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Descending control of locomotor circuits

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Animals have developed different locomotor strategies to explore and survive in their environment by walking, flying, or swimming. Even though the biomechanics are different, the neural control of these movements is very similar in all vertebrate species. In this review, we provide an overview of the descending central control of locomotion in vertebrates with an emphasis on recent findings in the field. We discuss how different cell populations in the spinal cord control the intensity of locomotion. We then outline exciting findings on the heterogeneity of reticulospinal cells and their role in controlling different locomotor aspects. Furthermore, we review specific roles of different cell groups in the mesencephalic locomotor region (MLR) and describe newly found descending inputs to the MLR.

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Introduction

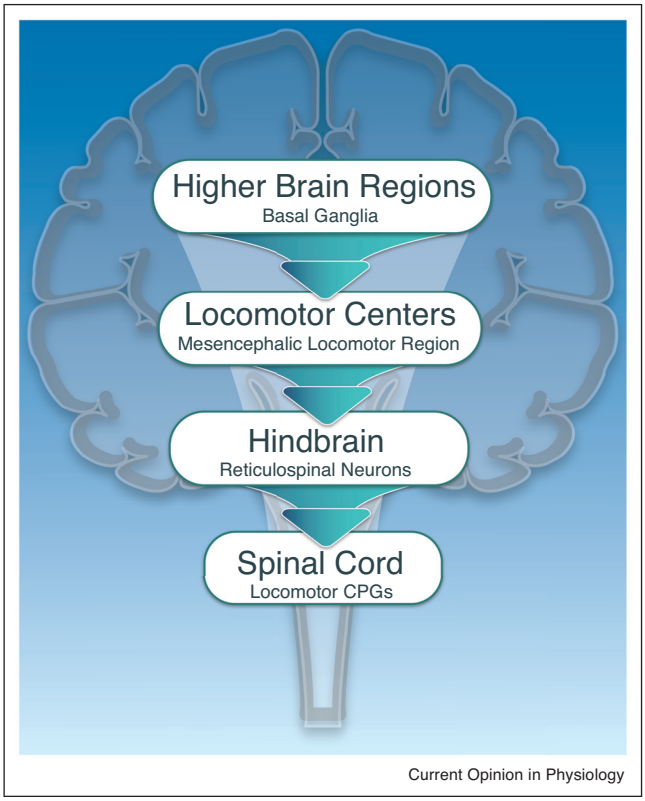
The control of locomotion is organized mostly in a linear fashion in all animal species including invertebrates and vertebrates [1,2]. In vertebrates, spinal central pattern generators (CPGs) receive synaptic inputs from brainstem reticulospinal (RS) neurons [3,4], which act as command cells for locomotion and are themselves controlled by upstream locomotor centers such as the mesencephalic and the diencephalic locomotor regions (MLR and DLR, respectively) [3]. The MLR initiates locomotion and controls the intensity of the output in a graded fashion [5]. It receives inputs from higher brain regions, including the basal ganglia, which play a key role in selecting motor programs [6]. In addition to this linear organization within the central nervous system (Figure 1), sensory information plays a crucial role in controlling locomotion. In this review, we will focus mainly on the central mechanisms controlling locomotion.

Before the mid-1980s, cats were the mostly used animal model for examining the neural mechanisms responsible for locomotion. Studies in cats provided the foundation for the present knowledge relative to the neural control of locomotion. For instance, the concept of locomotor CPGs, first introduced in relation to locust flight [7], was applied by Sten Grillner and his group to describe the spinal neural organization generating locomotion in cats [4,8]. The MLR was also first discovered in cats [5], but the identification of the cellular mechanisms involved in controlling locomotion remained highly challenging due to the complexity of the mammalian central nervous system (CNS). Other animal models with a simpler CNS were developed such as the *Xenopus* tadpole and the lamprey. In the 1980s, the group of Sten Grillner identified the detailed cellular connectivity comprising the locomotor CPG in lampreys [9]. Concomitantly, Allan Roberts and his group characterized rhythm generating networks for swimming in the spinal cord of *Xenopus* tadpoles [10]. The subsequent development of *in vitro* preparations and the establishment of new techniques in the neonatal rat stimulated an additional interest for mammalian models. Optogenetic techniques are now used to study the role of different cell populations in the control of locomotion [11••,12•,13•,14••]. Neuroimaging techniques facilitate the characterization of neural activity of specific cell populations [15,16•,17]. Anatomical tracing with viruses have considerably helped to detail the neural projections involved in locomotor control [18••,19–21]. Technological advances have thus improved the accessibility of brain regions to define in more detail the descending control of locomotor circuits in vertebrates.

Generation of locomotor rhythm: the central pattern generators

In the mid-80s, the development of *in vitro* preparations in rodents [22–24] has allowed the identification of neurons comprising the mammalian spinal CPGs. Several groups of spinal interneurons were later identified using genetic tools and the role of some of them was established in controlling locomotion [25]. For instance, V0 neurons were shown to control left–right limb alternation and in their absence, mice perform quadrupedal hopping movements only [26]. Studies carried out in the zebrafish revealed a topographic organization of spinal motoneurons and interneurons that was involved in neural

Figure 1



Descending control of locomotion in vertebrates.
Schematic overview of the central neural organization responsible for the control of locomotion from higher brain structures down to the spinal cord.

recruitment during fast and slow swimming activity [27]. Furthermore, a modular organization of spinal V2a interneurons that project specifically to slow, intermediate, and fast motoneurons was discovered. These modules are activated in a stepwise manner from slow to intermediate and finally to fast locomotor frequencies [28,29].

Locomotor command cells: the reticulospinal neurons

The spinal CPGs receive powerful inputs from RS cells, and early studies in the cat demonstrated that these brainstem neurons project directly to spinal interneurons and motoneurons [[39•],30]. Studies of lamprey RS cells have provided a better understanding of their role in locomotor control. Lamprey RS cells are functionally heterogenous, including excitatory and inhibitory neurons [31,32] and specific populations of RS cells were shown to initiate or maintain locomotion, control locomotor speed, adjust posture, or produce forward versus backward swimming [33–37]. These findings paved the way for studies on the mammalian reticulospinal system where excitatory and inhibitory RS cells were also found to be highly intermingled [12•,19]. Studies in different vertebrate models confirmed that there are several populations of RS cells controlling a variety of motor behaviors. In the zebrafish, glutamatergic V2a neurons in the hindbrain were identified by their expression of the transcription factor Chx10 [38]. They were shown to project to the spinal cord, and their optogenetic activation initiated locomotion while their inactivation stopped it. Recordings of these neurons revealed that they are rhythmically active during swimming [38]. In mice, glutamatergic V2a neurons were also identified in the bulbar reticular formation and shown to project to the spinal cord. They receive synaptic inputs from the MLR and are active during locomotion [39•]. Recently, Ole Kiehn and his group showed that V2a neurons located in the mouse at the ponto-medullary border act as 'stop neurons'. They halt locomotion when optogenetically activated, whereas they decrease the occurrence of spontaneous stopping when their synaptic output is blocked [18••]. In the lamprey, three different populations of RS cells were identified according to their activity pattern during locomotion. 'Start cells' are transiently active at the beginning of the locomotor bout, 'maintain cells' are active throughout the locomotor bout, and 'stop cells' are transiently active at the beginning and the end of a locomotor episode [16•]. The activity pattern of the latter cell group was not only present when locomotion was elicited by MLR stimulation, but also during sensory evoked or spontaneous locomotion. Pharmacological activation of these cells was shown to stop ongoing locomotion, whereas their inactivation impaired the termination process [16•]. Similar to what was reported in mice, these 'stop cells' in lamprey are predominantly located in an area homologous to the caudal pons of mammals. Inhibitory RS cells have also been shown to stop ongoing locomotion in the *Xenopus* tadpole and in mice. In *Xenopus*, these cells receive sensory inputs that play a crucial role in their activation [40]. In mice, optogenetic activation of inhibitory neurons in various reticular nuclei of the caudal brainstem stops movement [12•].

A recent study in lampreys has shown that RS neurons do not only play a role in activating the spinal neurons responsible for generating locomotion, but they also activate interneurons involved in phase-dependent modulation of reflexes or reflex reversal. These observations demonstrate that descending inputs from the brainstem also control the flux of sensory information reaching spinal interneurons involved in generating locomotion [41].

Locomotor centers: the mesencephalic locomotor region

As indicated above, Grigori Orlovskii and his group discovered in the 1960s that local stimulation at the junction between the midbrain and the hindbrain initiated locomotion in resting cats. This functional brainstem

region was named the mesencephalic locomotor region (MLR) [5]. Another locomotor region was later found in the diencephalon and named the diencephalic locomotor region (DLR). During the following decades, the MLR was found in several other vertebrate species, from lampreys to humans [42]. The key characteristic of the MLR is the graded control it exerts on the intensity of the locomotor output; increasing the simulation strength results in a more powerful locomotor output. The mammalian MLR comprises cholinergic, glutamatergic, and GABAergic neurons, which are located in two nuclei, the pedunculopontine nucleus (PPN) and the cuneiform nucleus (CuN) [20,42]. It has not yet been resolved whether different subnuclei of the MLR control different motor functions, but it was proposed that locomotion generated under different behavioral contexts such as food seeking, escape, or exploration was initiated by different parts of the MLR [43].

Recently, genetic tools were used in the mouse MLR and optogenetic stimulation was shown to initiate stable locomotor bouts [11••,13•,14••,44]. Subpopulations of MLR neurons were examined and glutamatergic cells were found to be necessary and sufficient for locomotion, whereas cholinergic cells were found to modulate the locomotor output. Furthermore, it was shown that locally projecting GABAergic cells inhibit glutamatergic MLR neurons [14••]. Glutamatergic neurons in both the PPN and the CuN were found to contribute to slow exploratory movements, whereas the selective activation of glutamatergic CuN neurons was able to elicit high-speed synchronous-gait locomotion [11••]. In addition, Frédéric Bretzner and his group [13•] found that optogenetic stimulation of glutamatergic CuN neurons induces fast locomotion as in escape behavior and that activation of glutamatergic and cholinergic PPN neurons produces slow walking in mice, as observed during exploratory behavior [13•]. In cats, it was shown that electrical stimulation of non-cholinergic neurons in the CuN and PPN triggers locomotion and stimulation of cholinergic PPN neurons stops spontaneous walking and induces muscle atonia [45]. Interestingly, it was recently shown in lampreys, that stimulation of a same MLR site can either start or stop locomotion [46]. When locomotion is triggered by electrical MLR stimulation, a second MLR stimulation stops it if the intensity is lower than that initially used to trigger locomotion. When the intensity of the second stimulation is higher, the ongoing locomotor bout is prolonged. It was hypothesized that a subpopulation of MLR neurons would transmit a stop signal to downstream targets. These neurons would display a build-up of excitation during ongoing locomotion. Other MLR neurons starting or maintaining locomotion would display a decrease in their excitability [46].

The MLR has recently received increasing interest in the clinical field because 'Deep Brain Stimulation' (DBS) of this region is now used to treat locomotor deficits in patients with neurodegenerative diseases, such as Parkinson's disease [42]. As of now, mixed results were obtained in Parkinson's patients. It was also proposed that DBS in the MLR could be used as a rehabilitation approach for spinal cord injured patients [47]. A clinical trial is presently ongoing to examine the effects of DBS in the MLR on 5 patients with an incomplete spinal cord injury [48]. A detailed understanding of the cellular organization of the MLR should clearly help to improve these clinical approaches.

Selection of motor programs: the basal ganglia

The MLR receives inputs from the basal ganglia, which are involved in the selection of motor programs [[49••]]. The organization of the basal ganglia is highly conserved throughout the vertebrate phylum and the lamprey has been shown to be a blueprint model for these forebrain regions [49••,50,51]. As in mammals, the striatum is the input structure of the lamprey basal ganglia, receiving projections from the thalamus, the pallium (homologous to the mammalian cortex [52,53]), and the posterior tuberculum (homologous to the mammalian *substantia nigra pars compacta* (SNc) and the ventral tegmental area [[49••],54]). The *substantia nigra pars reticulata* (SNr) and *globus pallidus interna* (GPi) constitute the output regions of the basal ganglia, which keep downstream brain structures, such as the MLR under tonic inhibition when no locomotion occurs. Within the basal ganglia, a direct pathway (striatal neurons projecting directly to SNr/GPi) and an indirect pathway (striatal neurons that project to SNr/GPi via the globus pallidus externa) regulate locomotor activity in an opposing manner. In order to initiate or suppress goal-directed locomotion, the direct and indirect pathways are, respectively, recruited [49••]. In mice, it has been shown that neurons of the direct and indirect pathways project to glutamatergic MLR neurons and thus control the locomotor output [14••]. Recently, it has been demonstrated in lampreys that the MLR also receives dopaminergic and glutamatergic inputs directly from a brain region homologous to the SNc [[49••],55••,56]. Moreover, a direct dopaminergic projection from the *zona incerta* to the MLR has been identified in mice [57]. These findings are described in more detail in another review in the present issue [58].

Over the past decades, studies in different animal models have yielded important advances in the motor control field. Studies in animal models with a simpler CNS have paved the way for new discoveries in mammals. With the establishment of optogenetic techniques, it is now possible to get a better picture relative to the function of neurons expressing different transcription factors. This has been particularly useful to investigate intermingled

cell populations. However, recording the activity of these cells remains very challenging in the mammalian CNS, especially during active locomotion. Altogether, there has recently been impressive progress in our understanding of the descending control of locomotor behavior through complementary approaches from preparations allowing physiological access to single neurons (e.g. the lamprey) and preparations allowing neurogenetic access to populations of neurons (e.g. the mouse).

Conflict of interest statement

Nothing declared.

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The authors examine in an elegant set of experiments the functional role of glutamatergic neurons in two midbrain nuclei that comprise the mammalian MLR, the cuneiform (CuN) and pedunculopontine (PPN) nuclei. They find that glutamatergic neurons in both nuclei contribute to low speed locomotion, whereas glutamatergic neurons in the CuN are able to elicit fast locomotion. These results underscore the multifunctionality of the MLR and how this region controls different gaits.

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