Modelling spinal circuitry involved in locomotor pattern generation: insights from the effects of afferent stimulation

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A computational model of the mammalian spinal cord circuitry incorporating a two-level central pattern generator (CPG) with separate half-centre rhythm generator (RG) and pattern formation (PF) networks has been developed from observations obtained during fictive locomotion in decerebrate cats. Sensory afferents have been incorporated in the model to study the effects of afferent stimulation on locomotor phase switching and step cycle period and on the firing patterns of flexor and extensor motoneurones. Here we show that this CPG structure can be integrated with reflex circuits to reproduce the reorganization of group I reflex pathways occurring during locomotion. During the extensor phase of fictive locomotion, activation of extensor muscle group I afferents increases extensor motoneurone activity and prolongs the extensor phase. This extensor phase prolongation may occur with or without a resetting of the locomotor cycle, which (according to the model) depends on the degree to which sensory input affects the RG and PF circuits, respectively. The same stimulation delivered during flexion produces a temporary resetting to extension without changing the timing of following locomotor cycles. The model reproduces this behaviour by suggesting that this sensory input influences the PF network without affecting the RG. The model also suggests that the different effects of flexor muscle nerve afferent stimulation observed experimentally (phase prolongation *versus* resetting) result from opposing influences of flexor group I and II afferents on the PF and RG circuits controlling the activity of flexor and extensor motoneurones. The results of modelling provide insights into proprioceptive control of locomotion.

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The mammalian spinal cord contains neuronal circuitry that can generate the basic locomotor rhythm and produce alternating flexor and extensor motoneurone activities underlying locomotion. Although this locomotor central pattern generator (CPG) can operate in the absence of sensory feedback (reviewed by Grillner, 1981; Rossignol, 1996; Orlovsky *et al.* 1999; Rossignol *et al.* 2006), afferent activity plays a crucial role in adjusting the locomotor pattern to the motor task, the environment and the biomechanical characteristics of the limbs and body (e.g. Pearson, 2004; Rossignol *et al.* 2006).

Perhaps the most studied hindlimb afferent system controlling locomotor activity is that from extensor group Ia muscle spindle and Ib tendon organ afferents (collectively referred to as group I afferents). Activation of extensor group I afferents, and particularly those from ankle muscle nerves, results in a strong excitation of extensor motoneurones during extension (Conway *et al.* 1987; Pearson & Collins, 1993; Guertin *et al.* 1995). This proprioceptive feedback contributes to a substantial portion of stance-phase extensor activity in cats during treadmill locomotion (e.g. Hiebert & Pearson, 1999; Donelan & Pearson, 2004), and in man (Sinkjaer *et al.* 2000). In reduced preparations, activity in extensor group I afferents can also control the transition from stance to swing (Duysens & Pearson, 1980), regulate the duration of the stance phase, and entrain the step cycle period (references in Pearson, 2004; Rossignol *et al.* 2006). In contrast, activation of group II afferents in the same extensor nerves appears to contribute little to the control of locomotion (Conway *et al.* 1987; Guertin *et al.* 1995; Donelan & Pearson, 2004).

Cutaneous reflexes also have an important role in controlling locomotion (e.g. Zehr & Duysens, 2004;

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Rossignol *et al.* 2006). For example, stimulation of tibial nerve cutaneous afferents during the extensor phase of fictive locomotion enhances the activity of extensor motoneurones and prolongs the ongoing extensor phase. The same stimulation during flexion produces a premature initiation of the extension phase (Conway *et al.* 1994; Guertin *et al.* 1995). In addition to these widespread effects on hindlimb motoneurones, specialized cutaneous reflexes such as the stumbling correction reaction produce a specific and more limited pattern of motoneurone excitation and inhibition in intact cats (e.g. Buford & Smith, 1993) and during fictive locomotion (Quevedo *et al.* 2005*a*) evoked through both restricted cutaneous reflex pathways and through CPG circuitry (Quevedo *et al.* 2005*b*).

Activation of hindlimb flexor muscle group I afferents during the flexor phase of locomotion can enhance hindlimb flexor activity in a manner analogous to the extension-promoting effects of extensor group I afferents (e.g. Perreault *et al.* 1995; Stecina *et al.* 2005). However, unlike group II fibres in extensor nerves, group II afferents in flexor nerves evoke powerful effects on the activity of motoneurones and on step cycle timing during fictive locomotion. Depending on the nerve tested and the preparation used, activation of flexor group II fibres during the flexor phase can either prolong flexion (e.g. stimulation of the extensor digitorum longus (EDL) nerve; Stecina *et al.* 2005) or terminate flexion and initiate extension (e.g. tibialis anterior (TA); Perreault *et al.* 1995; Stecina *et al.* 2005). An important feature of the reflex actions of flexor group II afferents evoked during fictive locomotion is that spontaneous reflex reversals can occur. In those cases, TA stimulation prolongs flexion and EDL stimulation resets the step cycle to extension for a few stimulus trials (Stecina *et al.* 2005). During treadmill walking, activation of group II afferents in both nerves (TA or EDL) usually enhances flexor activity (Hiebert *et al.* 1996) although variability in flexor group II actions has also been reported (Lam & Pearson, 2002). Thus the effects of hindlimb flexor muscle afferents on locomotion can be more variable than those from extensor nerves and depend upon the involvement of group II fibres, the particular nerve stimulated and the preparation.

Based primarily on observations obtained during fictive locomotion, it would appear that most hindlimb reflex pathways are altered with the onset of locomotion. For example, monosynaptic Ia excitation of homonymous and synergist motoneurones (Gosgnach *et al.* 2000) and transmission from group II afferents (Perreault *et al.* 1999) are reduced by a presynaptic inhibition. The nature of reflexes may also change with the onset of locomotion. For example, group I non-reciprocal inhibition of motoneurones is suppressed during fictive locomotion (Gossard *et al.* 1994; McCrea *et al.* 1995; Angel *et al.* 1996, 2005) and in many preparations replaced by a group I-evoked, phase-dependent, disynaptic excitation of extensor (McCrea *et al.* 1995; Angel *et al.* 1996, 2005) and flexor (Degtyarenko *et al.* 1998; Quevedo *et al.* 2000) motoneurones. Both in cats and in man, the control of motoneurone activity by sensory feedback during locomotion involves significant changes in the reflex circuitry operating in quiescent or non-locomoting motor states (McCrea, 2001; Rossignol *et al.* 2006).

The ability of afferent stimulation to simultaneously affect activity in flexor and extensor motoneurone pools throughout the limb and to control locomotor cycle timing is strong evidence for afferent actions exerted through a common network, such as the CPG, rather than through a system of private reflex pathways acting on a limited set of motoneurones (Conway *et al.* 1987; Gossard *et al.* 1994; McCrea, 2001; Pearson, 2004; Rossignol, 2006). Accordingly, it appears that CPG and reflex circuits are deeply integrated within the spinal cord and can influence and modify the performance of each other (Jankowska *et al.* 1967; McCrea, 2001; Angel *et al.* 2005).

According to classical views, the locomotor CPG consists of two half-centres that reciprocally inhibit each other and directly excite antagonist groups of motoneurones (e.g. Lundberg, 1981). In this organization, a single network controls the locomotor rhythm and patterns of motoneurone activity during locomotion (discussed in Lafreniere-Roula & McCrea, 2005; and the accompanying paper, Rybak *et al.* 2006). Therefore, any afferent stimulation that produces a premature or delayed phase switching would be expected to change the ongoing step cycle duration and hence shift the phase of the following locomotor rhythm (i.e. produce resetting). However, the effects of afferent stimulation observed during fictive locomotion are often inconsistent with this expectation. For example, stimulation of extensor group I afferents during flexion can produce a premature switching to extension with a compensatory shortening of the subsequent extensor phase so that there is no change in step cycle duration and timing of the following step cycles (Guertin *et al.* 1995). Thus despite changes in phase duration, the system can 'remember' and maintain the original cycle period timing. Similarly, when extensor afferent activation prolongs the extensor phase, step cycle duration is often maintained by a corresponding shortening of the subsequent flexion phase (Guertin *et al.* 1995; see also Kriellaars *et al.* 1994).

In the present report we propose a neuronal organization of the mammalian spinal cord circuitry that can accommodate the variety of sensory-evoked changes in locomotor activity described above including spontaneous and preparation-dependent reflex reversals of group II actions (see Stecina *et al.* 2005). This spinal circuitry incorporates our recently developed computational model of the mammalian spinal cord circuitry that incorporates the locomotor CPG (Rybak *et al.* 2006) that has a

two-level architecture consisting of a half-centre rhythm generator (RG) and a pattern formation (PF) network with reciprocal inhibitory interactions between antagonist groups of neurones at several levels. The model is presently limited to describing the activity of only one pair of antagonist motoneurone pools. Here we incorporate hindlimb afferent inputs into this model to examine how these inputs control the locomotor CPG. Specifically, we describe the results of modelling the effects of stimulation of extensor group I afferents, cutaneous posterior tibial nerve afferents and flexor muscle nerve group I and II afferents on the firing patterns of motoneurones, the timing of phase transitions and the locomotor cycle period. We begin by discussing the reorganization of group I reflex pathways that occurs with the transition to the locomotor state. This reorganized circuitry is then incorporated into our CPG model to reproduce the actions of hindlimb nerve stimulation observed in experimental studies during fictive locomotion. Some results have been presented in abstract form (McCrea *et al.* 2004; Rybak & McCrea, 2005).

Methods

The present model extends the model of mammalian spinal locomotor circuitry described in detail in our preceding paper (Rybak *et al.* 2006). This model includes a two-level locomotor CPG consisting of a half-centre rhythm generation (RG) and a pattern formation (PF) network. All neurones were modelled in the Hodgkin-Huxley style. Each type of neurone was represented by a population of 20 neurones in which heterogeneity was created by a random distribution of the leakage current reversal potential. The RG was modelled as two interacting neural populations (half-centres) coupled by mutual excitation and inhibition (via inhibitory interneurone populations). The endogenous rhythmogenic properties of RG neurons were based on the persistent sodium channels incorporated. RG activity in the model generated the locomotor rhythm with alternating flexor and extensor phases whose durations defined by the intrinsic neuronal properties, mutual inhibition and tonic excitatory drives to the half-centres. Motoneurones were modelled based on a two-compartment model (Booth *et al.* 1997). All interneurones were simulated as one-compartment models. A complete description of the neurone models and their parameters may be found in the preceding paper (Rybak *et al.* 2006).

In the present paper, additional interneurone populations were incorporated in the model to mediate effects of afferent stimulation. These included interneurones meditating afferent input to extensor and flexor portions of the rhythm generator and pattern formation networks (Irg-E, Irg-F and Ipf-E, Ipf-F, respectively; see Fig. 2 and 6) and interneurones mediating locomotor-dependent disynaptic excitation of extensor motoneurones from extensor group I afferent (Iab-E; see Figs. 1*B* and 2). The schematic of interactions between neural populations in the model used for simulation of the effects of extensor and cutaneous afferent stimulation is shown in Fig. 2 and for flexor afferent stimulation in Fig. 6. The weights of connections to and from interneurone populations mediating the effects of afferent stimulation (e.g. Irg-E, Irg-F, Ipf-E, Ipf-F, In-E and Iab-E) were adjusted to replicate afferent-evoked changes in electroneurogram (ENG) activity recorded during midbrain locomotor region (MLR)-evoked fictive locomotion in decerebrate adult cats. The relative weights of all synaptic connections, including the connections to the populations incorporated in the extended model, are shown in Table 1 in the Appendix.

Records of motoneurone activity from previously published experiments (Guertin *et al.* 1995; Perreault *et al.* 1995; Stecina *et al.* 2005) obtained during fictive locomotion in decerebrate cats were used as target templates for the simulations. Details concerning the fictive locomotion preparation and data collection have been previously provided (Guertin *et al.* 1995; Perreault *et al.* 1995; Stecina *et al.* 2005). Briefly, all surgical and experimental protocols were in compliance with the guidelines set out by the Canadian Council on Animal Care and the University of Manitoba. Fictive locomotion was evoked by electrical stimulation of the MLR following neuromuscular blockade. In those experiments, short duration (100–200 ms) trains of stimuli (typically at 200 Hz) were delivered to hindlimb nerves to activate only group I afferents (with intensity of stimulation about twice threshold for the largest diameter afferents) or groups I and II together (typically with five times threshold intensity, 5*T*). Stimulus delivery was triggered at particular phases of the step cycle using a computer-based window discriminator to detect activity in flexor or extensor motoneurone pools from rectified and integrated peripheral nerve recordings (electroneurograms, ENGs). In most cases, stimulus trains were given once every few step cycles so that control and perturbed cycles could be readily compared under identical conditions of the preparation.

In the model, afferent stimuli were applied as rectangular pulses with the amplitudes and durations indicated in the corresponding figures and legends. To mimic the experimental conditions in which electrical stimulation of peripheral nerves at group I intensity recruits both Ia and Ib fibre types and stimulation at group II intensity recruits type Ia, Ib, and II sensory afferents, afferent stimuli were applied simultaneously either to Ia and Ib fibres of extensors (Ia(e) and Ib(e), respectively; Ia(e) = Ib(e)), or to Ia, Ib and group II fibres of flexors (Ia(f), Ib(f) and II(f), respectively; Ia(f) = Ib(f)), or to cutaneous afferents (Cut). Activation of flexor

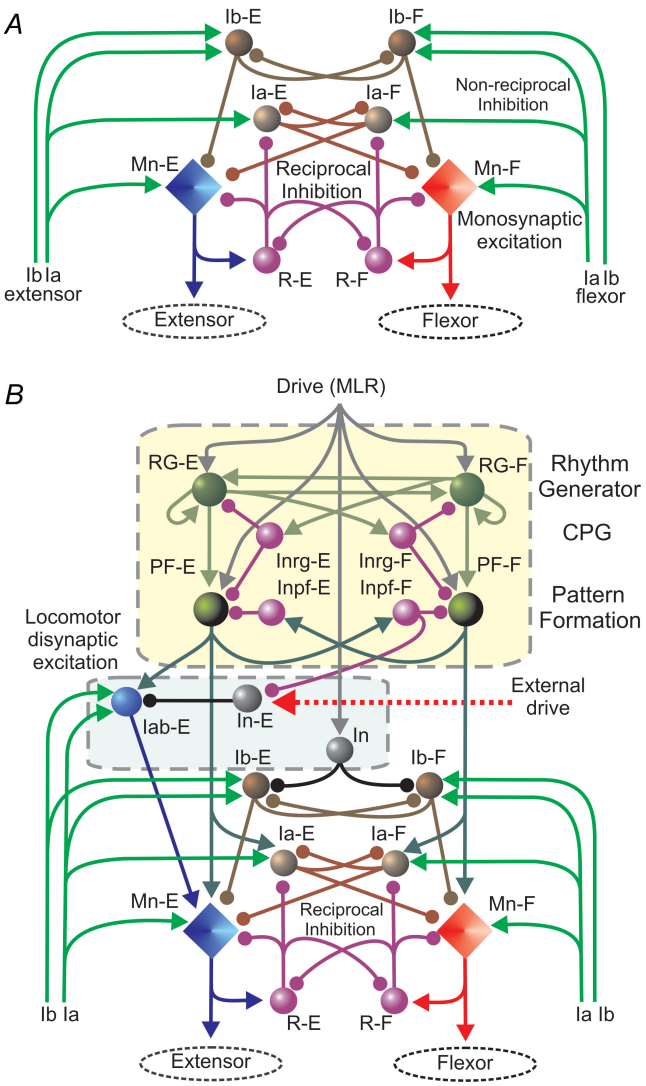

Figure 1. Reflex circuitry of group I afferents and its reorganization during locomotion
A, the simplified schematic diagram of the neural circuitry of spinal reflexes operating under non-locomotor conditions. *B*, reorganization of the spinal circuitry during (fictive) locomotion. Populations of interneurones are represented by spheres. Excitatory and inhibitory synaptic connections are shown by arrows and small circles, respectively. Populations of flexor (Mn-F) and extensor (Mn-E) motoneurones are represented by diamonds. Excitatory tonic locomotor drives are shown in grey. Connections of group I (Ia and Ib) sensory afferents are in green. In *B*, the upper area enclosed by dashed lines indicates the CPG circuits including the rhythm generator (RG) and pattern formation (PF) network. The full description of CPG architecture and performance can be found in the accompanying paper, Rybak *et al.* (2006). During the extensor phase of fictive locomotion, the Iab-E population (blue) is released from inhibition by the In-E population (grey) and mediates phase-dependent disynaptic excitation of extensor motoneurones by group I extensor afferents. During both locomotor phases, the In population (grey) inhibits both the Ib-E and Ib-F populations and hence suppresses non-reciprocal inhibition. See text for details and definitions.

group II afferents required stimulus amplitude to exceed some threshold (Thr(II)). Specifically,

$$\mathrm{II(f)} = S\{\mathrm{Ia(f)} - \mathrm{Thr(II)}\}, \quad (1)$$

where $S\{x\} = x$, if $x \geq 0$, and 0 if $x < 0$.

All simulations were performed using a simulation package NSM 2.0 (for Windows XP) developed at Drexel University by I. A. Rybak, N. A. Shevtsova and S. N. Markin. Differential equations were solved using the exponential Euler integration method (MacGregor, 1987) with a step of 0.1 ms (further details in Rybak *et al.* 2003).

Results

Reorganization of spinal reflexes during MLR-evoked fictive locomotion and afferent control of the locomotor CPG

In the cat, activation of group Ia muscle spindle afferents evokes a reflex monosynaptic excitation of synergist motoneurones (Eccles *et al.* 1957) and a disynaptic inhibition of antagonist motoneurones mediated by Ia interneurones (Jankowska, 1992). Activation of Ib tendon organ or group Ia muscle spindle afferents in non-locomoting preparations evokes a short latency inhibition of synergist motoneurones, the non-reciprocal group I inhibition (Jankowska *et al.* 1981; Jankowska, 1992). These and other reflex actions were incorporated into the scheme shown in Fig. 1. Figure 1*A* represents a simplified scheme of basic reflex circuitry under non-locomoting conditions. It shows two motoneurone (an extensor and a flexor) populations and six interneurone populations mediating reflex interactions. The Ia-E and Ia-F interneurone populations are excited by primary muscle spindle afferents from extensors and flexors, respectively, and mediate Ia reciprocal inhibition of antagonist motoneurones. They are also connected by mutual inhibition (see Jankowska, 1992). R-E and R-F are the populations of Renshaw cells which are excited by axon collaterals of the corresponding motoneurones and inhibit these motoneurones and the corresponding Ia inhibitory interneurones (Jankowska, 1992). In Fig. 1*A*, the group I afferents (from both tendon organs and spindles) activate pathways providing the non-reciprocal inhibition of extensors and flexors mediated, respectively, by the Ib-E and Ib-F populations of inhibitory interneurones, which also mutually inhibit each other (Brink *et al.* 1983; Jankowska & McCrea, 1983; Jankowska, 1992). Therefore during non-locomoting conditions, the reflex circuits described above produce (1) Ia-evoked monosynaptic excitation of homonymous and close synergist motoneurone pools, (2) Ia-evoked disynaptic reciprocal inhibition of antagonist motoneurone populations, and (3) group I (Ib and Ia)-evoked disynaptic non-reciprocal inhibition of homonymous motoneurone pools.

Figure 1*B* shows the spinal cord circuitry operating during fictive locomotion. The two-level locomotor CPG (described in our preceding paper, Rybak *et al.* 2006) and several additional interneurone populations (see areas enclosed by dashed lines) have been incorporated into the circuitry of Fig. 1*A* to provide interactions between the CPG and reflex circuits during locomotion. Activation of tonic excitatory drive to the RG and PF populations (e.g. by continuous MLR stimulation) initiates the generation of the basic locomotor rhythm (for details, see Rybak *et al.* 2006). During locomotion, alternating activity in the RG populations provides periodic alternating inhibition of excitatory interneurone populations in the extensor and flexor portions of the PF network (PF-F and PF-E, respectively), which in turn alternately excite flexor and extensor motoneurone populations as well as several interneurone populations including Ia-E and Ia-F that provide rhythmic inhibition of antagonist motoneurone populations.

With the onset of locomotion, the state of the spinal circuitry changes and the operation of the reflex circuitry is reorganized. First of all during fictive locomotion in decerebrate cats, the non-reciprocal inhibitory reflexes are suppressed (e.g. Gossard *et al.* 1994; McCrea *et al.* 1995). To reproduce this effect, the tonic MLR drive in the model provides a sustained excitation of the hypothetical interneurone population In (see centre portion of Fig. 1*B*) which inhibits the Ib-E and Ib-F populations thus suppressing the group I-evoked non-reciprocal inhibition of motoneurones during locomotion.

The Iab-E population has been included in the model (see Fig. 1*B*) to provide a disynaptic reflex excitation of extensor motoneurones from extensor group I afferents during extension. This group I-evoked disynaptic excitation of extensor motoneurones can be evoked during the extensor phase of fictive locomotion (Schomburg & Behrends, 1978; McCrea *et al.* 1995; Angel *et al.* 1996; Degtyarenko *et al.* 1998) and is mediated by a population of lumbar interneurones that cannot be activated in quiescent preparations (Angel *et al.* 2005). To reproduce these data, the hypothetical In-E population which inhibits the Iab-E population, has been included in the model (Fig. 1*B*). Under non-locomoting conditions (i.e. when the locomotor drive is zero), excitatory external drive produces tonic activity of this population that prevents sensory activation of the excitatory Iab-E interneurones (see Fig. 1*B*). However during the extensor phase of locomotion (i.e. when the PF-E population and the inhibitory Inpf-F population are active), the Inpf-F population inhibits In-E thereby removing the In-E inhibition of Iab-E. This disinhibition permits disynaptic excitation of extensors by group I extensor afferents. In keeping with experimental observations (e.g. McCrea *et al.* 1995; Angel *et al.* 1996, 2005), inhibition of Iab-E during flexion prevents the group I disynaptic excitation of extensor motoneurones during the flexion phase of locomotion. Finally, direct excitation of the In-E population from the PF-E population creates rhythmic extensor-phase activity in Iab-E interneurones. Such rhythmic activity has been found in candidate Iab-E interneurones recorded during fictive locomotion in the cat in the absence of sensory stimulation (Angel *et al.* 2005).

The organization of flexor nerve-activated reflex circuitry operating during fictive locomotion has several similarities to that of extensor reflex circuitry. Flexor afferent stimulation can also evoke disynaptic excitation in flexor motoneurones that is modulated with cycle phase (Degtyarenko *et al.* 1998; Quevedo *et al.* 2000). However, compared to the disynaptic excitation of extensors by extensor afferents, the disynaptic excitation of flexors has a more complex phase dependency and a more limited distribution to hindlimb flexor motoneurones (Quevedo *et al.* 2000). Therefore, a disynaptic excitation of flexors has not been included in the present simplified model containing only two motoneurone pools.

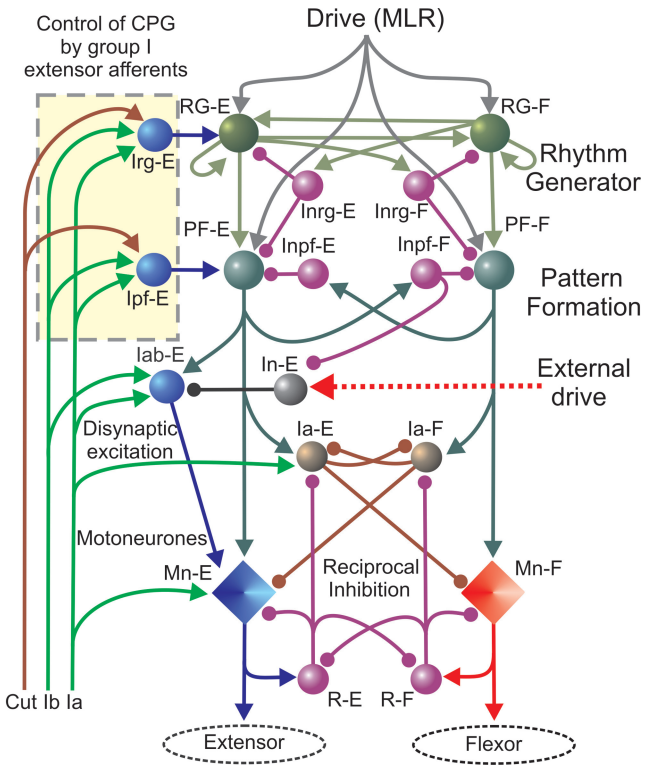

Figure 2. Model schematic diagram of the spinal cord circuitry integrated with the locomotor CPG used for simulation of the effects of extensor group I and cutaneous afferent stimulation during fictive locomotion

The non-reciprocal inhibition illustrated in Fig. 1 has been removed and interneurone populations Irg-E and Ipf-E (both blue) have been added to mediate the access of sensory information from extensor group I (Ia and Ib, green) and cutaneous (Cut, brown) afferents to the rhythm generator (RG-E) and the pattern formation (PF-E) networks. See text for details and definitions. The Iab-E population mediates phase-dependent disynaptic excitation of extensor motroneurons.

An additional change in the model in the locomotor state (not seen in Fig. 1*B*) is that the weights of monosynaptic excitatory inputs of Ia extensor and flexor afferents to the corresponding motoneurone populations (Mn-E and Mn-F, respectively) were set relatively small (see Appendix Table 1) to simulate the tonic presynaptic depression of Ia monosynaptic excitation of motoneurones occurring during fictive locomotion (Gosgnach *et al.* 2000; Rossignol *et al.* 2006). The additional circuitry incorporated into the model to mediate sensory actions on the CPG is discussed below (see Figs. 2 and 6).

In summary, the reorganization of reflex circuits in our model during locomotion includes: (1) reduction in the amplitude (i.e. weighting) of monosynaptic excitation of extensor and flexor motoneurones by the corresponding Ia afferents; (2) suppression of the non-reciprocal inhibition of extensor and flexor motoneurones by the corresponding group I extensor and flexor afferents; (3) emergence of the phase-dependent disynaptic excitation of extensor motoneurones by the same group I extensor afferents; and (4) emergence of the phase-dependent polysynaptic excitation of extensor motoneurones by extensor group I afferents via the CPG.

Taken together, the last three issues represent a 'global reorganization' of the afferent feedback from group I afferents to extensor motoneurones during locomotion. This feedback therefore switches from a negative type via the non-reciprocal inhibition under non-locomotor conditions, to a phase-dependent positive type during locomotion (see Pearson & Collins, 1993; McCrea, 2001; Pearson, 2004; Rossignol *et al.* 2006).

In the remainder of this paper, only the locomotor state is considered. Therefore the Ib-E, Ib-F and In populations and all connections involving the suppressed non-reciprocal inhibitory pathways have been removed (see Figs 2 and 6).

Control of the CPG at the PF and RG level: effects of extensor group I stimulation

Figure 2 shows the reduced circuitry used to model the effects of extensor group I afferent stimulation during locomotion. The locomotor rhythm is generated by the rhythm generator (RG) network. The mechanism for rhythm generation (described in detail in the accompanying paper, Rybak *et al.* 2006) is based on a combination of intrinsic bursting properties of neurons comprising RG-E and RG-F populations, mutual excitation and inhibition between these populations, and their excitation by external (MLR) drive. The rhythm generated by the RG causes alternating activity of PF-F and PF-E populations (within the PF network) which transmits the rhythm to the motoneurone level producing alternating activation of flexor and extensor motoneurones, respectively. One aspect of the model important for understanding the effects of afferent activation is that although both the RG and PF populations have intrinsic bursting properties, the locomotor pattern generated under normal conditions is critically dependent on the mutual inhibition within both the RG and PF networks. This inhibition is important for burst termination and causes the alternating activity bursts of antagonist populations at each level of the network to be tightly coupled.

In Fig. 2, two hypothetical interneurone populations (Irg-E and Ipf-E) have been included in the model to mediate the effects of extensor group I afferent stimulation on the CPG (at the RG and PF levels, respectively) and produce the afferent-evoked excitation of motoneurones that has been postulated to be mediated by the CPG (Conway *et al.* 1987; Gossard *et al.* 1994; Guertin *et al.* 1995; McCrea, 2001; Pearson, 2004; Rossignol *et al.* 2006).

An important feature of our model is that the extensor afferent stimulation can excite extensor motoneurones via both the RG and PF levels of the CPG as well as through local circuits producing disynaptic and, in the case of Ia afferents, monosynaptic motoneurone excitation. Afferent access to the RG-E and PF-F populations is mediated by the Irg-E and Ipf-E populations, respectively (see Fig. 2). According to the hypothesis explored here, the synaptic weighting of group I input (i.e. combining the Ia and Ib inputs) to the PF-E population (controlling extensor activity at the PF level) is stronger than that to RG-E (the extensor half-centre of the RG) (see Appendix Table 1).

Figure 3*A* shows a result of modelling the effects of group I extensor afferent stimulation delivered during flexion. All traces except the top one are average activity histograms of the labelled neuronal populations (see Fig. 2). In this example, a brief group I extensor afferent stimulation (top trace) is delivered to the RG-E and PF-E populations (via Irg-E and Ipf-E populations, respectively) when the flexor motoneurone population (Mn-F) is active (i.e. during the flexion phase). During flexion, both the RG-E and PF-E populations are inhibited by activity in the flexor half-centres (RG-F and PF-F, mediated by the Inrg-E and Inpf-E populations, see Fig. 2). The relatively weak synaptic input from group I extensor afferents to Irg-E is unable to overcome this flexion-related inhibition and excite the RG-E population. Thus rhythm generator activity (second and third traces in Fig. 3*A*) is unaffected by the afferent stimulation. But at the same time, the stronger synaptic weight of afferent input to Ipf-E (1.0 *versus* 0.4 to Irg-E, see Appendix Table 1) evokes a brief excitation of the PF-E population, which in turn inhibits PF-F activity (fourth and fifth traces from the top in Fig. 3*A*). As a result there is a resetting of the PF network to extension (without affecting the RG) that evokes a brief burst of extensor motoneurone activity and a corresponding inhibition (cessation of activity) of flexor motoneurones (see the two bottom traces in Fig. 3*A*).

Figure 3*B* shows the effects evoked during fictive locomotion by a brief duration stimulus train applied to group I ankle extensor (lateral gastrocnemius combined with soleus, (LGS)) afferents during the flexion phase. In this example (modified from Guertin *et al.* 1995), flexor motoneurone activity (TA trace) is truncated soon after stimulus onset (filled rectangle) and a burst of extensor activity occurs (hip, anterior biceps (AB), and knee, quadriceps (Quad) records are illustrated). In both the model (Fig. 3*A*) and the experiment (Fig. 3*B*) the duration of the evoked extensor activity and the following flexor phase are shortened such that a phase shift of the locomotor rhythm does not occur. In other words, the timing of the locomotor periods following the stimulus is the same as would have been expected without the sensory perturbation. This is illustrated in Fig. 3 by the dashed lines indicating intervals equal to the step cycle period preceding stimulus delivery and by the arrows at the bottom of the figure. According to our model, the fictive locomotor data in Fig. 3*B* can be explained by the suggestion that extensor group I afferent stimulation during flexion produces a temporary resetting to extension at the level of PF without affecting the RG and hence, without any change in the timing of the following step cycles.

During real locomotion, extensor group I afferent feedback would occur mainly during the extension phase when Ib afferents are active during extensor muscle contractions (Prochazka & Gorassini, 1998). Figure 4*Aa* and *Ab* shows the results of our simulations of the effects of stimulation of extensor group I afferents during the extension phase when both the RG-E and PF-E populations are active. The simulation in Fig. 4*Aa* had the same amplitude ($d_{\max} = 0.8$) as in Fig. 3. This moderate stimulation had little effect on the activity of the RG populations and hence did not change the ongoing locomotor rhythm generated by the RG (see the second and third traces in Fig. 4*Aa*). The applied stimulation did, however, enhance and prolong PF-E population activity. This increased PF-E activity delayed the switching to the flexion phase at the PF level (see fourth and fifth traces in Fig. 4*Aa*) and enhanced and prolonged extensor motoneurone firing (see the bottom trace in Fig. 4*Aa*). Because the rhythm generator was not affected, the subsequent flexion phase was shortened and the step cycle duration remained constant. This simulation is consistent with the experimental data shown in Fig. 4*Ba* where plantaris (Pl) nerve stimulation enhanced and prolonged extensor motoneurone activity (hip, AB; knee, Quad; and ankle, medial gastrocnemius (MG)). As in our simulation, there was a corresponding shortening of the subsequent flexor phase such that the step cycle period remained unchanged (see arrows at the bottom of Fig. 4*Ba*).

In Fig. 4*Ab*, the amplitude of stimulation was increased by 300% while maintaining the same relative weightings to PF-E and RG-E populations (Appendix Table 1). In contrast to the situation in Fig. 4*Aa*, stronger stimulation increased RG-E activity which in turn delayed the transition to flexion at the RG level (see second and third traces in Fig. 4*Ab*). This stimulation also enhanced PF-E

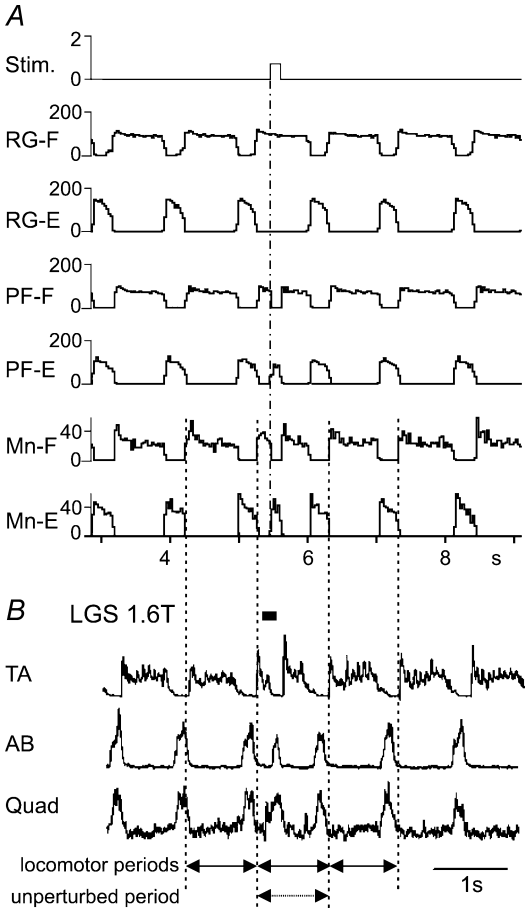

Figure 3. Modelling the effects of group I extensor afferent stimulation delivered during flexion
A, the stimulation applied to group Ia and Ib afferents is shown in the top trace. Other traces show activities of the neural populations in Fig. 2 represented by the average histograms of firing frequency (number of spikes per second per neurone, bin = 30 ms). Stimulus amplitude ($d_{\max}$) was 0.8. The tonic drives to RG-F ($d_{\text{rg-f}}$) and RG-E ($d_{\text{rg-e}}$) populations were 0.57 and 0.39, respectively. Note that here and in the subsequent figure legends, each subscripted variable *d* defines the normalized value representing the corresponding particular drive or afferent input, for details see eqn (10) in the preceding paper by Rybak *et al*. (2006). *B*, an example of the effect of stimulating extensor group I afferents in the lateral gastrocnemius and soleus (LGS) nerve (1.6*T*, where *T* is the threshold for activation of group I afferents; 20 shocks, 100 Hz, filled rectangle) during the flexion phase of MLR-evoked fictive locomotion (modified from Fig. 6*A* in Guertin *et al.* 1995). Stimulation produced a premature onset of extension as seen in the activities of the rectified and integrated hip (anterior biceps, AB) and knee (quadriceps, Quad) extensor electroneurogram (ENG) recordings and terminated the ongoing flexion phase (tibialis anterior, TA, an ankle flexor). Note in both *A* and *B*, the stimulation resulted in a short extensor burst that was followed by a shortened flexion phase so that the timing of the following step cycles did not change (i.e. the locomotor rhythm was not reset; see arrows at the bottom showing equal locomotor periods before, during and after application of stimulation).

activity (see fifth trace in Fig. 4*Ab*). The net effect was an increase and prolongation of extensor motoneurone firing. There was, however, no compensatory change in the duration of the subsequent flexor phase (see the bottom trace in Fig. 4*Ab*). Consequently, each stimulus prolonged the duration of the ongoing locomotor cycle and hence produced a phase shift of the post-stimulation locomotor rhythm. An experimental example of a group I extensor stimulation-evoked enhancement of extensor motoneurone activity in which the ongoing step cycle

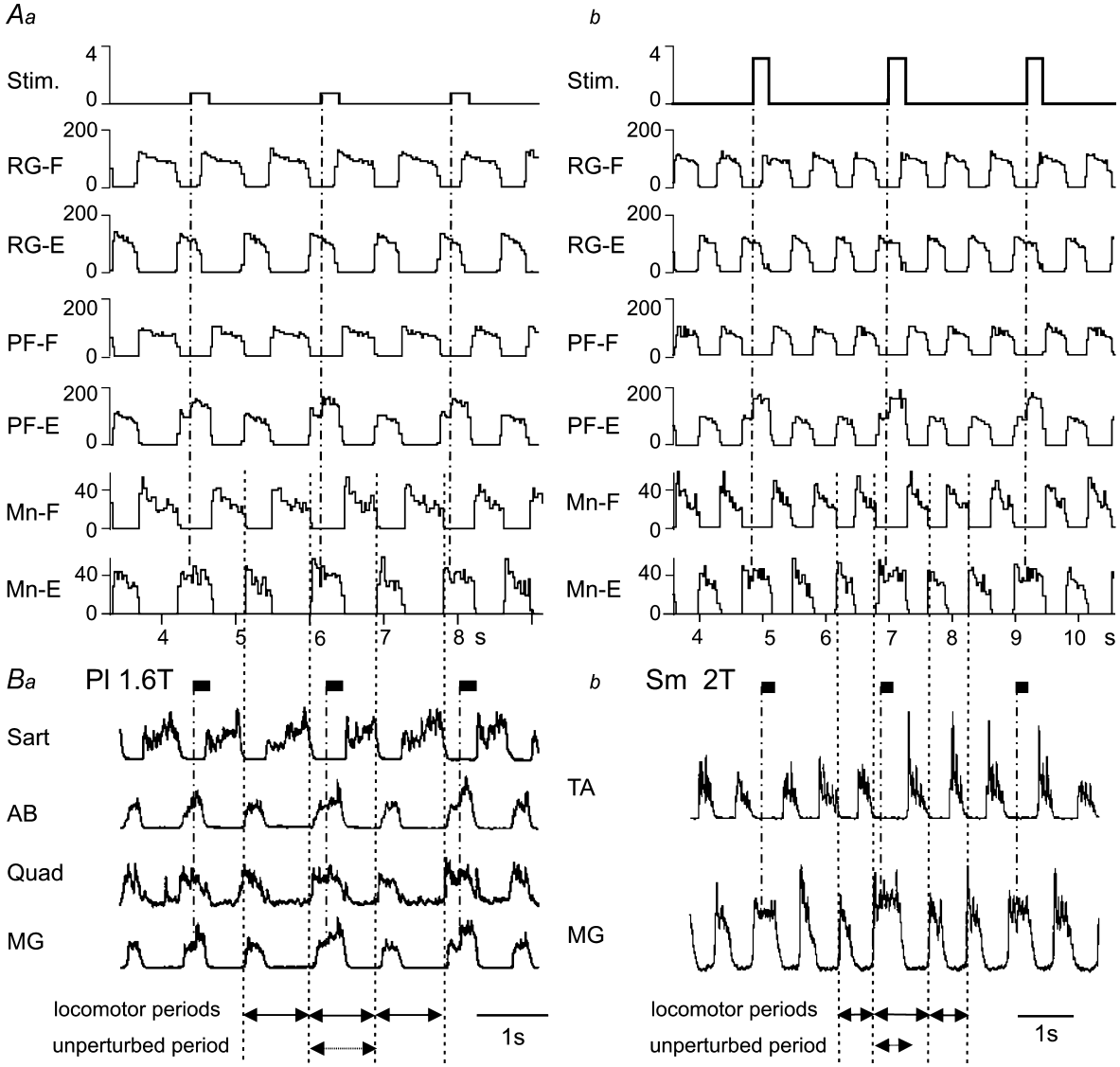

Figure 4. Modelling the effects of group I extensor afferent stimulation during extension
Aa and *Ab*, examples of modelling the effects of stimulation of the group I extensor afferents during extension (see text for details). The applied stimuli are shown in the top traces. The stimulus amplitude (d_{max}) was 0.8 in *Aa* and 3.2 in *Ab*. In *Aa*, drives to RG-F and RG-E populations were: 0.52 and 0.43, respectively; and in *Ab* were: 0.52 and 0.47, respectively. *Ba* and *Bb*, the effects of stimulation of extensor group I afferents during MLR-evoked fictive locomotion. In *Ba*, stimulation of plantaris (Pl) group I afferents during extension (1.6 times threshold (1.6*T*), 20 shocks, 100 Hz; adapted from Fig. 1*A* in Guertin *et al.* 1995) increased the size and duration of extensor motoneurone activity (medial gastrocnemius, MG) and shortened the duration of the following flexor phase as seen in the sartorius (Sart) ENG. Note that in both *Aa* and *Ba*, the duration of each flexion phase following the prolonged extension phase was shortened so that the locomotor periods did not change. The locomotor rhythm was not reset (see equal length arrows at the bottom). In panel *Bb*, hip extensor (semimembranosus, Sm) muscle afferents were electrically stimulated during extension (2*T*, 20 shocks, 100 Hz). This figure is from unpublished observations obtained during the experiments reported by Guertin *et al.* (1995). In contrast to the results shown in *Aa* and *Ba*, in *Ba* and *Bb* the flexion phase that follows the stimulus-evoked extension phase prolongation (see MG trace in *Bb*) was not shortened (see TA trace) and the step cycle period increased with each stimulus delivery (see arrows at the bottom).

period was increased is shown in Fig. 4*Bb*. In this example, each stimulus applied to group I extensor afferents (semimembranosus (Sm), a hip extensor) enhanced and prolonged extensor (MG) bursts. The following flexor phase had an unchanged duration and hence the locomotor rhythm was shifted in time (see arrows at the bottom of Fig. 4).

Based on the results of these simulations, we conclude that stimulation of group I extensor afferents during extension may prolong the current extension phase with or without changing the duration of ongoing locomotor cycle and the phase of post-stimulation rhythm. The exact effect in the model depends on how strongly the applied stimulation influences the rhythm generator.

Dominant control of the CPG at the RG level: effects of cutaneous tibialis nerve stimulation

In the cat, stimulation of cutaneous afferents in the tibial nerve (Tib, innervating plantar foot structures) during

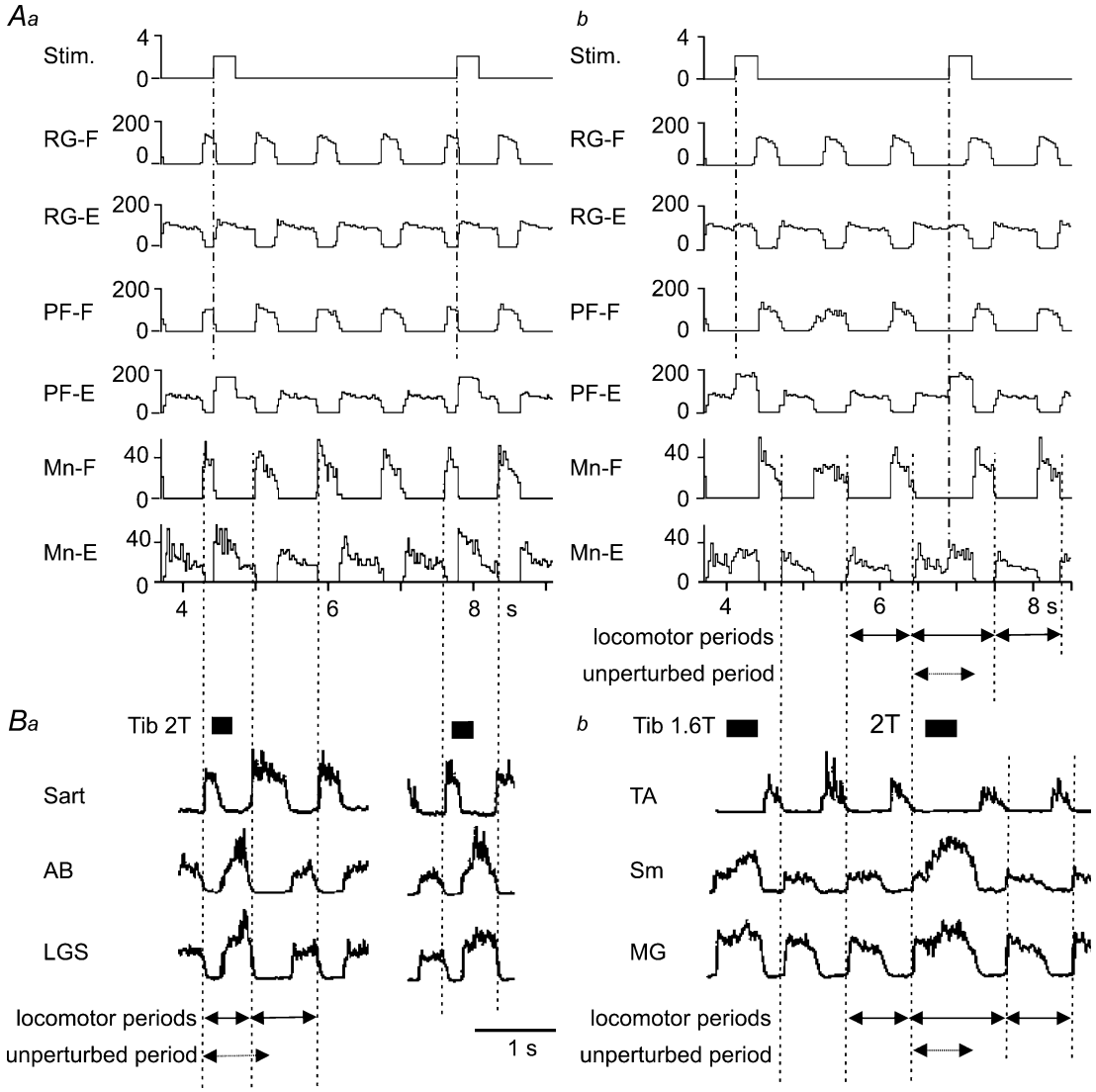

Figure 5. Modelling the effects of cutaneous nerve stimulation
Aa and *Ab*, using the schematic diagram shown in Fig. 2, sensory stimuli were applied to the cutaneous afferents during the flexor (*Aa*) and extensor (*Ab*) phases of locomotion. The applied stimulation affected both the PF and RG levels of CPG (on the extensor side, see Fig. 2). The applied stimuli are shown in the top traces ($d_{max} = 3.0$). Drives to RG-F and RG-E populations were: 0.43 and 0.53, respectively. *Ba* and *Bb*, experimentally recorded effects of stimulation of a cutaneous nerve during flexion and extension. The stimulations (20 shocks, 100 Hz) were applied to the distal portion of the tibial nerve. Stimulation applied during flexion (*Ba*) terminated the ongoing flexor phase (sartorius, Sart) and produced a premature onset of extension (seen in activities of anterior biceps (AB) and lateral gastrocnemius combined with soleus (LGS)). Stimulation applied during extension (*Bb*) prolonged the extension phase (seen in activities of semimembranosus (Sm) and medial gastrocnemius (MG)). The recordings are from Figs 7*C* and *D* of Guertin *et al.* (1995). Note that in *Aa* and *Ba*, the afferent stimulation shortened the cycle period, whereas in *Ab* and *Bb*, cycle period was prolonged (see arrows at the bottom of each part of the figure).

the extension phase of fictive locomotion promotes hindlimb extensor activity (Guertin *et al.* 1995). The same stimulation during flexion terminates the ongoing flexion phase and initiates extension (Guertin *et al.* 1995). To simulate these effects, we suggest that stimulation of Tib nerve afferents (the Cut lines in Fig. 2) activates the extensor part of the CPG via the corresponding interneurone populations (Inrg-E and Inpf-E) with an equal effect on the RG-F and PF-E populations (Appendix Table 1). In the model, these afferents have no monosynaptic or disynaptic actions on motoneurones or Ia inhibitory interneurones. Figure 5*Aa* and *Ab* shows simulations of the effects of delivering such stimulation during flexion and extension, respectively. Stimuli applied during flexion (Fig. 5*Aa*) reset the RG (and the entire pattern) to extension. Note the shortening of activity in the RG-F population and the advanced start of activity of the RG-E populations with the onset of stimulation (vertical dash-dot lines). The same stimuli applied during extension prolong activity in the RG-E and PF-E populations which then causes prolonged and increased extensor motoneurone activity with each stimulus presentation (Fig. 5*Ab*). The effect in both cases (resetting or prolongation) is produced at the level of RG with a resetting of the locomotor rhythm (see arrows at the bottom of Fig. 5*Ab*, *Ba* and *Bb*). The simulations closely reproduce the results of corresponding experimental studies (see Fig. 5*Ba* and *Bb*).

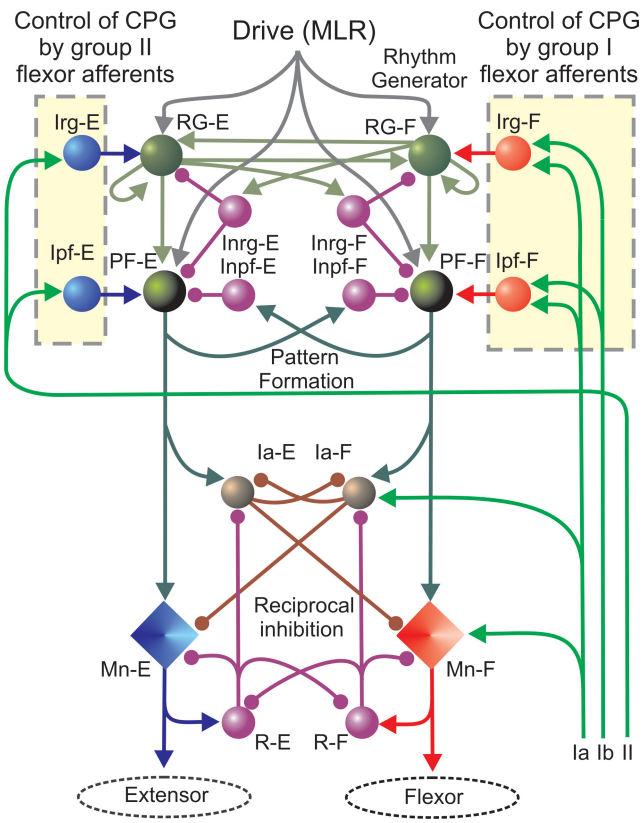

Figure 6. Schematic diagram of the model used for simulation of flexor afferent stimulation
Flexor group I afferents access the RG and PF elements on the flexor side of the CPG through interneurone populations (Irg-F and Ipf-F, respectively, both are shown red). Flexor group II afferents project to the extensor side of the CPG via the Irg-E and Ipf-E populations, respectively (shown blue). See text for details and definitions.

Competing actions of group I and group II flexor muscle afferents on the CPG: effects of flexor afferent stimulation

As outlined in the Introduction, activation of group II afferents in flexor nerves during fictive locomotion can either terminate the ongoing flexor phase and switch the step cycle to extension (e.g. following TA nerve stimulation) or prolong ongoing flexor activity (e.g. EDL nerve stimulation; Perreault *et al.* 1995; Stecina *et al.* 2005). Occasionally these actions spontaneously reverse (Stecina *et al.* 2005). In the same preparations, flexor group I afferent activation can enhance and prolong flexor motoneurone activity in a manner analogous to the extensor promoting actions of extensor group I afferents (Perreault *et al.* 1995; Stecina *et al.* 2005). These observations support the suggestion that the group I flexor afferents are excitatory to the flexor part of the CPG (i.e. to RG-F and PF-F populations in the model). Our hypothesis (see Stecina *et al.* 2005) is that flexor group I afferents excite the flexor part of the CPG (both RG-F and PF-F) while flexor group II afferents are excitatory to the extensor part of the CPG. Accordingly, the effects of simultaneous activation of group II and group I flexor afferents work against each other. The resulting effect is therefore dependent upon the interplay between the two influences on the CPG.

The schematic of the model used for flexor afferent stimulation is shown in Fig. 6. As in Fig. 2, hypothetical interneurone populations (Irg-F, Ipf-F, Irg-E and Ipf-F) have been added to mediate the effect of group I and II flexor afferent stimulation on the CPG. Similar to the organization postulated for extensor afferents, there is a relatively strong excitatory effect of flexor group I afferents on PF-F (via Ipf-F) and a weak effect on RG-F (via Irg-F) (see Appendix Table 1). In accordance with the above hypothesis, the flexor group II afferents are connected to the Irg-E and Ipf-E populations which mediate their excitatory effects on the extensor part of the CPG (RG-E and PF-E, respectively). Because of the strong weighting of group II afferent input to RG-E (via Irg-E), activation of these afferents may strongly affect the RG (e.g. reset the RG to extension).

Figure 7*A* shows an example of our simulation of the effects of flexor afferent stimulation during flexion. To match the experimental procedure, all stimuli were applied to both flexor group I (Ia and Ib) and group II inputs. The

first stimulus (left, top trace in Fig. 7*A*) strongly recruits both group I and II afferents. This stimulus terminated the ongoing flexion phase and reset the cycle to extension (see RG-F and RG-E activities in Fig. 7*A*). In order to mimic a less effective recruitment of group II afferents, the threshold for activation of group II flexor afferents was increased prior to the application of the second stimulus. This time the stimulation prolonged the ongoing flexor phase. This occurred because the relatively stronger group I-evoked excitation of PF-F (i.e. weaker group II activation of RG-F) prevented phase resetting at the level of pattern formation (see the fourth and fifth traces in Fig. 7*A*) and hence at the level of motoneurones. Therefore, the net result of strong activation of flexor group I and relatively weak activation of group II afferents was a prolongation of the ongoing flexion phase. It is important to notice that both stimuli reset the RG oscillator to extension (see the second and third traces in Fig. 7*A*).

These effects are quite similar to the experimental results illustrated in Fig. 7*B*. Stimulation of TA afferents at an intensity that recruits group II fibres (*5T*), terminated ongoing flexor phase activity (sartorius, Sart) and initiated extensor activity (hip, semimembranosus combined with anterior biceps (SmAB) and ankle, MG). Stimulation of EDL in the same run prolonged the flexion phase (Sart and peroneus longus (PerL) ENG activity). In both the simulation (Fig. 7*A*) and experiment (Fig. 7*B*), the first stimulus reduced the ongoing cycle period shifting the rhythm to the left. Increasing the threshold of group II afferents in the model reduced their input to Irg-E and Ipf-E and produced an effect similar to that of EDL nerve stimulation shown in Fig. 7*B*, namely a prolongation of the duration of both the ongoing flexion and the total cycle period (and the corresponding shifting of the rhythm to the right). According to these concepts, the reflex actions of group II afferents between different flexor nerves could vary according to either the numbers of group I and II afferents in each nerve or their central excitatory effectiveness.

Figure 8*Aa*–*Ae* shows the effects of a progressive increase in the influence of flexor group II afferents on RG-E and PF-E populations in the model. This was produced by a sequential reduction of the threshold for group II flexor afferent activation from panel *Aa* to *Ae* (see threshold value at the top of each panel). At the lowest level of group II activation (highest threshold, *Aa*), the stimulation had little effect on the RG populations and produced a mild enhancement and prolongation of flexor motoneurone activity due to the activation of PF-F by flexor group I afferents (see third and fifth traces in Fig. 8*Aa*). In both Fig. 8*Ab* and *Ac*, the group II activation reset the RG (see the first and second traces in Fig. 8*Ab* and *Ac*) but this resetting was not expressed at the PF level (see the third and fourth traces in Fig. 8*Ab* and *Ac*). As a result, flexor motoneurone activity was prolonged

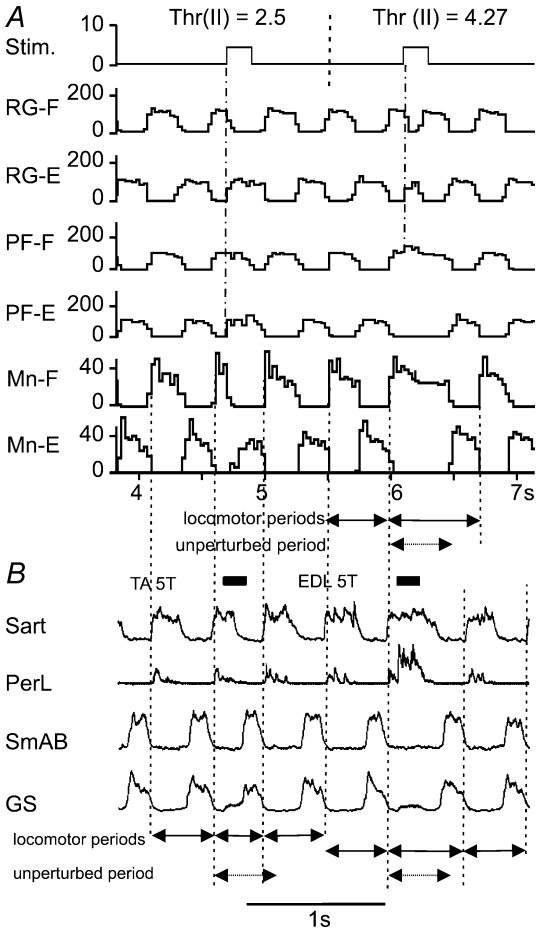

Figure 7. Modelling the effects of stimulation of flexor afferents during flexion
A, the applied stimuli are shown in the top trace (stimulus amplitude ($d_{max} = 5.0$). The first stimulus terminated ongoing flexion and initiated a premature switch to extension. At the 5.5 s time point in the simulation (i.e. before the second stimulus application), the threshold of group II flexor afferent activation (Thr(II), see eqn (1)) was increased from 2.5 to 4.27 (see labels at the top). As a result, group II afferent action on the extensor CPG circuitry was reduced and the second stimulus produced a prolongation of the ongoing flexion phase (see PF-F and Mn-F activity). Note that both stimulus presentations reset the locomotor rhythm (see RG-E and RG-F traces). Tonic drives to RG-F (d_{rg-f}) and RG- E (d_{rg-e}) populations were: 0.55 and 0.53, respectively. *B*, experimental effects of five times threshold (5*T*) stimulation of flexor afferents during flexion. Stimulation of tibialis anterior (TA) afferents terminated the flexion phase (sartorius, Sart and peroneus longus, PerL) and advanced the onset of extensor (semimembranosus combined with anterior biceps, SmAB and combined lateral and medial gastrocnemius and soleus nerves, GS) activity. Stimulation of another flexor nerve (extensor digitorum longus, EDL) in the same run of fictive locomotion prolonged the ongoing flexion phase (see activities of Sart and PerL). Data from Stecina *et al.* (2005). In both the simulated and experimental trials, the locomotor rhythm was affected by flexor nerve stimulation with the first stimulation shortening, and the second prolonging, the ongoing locomotor period (see arrows at the bottom of *A* and *B*).

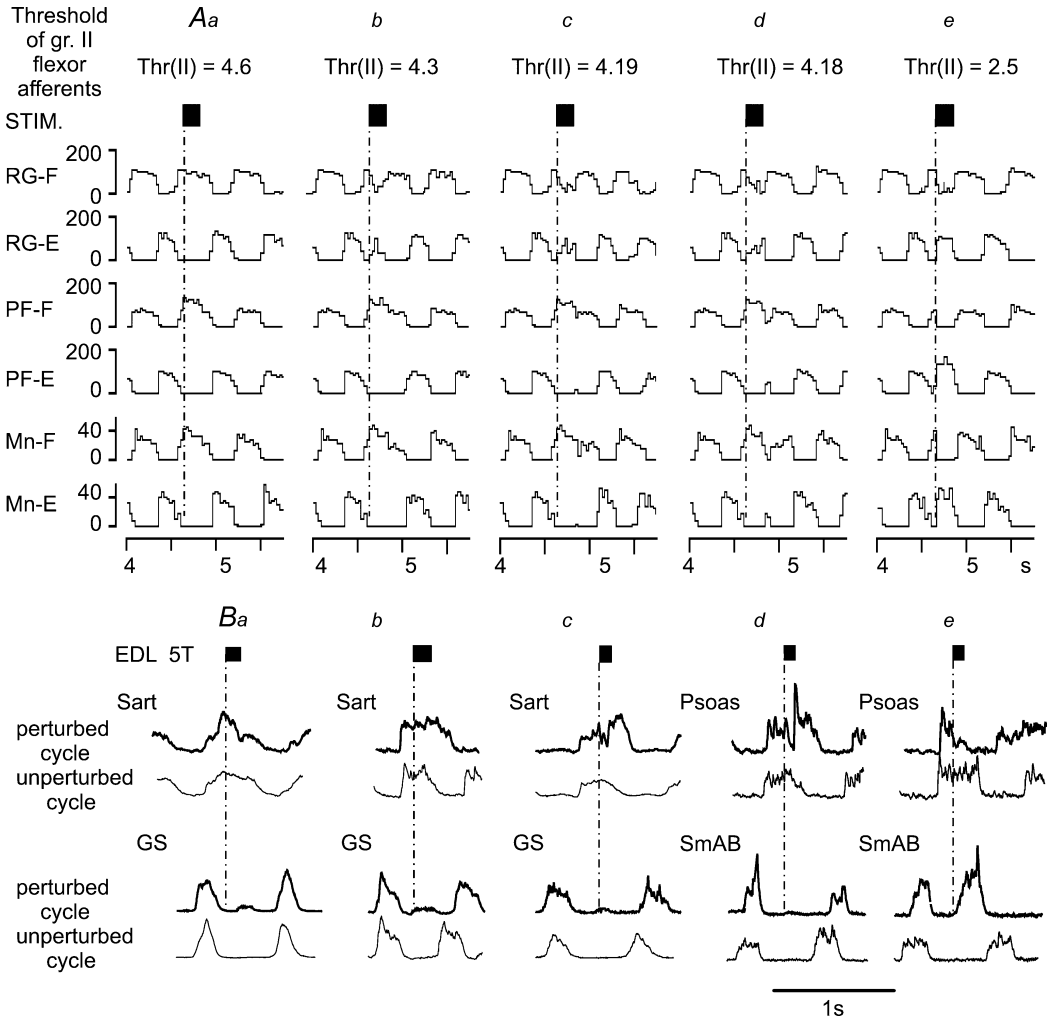

Figure 8. Modelling the variable effects evoked by flexor muscle afferent stimulation during flexion on locomotor output

Aa–Ae, results from modelling experiments illustrating variable effects produced by the activation of flexor afferents (filled rectangles) during the flexion phase of locomotion. All model parameters and parameters of stimulation were the same as in Fig. 7*A*, except for the threshold of group II flexor afferent activation Thr(II) (see eqn (1)), which was sequentially decreased from *Aa* to *Ae* (see values of the Thr(II) at the top of each panel). The filled rectangles at the top indicate the timing and duration of the stimuli. Note that the afferent stimulation resets the RG in all simulations except for *Aa* (see the top and second traces showing RG-F and RG-E population activities). In *Ab* and *Ac*, the concomitant activation of PF-F by flexor group I afferents (see Fig. 6) prevented resetting at the PF level (third and fourth traces in *Ab* and *Ac*) and the level of motoneurones (bottom two traces). The result therefore was a prolongation of the flexion phase. In *Ad*, the applied stimulus produced only a short break in the middle of flexor activity and a small, short extensor burst (Mn-E). In *Ae*, with the lowest Thr(II) (i.e. strongest group II actions), sensory activation produced a full resetting to extension (see text for details). *Ba–Be*, experimentally recorded effects of five times threshold (5*T*) stimulation of extensor digitorum longus (EDL) afferents during the flexion phase of MLR-evoked fictive locomotion. Averaged ENG records during cycles in which stimulation was applied (perturbed cycle) are shown in bold with control (unperturbed) cycles shown directly below. These observations were selected from different experiments (McCrea, 2001; Stecina *et al.* 2005) and formed the basis of the simulations shown in *Aa–Ae*. Note the variety of effects observed following 5*T* EDL stimulation in the different experiments. In *Ba*, EDL stimulation resulted in a slight increase in flexor (sartorius, Sart) activity with no effect on the timing of flexor or extensor motoneurone bursts. In *Bb*, there was a prolongation of the ongoing flexor phase and a delay in the activation of extensors. In *Bc* and *Bd*, flexor afferent stimulation also prolonged the flexion phase (see Sart in *Bc* and psoas (Psoas) in *Bd*) but there was also a brief reduction in flexor motoneurone activity in the middle of the flexor phase and a corresponding small but visible activation of extensors (see the hint of extensor activity in GS in *Bc*). Both these effects presumably indicate a short lived resetting of flexor activity. These experimental observations are similar to the modelled trials shown in *Ac* and *Ad*. *Be*, shows an example of a rarely observed effect of EDL stimulation in which flexion was terminated and a premature onset of extension initiated. This was another stimulus trial from the same run of fictive locomotion as shown in *Bd* and is an example of a spontaneous reversal of EDL actions (Stecina *et al.* 2005).

even though activity in the flexor portion of the rhythm generator (RG-F) was shortened. In Fig. 8*Ad*, the increased group II input (further threshold reduction) produced further excitation of the extensor side of the CPG. This partially overcame the group I actions on the flexor side, and a phase resetting occurred at both RG and PF levels. There was, however, only a small brief burst of extensor motoneurone activity and a short break in flexor activity. Further increase in group II flexor afferent activation (further reduction of their threshold) resulted in a much stronger effect of group II afferents on the CPG. In Fig. 8*Ae*, the threshold for group II flexor afferent activation was maximally reduced (to the same value as during the first stimulus application in Fig. 7*A*). As a result, stimulation terminated the flexion phase and produced a premature resetting to extension. Importantly, in all but one (Fig. 8*Aa*) of the simulations shown in Fig. 8*Aa–Ae*, the prolongation of flexion or resetting to extension was accompanied by a resetting of the rhythm at the RG level.

Figure 8*Ba–Be* shows experimentally recorded effects of EDL stimulation taken from different fictive locomotion experiments. During those experiments, the same intensity of EDL nerve stimulation (activating both group I and II afferents) resulted in a variety of effects on the step cycle. These variations in reflex actions may result from differences in the excitability of the CPG networks, or from the differences in the effectiveness of synaptic transmission from group I and II afferents to the CPG network (Perreault *et al.* 1999; Stecina *et al.* 2005). In the first example (Fig. 8*Ba*), EDL stimulation produced only a slight increase in hip flexor (Sart) activity and there was no effect on step cycle period (compare the cycle period in the perturbed cycle to that in the unperturbed cycle). In Fig. 8*Bb*, EDL stimulation prolonged the ongoing flexor motoneurone bursts (Sart) and delayed the onset of extensor bursts (gastrocnemius combined with soleus, GS). These effects can be compared to the modelled effects of flexor afferent stimulation shown in panels Fig. 8*Aa* and *Ab*, respectively. In Fig. 8*Bc* and *Bd*, flexor afferent stimulation also prolonged the flexion phase (Sart and psoas, Psoas), but there was also a brief reduction in flexor motoneurone activity in the middle of the flexor phase and a corresponding small but visible activation of extensors (Fig. 8*Bc*). Both of these effects presumably indicate a short lived resetting of flexor activity. These experimental observations are similar to the modelled trials shown in Fig. 8*Ac* and *Ad*. Fig. 8*Be* shows an example of the unusual effect of EDL nerve stimulation terminating flexion and initiating a premature onset of extension (Stecina *et al.* 2005). This example was from the same run of fictive locomotion as shown in Fig. 8*Bd* and represents an example of a spontaneous reversal of EDL actions. This 'reversed' extension-promoting action of EDL stimulation is similar to the common effect seen with TA nerve stimulation (Perreault *et al.* 1995; Stecina *et al.* 2005). As seen in Fig. 8*Ae*, this resetting to extension could be reproduced in the model by further recruitment of flexor group II fibres with a resulting stronger activation of RG-E.

Discussion

In the preceding paper (Rybak *et al.* 2006), we proposed a model of the mammalian spinal circuitry incorporating a locomotor CPG with a two-level architecture that included a half-centre RG producing the basic locomotor rhythm and a PF network distributing rhythmic excitation to different motoneurone populations. In the present study, basic reflex circuits were integrated into this model to account for the reorganization of group I reflex pathways during locomotion (see Fig. 1). The integrated model was then used for simulation of the effects of various phase-specific stimulations applied to different afferent nerves during MLR-evoked fictive locomotion in decerebrate cats (Guertin *et al.* 1995; Stecina *et al.* 2005).

The reorganization of reflex circuits during locomotion in our model results from interactions of these circuits with the locomotor CPG (Fig. 1) and includes the suppression of non-reciprocal inhibition (Gossard *et al.* 1994; McCrea *et al.* 1995; Angel *et al.* 1996; McCrea, 2001) and the emergence of phase-dependent, disynaptic excitation of extensor motoneurones by group I extensor afferents (McCrea *et al.* 1995; Angel *et al.* 1996, 2005). This reorganization results in the replacement of the non-reciprocal inhibition operating under non-locomoting conditions with a phase-dependent positive feedback to extensors during locomotion (Pearson & Collins, 1993; Gossard *et al.* 1994; McCrea, 2001; Donelan & Pearson, 2004; Rossignol *et al.* 2006). In the present simulations, the weights of Ia afferent inputs to extensor and flexor motoneurones were set at a relatively weak level to account for the presynaptic depression of monosynaptic Ia reflexes during locomotion (e.g. Gosgnach *et al.* 2000; Rossignol *et al.* 2006). We did not attempt to simulate all of the known hindlimb reflexes operating during fictive locomotion. For example, we did not consider the flexor afferent-evoked disynaptic excitation of flexor motoneurones (Degtyarenko *et al.* 1998; Quevedo *et al.* 2000) and the short-latency cutaneous reflexes involved in the stumbling correction reaction (Burke, 1999; Quevedo *et al.* 2005*a*,*b*). Nor did we simulate cutaneous reflexes evoked from nerves other than the tibial nerve (e.g. Guertin *et al.* 1995). These issues will be considered in our future modelling studies.

An important advantage of the two-level CPG structure considered here is that it allows sensory feedback to separately control (1) the amplitude and timing of flexor

and extensor motoneurone activities (via the PF level) and (2) the frequency and phase of locomotor oscillations (through the RG level). Specifically, the model suggests and identifies the conditions in which there can be a premature phase switching or a prolongation of the ongoing phase without (e.g. Figs 3 and 4*Aa*) or with (e.g. Figs 4*Ab* and 5) an alteration of the phase of post-stimulation rhythm. Furthermore, by regulating the relative degree to which flexor group I and group II afferents affect flexor and extensor components of the RG and PF, we could also simulate and suggest an explanation for the complex reflex actions of flexor afferents and the occasional reflex reversal observed during fictive locomotion (e.g. Figs 7 and 8; see Stecina *et al.* 2005).

The effects of extensor afferent stimulation

Modelling the effects of group I extensor afferent stimulation delivered during flexion shows that these afferents can produce a premature switching of ongoing flexion to extension without affecting rhythm generation (Fig. 3*A*). These simulation results are quite similar to the experimental data obtained during MLR-evoked fictive locomotion (e.g. see Fig. 3*B*). To our knowledge, such phase switching that does not affect the locomotor rhythm has not been considered before. The reciprocal inhibition between flexor and extensor components within the PF level as suggested by our model is critical for this behaviour.

There is substantial evidence (see Introduction) that during real locomotion, the activity of group I extensor afferents provides strong activation of extensor motoneurones and significantly contributes to the weight support during stance as well as to the control of the timing of stance–swing transition. In the context of our model, we suggest that these afferents contribute to weight support and the control of stance–swing transitions via separate pathways within the CPG. We hypothesize that the contribution of the activity of group I extensor afferents to weight support during stance is provided by a positive feedback loop via the PF network (in the model, via the activation of PF-E population) and, at a lower level, through the disynaptic excitation of extensor motoneurones. At the same time, the control of the transition from stance to swing (e.g. prohibiting swing until the limb is unloaded; see Duysens & Pearson, 1980) operates via an extensor group I afferent-evoked activation of the extensor half-centre of the RG (RG-E population). Our model also suggests that the effect of group I afferents on the RG is weaker than their effect on the PF. Therefore, moderate activation of extensor group I afferents would enhance and prolong the ongoing extension phase via actions at the PF level without resetting the locomotor rhythm (see Fig. 4*Aa*). At the same time, a stronger activation of RG-E may delay (or even 'prohibit') the transition from stance to swing at the RG level and shift the timing of the following step cycles. Our model predicts that such effects can be produced with an increase in the intensity of group I extensor afferent stimulation (see Fig. 4*Ab*) or with stimulus delivery closer to the expected time of transition to flexion. These predictions await experimental confirmation.

The effects of cutaneous afferent stimulation

In our model, stimulation of the tibial nerve was used as an example of reflex control exerted principally at the RG level of the CPG and not at the level of motoneurones and short-latency reflexes. Tibial nerve stimulation during the extension phase of fictive locomotion enhances the activity of extensor neurones and prolongs extension while the same stimulation during flexion terminates the ongoing flexion and initiates extension (Conway *et al.* 1994; Guertin *et al.* 1995). In both cases the stimulation strongly affects the duration of the ongoing locomotor period (see Fig. 5). Our simulation predicts that cutaneous afferents in the tibial nerve have direct access to the spinal rhythm-generating circuitry to control the timing of locomotor phase switching and increase extensor motoneurone activity throughout the limb. According to both the experimental data and our simulation, the effects of stimulation of these afferents on step cycle period are similar but stronger than the actions of group I extensor muscle afferents. In keeping with the important contribution of cutaneous afferents to the control of locomotion in both normal and spinal cats (Rossignol *et al.* 2006), the flexible organization of the model could also incorporate the reflex actions of other cutaneous afferents (e.g. superficial peroneal) postulated to have actions on the flexor side of the CPG (see Quevedo *et al.* 2005*a,b*).

The effects of flexor afferent stimulation

Our modelling studies on the effects of flexor nerve stimulation were motivated by the need to explain the variable, often opposing, and spontaneously reversing reflex actions of these afferents on the locomotor pattern (see Introduction). Here we explored the hypothesis (Stecina *et al.* 2005) that group I afferents in flexor nerves provide excitatory input to the flexor part of the CPG (RG-F and PF-F) whereas group II afferents in the same nerves are excitatory to the extensor part of the CPG (see Fig. 6). Based on our model, lower intensity stimulation that predominately activates group I flexor afferents should prolong the ongoing flexion phase and higher intensity

stimulation, activating group II afferents, may evoke a resetting to extension. This idea appears to be generally consistent with the fictive locomotion data in which raising stimulus intensity in some flexor nerves from 2*T* to 5*T* to recruit group II afferents changes the effect of flexor afferent stimulation from a flexor-phase prolongation to a resetting to extension (e.g. TA, posterior biceps combined with semitendinosis (PBSt) and Sart nerves; Perreault *et al.* 1995; Stecina *et al.* 2005).

According to our hypothesis, higher intensity electrical stimulation activating both group I and II flexor afferents causes a competition between opposing actions of these afferents on the CPG (see Figs 6, 7 and 8). Therefore, the opposite effect produced by activation of TA (and PBSt and Sart) *versus* EDL (and PerL and Psoas) afferents seen experimentally (see Fig. 7*B*) may be because of differences in the relative effectiveness of the inputs from group I and group II fibres in these nerves to central circuitry (as in Fig. 7*A*) and not because of qualitative differences in their anatomical projections to subpopulations of spinal interneurones. In addition, we suggest that the effectiveness of both group I and II afferent synaptic connections to the CPG are subject to control and variation during locomotion. Experimental support for this suggestion is that there is a strong centrally generated presynaptic control of synaptic transmission from group II afferents during MLR-evoked fictive locomotion in select spinal locations (Perreault *et al.* 1999; Stecina *et al.* 2002). Spontaneous variations in the effectiveness of group II and group I inputs to the CPG could explain the occasional reversal of reflex effects (e.g. those seen during EDL stimulation) (Fig. 8*Ba–Be*).

The two-level CPG model was able to reproduce the flexor nerve-evoked enhancement and prolongation of flexion (Fig. 7*A*, second stimulus, and Fig. 8*Aa–Ad*) as well as the resetting to extension (Fig. 7*A*, first stimulus, and Fig. 8*Ae*). We show that the resultant effect depends on the relative influences of group I and group II afferents on the CPG. An important conclusion from our simulations is that both effects (shortening or prolonging the current cycle period, as seen in the activity of motoneurones) may be produced with (and are a consequence of) the resetting of the RG by the group II afferents (see the RG-E and RG-F traces in Figs 7*A* and 8*Ab–Ae*).

The complex reflex effects of activation of group I and II afferents in flexor nerves require further analysis. The exact neuronal types and pathways operating during locomotion and their control remain unidentified. The variability of responses between and within preparations (see Introduction) may depend on the intensity of applied stimulation (and the number of group II afferents involved and the distribution of their thresholds) and on the timing of stimulus delivery (with respect to the anticipated phase switching). These factors will be subjects for future experimental and modelling studies.

The role of flexor afferent feedback during normal locomotion is poorly understood. It is known that feedback from hip flexor muscle afferents, particularly from the Sart muscle, can enhance flexor activity during treadmill locomotion (Lam & Pearson, 2001) and that hip position contributes to swing–stance transitions (McVea *et al.* 2005). Our simulations have demonstrated that simultaneous activation of both group I and group II afferents of flexors may enhance and prolong flexion (see Fig. 7, second stimulus, and Fig. 8*Aa–Ad*), which is consistent with the findings of Lam & Pearson (2001). On the other hand, and similar to the experimental data on fictive locomotion (Perreault *et al.* 1995; Stecina *et al.* 2005), the model shows that a stronger activation of group II afferents during flexion may promote a switch to the extension phase. Sorting out flexor afferent control of CPG operation will require an understanding of when these afferents are active during the step cycle as well as an appreciation of the presynaptic control of inputs from these afferents to their target interneurones.

Conclusion

In the preceding paper (Rybak *et al.* 2006), we proposed a model of mammalian spinal circuitry with the two-level locomotor CPG composed of RG and PF networks. Despite the relatively simple schematic, this model is able to generate locomotor oscillations with step cycle periods and phase durations spanning the range observed during fictive locomotion (Yakovenko *et al.* 2005) and reproduce various types of spontaneous deletions of motoneurone activity occurring during fictive locomotion (Lafreniere-Roula & McCrea, 2005). Here we show that this model can accommodate the reorganization of reflex circuits during locomotion and realistically reproduce and explain several experimentally observed effects of extensor, flexor and cutaneous afferent stimulation upon locomotor rhythm and motoneurone firing. The ability to separately control the durations of locomotor phases and the step cycle and the degree of motoneurone activity is an important feature of this model allowing it to reproduce experimental data that cannot be easily accommodated within the classical half-centre or the coupled unit-burst generator organizations. Efforts are underway to extend the model to the more complex locomotor activities of bifunctional motoneurones (Chakrabarty *et al.* 2004). We consider this model as a basis for future interactive experimental and modelling studies.

Appendix

Table 1. Weights of synaptic connections in the network

Target population	Source population or drive (weight of synaptic input to one neurone)
RG-E	MLR (1); RG-E (0.0125); RG-F (0.0125); Inrg-E (−0.115); Irg-E (0.05)
RG-F	MLR (1); RG-E (0.0125); RG-F (0.0125); Inrg-F (−0.115); Irg-F (0.05)
Inrg-E	RG-F (0.45)
Inrg-F	RG-E (0.45)
Irg-E	Ia(e) (0.1); Ib(e) (0.3); IIf(1.7); Cut (2)
Irg-F	Ia(f) (0.03); Ib(f) (0.09)
PF-E	MLR (1); RG-E (0.0075); Inrg-E (−0.05); Ipf-E (0.5)
PF-F	MLR (1); RG-F (0.0075); Inrg-F (−0.05); Ipf-F (0.5)
Inpf-E	PF-F (0.2)
Inpf-F	PF-E (0.2)
Ipf-E	Ia(e) (0.25); Ib(e) (0.75); IIf(1); Cut (2)
Ipf-F	Ia(f) (0.075); Ib(f) (0.225)
Iab-E	Ia(e) (0.05); Ib(e) (0.15); PF-E (0.2); In-E (− 0.5)
In-E	ED (1); Inpf-F (−0.35)
Ia-E	PF-E (0.4); Ia-F (−0.1); R-E (− 0.1); Ia(e) (0.1)
Ia-F	PF-F (0.4); Ia-F (−0.1); R-F (− 0.1); Ia(f) (0.1)
R-E	Mn-E (0.25); R-F (−0.1)
R-F	Mn-F (0.25); R-E (−0.1)
Mn-E	PF-E (0.5); Ia-F (−0.6); R-E (−0.2); Iab-E (0.08); Ia(e) (0.01)
Mn-F	PF-F (0.5); Ia-E (−0.6); R-F (−0.2); Ia(f) (0.01)

Values in brackets represent relative weights of synaptic inputsfrom the corresponding source populations (w_{ji}), or from external drives or afferent inputs (w_{dmi}); fordetails see eqn (10) in the preceding paper Rybak et al. (2006). Ia(e), Ib(e), Ia(f) and Ib(f) are, respectively,extensor and flexor Ia and Ib afferent inputs; II(f) is the group II flexor input; Cut is cutaneous input; ED(external drive to In-E population), $d_{ed} = 1$. MLR drives to PF-E ($d_{pf\text{-}e}$) and PF-F($d_{pf\text{-}f}$), $d_{pf\text{-}e} = d_{pf\text{-}f} = 0.5$; for MLR drives to RG-E and RG-F ($d_{rg\text{-}e}$and $d_{rg\text{-}f}$) see figure legends.

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