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Nervous mechanisms of locomotion in different directions

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Abstract

Locomotion, that is active propulsive movement of the body in space, is a vital motor function. Intensive studies of the main, for the majority of living beings, form of locomotion, forward locomotion, have revealed essential features of the organization and operation of underlying neural mechanisms. However, animals and humans are capable to locomote not only forward but also in other directions in relation to the body axis, e.g. backward, sideways, etc. Single steps in different directions are also used for postural corrections during locomotion and during standing. Recent studies of mechanisms underlying control of locomotion in different directions have greatly expanded our knowledge about locomotor system and can contribute to improvement of rehabilitation strategies aimed at restoration of locomotion and balance control in patients. This review outlines recent advances in the studies of locomotion in different directions in lower and higher vertebrates, with special attention given to the neuronal locomotor mechanisms.

Keywords

swimming; walking; backward; spinal networks; supraspinal control; reflexes

Introduction

Locomotion is an evolutionary old basic motor function. Neural mechanisms for control of the main form of locomotion, forward locomotion, have been studied in different species from simple animals to humans [1]. These studies revealed basic principles in the

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organization and operation of these mechanisms common for phylogenetically remote species.

Most vertebrates can locomote not only forward but also in other directions. Thus, lower vertebrates exhibiting axial locomotion can swim backward [2,3], and legged higher vertebrates can walk in any direction in relation to the body axis [4,5,6•]. These forms of locomotion are usually generated in the context of avoidance behavior (called “escape” in the lamprey and “struggling” in the zebrafish and Xenopus tadpole). Also, single steps in different directions are used for postural corrections during locomotion [7,8] and during standing [9•,10,11].

This review outlines recent progress in understanding the neural mechanisms underlying control of locomotion in different directions in lower and higher vertebrates.

Forward and backward locomotor movements

In general, backward locomotion could be considered as reversed forward locomotion. Thus, in low vertebrates during backward swimming the waves of periodic lateral body flexion propagate in a caudo-rostral direction during forward locomotion, while in a rostro-caudal - during backward locomotion [2,3]. In higher vertebrates and humans during stance and during swing phases of backward locomotion, a limb moves in directions opposite to those during forward stepping [4,5]. Although in both lower and higher vertebrates the muscle activity patterns of forward and backward locomotion differ, analysis of these patterns in higher vertebrates and humans revealed similar basic flexor-extensor synergies [6•,12,13]. This led to a suggestion that there are some common direction-independent neuronal mechanisms contributing to generation of both forward and backward locomotion.

Organization of spinal networks

In both lower and higher vertebrates, the neuronal mechanisms generating locomotion in different directions reside in the spinal cord [14,15,16,17]. The axial locomotor rhythm is generated by a chain of coupled segmental oscillators (Fig. 1a,b; [18,19,20]). Each oscillator generates rhythmically alternating bursts of activity in the right and left hemisegments. Recording of individual spinal interneurons during forward and backward swimming in the tadpole and larval zebrafish, revealed a group of excitatory interneurons with activity modulated in locomotor rhythm during swimming in both directions [3,21,22]. This suggests the presence of a core rhythmogenic kernel that is active independently of the particular direction of locomotion. In the tadpole, these neurons exhibit mutual excitation [22] and form two subpopulations preferentially active during forward and backward swimming, respectively [21]. Differences in biophysical properties of these subpopulations may explain differences in parameters of forward and backward rhythms [21,23•]

Two models have been proposed to explain the change in the direction of locomotor waves. The trailing-oscillator model with symmetrical intersegmental connections [24] suggests that the direction of propagation of locomotor waves is determined by a gradient of excitability of individual oscillators along the chain. In isolated lamprey spinal cord this gradient is rostrocaudal. In the tadpole, ascending glycinergic inhibitory interneurons are involved in the locomotor wave reversal [25,26] and presumably inverse this gradient (*I* in Fig. 1b) [27]. Such inhibitory interneurons (active only during backward locomotion) have been found in the zebrafish [3]. A model with asymmetrical intersegmental connections explains the reverse of the wave propagation from rostro-caudal to caudo-rostral by switching from activation of the descending coupling to activation of the ascending one [28].

Functional organization of networks generating stepping in different directions was studied by analyzing locomotor movements evoked by direct unspecific activation of these networks by epidural stimulation of the spinal cord in the decerebrate cat [29••]. It was demonstrated that during stimulation of certain sites, the direction of locomotion is determined by the direction of the treadmill belt motion, and on immobile surface or in the air, in-place stepping is observed, suggesting that the locomotor system includes two principal mechanisms (Fig. 1c,d). One mechanism generates the vertical component of step (VC, limb elevation and lowering), and the other generates the horizontal component (HC, limb transfer from one extreme point to the other). The latter includes networks generating the horizontal component of step in different directions. These circuits receive sensory input signaling limb motion in stance; reaching an extreme position triggers the limb lifting and transfer in the opposite direction. One can suggest that VC-mechanism contains rhythm-generating while HCmechanism – pattern formation networks.

Analysis of kinematics and EMG patterns of single corrective steps in different directions generated in response to postural disturbances during standing, revealed their similarity with those of locomotor steps in the corresponding direction [9•]. It was proposed that a corrective step is generated by the same (VC and HC) mechanisms, which generate locomotor steps in corresponding direction, but they are activated by sensory information caused by postural disturbance and signaling deviation of the limb in relation to the trunk. This hypothesis is supported by finding that training locomotion in different directions improves balance control in spinal cord injured and stroke subjects [17,30,31].

Mapping the efficacy of epidural stimulation of different sites of the lumbosacral enlargement to evoke forward and backward locomotion combined with c-Fos immunostaining [32•] led to a suggestion that networks generating the VC of steps and the HC for forward stepping are distributed throughout the whole lumbosacral enlargement, while the network generating the HC for backward stepping is confined to a zone from caudal L5 to L7 (Fig. 1e). Recording of the same individual spinal interneurons in L5-L6 during both forward and backward locomotion, revealed neurons with activity phase in the locomotor cycle independent of the locomotion direction and those modulated during forward or during backward locomotion only, presumably belonging to the VC and corresponding HC networks, respectively [33].

Though the basic principles of organization of axial and legged locomotor networks are similar, their neuronal compositions are different. In the zebrafish, spinal glutamatergic V2a interneurons are necessary and sufficient for the locomotor rhythm generation [34]. In contrast, in mice, glutamatergic non-V2a spinal interneurons contribute to generation of locomotor rhythm [35,36•], while V2a interneurons are involved in interlimb coordination [37]. In the zebrafish, an increase in the locomotor speed is associated with recruitment of new modules of locomotor network containing only excitatory (V0v) commissural interneurons [38]. By contrast, in mice, inhibitory V0d interneurons determine the left-right limb alternation at low frequencies characteristic for slow forward walking, while excitatory V0v interneurons – at higher frequencies characteristic for both fast forward and backward locomotion [39,40,41]. These findings suggest that though some populations of genetically identified spinal interneurons are elements of both axial and legged locomotor networks, they have different specific functional role in generation of locomotion. Most likely, the legged locomotor network cannot be considered as axial network updated with some new populations of neurons, and thus the axial network does not represent the core of the legged one.

Supraspinal control

In all studied vertebrates, forward locomotion can be elicited and the speed of progression controlled from mesencephalic locomotor region (MLR), which represents a command center for forward locomotion only [29••,42]. Its activation leads to formation of reticulospinal commands, which selectively activate a part of spinal locomotor networks necessary for generation of forward locomotion (Fig. 1a,c). Recent study in mice demonstrated that activation of glutamatergic neurons of MLR located in both the cuneiform (CnF) and the pedunculopontine nucleus evokes slow, alternating-gait locomotion, whereas activation of those in the CnF – high-speed synchronous-gait locomotion [43•]. One can hypothesize that some other forms of locomotion (e.g. backward and sideward) also have their command centers.

In both lower and higher vertebrates, backward locomotion can be initiated by continuous stimulation of the skin mechanoreceptors of the head [2,3,15,41]. Signals from these receptors are transmitted by specific populations of trigeminal nerve afferents [2].

In the lamprey and tadpole, reticulospinal neurons active exclusively during forward (Fgroup) or during backward locomotion (B-group), or active both during forward and backward locomotion (FB-group), were revealed [21,27]. It was suggested that the FB-group activates segmental oscillators during forward and during backward swimming (Fig. 1a,b; [27]). In the framework of the trailing-oscillator model with symmetrical intersegmental connections [24], activation of FB-group alone (due to intrinsic rostro-caudal gradient of excitability in the chain of segmental oscillators) evokes forward swimming. The F-group can contribute to stabilization or (in the framework of the model with asymmetrical intersegmental connections [28]) creation of the rostro-caudal gradient of excitability. The Bgroup inverses the excitability gradient in the chain of segmental oscillators presumably through the ascending inhibitory interneurons (*I* in Fig. 1b), and thus, co-activation of Bgroup and FB-group results in backward swimming. One may hypothesize that in higher vertebrates, signals from MLR and skin mechanoreceptors activate VC mechanism via FBgroup of reticulospinal neurons, and specific HC circuits determining forward and backward direction of locomotion via F- and B-populations of reticulospinal neurons, respectively (Fig. 1c,d).

Besides populations of reticulospinal neurons contributing to activation of locomotion [44••, 45,46•], reticulospinal neurons terminating forward locomotion were found in both lower and higher vertebrates [44••,47,48,49••]. In lampreys and tadpoles, glutamatergic and GABA-ergic reticulospinal neurons terminate forward locomotion, respectively. It was demonstrated that in tadpoles they do not stop backward locomotion. In mice, glutamatergic V2a reticulospinal neurons in the rostral medulla terminate forward locomotion through inhibition of interneurons of the rhythm-generating network [49••]. One can expect that they stop locomotion in other directions as well.

While supraspinal control of forward locomotion in higher vertebrates was studied in a considerable detail [1], only activity of corticospinal neurons was investigated during locomotion in different directions [50]. In intact cat, activity of almost all corticospinal neurons is phasically modulated in the rhythm of stepping during both forward and backward locomotion. However, the modulation pattern is direction-dependent. It is caused by inputs only from locomotor mechanisms of the projection girdle when this girdle is leading, and from locomotor mechanisms of both girdles when this girdle is trailing. This suggests flexibility of functional roles of individual corticospinal neurons during different forms of locomotion. Involvement of motor cortex in control of both backward and forward locomotion was also demonstrated in humans [51].

Sensory feedback

In lower vertebrates, a specific movement-related sensory feedback can be provided by intraspinal mechanoreceptors (stretch receptor neurons (SRNs) in the lamprey [52] and cerebrospinal fluid contacting neurons (CSF-cNs) in zebrafish [53]), while in higher vertebrates – by proprioceptors and cutaneous afferents [54].

Recent studies demonstrated that in the lamprey, the spinal reflex to body bending during forward swimming mediated by SRNs observed during forward locomotion is reversed during backward locomotion [55•]. This reflex reversal is aimed at reinforcement of the movements generated in each of these behaviors. It assists in initiation of contralateral bending during forward swimming and augments the body undulations amplitude during backward locomotion. A population of reticulospinal neurons transmitting commands causing modification of unilateral spinal networks processing signals from SRNs, which lead to the reflex reversal, has been revealed. They are activated by trigeminal nerve stimulation causing backward swimming and presumably belong to B-group. It was found that in the zebrafish CSF-cNs increase speed of forward locomotion [53], however, their role in control of backward swimming is unknown.

It was shown that in higher vertebrates, modulation of the efficacy of the soleus H-reflex during locomotor cycle, as well as cutaneous afferents reflex effects, which are characterized by a “reversal of actions” that depends on the step cycle phase, are similar during backward and forward locomotion [56,57], suggesting that phase-dependent changes of these reflexes most likely caused by a locomotor network common for forward and backward locomotion.

A critical point in the step cycle is onset of the swing phase. It was suggested that the swing onset in any direction is determined by the afferents signaling a critical limb deviation in the stance phase [29••,54]. One can expect that supraspinal command determining the direction of stepping, selects and activates a specific spinal network in HC-mechanism for processing this information (Fig. 1c,d).

Conclusions

The rhythm-generating part of locomotor networks, as well as neuronal mechanisms underlying left-right coordination are common and contribute to generation of locomotion in any direction. By contrast, networks determining direction of locomotion are different and specific for each direction. They contain neuronal mechanisms for specific processing of movement-related sensory feedback. A detailed analysis of these networks (including clarification of functional roles of genetically identified populations of neurons) and their interaction, is one of the major lines of future studies. Evidence of shared neuronal networks for locomotor and corrective steps in different directions provides a basis for rehabilitation strategies employing walking in different directions aimed at improvement of both locomotion and balance control in patients. Such strategies showed promising results [17,30,31]. Determining specific functions of genetically identified populations of neurons and subsequent well-controlled precisely targeted activation/inactivation of relevant populations will undoubtedly boost these efforts.

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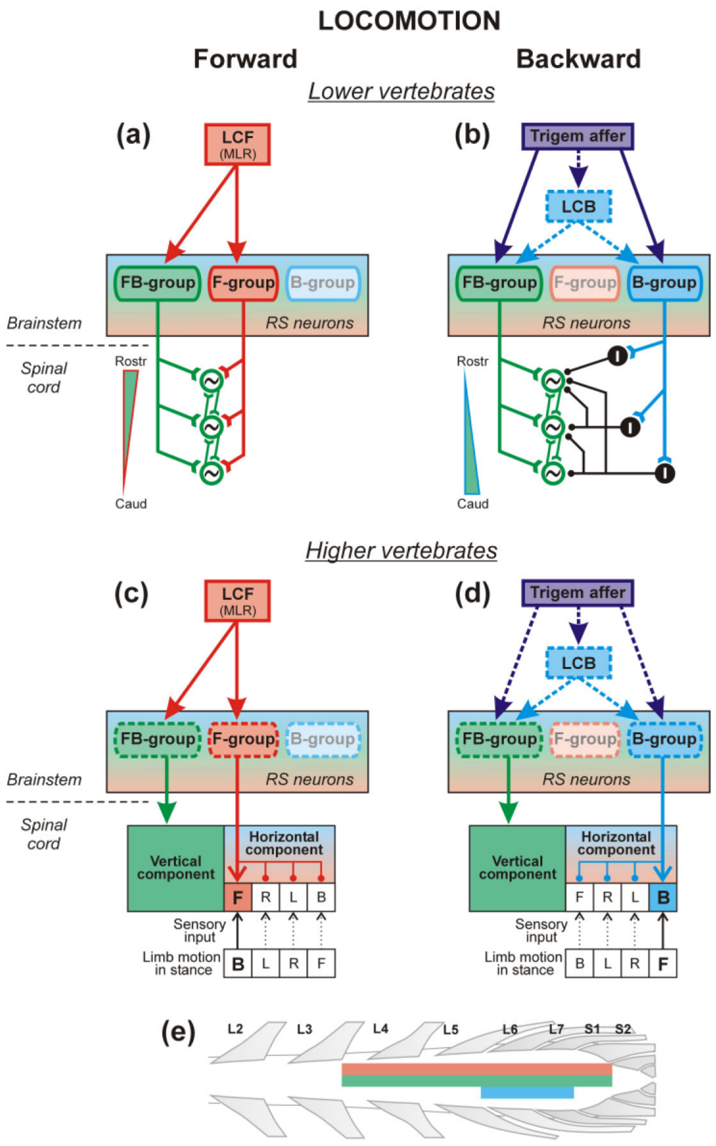
Highlights:

- Vertebrates can locomote not only forward but also backward, sideways, etc.
- Spinal rhythm-generating locomotor network is common for locomotion in any direction.
- Spinal networks determining direction of locomotion are specific for each direction.
- Each direction-determining network specifically process sensory feedback.
- Different supraspinal commands activate rhythm-generating and direction-determining networks.



Hypothetical neural mechanisms for the control of locomotion in different directions. **(a-d)** Hypothetical models of the spinal locomotor network and of the descending commands controlling forward **(a,c)** and backward **(b,d)** locomotion in lower **(a,b)** and higher **(c,d)** vertebrates. **(a,b)** The spinal locomotor network in lower vertebrates consists of segmental oscillators (green circles) that excite one another and thus form a chain, along which the waves of activity propagate. **(a)** Elicitation of forward swimming. The MLR, which is a locomotor center for forward locomotion (LCF), activates reticulospinal (RS) neurons of FBgroup and F-group. FB-group activates the chain of oscillators generating the swim rhythm. F-group stabilizes an intrinsic rostro-caudal gradient of excitability of oscillators or creates this gradient (green ramp with red outline). As a result, the waves of activity propagate in the caudal direction. **(b)** Elicitation of backward swimming. Trigeminal afferents activate RS neurons of FB-group and B-group (possibly, through the locomotor center for backward locomotion, LCB). FB-group activates the chain of oscillators generating the swim rhythm. At the same time, neurons of B-group activate inhibitory neurons (I) that invert the gradient of excitability (green ramp with blue outline). This results in the caudo-rostral propagation of locomotor waves. **(c,d)** Spinal cord of higher vertebrates contains two principal mechanisms, one generating the vertical component of step (limb elevation and lowering), and the other generating the horizontal component (limb transfer from one extreme point to the other). The latter includes networks generating the horizontal component of step in different directions (for simplicity, only the networks generating steps in four directions – F, forward; B, backward; R, rightward; L, leftward are shown). These networks receive sensory input signaling the limb motion during stance. **(c)** Elicitation of forward stepping. The MLR activates specific populations of RS neurons (presumably, FB-group and F-group). FB-group activates a network generating the vertical component of step. At the same time, neurons of Fgroup activate a network generating the horizontal component for forward stepping. Sensory input signaling that the limb reached the extreme caudal position during stance (B) assists in initiation of the forward swing. **(d)** Elicitation of backward stepping. Trigeminal afferents presumably activate RS neurons of FB-group and B-group (possibly, through LCB). FBgroup activates a network generating the vertical component of step. At the same time, neurons of B-group activate a network generating the horizontal component for backward stepping. Sensory input signaling that the limb reached the extreme rostral position in stance (F), assist in initiation of the backward swing. **(e)** Rostro-caudal distribution in the lumbosacral enlargement of networks generating vertical component of the steps, horizontal component for forward steps, and horizontal component for backward steps, are shown schematically by thick green, red and blue lines, respectively.