as a neural probe of CPG activity. As a salient example, the modulation of cutaneous reflexes during rhythmic movement has been suggested to infer activity of a central pattern generator during human walking (Duysens and Tax 1994; Zehr, Hesketh, and others 2001). Research suggests that this concept also obtains in leg cycling (Ting and others 1999). CPG activity could explain observations of phase and task dependency via premotoneuronal gating of afferent feedback (Duysens and Tax 1994; Duysens and Van de Crommert 1998; Dietz 2002a, 2002b; MacKay-Lyons 2002). It has also been shown recently that both cutaneous and H-reflexes are phase and task dependent during arm cycling (Zehr and Chua 2000; Zehr and Kido 2001; Zehr and others 2003) and during the natural arm swing of walking (Zehr and Haridas 2003). These observations support the suggestion that rhythmic arm movements are partly regulated by CPGs just as documented for the leg (Dietz and others 2001; Dietz 2002a, 2002b; Zehr 2004; Fig. 2).

Sensory Control of the Legs during Locomotion

An important question is what the role of these CPGs is in the gait of neurologically intact subjects. Most of our knowledge comes from cat studies. From these studies, it is known that sensory feedback, elicited during gait, acts directly on the CPG to aid the phase transitions during the step cycle (Duysens and Pearson 1980; Conway and others 1987). In particular, in many species, one can demonstrate load-resisting reflexes during the gait stance phase, and it is known that these reflexes help to control the onset of the ensuing swing phase (for review, see Pearson 1993; Duysens and others 2000). When limb

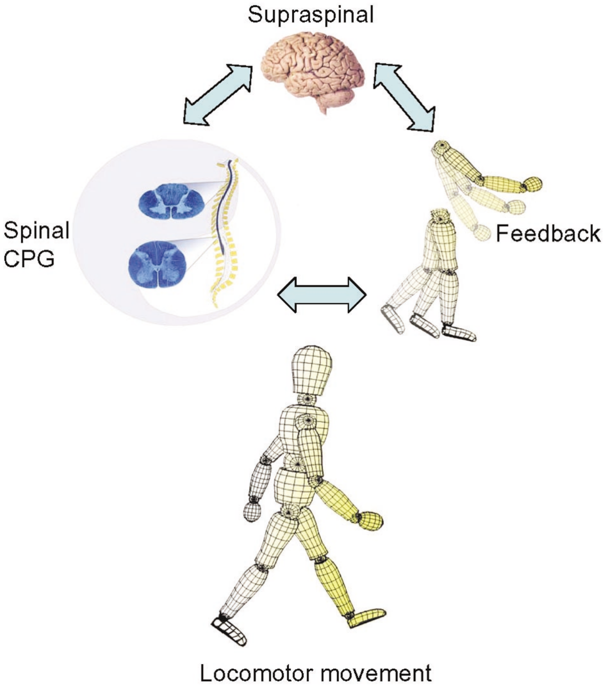

Fig. 1. General outline of the interrelationships between spinal central pattern generators (CPG) activity (spinal cord sections shown), supraspinal input (brain shown), and sensory feedback arising during movement (moving arms and legs) in creating and sculpting human locomotion (shown at bottom).

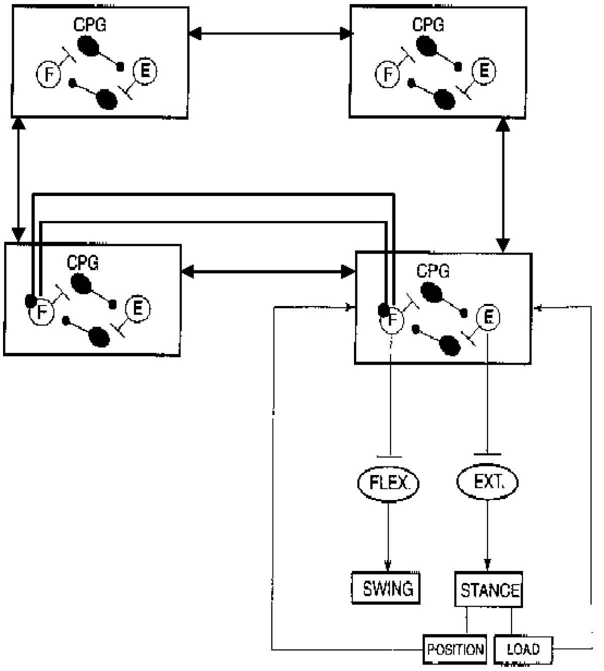

Fig. 2. Current hypothesis on the spinal organization of locomotion and its reflex regulation. The central pattern generator (CPG) contains flexor (F) and extensor (E) half-centers, controlling flexors (Flex) and extensors (Ext), respectively. Each limb is controlled by such a CPG (*top*, two arms, bottom two legs). Furthermore, there are interconnections between these various CPGs. Some of these are schematically shown for the legs. The main connections are such that activity in a flexor center on one side inhibits activity in the corresponding contralateral flexor center. Each leg separately also contains feedback loops as shown for the left leg only. These loops allow automated switching between the stance and swing phases (see text).

loading decreases, such as occurs at the end of the stance phase, the extensor reinforcing feedback is reduced and the onset of swing is facilitated in the unloaded leg. However, the problem is that this feedback can be demonstrated clearly only in animals with reduced descending control from the brain. In intact cats, the manipulation of just a single type of sensory feedback is almost never sufficient to affect phase switching (Duysens and Stein 1978; Whelan and Pearson 1997). The effects on force-feedback, as originally observed in decerebrate cats, were either not seen in the intact cat or when seen, they appeared much weaker than in the decerebrate animal.

Not surprisingly, in humans, the best evidence comes from newborns, in whom descending supraspinal control is not yet fully developed. Infant stepping occurs in the near absence of mature corticospinal connections, yet infants show well organized and location-specific reflex responses to mechanical disturbances during walking in various directions, although these require very different interlimb coordination (Lamb and Yang 2000; Pang and Yang, 2000, 2002; Pang and others 2003). It was shown that limb loading and hip position are powerful signals for regulating the stepping pattern in human infants (Yang and others 1998; Pang and Yang 2000), in much the same way as that reported in decerebrate and spinal cats (Grillner and Rossignol 1978; Duysens and Pearson 1980; Hiebert and others 1996). Adding manual loading during the stance phase of gait delayed the onset of the swing phase (Pang and Yang 2000). On the other hand, limb unloading was shown to be an important cue for the stance to swing transition not only during forward walking (Pang and Yang 2000, 2001) but also during walking sideways or backward (Pang and Yang 2002). Unloading effects were studied by placing a piece of cardboard under the foot and pulling the cardboard.

In contrast, similar transient loading or unloading experiments performed on adult humans have yielded relatively minor effects, at least in terms of phase transitions. Increased loading increased the extensor electromyography (EMG) amplitude but did not change the duration of the step cycle (Stephens and Yang 1999). Why is there this difference between intact and nonintact or “incomplete” cats or humans? For many motor functions, such as respiration, mastication, or micturition, the cortex is known to be able to control automated functions executed at lower CNS levels. In all these cases, the lower control levels can still function under some circumstances, but voluntary control can take over. For locomotion, this is also very likely to be the case. Under normal conditions, gait is highly automated and requires few cognitive resources. However, cortical control is increasingly important for gait under difficult conditions (uneven terrain and changes in internal biomechanical constraints). In pathology, this is often overly obvious as patients lose the automaticity of gait and become dependent on cortical control. Under cognitive load (e.g., double task), the gait in these patients deteriorates (de Visser and others 1998). A second reason why it will be difficult to demonstrate the use of reflex cues, such as unloading at end stance, is that such cues normally do not operate in isolation. The decision to initiate flexion is likely to be controlled by a multitude of elements, only one of which is the load feedback (others could involve hip position signals, for example, as demonstrated by Andersson and Grillner 1981). From there, to conclude that one single type of input is not effective for the control of locomotion is dangerous. For many years, for example, it was believed that cutaneous input from the foot was unimportant for the control of gait because Sherrington (1910) failed to see gross gait abnormalities after denervation of foot pad afferents and concluded that cutaneous reflexes are not indispensable to locomotion. Recently, however, these experiments were repeated, and it was found that deficits were indeed small during level treadmill walking early after the denervation (1–3 days), but under more difficult situations, there were clear abnormalities (Bouyer and Rossignol 2003a, 2003b). The cats could not walk across a ladder, for example, or they had difficulties walking on inclines. When the same cats were spinalized, these cutaneous inputs became even more critical for foot placement during locomotion (Bouyer and Rossignol 2003b). After spinalization, the completely denervated cats never recovered plantar foot placement or normal weight bearing of the hindquarters despite an extensive period of treadmill training. If only partial denervation was applied, then there was a substantial recovery. These experiments indicate that deficits are more clearly expressed in the absence of supraspinal influences. The same is true for the inverse type of experiments in which afferents are activated rather than eliminated. In animals with reduced supraspinal control, the activation of cutaneous afferents from the foot has dramatic effects on the locomotor cycle and there is therefore little doubt that it has rather direct connections with the CPGs (Duysens and Pearson 1976; Duysens 1977).

Because cutaneous input is so important, it is no surprise that cutaneous reflexes are tightly controlled during locomotion and that phase-dependent modulation is present even in "fictive locomotion" when actual movement is absent (Andersson and others 1978; LaBella and others 1992). Indeed, afferent feedback not only affects CPGs but is also more directly connected to motoneurons through various reflex pathways, which are largely under the control of the CPG (Burke 1999). In this way, it is ensured that reflex activations of given muscles occur at the appropriate times in the step cycle and are suppressed at other times. This phase-dependent modulation was extensively studied for human walking through electrical stimulation of cutaneous afferents in the foot (Yang and Stein 1990; Tax and others 1995; Van Wezel and others 1997; Zehr and others 1997). Such stimulation elicits responses at a latency of about 75 to 80 ms in both ipsilateral and contralateral leg, and the amplitude of these responses was dependent on the phase of stimulation. The amplitude of these so-called P2 or middle latency responses could even change from facilitatory into suppressive responses within the step cycle (Yang and Stein 1990; Tax and others 1995; Van Wezel and others 1997; Zehr and others 1997). These P2 responses were mostly evaluated during gait because it is known that cutaneous reflexes are facilitated during walking as compared to standing (Duysens and others 1993; Komiyama and others 2000). Furthermore, it was shown that stimulation of different cutaneous nerves in the foot (sural, peroneal, and posterior tibial nerves) yielded P2 responses with both nerve-specific and nerve-aspecific features (Van Wezel and others 1997; Zehr and others 1997; Zehr, Stein, and others 1998). Facilitatory P2 responses were present in the ipsilateral (i) tibialis anterior (TA) at the end of the stance phase when the sural nerve was stimulated but not, or very little, when the other cutaneous nerves (peroneal and posterior tibial nerves) were activated (Yang and Stein 1990; Van Wezel and others 1997; Zehr and others 1997). In contrast, suppressive P2 responses occurred in the TA at the end of the swing phase independent of the nerve stimulated. The striking observation that suppressive responses, obtained at end swing and early stance, were a very constant feature of various forms of stimulation is summarized in Figure 3.

The responses shown are subtracted responses, obtained when background activity is subtracted from the reflex responses. Stimulation of the three main nerves to the foot (sural, peroneal, and tibial) yielded a variable amount of TA facilitation at end stance. However, all three types of stimulation produced consistent suppressive responses at end swing. More recently, it was found that similar responses can be obtained for stimuli not related to the foot. Stimulation of the rectus femoris (RF) yielded some facilitation in TA at end stance, but at end swing, the responses were suppressive (Van de Crommert and others 2003); see Fig. 3). Stimulation of the nerve innervating the skin above the RF also gave similar responses (not illustrated), but they were much smaller than those obtained with foot nerve stimulation or with RF pulses. It has been shown that stimulation during walking of a cutaneous nerve innervating the hand also yields suppression in TA at end swing (Haridas and Zehr 2003). Hence, the suppressive response in TA emerges as a very constant feature, regardless of the type of stimulation. The presence of suppressive P2 responses in TA at the end of the swing phase following stimulation of afferent sites in the upper and lower leg during human walking indicates that there is widespread convergence of suppressive pathways to TA. During unperturbed walking, the TA shows two activity periods, one at end stance and one at end swing.

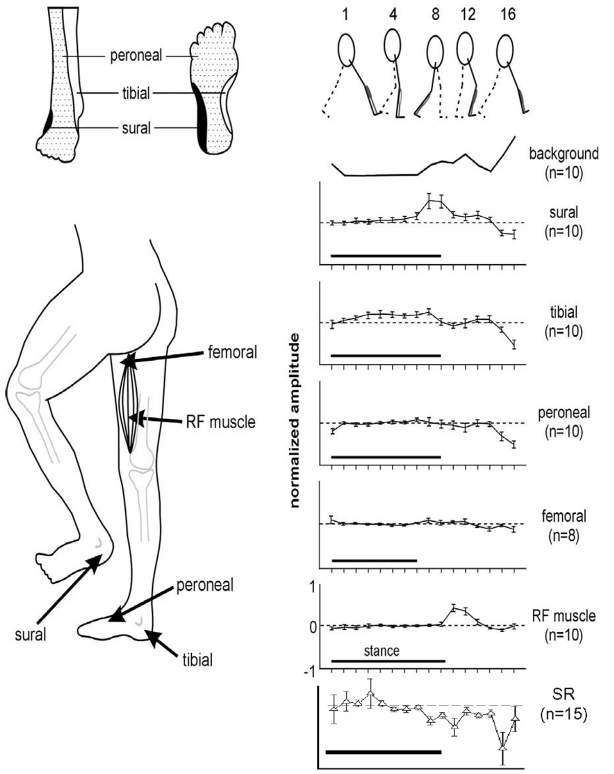

Fig. 3. Summary of reflex reversals obtained by stimulating different nerves or a muscle. The right figure shows the places of stimulation, the left the different reflex responses, obtained in the whole population. The black horizontal line indicates the stance phase. In all stimulations, a suppression of responses can be observed at the end of the swing phase. RF = rectus femoris. Adapted from Duysens and others (2004).

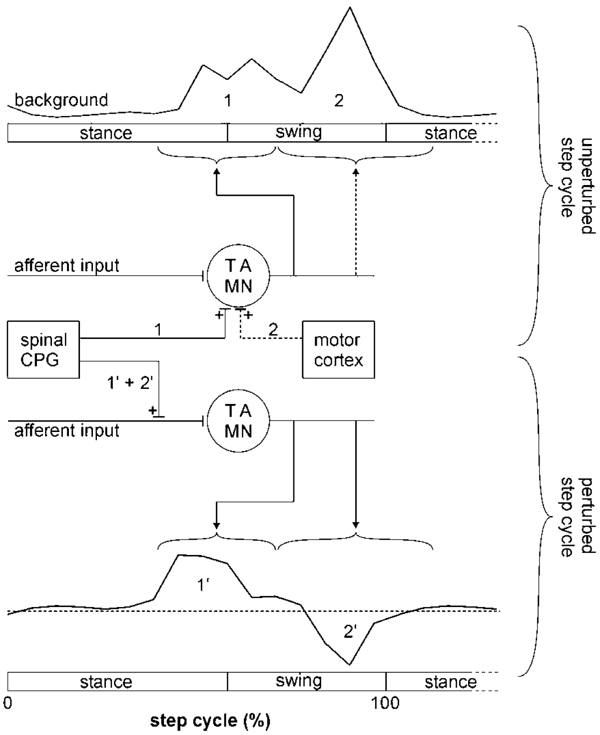

Fig. 4. Scheme explaining the origin of tibialis anterior (TA) background activations during gait and the phase-dependent modulation of P2 responses. Model of the possible structures involved in the control of the different parts of the background and reflex activity. The dotted line is the influence from the cortex, and the solid line is the spinal central pattern generator (CPG). Adapted from Duysens and others (2004).

It is suggested that the first burst is primarily due to output of a spinal CPG whereas the second is more of cortical origin (see Fig. 4).

The support for the latter proposal stems from several lines of evidence. Clinical observations on stroke patients clearly show that especially the second burst (end swing) is affected after damage to the motor cortex. The transcranial magnetic stimulation studies during gait have also pointed toward a strong involvement of the motor cortex in the generation of this activity (Schubert and others 1997; Pijnappels and others 1998; Capaday and others 1999; Christensen and others 1999). During perturbed gait, that is, after stimulation of various skin sites, the main effect at end stance is a facilitation, and it is thought that the spinal CPG plays an important role here. In studies on motionless or spinal cats, the facilitation of cutaneously evoked responses persists, indicating that it can occur in the absence of movement and/or corticospinal connections (Andersson and others 1978; Schomburg and Behrends 1978; LaBella and others 1992). However, these responses are equivalent to earlier (P1) responses and not to the P2 responses, which have been studied extensively in humans. In cats, there is no strong evidence for spinal P2 responses.

Whatever the mechanism of the modulation, it is clear that the observed changes in reflex responses have behavioral consequences in humans.

As illustrated in Figure 5, the facilitatory TA responses in early swing lead to increased dorsiflexion following sural nerve stimulation. In contrast, in late swing, the responses in TA are suppressive, and this results in increased dorsiflexion. For the tibial nerve, the results are comparable, but for the peroneal nerve, innervating the foot dorsum, the main result is plantar flexion, irrespective of whether the responses occur in early or in late swing (Box 2).

A separate question is whether phase-dependent modulation also depends on corticospinal input. All studies with patients with defective corticospinal pathways have shown a decrease in the depth of the phase-dependent modulation, but this can largely be contributed to two factors, namely, the general decrease in the amplitude of the responses and the reduction or disappearance of the suppressive responses at end swing in muscles such as TA. In patients with spinal cord injury (SCI), the main difference, in comparison with normal subjects, was an absence of the suppressive responses in TA at end swing (Jones and Yang 1994). In general, the end stance facilitations of cutaneous reflexes persist relatively better in

Box 2. Clinical Implications

Because cutaneous reflexes appear important for the regulation of gait and because these responses require an intact cortex in animals such as the cat, the question arises whether for humans, the P2 responses also depend heavily on an intact corticospinal pathway and whether lesions in this pathway affect reflex modulation and gait. After stroke, Zehr, Fujita, and others (1998) observed that P2 responses were small or absent during walking. Patients with hereditary spastic paraparesis have a lesion in the corticospinal tract, and they also show decreased P2 reflexes (Duysens and others 2004). Jones and Yang (1994) used tibial nerve stimulation to study phase-dependent modulation of P2 responses during gait in spastic patients (mildly affected spinal cord injury), and they reported that responses were smaller than normal. Inversely, several studies have shown that cortical stimulation facilitates P2 responses. In parallel, Nielsen and others (1997) showed that during tonic voluntary contractions in immobile subjects, the discharge probability of tibialis anterior motor units following combined electrical sural and magnetic cortical stimulation was larger than the algebraic sum of the discharge probability following each of the two stimuli separately. This facilitation was not present when electrical (direct) cortical stimulation was applied instead of magnetic cortical stimulation. Nielsen and others (1997) concluded that the magnetic facilitation was due to increased susceptibility of the corticomotoneuronal cells rather than to an interaction between the cutaneous and corticospinal volleys at a subcortical site. In other words, it was suggested that facilitation of corticospinal input onto cutaneous reflex pathways was enhanced. Later, these results were confirmed for gait. Motor-evoked potentials (MEPs) were more facilitated by prior sural-nerve stimulation than the algebraic sum of the control potentials and the cutaneous facilitation in the EMG when evoked separately, suggesting a transcortical pathway contributing to cutaneous reflexes during walking. Similar results were obtained during gait. At end stance, the sural nerve–induced responses are facilitated when combined with transcranial magnetic stimulation (Pijnappels and others 1998; Christensen and others 1999).

humans with reduced supraspinal control. For this reason, it is proposed in the scheme shown in Figure 4 that the modulations of the reflexes are primarily due to actions of the CPG and not of the cortex.

For muscle spindle reflexes, there are also clear indications for phase-dependent modulations, but these often follow different rules than those observed for cutaneous stimulation. In biceps femoris, for example, the tendon jerk reflex is at a maximum near the end of the swing phase (Van de Crommert and others 1996; Faist and others 1999). This facilitated stretch reflex lends support to the hypothesis that activation of this muscle at end swing may be partly generated through stretch reflexes (Prochazka and others 1979; Perret and Cabelguen 1980; Wisleder and others 1990; Van de Crommert and others 1996; Verschueren, Swinnen, and others 2002). The facilitation occurs in a period when this muscle is normally very active, when sensitivity to cutaneous stimuli from the foot is at a maximum (Duysens and others 1995) but when cutaneous reflexes to this muscle are suppressed (Duysens and others 1996). During this critical period, just prior to foot placement, there apparently is a highly specialized control of sensory and reflex pathways.

The same applies for early stance. A tendon tap study on human quadriceps showed that for this muscle, the reflex amplitudes were at a maximum in early stance, in agreement with increased H-reflex amplitude in the same period (Dietz, Discher, and others 1990; Dietz, Faist, and others 1990). This is functionally meaningful because these strong proprioceptive reflexes can contribute to the sudden loading in this period just after weight acceptance (as first proposed for running by Dietz and others 1979). Presumably for the same reason, the soleus stretch reflexes are at a maximum in this part of the step cycle. However, one can question whether this soleus contribution is important for the normal soleus activity during stance. Vibration of the triceps surae tendon has very little effect (Ivanenko and others 2000; Courtine and others 2001; Verschueren, Brumagne, and others 2002; Verschueren, Swinnen, and others 2002). Furthermore, during human gait, there is a general suppression of soleus H-reflexes when compared to standing (Morin and others 1982; Capaday and Stein 1986). These negative findings are possibly due to the selective activation of group I afferents. There is growing evidence that group II afferents are much more important in providing functionally important feedback during the stance phase (Sinkjaer and others 2000; Grey and others 2001, 2002; Nielsen and Sinkjaer 2002). This confirms earlier suggestions that these afferents are important in reactions to perturbations during gait (Berger and others 1984; Dietz 1992) or standing (Schieppati and Nardone 1999). Activation of these group II afferents possibly explains why stretches of these muscles elicit such large reflexes during gait. Yang and others (1991) used a pneumatic device to deliver brief ankle rotations during walking and estimated that the stretch reflex could contribute up to 30% to 60% of the activation of soleus during walking, especially during the early part of stance. A similar conclusion was reached by Sinkjaer and others (2000), who used a semi-

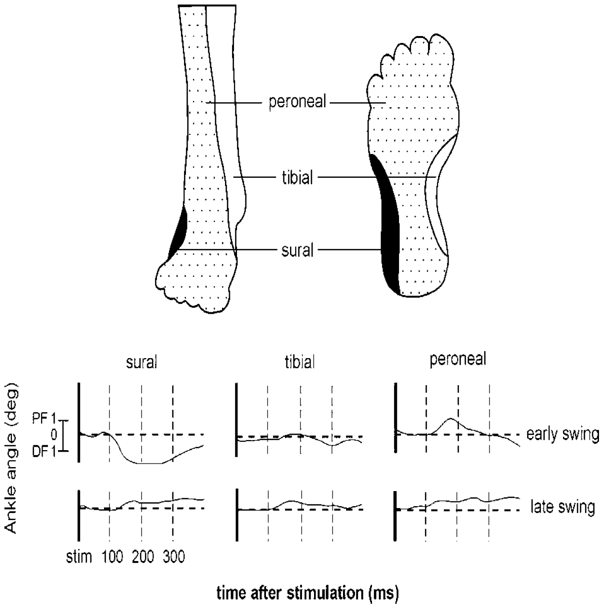

Fig. 5. Kinematics of reflex reversals. Changes in ankle joint during different cutaneous stimulation during gait. The figure is based on results from only two studies (Van Wezel and others 1997; Van de Crommert and others 2003), but other studies have yielded similar results (Yang and Stein 1990; Zehr and others 1997; Zehr, Stein, and others 1998; Haridas and Zehr 2003; Duysens, Tax, and others 1992). *Top*, the innervation sides of the different nerves. PF = plantarflexion, DF = dorsiflexion. Adapted from Duysens and others (2004).

portable stretch device to study soleus stretches in various phases of the step cycle.

Reflex Control of the Arms during Locomotor Movement

Until quite recently, it has not been very clear to what extent CPGs or reflex control are involved in the control of rhythmic upper limb movement. It has been shown clearly (see above) that reflexes in leg muscles during walking show extensive modulation during the locomotor cycle. Phase and task dependence of reflexes evoked in leg muscles by stimulation in the leg are clearly expressed during both walking and leg cycling and may relate to the function of the reflexes. However, the extent to which these observations apply to responses in the arms has been less clear. In the quadrupedal cat, this concept was extended to the forelimb (Drew and Rossignol 1987). It was shown that there was a similar modulation pattern for the cat forelimbs as was documented in the hindlimb. Thus, despite the obvious differences in use of the forelimbs and hindlimbs (e.g., exploratory reaching and manipulation with the forelimbs vs. locomotion with the hindlimbs), there was seen a similar underlying set of neural mechanisms to regulate reflexes during rhythmic movement of the cat forelimb. This has significant behavioral relevance during quadrupedal locomotion where it is necessary to control rhythmic movements of both forelimbs and hindlimbs. However, during human locomotion, there is no obvious need to move the upper limbs in concert with the lower limbs. In fact, we can walk quite easily with no obvious arm movement whatsoever. Yet we do naturally move our upper limbs in rhythmic patterns while running and walking, and it may be that similar mechanisms regulate the modulation of reflexes in our upper limbs as we have seen in the lower limbs.

A series of investigations into this issue has recently been conducted (reviewed in Zehr 2004). In these experiments, participants were asked to perform rhythmic locomotor-like arm cycling motions or walk naturally on a treadmill. It was shown that both cutaneous and H-reflexes in arm muscles depend strongly on the portion of the movement in which they are evoked (phase dependent) and on the specific motor behavior performed (task dependent) during arm cycling (Zehr and Chua 2000; Zehr and Kido 2001; Zehr and others 2003). Furthermore, it was also documented that there is extensive modulation of cutaneous reflexes in arm muscles during the natural arm swing of walking (Zehr and Haridas 2003). A full cutaneous reflex reversal can also be seen in some arm muscles in which reflexes may be excitatory during static contraction but inhibitory during arm cycling (see Fig. 6, *top*). H-reflexes are also affected by task. During arm movement, H-reflexes in the forearm flexor carpi radialis were strongly inhibited compared to the amplitude expressed during static contraction (see Fig. 6, *bottom*). Thus, extensive task dependence is seen during rhythmic arm movement in different reflex pathways.

As described in the previous section, the issue of the location of nerve stimulation (nerve specificity of cutaneous reflexes) in leg muscles during walking has fundamental implications for reflex function. This issue was also addressed during arm cycling (Zehr and Kido 2001). Nerve specificity was seen when stimulating three different cutaneous nerves innervating the hand (median, ulnar, superficial radial) during human cycling. Earlier, it had been indirectly shown by Cavallari and others (1985) that some portion of nerve specificity may be seen in the human upper limb. It was shown that there was an interaction between cutaneous and Ib input that depended on the site of cutaneous stimulation. Ib facilitation from wrist extensor muscles to wrist flexor muscles was increased by dorsal hand cutaneous stimulation but not by stimulation of the palm (Fig. 7).

Contralateral movement has a very strong effect on H-reflexes in the legs (for review, see Brooke and others 1997). During rhythmic arm cycling, we found that contralateral movement (whether active or passive) did not have a significant suppressive effect on the forearm H-reflex but that movement of the ipsilateral arm did modulate the H-reflex (Zehr and others 2003). Motion at the wrist in the stimulated arm has also been shown to alter forearm H-reflexes (Carson and others 1999), but this may have been due to changes in EMG activity of the forearm muscles. Asymmetrical flexion-extension at the wrist or elbow were also shown to significantly reduce

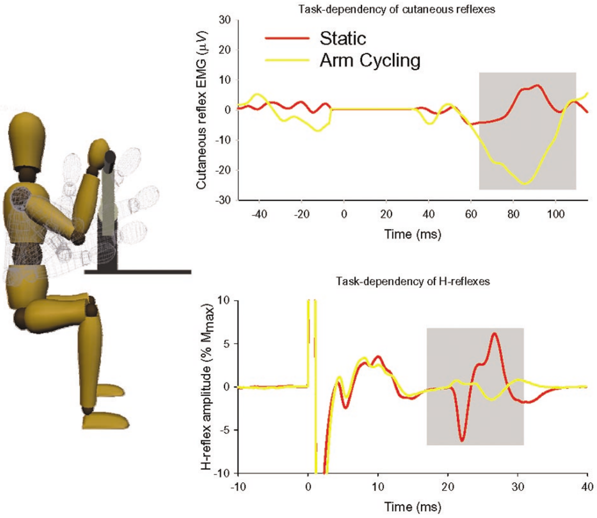

Fig. 6. Reflex amplitude depends strongly on the motor task. Rhythmic arm cycling was performed (see cartoon at right), and task dependency of cutaneous (*top*) and H-reflexes (*bottom*) was observed. Note the attenuation of forearm H-reflex amplitude during cycling (adapted from Zehr and others 2003) and the reversal in the sign of the middle latency cutaneous reflex in anterior deltoid muscle (adapted from Zehr and Kido 2001) highlighted by the rectangles.

flexor carpi radialis H-reflex amplitude (Brooke and others 2000). These observations represent a difference in the reflex linkages seen between the arms as compared to those shown between the legs. It may be that this reflects a weaker coupling between neural circuits (i.e., CPGs) for the arms as compared to those for the legs. This flexibility of coupling may be functionally related to the more common individuated use of the arms as compared to that seen for the legs during daily motor behaviors. It is also possible that this reflects a larger bimanual coordinative role of the cortex in assisting with coupling between the CPGs regulating each arm.

Cutaneous reflexes are modulated with position in the movement cycle (i.e., phase dependent) when active leg cycling is performed (Brown and Kukulka 1993), but this phase dependency is absent during passive movement of the stimulated leg (Brooke and others 1999). Cutaneous reflexes are typically of larger amplitude during arm cycling as compared to static contraction, and sometimes the task dependency can also be expressed as a switch in the sign of the cutaneous reflexes from facilitatory during static contraction to inhibitory during movement. Interestingly, this task dependency is very similar to that seen during leg cycling (Zehr, Hesketh, and others 2001) and suggests the possibility of similar underlying neural mechanisms.

Data on the mechanical outcomes of reflexes in arm muscles during locomotor movement are currently lacking. However, based on the very similar organization of reflexes in the arms and legs, it is probable to anticipate similar mechanical outcomes.

Interlimb Coordination during Walking: Putting the Arms and Legs Together

Sir Charles Sherrington (Sherrington and Laslett 1903) demonstrated reflex interconnections between the cervical and lumbar spinal cord in the cat (interlimb reflexes). More detailed information on this issue was provided by Lloyd and McIntyre (1948), but it was not until much later that the extensive propriospinal interlimb connections in the cat were revealed (Gernandt and Megirian 1961; Gernandt and Shimuamura 1961; Miller and others 1973; Skinner and others 1980). Interlimb reflexes were suggested to assist in the coordination of upper and lower limbs (or forelimbs and hindlimbs in the cat) during locomotion. Indeed, based on the study of coordination of the forelimbs and hindlimbs during swimming, walking, and air stepping, it has been suggested that propriospinal interlimb reflex pathways are the primary locus of quadrupedal interlimb coordination (Miller and others 1975). There is a demonstrable linkage between rhythmic hindlimb and forelimb movements resulting in coordinated movement in the cat (Miller and others 1975). It has been shown that both ascending (Gernandt and Megirian 1961) and descending (Skinner and others 1980) pathways may assist in this coordination between the cervical and lumbar spinal cord. Interestingly, several studies of interlimb reflexes during movement have shown many of the same characteristics of modulation that are observed in segmental reflex pathways. Phase-dependent reflex transmission from the forelimbs to hindlimbs has been shown during fictive locomotion in the cat (Schomburg and others 1977), and a reflex reversal of inputs from the forelimb onto the hindlimb was shown during stepping in decerebrate cats (Miller and others 1977).

Reflexes from forelimb afferents onto hindlimb motoneurons were modulated according to the phase of movement during fictive locomotion in the cat (Schomburg and others 1977). Furthermore, during treadmill stepping, interlimb reflexes were modulated according to the step cycle and were shown to reverse in sign (Miller and others 1977). These reflex connections make functional sense in the rapid transmission of information about the terrain from the forelimbs (the first to contact the environment in a quadruped) to the hindlimbs so that appropriate compensations can be made. When extrapolating to the human, the concept is that the feet are the first to make contact with the environment, and rapid pathway signaling corrections and protective responses to the upper limbs would be desirable.

Delwaide and others (1977) observed that changes in the posture of the upper limb could alter the tendon reflexes in soleus, quadriceps, and biceps femoris muscles, suggesting that propriospinal connections could link rhythmic movement and reflexes between the upper and lower limbs. The pattern of responses was reciprocal in that forward flexion of the arm on the ipsilateral side or backward extension of the contralateral arm similarly

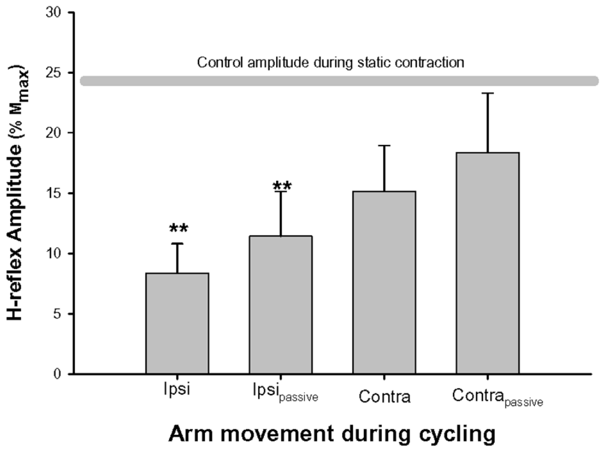

Fig. 7. Movement of the ipsilateral arm has the largest effect on H-reflexes in forearm muscles. Note that both active and passive movements significantly reduce reflex amplitude compared to control condition (shown by horizontal gray line). Movement of the contralateral arm had a nonsignificant effect. These observations contrast with those seen in the leg during rhythmic leg movement and suggest relatively weaker coupling between the arms than that seen between the legs. Data adapted from Zehr and others (2003).

affected the reflexes. This pattern was reversed when the arm positions were switched. Delwaide and Crenna (1984) were the first to show that stimulation of tactile afferents in the human median and sural nerves could evoke reflex changes in the upper and lower limbs. Median nerve stimulation caused a large facilitation of the soleus H-reflex at ~70 ms latency. A similar facilitation of the biceps brachii tendon jerk was found at ~90 ms in concert with a suppression of triceps brachii tendon jerk after sural nerve stimulation. Thus, there was a reciprocal pattern between flexor and extensor muscles, suggesting a coordinated and possibly functional linkage. Piesiur-Strehlow and Meinck (Piesiur-Strehlow and Meinck 1980; Meinck and Piesiur-Strehlow 1981) also demonstrated propriospinally mediated reflex conditioning of muscles in the lower limb after painful cutaneous stimulation of arm nerves using H-reflex and measurement of changes in tonic EMG. However, in the case of these noxious cutaneous inputs, the pattern was quite similar in all muscles: Inhibition occurred, followed closely by excitation with no reciprocity between antagonist muscles. Kearney and Chan (1979, 1981) showed that large reflexes, reciprocal in sign between antagonists, could be evoked in upper limb flexor and extensor muscles after both cutaneous and muscle afferent stimulation. A descending connection from brachial to lumbosacral muscles was also demonstrated by the intrathecal measurement of lumobsacral cord potentials (Sarica and Ertekin 1985). Thus, despite some differences in the specific nature of any reflex responses in humans, the available data suggest that interlimb reflex connections are present in human subjects. Calancie and colleagues (Calancie 1991; Calancie and others 1996) studied reflexes arising from both cutaneous (distal tibial nerve) and muscle afferent inputs (tibial and median nerves) in neurologically intact and spinal cord–injured subjects. Interlimb reflexes, particularly cutaneous reflexes, were large and widespread after SCI. Zehr, Collins, and others (2001) stimulated the superficial peroneal (SP; innervating the foot dorsum) and superficial radial (SR; innervating the later margin of the dorsum of the hand) nerves in subjects maintaining tonic contractions and observed interlimb cutaneous reflexes in leg muscles (particularly those acting at the knee and ankle) after stimulation of the SR nerve in the hand as well as in arm muscles (particularly the shoulder and wrist muscles) after stimulation of the SP nerve in the foot.

Because a strong perturbation to the human swing limb can easily result in a fall, thus necessitating the use of the upper limbs to break the fall, reflex activation of upper limb muscles should be observed after SP stimulation during locomotion. That is, when we trip or stumble while walking, we must put our arms out to help brake our fall or to help regain our balance. McIlroy and Maki (1995) described compensatory arm muscle activation during perturbation of upright stance and suggested that the arms were being used to stabilize posture. Furthermore, phase-dependent modulation of postural activity of upper and lower limb muscles during walking has been documented (Hirschfeld and Forssberg 1991). However, although anticipatory reactions were studied in that study, it is tempting to speculate that reflexes acting via propriospinal or transcortical pathways may be active in a truly coordinated whole-body response to the perturbation. That is, interlimb reflexes evoked by stimulation of the foot surface may act to coordinate protective responses in the upper body.

During treadmill walking, it was recently shown that interlimb cutaneous reflexes in both the arms and legs evoked by stimulation at the hand (SR) and foot (SP) were phase modulated during the walking cycle and were also task dependent (Haridas and Zehr 2003). Large cutaneous reflexes were evoked in shoulder muscles by stimulation at the foot during walking. It was also observed that there is a reciprocally organized pattern and coordination of reflex responses from hand to foot and from foot to hand. In arm muscles such as the posterior deltoid, SP nerve stimulation evoked inhibition in ipsilateral posterior deltoid muscle during stance whereas facilitation was seen in the contralateral posterior deltoid muscle during contralateral stance. These so-called crossed effects were seen in the same relative part of the step cycle for each arm as has been documented for the leg. With stimulation at the wrist (SR n), interlimb cutaneous inhibition was recorded in ipsilateral and contralateral TA during late swing, consistent with SP nerve stimulation (see also the third section of this article). In the ankle extensor contralateral medial gastrocnemius muscle, a reversal between the two different nerve stimulation protocols was observed. With SR stimulation, inhibition was seen in the contralateral medial gastrocnemius muscle during stance, but with SP stimulation, facilitation was seen in the same muscle at the same part

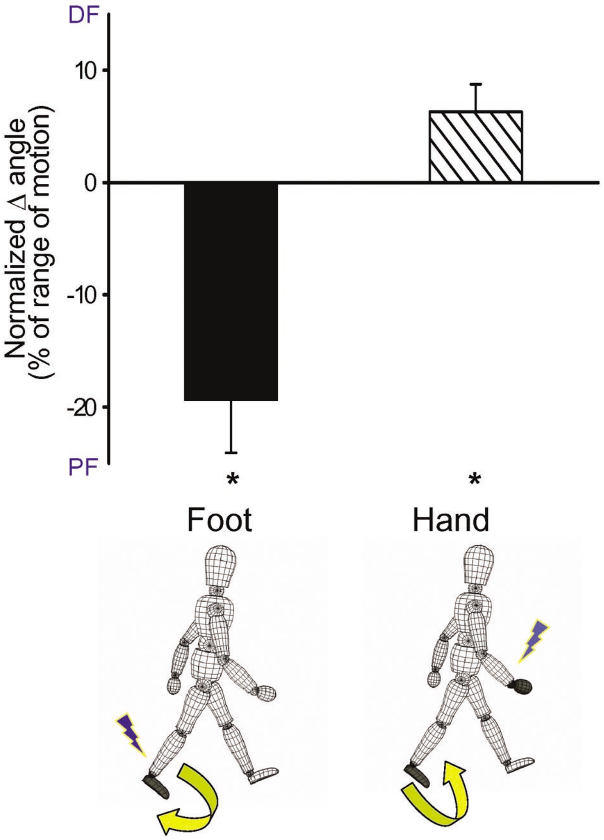

Fig. 8. Mechanical outcomes of cutaneous interlimb reflexes during walking. During walking, stimulation of the superficial peroneal nerve at the ankle (labeled as *foot* and shown by the lightning bolt in the cartoon at bottom left) produces plantarflexion (see also Fig. 5). Stimulation of the superficial radial nerve at the wrist (labeled as *hand* and shown by the lightning bolt at bottom right) produces dorsiflexion during the same portion of the walking cycle. Data adapted from Haridas and Zehr (2003).

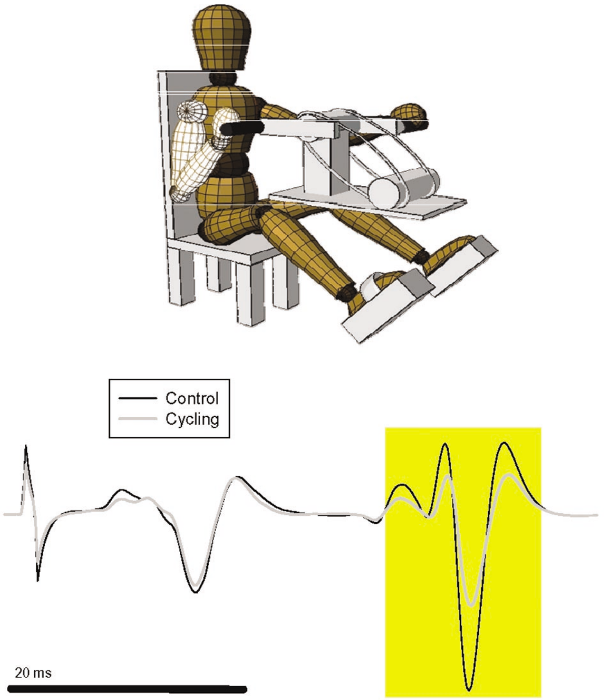

Fig. 9. Rhythmic arm movement affects reflex transmission in the legs. When arm cycling was performed during a tonic plantarflexion contraction (see cartoon at top), soleus H-reflex amplitude was inhibited compared to control level (see highlighted rectangle). Thus, neural mechanisms associated with rhythmic arm cycling modulate transmission in reflex pathways to the legs. Adapted from Frigon and others (2004).

of the step cycle. It was proposed that this may be evidence for a somewhat different form of reflex organization from cutaneous nerves in the hand and foot onto motoneurons innervating muscles in the arms and legs. Interlimb cutaneous stimulation also evoked significant changes in ankle movements (see Fig. 8). The mechanical responses to stimulation at the foot during early swing likely represent the stumbling corrective response (see above), whereas the responses after stimulation of the nerve innervating the hand were suggested to represent an attempt to defer or reduce forward progression as the hand contacts an obstacle during swing (Haridas and Zehr 2003).

It is difficult to determine the specific locus of any mechanisms regulating interlimb reflexes during locomotion because of the possible "interference" of rhythmic arm and leg activity. That is, it is not simple to determine if the modulation of reflexes in leg muscles evoked by stimulation in the hand during walking (e.g., Haridas and Zehr 2003) is due to rhythmic arm or leg activity. To investigate this, the remote effect of rhythmic arm cycling on reflex excitability in stationary legs has been studied (Frigon and others 2004). Earlier research suggested that arm position could have an effect on soleus H-reflexes (Delwaide and others 1973; Delwaide and others 1977; Eke-Okoro 1994). It was shown that passive flexion-extension at the elbow facilitated (Hiraoka and Nagata 1999) and arm swing reduced soleus H-reflex amplitudes (Hiraoka 2001). Rhythmic arm cycling was recently shown to have a significant inhibitory effect on soleus H-reflexes, probably via modulation of Ia presynaptic inhibition (Frigon and others 2004). Subjects performed rhythmic arm cycling, and H-reflexes were significantly reduced as compared to reflexes evoked when no arm movement was performed (see Fig. 9).

Because there was an interaction between this movement-induced conditioning and that seen by segmental alteration of soleus H-reflex excitability, it was determined that this modulation arises prior to the motoneuronal membrane, probably by presynaptic inhibition of IA afferent terminals (Box 3).

Furthermore, although humans are bipeds, it has been suggested that we use vestigial quadrupedal mechanisms of coordination (Dietz and others 2001; Dietz 2002a). Thus, a further requirement is evaluating pathways and mechanisms linking CPGs controlling arm and leg

Box 3. Development of Interlimb

In infants, the basic coordination patterns are very similar to those found in the cat. Infants crawling on hands and knees use mostly a diagonal interlimb pattern (diagonally opposite limbs move synchronously; Freedland and Bertenthal 1994). Infants first hold their arms in a high guard position (arm position at onset step cycle is with the shoulder in exorotation and with the elbow in flexion) when they start to walk upright. This pattern continues in the first 10 weeks of independent walking (Ledebt and Bril 2000). It is presumably related to the characteristic instability of this period of walking (Breniere and Bril 1998). Later, at around 1.5 years of age, the infants show normal "adult" arm swings when gait becomes more stable and step width decreases (Sutherland and others 1980). Further maturation occurs in the period of 6 years or longer after the onset of independent walking (Okamoto and Kumamoto 1972; Sutherland and others 1980; Berger, Altenmueller, and others 1984; Berger and others 1987; Stolze and others 1997). Recently, it was suggested that upper limb movements during walking are produced by CPG centers within the spinal cord (see main text and Dietz 2002a; Zehr 2004).

Box 4. Neuronal Interconnections

What are the neuronal elements involved in the central pattern generator (CPG) coupling? In various species, propriospinal neurons have been described that connect CPGs either at the same or at different segmental levels. These neurons can be either inhibitory or excitatory, and they can provide either out-of-phase or in-phase synchronization. Mammalian commissural interneurons make polysynaptic rather than monosynaptic connections (Butt and others 2002). It is thought that the extra synapses in mammals allow for a greater integration of information. In the neonatal rat, one distinguishes between short-range inhibitory and excitatory commissural interneurons (short-range interneurons for left-right coordination and long-range ones for intersegmental coordination; Butt and others 2002). In the cat, Jankowska and others (2003) claimed that commissural neurons can contribute to spinal coordination of the two sides and that they can also mediate reticulospinal signals. Indeed, at the lumbar level, the commissural neurons are monosynaptically activated from the ipsilateral reticular formation. These neurons, located in Rexed's lamina VIII, are thought to underlie the close coupling between spinal interneuronal systems such as CPGs.

movements. Recently, the issue of coordination between the arms and legs of humans during locomotion has been addressed in several laboratories (Dietz 2002a, 2002b; Dietz and others 2001; Haridas and Zehr 2003; Zehr, Collins, and others 2001). It has also been suggested that the concept of a discrete CPG is insufficient and that a distributed network model wherein portions of the neural CPG network can be found spanning spinal segments of the human CPG is more accurate (Dietz and others 1999). Furthermore, it has been directly suggested that the pattern of arm to leg coordination during walking, creeping, and swimming tasks in humans is due to the activity of coupled neural oscillators: two controlling arm movements and two controlling leg movements (Wannier and others 2001).

Evidence for linkages between human CPGs comes from different sources. Barbeau and colleagues showed that patients with incomplete SCI have greater gait symmetry and more normal EMG while walking on a treadmill when body weight support (BWS) was provided and arm swings were allowed than when arm swings were absent because of the use of parallel bars for the same amount of weight support (Visintin and Barbeau 1994). More generally, it is recognized that in the case of neurologic pathology, the impaired arm function during gait using a walker adds to the neural limitations that already are present due to the pathology (Behrman and others 1998).

In intact humans, there is also some evidence for strong coupling between leg CPGs. One group has used split-crank pedaling to study interlimb interactions. This method allows decoupling of the two legs and control of the mechanical loading of each leg (see Ting and others 2000). Subjects pedaled a modified cycle ergometer in a two-legged (bilateral) and a one-legged (unilateral) pedaling condition. The loading on the leg during unilateral pedaling was adjusted such that it was nearly identical to the loading experienced by the leg during bilateral pedaling. This was done by having a trained second subject pedal along with the experimental subject. The second subject exerted on the opposite crank the torque that the subject's contralateral leg normally generated in bilateral pedaling. If the cycling was done with totally independent "generators" for both legs, then this would lead to exacly the same muscle coordination pattern in both legs. If, instead, the generator actions were coupled, then the active contralateral cycling would facilitate the ipsilateral cycling. In the latter case, one would predict higher EMG activity in unipedal cycling, as was indeed observed.

These data indicate that there is a facilitation of the output on one side due to the pedaling of the other side during bipedal pedaling. Further experiments (Kautz and others 2002) showed that pedaling is not completely essential to obtain this contralateral facilitation because rhythmic isometric contractions in a motionless leg can produce similar results. In conclusion, these various pieces of evidence support the hypothesis that in humans, the rhythmic locomotor output on one side facilitates the rhythm on the other side (Box 4).

Summary

Walking can be a very automated process, but it can also be achieved under a high degree of conscious control. In the automated gait mode, it seems likely that CPGs play a dominant role, as does the sensory regulation of these CPGs. In humans, it has been particularly difficult to provide evidence for CPGs and their regulation, but some data are now available, paricularly from newborns. In adults, there are also clear indications not only for control of the legs but also for the arms. These observations support the suggestion that rhythmic arm movements are largely controlled by CPGs just as documented for the leg. Although there are some differences in the strength of coupling between the arms compared with that between the legs, arm and leg movements are similarly regulated by CPG activity and reflex control during locomotion.

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