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The special nature of human walking and its neural control

Charles Capaday

Walking the way we do is inherently unstable. Sophisticated neurological control systems are required to ensure that we progress and maintain our balance at the same time. Most of what is known about the functional organization of these neurological control systems is inferred from studies on animals. Here, I compare selected studies on the neural control of human walking with similar studies in reduced animal preparations. The simple monosynaptic reflex appears to be controlled by comparable mechanisms in walking cats and humans. However, peripheral feedback mechanisms suggested to contribute to the switch from stance to swing on the basis of experiments in reduced cat preparations have little influence during human walking. A cat whose spinal cord has been completely transected can be made to walk on a treadmill by drug injections, but such an immediate effect of pharmacological intervention is not seen in humans. However, there have been reports that pharmacological intervention can improve the walking of patients with incomplete spinal cord injury, especially when pharmacological treatment is combined with training.

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Human walking has three main gait characteristics: (1) humans walk erect on two legs, (2) at the moment of contact with the ground, the leg is almost fully extended, and (3) the foot strikes the ground initially with the heel – these characteristics are unique to human walking. As a consequence, a mixture of extensor and flexor muscles is activated at heel contact, and the activities of leg extensors are not in phase (as is typical for other mammals, such as cats). Ankle extensor activity is delayed by some 50–100 ms after heel contact, when the activity of most other leg extensors has ceased (Fig. 1). These facts imply that the motor pattern – and thus, the functional organization of the underlying neural control – cannot be simply summarized as a reciprocal activation of flexors (during swing phase) and extensors (during stance phase). Birds walk on two legs, but in a squatted position. Penguins walk with a more erect posture than other birds, but they still walk in a squatted position and, like other birds, walk on their toes. Their short legs, conspicuous forward body inclination, marked side-to-side waddle and high oxygen consumption do not make them good models of human walking [1]. Nonetheless, human walking shares important biomechanical principles with other walking animals, including penguins [2,3]. The exchange of gravitational potential energy and forward kinetic energy during the step cycle – similar to an inverted pendulum – conserves total body energy. As a result, less 'new' energy need be supplied at each step, reducing considerably the metabolic cost of walking. Margaria and Cavagna were the first to deduce this important principle of human walking physiology [4]. Additionally, Alexander [5] suggested that the human characteristic of walking with the legs nearly fully extended also minimizes muscle activity, and thus energy expenditure, with the legs being used more like struts.

Anyone observing a visual display of the electrical activity (electromyographic activity, EMG) of leg muscles while a subject is walking is struck by the pattern of the individual EMG bursts and by their timing relations. What part(s) of the CNS generates

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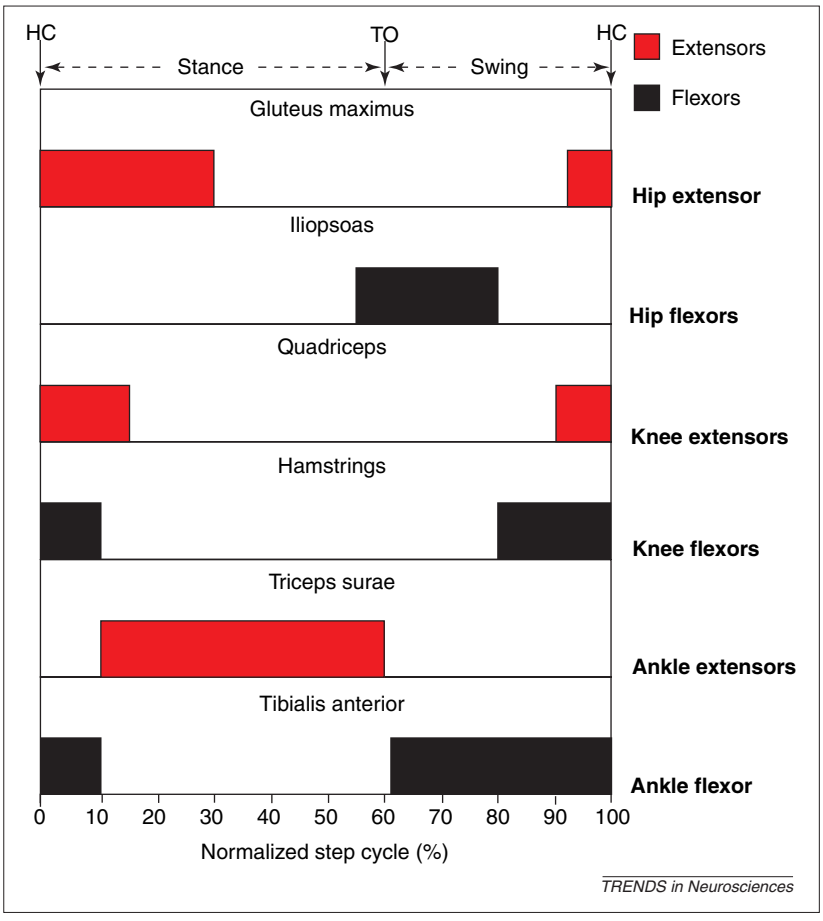

Fig. 1. Timing of electromyographic (EMG) activity in leg muscles during human walking. Despite variations between subjects, a reasonable average profile can be constructed. Here, the duration of activity of the most important leg muscles is shown on a normalized time scale, from heel contact to heel contact (HC to HC; i.e. one stride). Note that during human walking, the activity of extensors is not in phase and the pattern as a whole is not one of reciprocal activation of flexors and extensors. At HC, the hip extensor gluteus maximus and the knee extensor quadriceps, as well as the ankle flexor tibialis anterior, stiffen the leg and ankle. The gluteus maximus continues its activity and extends the hip during early stance (note that its activity begins in late swing, before HC). After the foot is lowered to the ground, the ankle extensors become active and in late stance they propel the body upward and forward. At around the time of toe off (TO), the hip flexor iliopsoas and the ankle flexor tibialis anterior become active, flexing the hip and ankle so that the leg can swing through. At normal walking speeds knee flexion is produced, partly by flexion at the hip and partly by the biarticular gastrocnemii muscles in the calf (i.e. it is not produced by knee flexor activity). The simple description of isolated muscle action given here is not necessarily the function of the muscle during walking: for example, ankle extensors control the rotation of the body about the ankle joint during most of the stance phase, and only extend the ankle in late stance. Similarly, the hamstrings decelerate leg extension at the end of swing rather than contribute to knee flexion during swing.

these locomotor bursts? We have no direct answer to this question, but inferences have been made from quadrupedal mammals, such as the rat and, notably, the cat. In their recent comprehensive book on the neural control of locomotion Orlovsky *et al.* stated '*…the locomotor activity in humans has been much more thoroughly studied than its neural control and in this matter we have to rely mainly on extrapolations from simpler animal models*' [6]. This is an explicit statement of what is a widely held, tacit assumption. The purpose of this article is to critically examine the extent to which results from 'simpler' animal models can be extrapolated to normal human walking. To this end, I will compare selected studies on the neural control of human walking with similar studies in reduced animal preparations. I begin with work on the monosynaptic reflex, probably the most studied neural mechanism of human and animal walking. Related to this, I will also examine reflex interactions across spinal cord segments. Next, I will deal with the neural mechanisms that have been proposed to contribute to the stance-to-swing transition. Finally, I will examine the possibility that central pattern generators (CPGs) located in the spinal cord produce the motor output during human walking. Absent from this review is a discussion of cutaneous reflex pathways, which have been reviewed and commented upon elsewhere [7].

Modulation of monosynaptic reflexes

Forward propulsion of the body is mainly powered by contraction of the calf muscles (the soleus and the two gastrocnemii), with a contribution from the knee extensors [8,9]. The stretch reflex has been suggested to make a substantial contribution to the motor output during human walking [10,11] and running [12] (but see Ref. [13]). Thus, understanding the reflex control of the ankle extensors, and particularly the stretch reflex, is of obvious importance. To make comparisons with work on animals, I will restrict the discussion to the monosynaptic component of the stretch reflex elicited electrically [14], which is known as the H-reflex (Box 1). The relation between the amplitude of the soleus H-reflex and the background level of motor activity is not fixed, but is strongly dependent on the motor task [15–21]. For example, the amplitude of the H-reflex decreases from standing to walking, and decreases further during running (reviewed in Ref. [22]). The reduction of the H-reflex between standing and walking is known to be of central origin [23,24]. The task-dependent control of the H-reflex has been suggested to reflect adaptive control of the stretch-reflex parameters in accordance with the biomechanical exigencies of the motor task [17,25,26]. Neural mechanisms that modulate the soleus H-reflex during the normal step cycle include increased activity of α-motoneurons during the stance phase [15], increased postsynaptic inhibition of α-motoneurons during the swing phase [27,28] and a tonic increase in presynaptic inhibition of group Ia afferent terminals projecting to the α-motoneurons [29–31]. Indeed, such a tonic increase of presynaptic inhibition was recently observed during fictive locomotion in cats [32], reducing monosynaptic EPSPs by ~30%. This seems to be an example of data from reduced animal preparations being consistent with, and providing an explanation for, data obtained in normal human walking.

However, a recent study in decerebrate cats [33] showed that the relationship between monosynaptic reflex amplitude and EMG was similar during episodes of walking on a treadmill and spontaneous bouts of tonic activity. The authors concluded that the component of the locomotor CPG that generates extensor bursts does not presynaptically inhibit the

Box 1. Basic neural circuits of the spinal cord and their corticospinal control

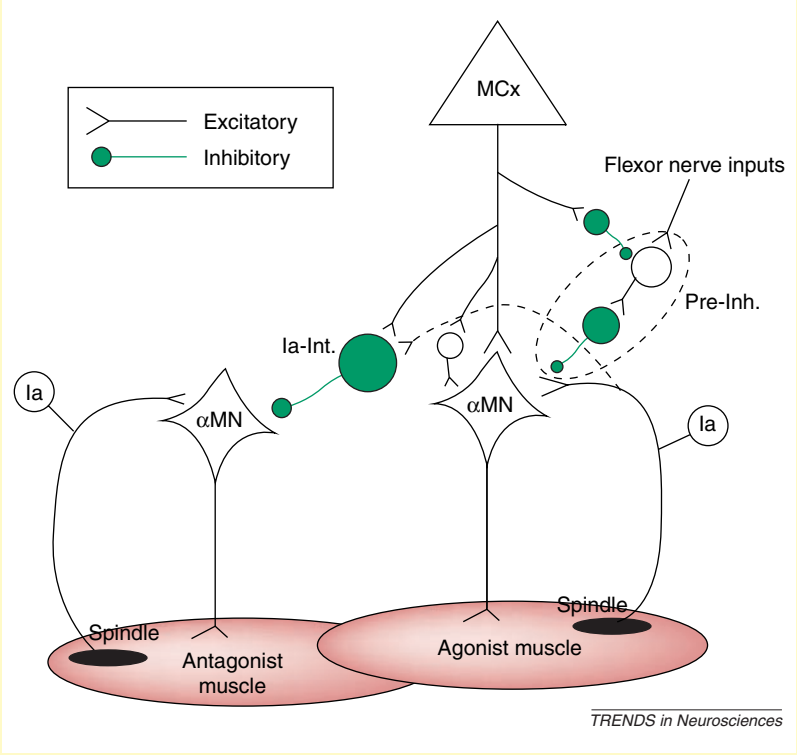

Fig. I. Basic spinal circuitry and its corticospinal control

The simplest spinal cord circuit is the monosynaptic connection between the muscle group Ia-afferents and the α-motoneurons (αMN) (Fig. I). This pathway subserves in large measure the stretch reflex [a]. The stretch reflex might have an oligosynaptic contribution, but no specific interneuronal circuit has yet been identified (although see Box 2). In humans, electrical stimulation of Ia fibres in peripheral nerves elicits a monosynaptic reflex that can be recorded from the muscle as a compound action potential (H-reflex) [b]. This description of the stretch reflex is a simplified abstraction. This circuit is inextricably embedded in a complex neural system; consequently, its behaviour reflects the integrated activity of the whole. At the peripheral end, the sensitivity of the receptor organ, the muscle spindle, to muscle stretch is controlled by the independent γ-motoneuron system [c] (not shown). Centrally, collaterals of group Ia afferents from muscle spindles inhibit the antagonistic α-motoneuron pool, via Ia-inhibitory interneurons (Ia-Int.). These form part of the neural circuits that mediate reciprocal inhibition between antagonistic muscles. For simplicity, the connection in the figure is shown only from agonist to antagonist. Additionally, a presynaptic inhibitory network (Pre-Inh.) controls the efficacy of synaptic transmission from the Ia-afferent terminals to α-motoneurons. This circuit includes at least two synapses and can be activated from the periphery by stimulation of muscle flexor nerves [d,e]. The last order interneuron(s) directly inhibits the group Ia afferent terminals projecting to α-motoneurons. This reduces neurotransmitter release and decreases reflex response. More specifically, presynaptic inhibition of group Ia-afferents increases the stretch reflex threshold (i.e. minimum stretch required) and decreases the reflex stiffness (i.e. increase of force per unit length change) independently of force the muscle is exerting [f]. Control of presynaptic inhibition has been suggested to adapt the stretch reflex output to the biomechanical exigencies of the motor task [f,g]. For example, walking might require a more compliant (i.e. less stiff) interface between the ankle extensors and the ground [g], whereas during standing, increased stretch reflex stiffness contributes to maintenance of the upright position [h].

Experiments using magnetic stimulation of the motor cortex have shown that most, if not all, human muscles are controlled by a fast direct corticospinal pathway [i]. In all cases, including that of the leg muscles, there is a strong monosynaptic component to this projection. The corticospinal neurons that project to a given motoneuron pool also inhibit the antagonistic motoneuron pool via Ia-inhibitory interneurons [d], adding an extra layer of complexity to the reciprocal inhibitory pathway. Stimulation of the motor cortex reduces presynaptic inhibition (i.e. inhibits presynaptic inhibition) [e]. It should be noted that branches of the same corticospinal fibre do not necessarily control the Ia-inhibitory interneurons and the presynaptic inhibitory network. Several other circuits could be added to the figure, but what is important is that descending pathways act simultaneously on α-motoneurons and interneurons. The facultative actions of descending pathways on spinal interneurons provide a final level of adaptive control of motor activity. For example, reciprocal inhibition between antagonistic muscles is much stronger during the swing phase of walking than during voluntary or postural motor activities [j]. During co-contraction of antagonistic muscles, as occurs when we clench a fist, reciprocal inhibition is symmetrically reduced between the antagonists [k]. The monosynaptic reflex decreases in the transition from standing to walking, and further during running [g]. This is thought to reflect increased presynaptic inhibition of the group Ia-afferents [g,l,m]. It is important to appreciate that these insights on how spinal circuits actually operate during motor activity were derived from neurophysiological experiments on normal human subjects.

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group Ia-afferent terminals projecting to the α-motoneurons presynaptically. How are these results related to the results from humans described above? Spontaneous bouts of tonic activity in decerebrate cats have no known behavioural counterpart in normal animals and cannot be equated with standing or

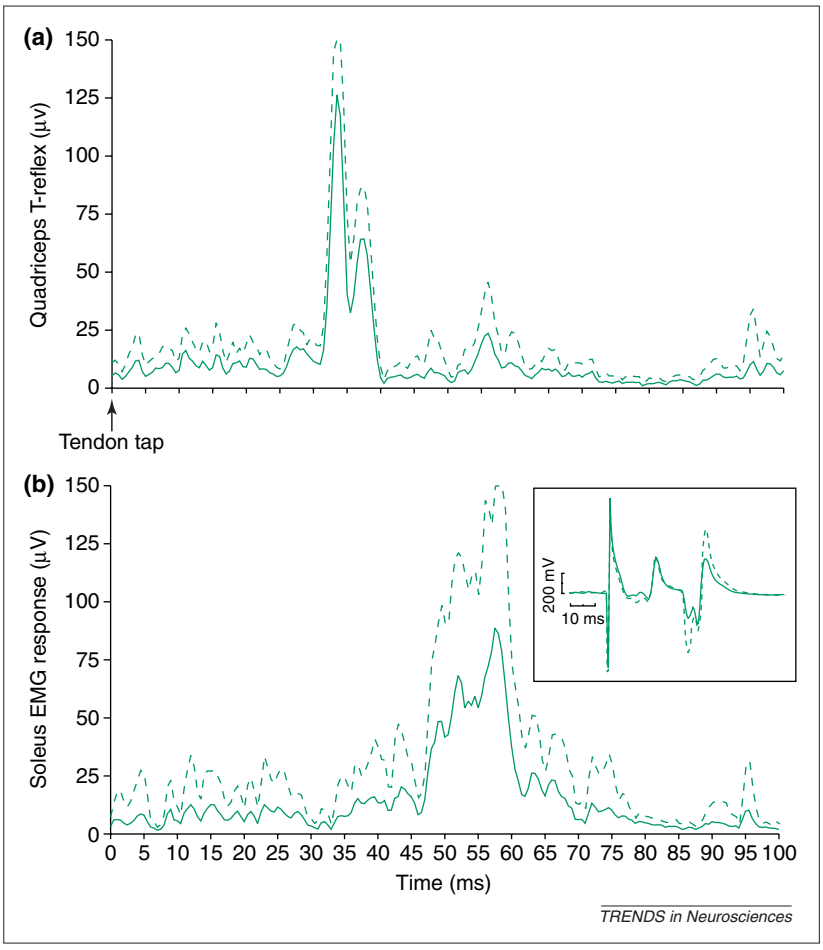

Fig. 2. A tap to the patellar tendon in a standing subject elicits a monosynaptic reflex response recorded electromyographically (T-reflex) in the quadriceps (a). Some 10 ms or so later, a reflex response is also observed in the soleus, an ankle extensor and anti-gravity synergist of the quadriceps (b). The inset shows that the H-reflex of the soleus, elicited 45 ms after the tendon tap, is facilitated (dotted waveform) as expected, precluding the possibility that the soleus group Ia-afferents are presynaptically inhibited by stretch of the quadriceps. Each trace is the average of eight individual responses and the dashed curves represent one standard deviation above the mean.

postural maintenance in humans. Differences in gait pattern (e.g. cats make ground contact with their toes) and biomechanics might also invalidate cross-species comparisons. Furthermore, one should not rush to infer from such studies how monosynaptic reflexes might be modulated in the behaving animal, or in a different experimental preparation of the same animal. For example, in spinalized cats treated with the α-2 noradrenaline-receptor agonist Clonidine to initiate rhythmic locomotor activity, stretch reflex gain was lower during locomotion than when the animal was still [34] (see Ref. [33] for a discussion of potential reasons for the differences). McCrea [35] offers an interesting explanation of the results in decerebrate animals [33]. The persistence of tonic presynaptic inhibition [32] followings bouts of locomotor activity – presumably owing to activation of $GABA_B$ receptors on the Ia-afferent terminals – might explain why H-reflexes and stretch reflexes were similar during locomotion and following bouts of locomotion. Thus, in addition to particular characteristics of different experimental preparations and species differences, methodological issues (such as the order of experimental observations) also limit generalization of results. Nonetheless, overall there is remarkable agreement – especially when considering the gap in going from fictive cat locomotion to normal human walking. This is also a nice example where observations made initially in humans have driven animal research.

Interaction of quadriceps and soleus spinal neural circuits

Stretch of the decerebrate cat quadriceps has been reported to inhibit the soleus H-reflex, with this inhibition persisting during bouts of walking on a treadmill [36]. There is also evidence that quadriceps group-Ia afferents mediate this effect via presynaptic inhibitory networks [36]. Thus, cyclic afferent information from the quadriceps has been suggested to amplitude-modulate the soleus stretch reflex during walking. However, in standing humans, stretch of the quadriceps elicits a homonymous stretch reflex as well as overt excitation of soleus α-motoneurons, without presynaptic inhibition of the H-reflex (Fig. 2). Thus in humans, Ia afferents of the quadriceps contribute to excitation of their own α-motoneurons as well as to that of soleus α-motoneurons [37]. This inter-segmental excitatory link makes sense because these muscles act as anti-gravity synergists. But this is equally true in humans and cats. Therefore, it appears that this is an example of a difference between results obtained from reduced animal preparations and normal human subjects. This should be seen as an opportunity, as determining the reason for the discrepancy will certainly further our understanding of the supraspinal control of spinal neural circuits.

Stance-to-swing transition

There are currently two hypotheses on the peripheral mechanism(s) contributing to the stance-to-swing transition. One states that the transition is promoted when the hip reaches a critical extended position during stance [6]. The promoting signal is likely to be transmitted by hip muscle-spindle afferents [38]. Unloading (decrease in force) of ankle extensors at the end of stance, which is signalled by group I afferents from spindles and Golgi tendon organs (Box 2), has also been proposed to contribute to the transition from stance to swing [39,40]. The issue is whether these peripheral effects observed in reduced animal preparations are necessary to initiate the swing phase of normal human walking.

The bulk of evidence shows that group-I afferent feedback (i.e. signalling unloading) from ankle extensors is not involved in the stance-to-swing transition of normal human walking [41–45] (reviewed in Ref. [22]). There is some evidence that loading during the stance phase of infant stepping increases the amplitude and duration of stance [46]. However, in adult cats this mechanism contributes

Box 2. Effects of group I muscle afferents during locomotion

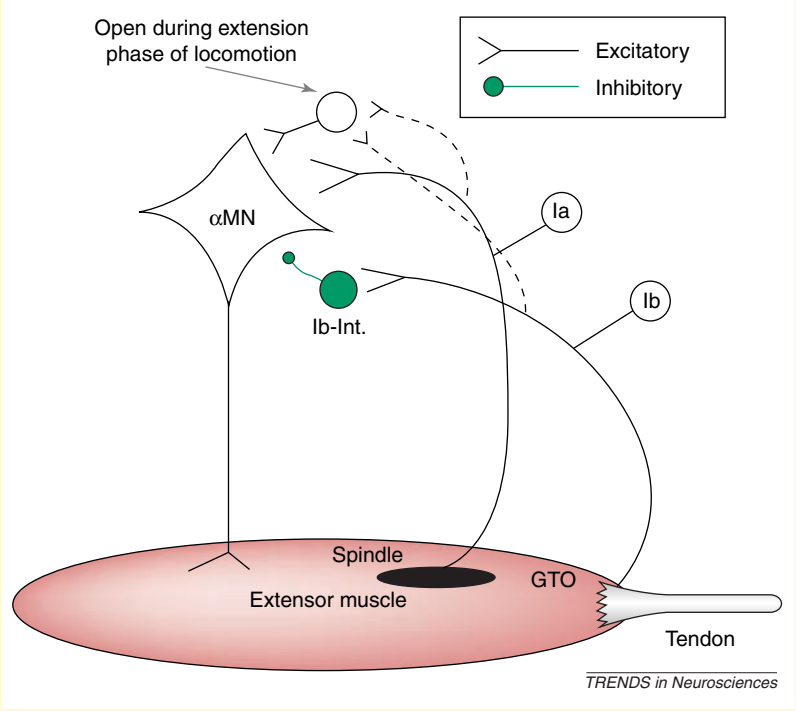

Fig. I. Effects of group I inputs during locomotion.

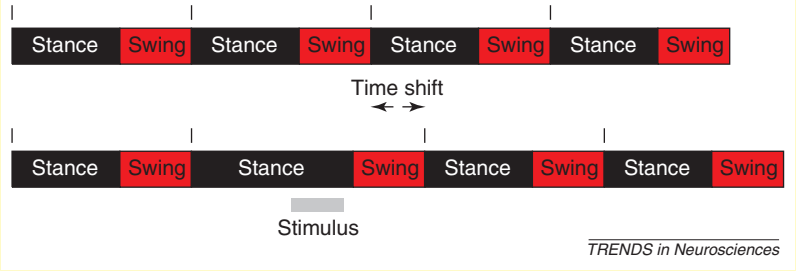

Fig. II. Group I effects on step-cycle timing.

Golgi tendon organs (GTO) are located at the musculotendinous junctions in muscles, and are sensitive to muscle force and to the rate of change of force [a]. The classic description of their reflex action is inhibition of the α-motoneurons (αMN) by way of Ib-inhibitory interneurons (Ib-Int.) (Fig. I). The closed loop thus has the characteristics of a negative force feedback system. In reduced cat preparations, the inhibition is decreased during the extension phase of locomotion [b,c]. Additionally, a disynaptic excitatory pathway is opened, allowing Ia and Ib afferents to excite the α-motoneurons. Thus, during the extension phase of locomotion, the α-motoneurons are depolarized by monosynaptic and disynaptic reflex pathways. Stimulation of group I afferents during locomotion in reduced animal preparations has another interesting effect: it prolongs the extensor phase and delays the onset of the flexor phase [d,e]. In the schematic example (Fig. II), the top tracing represents a series of normal unperturbed step cycles with a vertical marker indicating the start of the stance phase. In the lower tracing, group I afferents are stimulated in late stance of the second step. This prolongs the stance phase and delays the swing phase. Additionally, subsequent steps occur at times different than expected (time shift). This shows that the group I inputs, aside from acting via the two pathways illustrated above, also affect the neural system involved in timing the step cycle.

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little to the stance-to-swing transition [47]. Thus, there can be differences between different experimental preparations in a single species as well as across different species. The influence of group-I-afferent activity on the step cycle is an example of phase resetting of a neural oscillator (Box 2). This means that the group-I afferents have access to the neural circuits involved in the timing aspects of the step cycle [39,48]. Thus, continued studies in reduced animal preparations are important, as they can contribute to elucidating the neural circuitry of a mammalian spinal CPG.

What of the hip-position mechanism? As was the case the case for the unloading mechanism, results from infant stepping are generally consistent with the hip-position hypothesis. During supported infant stepping, extending the hip shortens the stance phase and initiates swing [46]. It has also been shown that there is not a unique value of hip position or load that must be reached to initiate swing, but rather, that a combination of the two factors is important. In adults, vibration of the quadriceps muscle group (to increase muscle-spindle-afferent discharge) during human walking had no effect and, in particular, did not hasten the transition from stance to swing. But, by contrast, vibration of the hamstrings increased walking speed when walking forward and decreased walking speed when walking backward. Conversely, vibration of the quadriceps increased walking speed when walking backward. The authors concluded that proprioceptive inflow from thigh muscles conveys information on foot velocity relative to the trunk [49]. These effects in adult humans are very different from those observed in the spinalized or decerebrate cat or in infant stepping, emphasizing the importance of the ensemble of operating neural systems in determining what effects will be observed. The results obtained with vibration during walking are consistent with the idea that movement-related proprioceptive feedback is mainly derived from the lengthening antagonist muscles, as previously shown in studies of arm movements [50–53]. Biomechanical measurements

made at different speeds in normal and altered gravity conditions have also shown that the transition from stance to swing does not occur at a fixed hip angle [54,55].

CPGs and the neuro-rehabilitation of walking deficits

In non-mammalian vertebrates and quadrupedal mammals, such as rats and cats, the isolated spinal cord can generate spontaneous locomotor bursts in the complete absence of peripheral feedback [6]. CPGs are the ensemble of spinal cord neural networks that generate these locomotor bursts. An obvious question is whether there is a CPG for human walking. There is now sufficient evidence to suggest that the human spinal cord with intact sensory inputs is capable of generating rhythmic motor bursts [56–59]. The experimental procedures involved in these demonstrations include partial body-weight support by a harness system, as well as direct assistance of the leg movements by therapists. However, it is not clear whether these represent locomotor bursts, or whether they are rhythmically entrained stretch reflexes. The studies of Stewart *et al*. [56] and Rossignol and Barbeau [60] suggest that the motor bursts seen in patients with clinically complete spinal cord injury (SCI) reflect muscle stretch imposed by the therapists. Harkema *et al*. have shown that the amplitude of the motor bursts is more closely correlated with the load on the lower limb (i.e. the percentage of body weight directly supported by the patient) than with muscle stretch [59]. However, it is not easy to separate load *per se* from the associated muscle stretch. Thus, the increased initial muscle stretch as a result of loading, together with greater stretch reflex excitability in SCI subjects, might prevent observation of a correlation between motor burst amplitude and muscle length changes. It is also important to keep in mind that flexion reflexes can be elicited by non-noxious cutaneous stimuli, and that crossed-extensor reflexes in the opposite leg can accompany them [61]. Thus, the generalized reflex excitability seen in SCI subjects makes it difficult to separate unequivocally patterned reflex actions from true locomotor pattern generation. In any case, the region of the human CNS in which the locomotor bursts are generated certainly warrants further investigation. The issue is important because it is generally thought that if human walking is generated by a spatially localized CPG (e.g. at the spinal level), neuropharmacological and neuro-rehabilitation methods could be selectively targeted. If the neural system that controls human walking is more widely distributed across the CNS, therapeutic intervention would be much more daunting. What is apparent is that the human spinal CPG, if it exists, is much less robust than those of mammals such as rats and cats. For example, in acutely spinalized cats, Clonidine induced locomotion when the animals were made to walk on a treadmill (reviewed in Refs [62,63]). By contrast, similar intervention in marmosets has shown that the spinal locomotor CPG is more difficult to activate [64]. In humans with clinically complete SCI, pharmacological interventions do not immediately induce or improve walking [63]. In subjects with incomplete SCI who were able to walk for a short distance with handrail support, intrathecal Clonidine injection improved the walking speed of three out of eight patients [65]. It is not clear however, whether this was due to activation of spinal circuits or the reduction of spasticity produced by Clonidine [65]. Training of chronic spinalized cats on a treadmill, without the use of drugs, leads to a stable locomotor pattern; once this is achieved, Clonidine administration can further enhance movement amplitude and speed [62,63]. As a result of these observations in animals, several studies on SCI subjects are currently under way to determine the efficacy of individual or combined therapeutic approaches to improving walking capacity [66]. These include training with partial body weight support, functional electrical stimulation of muscles and the use of pharmacological agents.

Conclusion

Studies of the neural control of animal locomotion certainly provide an important basis for such work on human walking. Conversely, results obtained in humans should, and have begun to, contribute to problem formulation in animal studies. The continued interplay of animal and human research is necessary, but we should not expect that the results would inevitably be comparable. Decerebrate animals do not have the full gamut of descending inputs, and spinalized preparations have none. Under these conditions, it is not surprising to observe strong influences of afferent inputs on spinal cord neural circuits. Furthermore, removal of descending inputs can upset the balance of spinal cord circuits, leading to responses not normally observed. A classic example is the positive Babinski response that appears following damage to the corticospinal tract [67]. In summary, what emerges from the results reviewed here is that the neural control of human walking needs to be understood in its own terms.

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