Sensory pathways and their modulation in the control of locomotion
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Recent experiments have extended our understanding of how sensory information in premotor networks controlling motor output is processed during locomotion, and at what level the efficacy of specific sensory–motor pathways is determined. Phasic presynaptic inhibition of sensory transmission combined with postsynaptic alterations of excitatory and inhibitory synaptic transmission from interneurons of the premotor networks contribute to the modulation of reflex pathways and to the generation of reflex reversal. These mechanisms play an important role in adapting the operation of central networks to external demands and thus help optimize sensory–motor integration.

Introduction

It is well established that sensory signals contribute to shaping locomotor output and to adapting it to environmental demands. In recent years, we have gained deeper insight into the sensory control mechanisms used by vertebrates and invertebrates in the regulation of locomotion. In this review, we will summarize recent progress in this field using specific examples from both vertebrate (e.g. cat, human, lamprey, mudpuppy, rat and Xylenopus) and invertebrate (e.g. crayfish, leech, locust and stick insect) model systems. More specifically, we will examine four areas of particular interest: first, modification of efficacy and sign of reflex pathways during locomotion or locomotor-like rhythms; second, locomotor-related presynaptic modulation of sensory synaptic transmission; third, sensory feedback in the control of movement direction during locomotion; and finally, reorganization of proprioceptive regulation of locomotor rhythms following partial deafferentation. Detailed accounts of previous work not cited here can be found in various reviews [1–7].

Modification of the efficacy and sign of reflex pathways during locomotion or locomotor-like rhythms

When locomotor systems become active, reflex pathways switch from a posture control mode that is present at rest to a movement control mode that contributes to the reinforcement of the motor output generated during locomotion. This change in operation is mirrored by the different reflex responses (e.g. reflex reversal) that are elicited by the same proprioceptive signals in both situations. Figure 1a summarizes schematically our present understanding of the generation of reflex reversal; in this review, we will focus on the mechanisms indicated by arrows 1–3. Figure 1b describes schematically the changes in reflex responses. At rest, sensory input signaling the movement of a leg elicits resistance reflex responses that oppose the movement being performed and thus ensure the postural stability of the limbs. When the locomotor network becomes active, the reflex response to the same sensory input can switch in sign, thus producing an assistance reflex that reinforces the ongoing movement. This phenomenon is termed reflex reversal and can occur either state- or phase-dependently. At present, reflex pathways are known to be subject to three kinds of alterations that can contribute to the generation of a reflex reversal [4]: first, the efficacy of specific reflex responses involved in postural control can be decreased when the locomotor networks switch from a postural to a locomotor state; second, other pathways that contribute to reinforcement of movement (e.g. reflex reversal) can be activated; and third, the gain of reflex pathways can be modulated in a phase-dependent manner during locomotor activity, and thus display variations between different phases of the locomotor cycle.

In the cat, locomotion induced by stimulation of the mesencephalic locomotor region (MLR) profoundly alters transmission in reflex pathways from extensor group I afferents onto extensor motoneurons. The amplitude of short-latency group I inhibition to synergistic extensor motoneurons, which is present at rest, is depressed [8]. This is thought to result from the inhibition of inhibitory interneurons that operate when the locomotor network is at rest. Locomotor-related depression of reflex pathways present at rest has also been described for the triceps surae stretch reflex in the cat [9]. In addition, extensor group I afferent evoked short-latency disynaptic excitation of synergistic extensor motoneurons, which is normally absent at rest, is evoked when fictive locomotion is induced (Figure 2). This disynaptic excitation, which may result from disinhibition of excitatory interneurons, is of maximal amplitude during the stance phase (extension) of the locomotor cycle [8,10]. Recent studies show that some aspects of these mechanisms...
Mechanisms involved in the generation of reflex reversal. (a) Diagram summarizing the mechanisms involved in the control of locomotor output by central and peripheral signals. The diagram focuses on reinforcement of movement (e.g. flexor activity) by sensory signals (SNs), such as flexion signals from a joint (for details, see [4]). Arrows denote the direction of influence between different elements; white lines ending with open triangles denote excitatory synaptic connections; filled lines ending with circles denote inhibitory synaptic connections. When the locomotor system (central rhythm generator [CRG]) is active, phase- or state-dependent priming of monosynaptic and polysynaptic sensory–motor pathways (via interneurons [INS]) between sensory neurons and motoneurons (MNs) takes place (as discussed in this review and [2,4]). Four influences are depicted as arrows numbered 1–4, three of which (1–3) are described in this review. Arrow 1 represents state- or phase-dependent alterations in the processing of sensory information at the level of premotor interneurons. The parallel excitatory and inhibitory premotor IN connections to the MNs are depicted as dashed lines. Arrow 2 represents the influence of premotor INS in sensory-motor pathways on the CRG. Arrow 3 represents the presynaptic inhibition of afferent terminals in the CNS. Arrow 4 represents the signals from SNs, which can affect locomotor output by entraining the CRG. (b) Schematic depicting the role of proprioceptive signals in controlling motor activity during standing and locomotion. The scheme is based on the situation in the stick insect leg muscle control system of the knee joint [7], but also reflects the situation in other locomotor systems in which proprioceptive signals have been shown to be used to control motor output by reinforcing movement [4,5]. When standing (i.e. in posture control mode), sensory information signaling knee flexion (small arrow) elicits resistance reflex action (large arrow) in motoneurons and muscles of the joint (left). The time course of the activity in knee extensor and flexor motoneurons (extensor activity and flexor activity) and muscles is given schematically. The resulting motor output (resistance reflex) tends to oppose the flexion of the joint, thus ensuring postural stability of the appendage. During walking (i.e. in movement control mode), the same sensory signals (flexion) are used to control movements of the joint (right). Flexion signals from the leg joint (small arrow) are utilized to reinforce the ongoing movement (large arrow). This is most obvious from the generation of an assistance reflex response that reinforces flexion of the joint.

operate in humans [11,12]. Processing of sensory information is reorganized in a phase-dependent manner to help reinforce ongoing activity during the stance phase and thus promotes weight support and forward propulsion (arrow 1 in Figure 1a; reviewed in [13]).

In the crayfish thoracic locomotor system, the sign of reflex responses switches from resistance in quiescent preparations to assistance during fictive locomotion [14]. Le Ray and Cattaert [15*] have recently analyzed the alterations in sensory transmission underlying the generation of reflex reversal in depressor motoneurons controlling downward movement of a walking leg. In quiescent preparations, sensory signals from a joint stretch receptor (coxo-basal chordotonal organ [CBCO]) corresponding to upward (elevation) movement of the leg induce a resistance reflex in depressor motoneurons. This reflex response is mediated through monosynaptic connections between sensory afferents and depressor motoneurons. Le Ray and Cattaert [15*] also characterized a class of interneurons that are involved in generating reflex reversal. These interneurons are non-spiking, are excited during depression of the leg, and make monosynaptic excitatory connections with depressor motoneurons. It appears that reflex reversal involves inhibition of resistance reflex pathways and activation of assistance reflex by increasing the activity of assistance reflex interneurons, a mechanism similar to that observed in the cat ([8,10*]; arrow 1 in Figure 1a). Presynaptic inhibition, which has been shown to exist in the CBCO sensory terminals, can also contribute to switching
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Diagnosis illustrating our present understanding of the pathways from muscle afferents of flexor and extensor muscles that influence the timing and magnitude of motor output during walking in the cat hindlimb. Feedback from extensor muscle spindle (group 1a) and tendon (group 1b) organs reinforce extensor activity through at least three pathways during stance; feedback from flexor spindle afferents (group Ia/lI) shorten stance. Inhibitory synaptic connections are depicted as closed circles; excitatory synaptic connections are depicted as open triangles. Dashed pathways are assumed and have not yet been identified. E/Ext, extension; F/Flex, flexion. Adapted from [13].

between the two reflex responses (see below). In quiescent preparations of crayfish thoracic ganglia, reflex reversal can also be induced by neuromodulators [16]. The amine octopamine induces a steady-state switch in reflex responses by suppressing assistance reflex responses and enhancing the resistance reflex. This study shows that modulators can reorganize sensory pathways and change the reflex responses to specific sensory inputs.

Finally, experiments on the locomotor system of the stick insect also emphasize the role of polysynaptic pathways in altering sensory–motor processing during state-dependent reflex reversal in the joint control network of the femur–tibia (FT) joint. At rest (i.e. in standing animals), flexion signals from the femoral-chordotonal organ (fCO), which is the transducer of this joint, elicit resistance reflex activation in tibial extensor and inhibition in flexor motoneurons. In active animals (i.e. in the locomotor state), flexion signals induce the 'active reaction', part of which is a reflex reversal [7,17]. Flexion signals from the fCO inhibit extensor motoneurons and activate flexor ones. Recordings from premotor interneurons reveal that alterations of the synaptic inputs from the fCO to identified premotor nonspiking interneurons contribute to the generation of reflex reversal. As a result, the balance between parallel inhibitory and excitatory synaptic drives from premotor interneurons onto motoneurons tips towards generating reflex reversal (arrow 1 in Figure 1a; Figure 3; [18]). This mechanism shares similarities with the generation of gain changes by sensory–motor pathways in posture control at rest [19,20]. Interestingly, implementing a biologically based 'reinforcement of movement' as a control mechanism in walking robots results in a superior locomotor performance compared to other control mechanisms available [21].

In summary, recent results have started to unravel the role of specific pathways in the premotor network that adapt sensory–motor processing during locomotion. The evidence suggests that alterations contributing to the change in sign of reflex responses are executed at the level of interneurons.

For us to gain further understanding of the afferent control of locomotion, specifically with regards to walking pattern generation, several gaps in our knowledge need to be filled. Firstly, it is not clear whether the pathways involved in the generation of reflex reversal are also elements of the central rhythm generating networks. There is some indirect evidence to support the assumption that they are: in the stick insect, interneurons involved in the generation of reflex reversal can re-set the activity of motoneurons in fictive rhythmic preparations (arrow 2 in Figure 1a; [22]). Secondly, in order to identify in detail how sensory signals interact with central rhythm generators, some knowledge of basic principles of network connectivity of the neuronal oscillators, such as that achieved in some invertebrate and
lower vertebrate preparations, is needed (see [3,23,24]). Finally, in order to address specific questions related to the function of sensory signals arising from ensembles of sensory receptors, more information is needed on actual afferent activity during the locomotor cycle [25,26].

One preparation that might be appropriate for tackling some of these questions in a multi-joint limb is the in vitro preparation of the mudpuppy [27]. Cheng et al. [28**] have recently reported the existence of individual elbow flexor and extensor rhythm generators controlling the forelimb (see also [1,7]). In this preparation, low-threshold electrical stimulation of afferent axons from the limb muscle in the dorsal roots affects locomotor rhythm in a similar manner to specific stimulation of group I extensor afferents-in the cat and rat hindlimb [13,29].

**Presynaptic inhibition as a mechanism for modulating reflex responses during locomotion**

Several mechanisms can contribute to the modulation of the efficacy of sensory transmission and thus mediate reflex reversal. One such mechanism consists of presynaptic inhibition of sensory feedback by the active neuronal network, which acts as a filter to bias specific sensory inputs in relation to others during given phases of the locomotor cycle [31]. In both vertebrate and invertebrate preparations, intracellular recordings from sensory afferents have revealed the presence of primary afferent depolarizations (PADs) that occur in phase with the locomotor activity pattern.

In cats, axons of both cutaneous and muscle afferents receive waves of PADs during the flexor phase (swing) and a smaller wave during the extensor phase (stance). The amplitude of monosynaptic EPSPs recorded in motoneurons shows phase-dependent modulation during fictive locomotion, reaching a maximum during depolarization [31]. The PADs may be at least partially responsible for changing the gain of reflex pathways during the different phases of the locomotor cycle. Locomotor-related PADs are not effective, however, in inhibiting synaptic transmission from Ia afferents [31].

A direct link between PADs and the depression of monosynaptic EPSPs has been demonstrated in the crayfish thoracic locomotor system [32–34]. During fictive locomotion, the terminals of sensory axons from leg joint stretch receptors receive bursts of GABAergic PADs that take place at a fixed phase in the locomotor cycle. Simultaneous intracellular recordings from a presynaptic sensory axon and its postsynaptic motoneuron revealed that the PADs reduced the amplitude of orthodromic afferent spikes through a shunting mechanism. This, in turn, decreased transmitter release, and thereby reduced the amplitude of EPSPs in the motoneurons. This locomotor-related presynaptic inhibition may be involved in reducing the efficacy of resistance reflex pathways that would oppose the motor output during the locomotor program, thus allowing assistance reflex pathways to be functional. Similar results have been obtained in the locust thoracic locomotor system during walking [35]. Locust sensory axons receive both tonic and phasic PADs during walking, which might be responsible for a phase-dependent modulation of sensory transmission.

During fictive locomotion in the lamprey spinal cord, intracellular recordings from intra-spinal cutaneous afferent dorsal cells show phasic PADs that originate in the axon and occur in phase with the ipsilateral ventral root burst in the same segment [36**]. The amplitude of the postsynaptic EPSPs evoked by sensory dorsal cells in giant interneurons, which do not receive any input from the central pattern generator circuits, is modulated in a phase-dependent manner. It is significantly smaller on the peak of the axonal depolarization, which coincides with the midpoint of the ipsilateral ventral root burst. In addition, sensory-evoked resetting of the locomotor rhythm is less effective when delivered at the mid-burst. Thus, sensory input from cutaneous neurons is phasically gated during fictive locomotion. Such presynaptic locomotor-related modulation of sensory transmission may represent a mechanism for phasic gain control, which gates sensory inputs activated by the ongoing motor activity.

**Sensory feedback in the control of movement direction during locomotion**

In Xenopus tadpoles, stimulation of the tail skin elicits swimming, with the contralateral side contracting first, thus directing the animal away from the stimulus [37]. The sensory pathway mediating this avoidance response has recently been investigated both experimentally and in simulations [38**]. The direction of the movement following skin stimulation is attributable to an asymmetry in the sensory pathway that occurs at the first synapse between sensory neurons and interneurons, with the contralateral pathway being more effective.

In the leech, a population coding strategy has been shown to underlie the integration of sensory inputs in a neuronal network function [39**]. Touching the body of the leech elicits a local bend in the opposite direction. The sensory input is encoded by mechanosensory neurons that provide the major inputs to the local bend network. The direction of bending is correlated with the population activity of the active sensory neurons. The network interneurons can extract the information encoded in the population vector provided by the sensory neurons and thereby produce motor activity that moves the animal away from the stimulus.

In the lamprey, the dorsal fin plays a role in body orientation during swimming. The dorsal fins are controlled by motor units activated in antiphase with the myotomal motoneurons of the trunk locomotor system and are subject to different perturbations than the trunk; they should, therefore, be under different sensory control than the
trunk. Sensory control of fin motoneurons occurs via direct monosynaptic connections from primary mechanosensory neurons (dorsal cells), whose cell bodies are in the spinal cord [40]. This monosynaptic reflex pathway between dorsal cells and the ipsilateral fin motoneurons may mediate a resistance reflex similar to the one described between stretch receptor neurons and myotomes (see [3]). This reflex pathway would reinforce the compensatory movement of the fin and thus help maintain a vertical position of the fin and the dorsal side-up position of the animal during swimming (see Figure 4).

**Reorganization of proprioceptive-regulated locomotion following partial deafferentation**

Because sensory feedback is vitally important for generating appropriate motor patterns, mechanisms must exist in the CNS to compensate for the loss of sensory cues after injury. The time-course and the site of plasticity of some reflex pathways controlling locomotor activity have recently been analyzed in both the cat and the locust.

In the cat, stimulation of group I excitatory pathways can regulate the stance-to-swing transition during walking, with the lateral gastrocnemius and soleus (LGS) nerve being more efficient than the medial gastrocnemius (MG) nerve. After transection of the LGS nerve, stimulation of the LGS nerve is less effective at controlling the step cycle, whereas stimulation of MG nerve becomes more effective [41]. These changes are paralleled by modifications in field potentials from LGS and MG nerves in the intermediate nucleus of L6/L7 [42]. The decrease in efficiency of LGS afferents appears progressively over several weeks and occurs at the spinal level, whereas the increase of the enhancement of MG effect occurs relatively rapidly and may involve supraspinal mechanisms.

The locust flight system can adapt to the loss of the hindwing tegulae, wing proprioceptors that determine the timing of wing elevation in the flight cycle [43]. During regeneration, following ablation of the hindwing tegulae, function and proper connections of these tegulae within the flight pattern generator are replaced by afferents from other proprioceptors, the forewing tegulae [44]. This plastic capability is independent of maturation of the adult locomotor system [45]; however, it may not necessarily lead to complete restoration of flight ability [46]. By investigating changes in synaptic connectivity in the flight pattern generating circuitry underlying these plastic modifications, Wolf and Büschges [47] found that retrograde signals from postsynaptic targets (i.e. the interneurons within the central pattern generator for flight) can contribute to the reorganization of the afferent connectivity within a locomotor network.

**Conclusions**

Our understanding of the afferent control of locomotion has increased substantially in recent years, with detailed descriptions of how sensory signals influence the phase and magnitude of motor output, and how these influences are modulated in the locomotor cycle. Recent insight into the neuronal mechanisms underlying the generation and control of locomotion has allowed descriptions of the pathways and mechanisms involved. The role of premotor interneurons and presynaptic inhibition in regulating the efficacy of

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**Figure 4**

Scheme depicting the sensory control of myotomal and fin motoneurons in the lamprey spinal cord. (a) Fin and trunk movements are generated by separate sensory control mechanisms. Fin motoneurons (fMN) receive monosynaptic input from dorsal cells (DC) innervating the dorsal fin, whereas myotomal motoneurons (MN) receive sensory input from stretch receptor neurons (SR) sensing the lateral bending of the body. CPG, central pattern generator. (b) Schematic illustrating the laterally directed movements of the trunk and the dorsal fin upon contraction of the myotomal musculature on the right side. The inset depicts a cross-section of the trunk; the dark grey shading indicates the simultaneous contraction of the right myotome and left fin musculature. Contraction of the right myotome pushes the body towards the left (arrows) and as a consequence, the fin bends passively towards the right (dashed line). Dorsal cells on the stretched side of the fin will provide activation of the ipsilateral fMN, which will add to their central activation and thereby restore the upright position of the fin.
sensory–motor pathways has been emphasized. Particularly, in walking pattern generation, with its complex sensory control features, further information is needed on the basic action and construction of the central rhythm generating networks in order to identify the neuronal mechanisms involved in the afferent control of locomotion.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as
• of special interest
**of outstanding interest
During fictive locomotion, stimulation of group I afferents from ankle extensor muscles induces disynaptic EPSPs in extensor motoneurones of ankle, knee and hip joint. This extends previous findings on the contribution of phasic disynaptic EPSPs in infraglottic extensor motoneurones contributing to reinforcement of [reviewed in 13)]. The evidence suggests that the phasic appearance of EPSPs is mediated by cyclic disinhibition of an unidentified population of excitatory spinal interneurones in the premotor network.
Identification of individual neural networks for the generation of rhythmic motor activity for both elbow flexor and elbow extensor motoneurone pools of the mudpuppy forelimb. The data presented support the 'unit-burst generator' hypothesis for locomotion (see [1]) and indicate similarities to the composition of an invertebrate walking pattern generator [7]. Dorsal root stimulation exhibits similar re-set properties as in the cat and rat [13,27], thus making the mudpuppy preparation a useful model system for the investigation of neuronal mechanisms underlying rhythm generation and its sensory control.
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36. El Manira A, Tegnér J, Grillner S: Locomotor-related presynaptic modulation of primary afferents in lamprey. Eur J Neurosci 1997, 9:696-705. Demonstrates a clear correlation between the occurrence of PADS and the decrease of sensory synaptic transmission during fictive locomotion in a vertebrate spinal locomotor network. Intracellular recordings from sensory neurons and their axons showed that phasic PADS originating in the axon occur in phase with the ipsilateral ventral root burst during fictive locomotion. The amplitude of monosynaptic sensory EPSPs is reduced at the phase where the PADS reach their maximum amplitude.


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41. Whelan PJ, Pearson KG: Plasticity in reflex pathways controlling stepping in the cat. J Neurophysiol 1997, 78:1643-1650. Axotomy of the LGS muscle in the cat hindlimb results in weakening of LGS group I afferent pathways in relation to MG group I afferents pathways in the control of the step cycle within 31 days following the operation. Alterations in reflex pathways following transaction of the spinal cord indicate that the changes in tuning of reflex pathways after axotomy of LGS nerve are attributable to both spinal and supraspinal mechanisms. This result is paralleled by the increased group I field potential of MG afferents in the intermediate nucleus of L6/L7 segments [42].


47. Wolf H, Büsches A: Plasticity of synaptic connections in sensory-motor pathways of the adult flight system. J Neurophysiol 1997, 78:1276-1284. After unilateral ablation of the hindwing tegulae, important wing proprioceptors, specific patterns of changes in connectivity occur between the remaining wing afferents and interneurons of the central pattern generator in the locust flight system. Up- and downregulation of synaptic connectivity on the intact side of the animal provides the first clear evidence that retrogade signaling between flight interneurons and presynaptic sites (i.e. sensory afferents) takes part in establishing and maintaining synaptic connectivity in a locomotor network.