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REVIEW

Now and Then

Locomotor pattern generation and descending control: a historical perspective

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Abstract

The ability to generate and control locomotor movements depends on complex interactions between many areas of the nervous system, the musculoskeletal system, and the environment. How the nervous system manages to accomplish this task has been the subject of investigation for more than a century. In vertebrates, locomotion is generated by neural networks located in the spinal cord referred to as central pattern generators. Descending inputs from the brain stem initiate, maintain, and stop locomotion as well as control speed and direction. Sensory inputs adapt locomotor programs to the environmental conditions. This review presents a comparative and historical overview of some of the neural mechanisms underlying the control of locomotion in vertebrates. We have put an emphasis on spinal mechanisms and descending control.

brain stem; central pattern generator; locomotion; spinal cord

INTRODUCTION

Locomotion is one of the most fundamental behaviors. It allows animals to move in their environment for different purposes such as social interactions, food seeking, reproducing, or escaping from predators. The neural mechanisms underlying locomotion have been examined in several animal species for more than a century. Because locomotion is a rhythmical motor activity, early neuroscientists used this easily identifiable output to design correlative and causal experiments to understand how the brain and spinal cord control behavior. This visionary idea is still used to this day by neuroscientists, who are now deciphering the genetically defined cell types controlling locomotion. Interestingly, the organization of the neural networks controlling locomotion is very similar in different vertebrate species (Fig. 1; for review see Ref. 1). Although not covered here, these networks share common principles with those described in invertebrates, which also generate standardized rhythmic and patterned motor activities in many circumstances (for review see Refs. 2, 3).

In the absence of sensory inputs and supraspinal structures, the neural networks located in the spinal cord can independently generate the rhythmic pattern of muscle contractions responsible for locomotion (Fig. 1). There was an intense debate in the 1970s relative to the complexity of the neural activity that is programmed centrally. Some suggested that the central program consists of a simple alternate activity between a flexor and an extensor component without the complex timing seen in different flexor muscles and different extensor muscles during natural locomotion. On the other hand, it was suggested that a central program produces detailed and complex muscle synergies as seen during natural locomotion (Refs. 4–8; reviewed in Ref. 9). Graham Brown (10, 11) had provided the first evidence that the locomotor rhythm and pattern were generated centrally, whereas Sherrington (12) proposed that locomotor movements resulted from a series of

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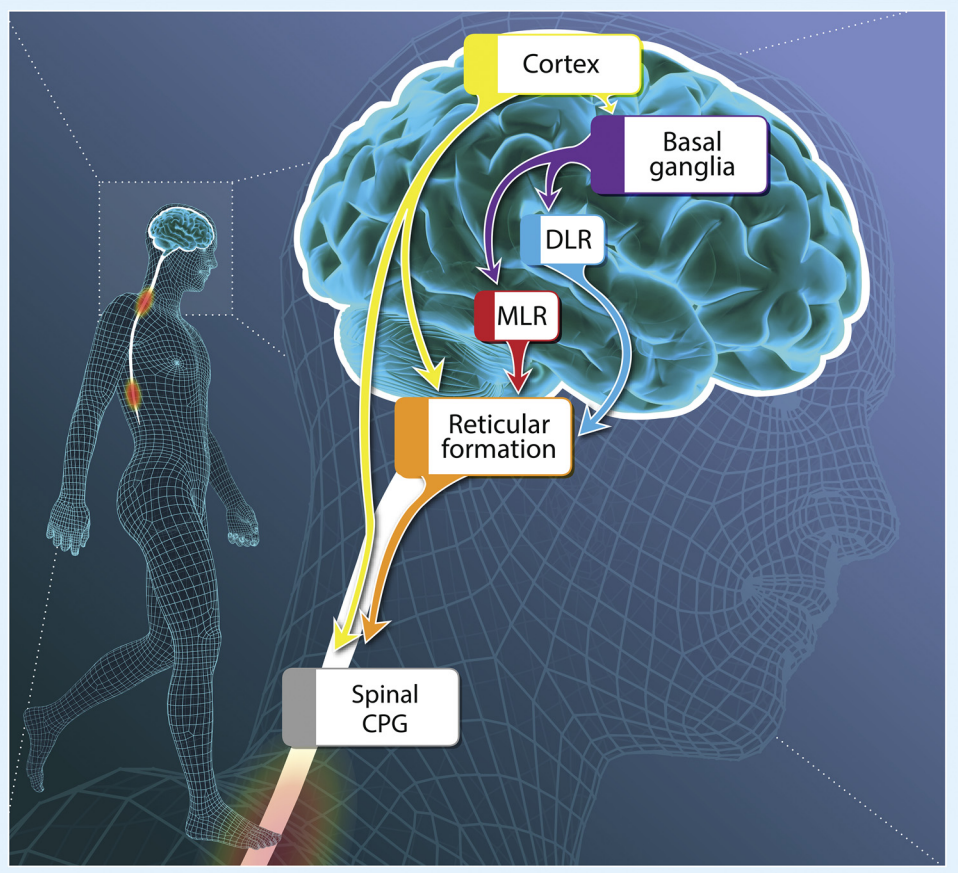

Figure 1. Schematic representation of the main supraspinal structures involved in the control of locomotion in vertebrates. The reticular formation contains the reticulospinal command neurons for locomotion initiation, speed control, steering, and locomotor termination. These command neurons are under control of the mesencephalic locomotor region (MLR) and of the less known diencephalic locomotor region (DLR). The basal ganglia send tonic inhibition to the locomotor centers, and such inhibition is temporarily decreased during locomotion initiation. The motor cortex can provide inputs at all levels of the circuitry described above. CPG, central pattern generator.

sensory reflexes. After removing the descending and sensory inputs, Sten Grillner and colleagues (5, 6, 13) showed that the spinal locomotor networks could still generate an elaborate complex sequence of muscle activations that was remarkably similar to that seen during locomotion in natural conditions. Consequently, the spinal neural networks generating this detailed locomotor pattern were named central pattern generators (CPGs; Refs. 5, 6, 14), as previously proposed from studies performed in invertebrates (3, 16, 17).

While the roles of spinal cord in the control of locomotion were being clarified in the 1960s and 1970s, researchers were acquiring new information on the role of supraspinal structures. A group of Russian scientists headed by Grigori Orlovsky discovered in cats that a specific area of the brain stem, the mesencephalic locomotor region (MLR), plays a crucial role in controlling the locomotor output (18). Stereotyped locomotor movements can be induced in response to electrical or chemical stimulation of the MLR. Similar findings were later obtained in several species (reviewed in Ref. 19 and more recently in Refs. 20–23). The strength of the MLR stimulation determines the speed, the gait (e.g., walk/trot/gallop in cat; Ref. 18), and the locomotor mode (e.g., stepping and swimming in salamander; Ref. 24). In recent years significant progress was made in our understanding of the roles of spinal and supraspinal structures in the control of locomotion, and some of the key findings are summarized below.

SPINAL MECHANISMS RESPONSIBLE FOR THE GENERATION OF LOCOMOTOR RHYTHM

A Century of CPG Models

In lower vertebrates that use their axial body parts to swim, a conceptual organization of the CPG was inherited from the "half-center CPG model" proposed by Graham Brown (11), which was further supported by Lundberg (7, 8). According to this model, rhythmic left-right alternated activity can be generated in each spinal segment by two hemisegments interconnected by mutual inhibition, and removal of mutual inhibition abolishes the rhythm (Fig. 2*A*). This view is supported by some studies in which acute surgical destruction of commissural connections was done (33, 34). However, the vast majority of other studies in lamprey and other vertebrates are in accordance with another conceptual organization proposed by Sten Grillner and referred to as the "unit burst generator" CPG model (Fig. 2*B*) (25). According to this model, the hemisegmental networks are able to produce rhythmic activity in isolation from one another, i.e., independently of mutual inhibition. In lamprey and amphibians a single spinal hemisegment carefully isolated surgically can generate rhythmic activity when tonically stimulated pharmacologically or electrically (Refs. 35–45, for review see Ref. 46; see also Ref. 47). The exact anatomical boundaries of these oscillatory centers are unresolved. Some authors proposed that the swimming CPG in larval zebrafish could also

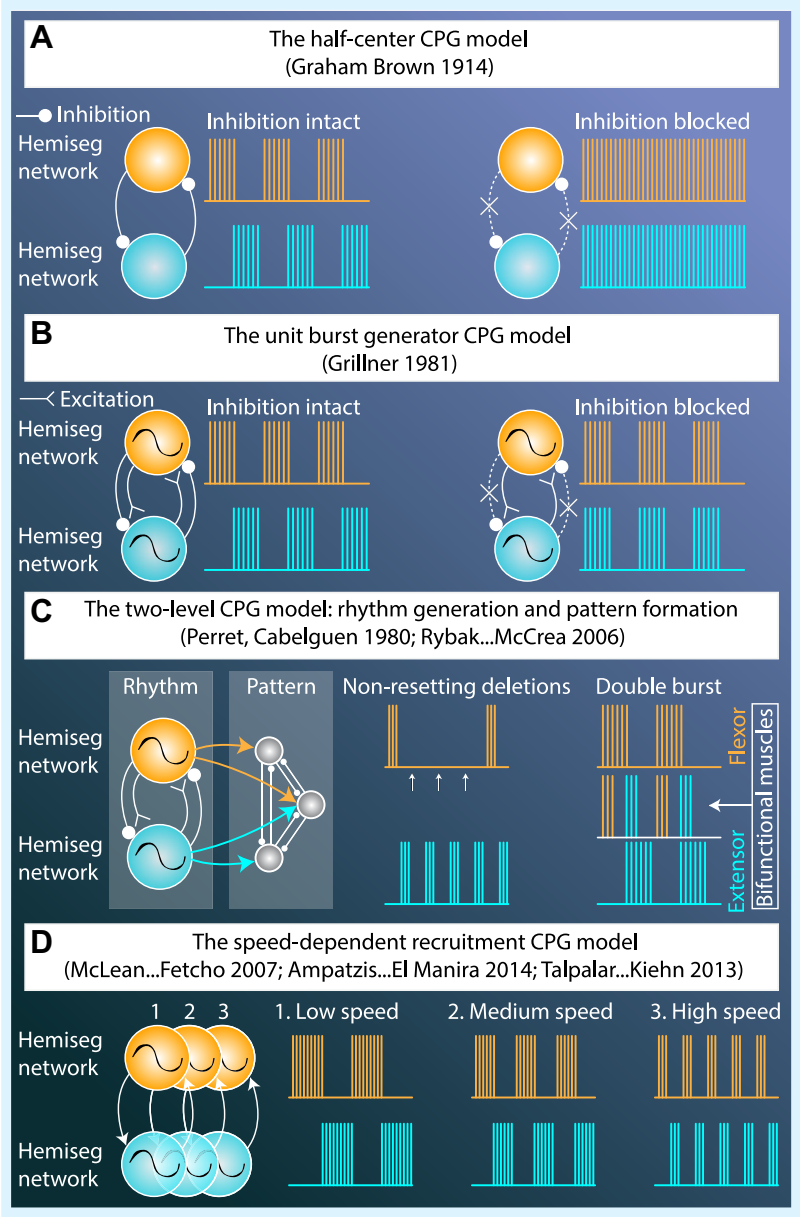

Figure 2. Main conceptual models of central pattern generators (CPGs) for locomotion over the last century. *A*: the "half-center CPG model." In this model proposed by Graham Brown in 1914 (11), and further supported by Lundberg (9), mutual inhibition between two hemisegments of the CPG (i.e., either flexor or extensor within a limb controller or left and right hemisegments in the body axis controller) is necessary for the rhythm to be generated. A prediction from this model is that isolated hemisegments cannot oscillate. Flexible coordination of multiple segments is limited with this model. *B*: the "unit burst generator CPG model." In this model proposed by Grillner in 1981 (25), each unit burst generator controls a group of close synergists (flexors or extensors, left or right axial muscles) at a given joint (hip/knee/ankle/digits or vertebra). Mutual inhibition between two hemisegments of the CPG is not necessary for the rhythm to be generated. A prediction from this model is that isolated hemisegments can oscillate. The bursting units at different joints can be combined in different ways, depending on afferent/descending inputs onto their connectivity, to generate the various limb or axial motor patterns associated with the different locomotor gaits. *C*: the "two-level CPG model." In this model proposed by Perret and Cabelguen in 1980 (26; see also Ref. 27), and supported by Rybak et al. in 2006 (28), two layers of neurons can independently generate the rhythm and the pattern. This model explains the nonresetting deletions and the double burst recorded in bifunctional muscles and in their motoneurons. It provides a relevant framework to integrate descending and sensory inputs on different network components, thereby allowing high reconfigurability of the coordination. *D*: the emerging "speed-dependent recruitment CPG model." This model was proposed by McLean et al. in 2007 (29) and further supported by the teams of El Manira (30, 31) and Kiehn (32). In this model, different layers of interneurons are recruited as a function of speed. Some components of the network can be added or derecruited as a function of speed.

consist of an unsegmented, "continuous" network of rhythmogenic microcircuits (48, 49).

In quadrupeds, the neural circuits controlling each limb appear to be distributed, and therefore the unit burst generator CPG model has been proposed to account for the complexity and flexibility of the limb locomotor pattern (Refs. 25, 50, 51; see also Refs. 52–54). The neural networks generating locomotor movements of forelimbs and hindlimbs are in the cervical and lower thoracic/lumbar regions of the spinal cord (55–61). Spinal sections and pharmacological manipulations further show that these rhythmogenic regions consist of neural networks distributed on the left and right sides, which independently control each limb and are linked by commissural connections coordinating the limbs at different locomotor speeds (62–64). This model could be improved to account for spontaneous deletions of motoneuron activity (65) and the phasic gating of reflex pathways during locomotion (66).

Studies based on optogenetics in newborn mice revealed that rhythm generation in hindlimb spinal segments is mediated by multiple subpopulations of excitatory interneurons able to generate the rhythm on each side independently, or flexor and extensor activity independently, as predicted by the unit burst generator CPG model (Ref. 54; reviewed in Ref. 67). Within the segments controlling a single hindlimb, a minimal neural circuit sufficient to generate reciprocal inhibition between flexor and extensor bursts has been identified in newborn mice (68, 266). It comprises two classes of genetically defined inhibitory interneurons: V1 neurons (69) and V2b neurons (70). Some of these neurons could correspond to the Renshaw cells and reciprocal Ia inhibitory interneurons previously defined in the cat (71–74). The latter interneurons were found to be rhythmically active during MLR-induced fictive locomotion in the cat (75).

Beyond Flexion and Extension: Bifunctional Muscles Reflect the Complexity of CPG Organization

During fictive locomotion, the limb motor pattern has been shown to be more complex than a simple synchronous activation of all flexor motoneurons alternating with a synchronous activation of all extensor motoneurons in cats (Ref. 6; for review see Refs. 76, 77) and in neonatal rodent preparations (78). The nerves of some hindlimb or forelimb muscles ("monofunctional muscles") discharge simply as flexors or extensors with one single burst of activity per cycle, whereas the nerves to other muscles ("bifunctional muscles") display more complex and versatile discharge patterns, including double bursts, during each locomotor cycle (Fig. 2*C*) (6, 26, 79–84). The different fictive patterns displayed by nerves of hindlimb bifunctional muscles have been related to different gaits (e.g., walk/gallop, forward/backward walking). Therefore, each limb CPG can generate the complex and detailed pattern of activation of the different limb muscles seen during different gaits, indicating that each limb controller is more complex than a simple neural network producing synchronous activation of all flexor muscles alternating with synchronous activation of all extensor muscles (half-center CPG model; see Refs. 7, 8). The complexity of the CPG output was well illustrated by recordings of motoneurons of bifunctional muscles, which display complex membrane potential oscillations during fictive locomotion (26, 84, 85). These complex oscillations result from a mixture of excitatory and inhibitory synaptic inputs from the limb CPGs during both the flexor and extensor phases of the fictive step cycle (83, 84). Changing the balance between flexor and extensor synaptic influences through descending or afferent inputs appears to be a simple and subtle way to shift the motor pattern expressed by bifunctional muscles according to demand (26).

The Emergence of a Two-Level CPG Model

The idea that the CPG controlling limb movements can be subdivided into two functionally independent, but hierarchically connected, subcomponents (two-level CPG model) was suggested on the basis of the variations of the fictive locomotor pattern in the thalamic cat (all brain tissue removed above the thalamus), occurring spontaneously or consecutively to exteroceptive limb stimulation (Refs. 26, 86, 87; Fig. 2*C*). In this conceptual model, a first component ("rhythm generator" or "clock") sets the locomotor rhythm and acts on a second component ("pattern-formation network") that produces the individual pattern of activity within the cycle. Interestingly, specific location of interneurons responsible for rhythm generation or pattern formation was characterized in the lumbar spinal cord of neonatal mice (88). Several findings suggest that some of the interneurons comprising reflex pathways like those activated by flexor reflex afferents belong to the pattern-formation network (79, 87). Studies on the rhythmic modulation of reflex responses during fictive locomotion have provided indirect evidence that proprioceptive and cutaneous inputs control differentially the two subcomponents of the limb CPG (for review see Ref. 66). Whether the two-level CPG concept applies to the axial locomotor circuitry (e.g., in zebrafish, tadpole, or lamprey) is unclear. In zebrafish for instance, the subpopulations of segmental V2a interneurons are necessary and sufficient to generate locomotor activity (see for review Ref. 1).

A computational model of the hindlimb CPG based on a two-level CPG organization (Fig. 2*C*) and incorporating afferent signals was shown to reproduce the patterns of activity of hindlimb flexors and extensors and most of the effects of proprioceptive inputs during stepping (89). Genetically identified neuronal types of the hindlimb CPG were recently added to the model (90–93). In the future, these modeling studies will likely include models of muscles that exhibit complex and variable locomotor patterns (cf. Ref. 94). The flexibility of the locomotor patterns displayed by bifunctional limb muscles strongly suggests that these muscles play a crucial role in the adaptation of limb movements to changing environment and goal. This implies that they are the main targets of peripheral and supraspinal inputs (see Ref. 66 for in-depth review). Importantly, the unit burst generator CPG model can also account for complex motor patterns as summarized in Ref. 95.

SUPRASPINAL STRUCTURES CONTROLLING LOCOMOTION

Overview

Locomotion is controlled through the activation of an ensemble of supraspinal regions playing different roles (Fig. 1). A significant part of these regions are connected in a linear fashion from forebrain to lower hindbrain. There is now growing evidence that supraspinal structures play a crucial role in starting, maintaining, and stopping locomotion. These structures can also integrate sensory inputs to adapt locomotor behavior according to both internal and external environmental conditions. Steering and speed control result from the interplay of supraspinal and spinal neural mechanisms.

The role of forebrain structures in the control of locomotion is not fully resolved. It has been suggested that the posterior parietal cortex contributes to planning locomotion by providing an estimate of the position of an animal with respect to objects in its path. In contrast, motor cortex would contribute primarily to the execution of gait modifications by modulating the activity of groups of synergistic muscles active at different times during the gait cycle (Refs. 96–98; for review see Refs. 99, 100). In addition, the basal ganglia send descending projections to the brain stem for controlling locomotion (Refs. 101–103; for review see Ref. 20). These are believed to play a crucial role in the selection of locomotor behaviors (Refs. 104–106; see also Ref. 107).

The MLR: an Emerging Target for Parkinson's Disease and Spinal Cord Injury

A striking feature of the supraspinal control of locomotion is the presence of locomotor centers specifically dedicated to initiating and controlling locomotion (for review see Refs. 76, 104, 108–114). As indicated above, one such region is the MLR. Its existence has been confirmed in several vertebrate species (for review see Refs. 19, 104, 112, 114, 115; for more recent review see Refs. 20–23, 116). Stimulation of the MLR induces swimming in fishes and lampreys, flying in birds,

and walking in tetrapods. The MLR controls locomotion not by projecting directly to the spinal cord but via projections to reticulospinal (RS) neurons in the pons and medulla, which, in turn, project to the spinal cord (104, 117–125). In lamprey, MLR neurons provide glutamatergic and nicotinic inputs to reticulospinal neurons (126, 127). An important aspect is that the MLR provides bilateral inputs on downstream reticulospinal neurons while inducing locomotion (128). The MLR also sends cholinergic input to a group of muscarinoceptive interneurons that in turn provide glutamatergic input to reticulospinal neurons (129). Recent studies in mice uncovered the genetic identity of MLR neurons and their role in the control of locomotor movements in vivo (Refs. 102, 124, 130–134; for review see Refs. 20, 22, 23). Interestingly, some MLR neurons encode aspects of behavior beyond locomotion (for review see Ref. 116). Some neurons projecting to the respiratory centers increase respiratory activity in lamprey (135) and mice (136). Some neurons projecting to the spinal cord control rearing, and others projecting to basal ganglia output station encode forelimb movements (137).

The MLR plays a role in locomotor control in humans. Damage to the MLR produces marked locomotor deficits (Refs. 138, 139, reviewed in Ref. 140). Functional MRI revealed that the MLR is active during mental imagery of walking and running in healthy volunteers (141). Deep brain stimulation is now carried out in the MLR as a target to improve locomotor function in patients with Parkinson's disease (Refs. 142–150; for review see Refs. 23, 151) as well as in patients suffering from other gait disorders such as primary progressive freezing of gait (152, 153) or progressive supranuclear palsy (154). In Parkinson's disease, deep brain stimulation of the MLR led to conflicting results that may result from the diversity of genetically defined MLR cell types, as uncovered in recent rodent studies (for review see Ref. 23). Some MLR cells induce locomotion, whereas others stop it. Therefore, selective stimulation of a subset of glutamatergic neurons in subparts of the MLR (cuneiform nucleus and caudal pedunculopontine nucleus) is needed to improve locomotor function in rodent models of Parkinson's disease (155, 156). Overall, the recent increase in interest for the MLR in the clinical field stresses an urgent need for understanding its function.

In rats with a partial spinal cord lesion, electrical stimulation of the MLR was shown to improve locomotor function (157, 158). Recently, optogenetic stimulation of glutamatergic neurons of the cuneiform nucleus, the dorsal part of the MLR, was shown to improve locomotor recovery after spinal cord injury in mice (159). The activity of these MLR neurons appears to be necessary for recovery (159). These studies will likely motivate the use of MLR stimulation to improve locomotor function in spinal cord-injured patients.

The inputs and outputs of the MLR have been identified in several animal species. The basal ganglia involved in the selection of motor programs project to the MLR. The organization of the basal ganglia is highly conserved throughout the vertebrate phylum, including lampreys (160). It has been demonstrated that the MLR of lampreys receives direct dopaminergic and glutamatergic inputs from a brain region homologous to the substantia nigra compacta (161, 268). This projection was confirmed in salamanders and rats (162). In addition, a direct dopaminergic projection from the zona incerta to the MLR has been identified in mice (163). The MLR is thus under descending dopaminergic and glutamatergic control. In lamprey, the dopaminergic component amplifies the glutamatergic component through the activation of D1 receptors, resulting in faster locomotor movements (140, 161). In mammals, the specific contribution of these two neurotransmitter systems remains to be established. The hypothalamus also projects to the MLR (110, 164), with additional direct projections to reticulospinal cells (164).

Other locomotor centers have been reported, although in a less detailed manner. The diencephalic locomotor region (DLR), which sends input to reticulospinal neurons, was shown to initiate and control locomotion in lamprey (165, 166) (Fig. 1). In mammals the DLR region likely corresponds to the subthalamic locomotor region (167, 168). In those experiments, it is unclear whether the subthalamic nucleus was stimulated or the closely located zona incerta, whose stimulation is also associated with locomotor activity and postural adjustments (169–172) and which is known to send projections to the MLR, including dopaminergic ones (163). The subthalamic nucleus sends direct and indirect projections to the MLR (for review see Ref. 19) and is therefore also an interesting substrate to control locomotor activity. The inputs and outputs of the DLR have been better documented in the lamprey than in other vertebrate species. Stimulation of the DLR elicits monosynaptic excitatory postsynaptic potentials, polysynaptic excitatory postsynaptic potentials, and inhibitory postsynaptic potentials in hindbrain reticulospinal neurons. Stimulation of the DLR was shown to induce rhythmic firing of reticulospinal neurons as well as rhythmic bursts of discharge in spinal ventral roots (165). Injection of GABA agonists in the DLR inhibits locomotion, whereas GABA antagonists facilitate the induction of locomotion, indicating that GABAergic projections provide tonic inhibition of the DLR that once turned off can release locomotion (166). It was shown by the same authors that populations of GABAergic neurons in the pallium and striatum project to the DLR.

Another locomotor center is the cerebellar locomotor region, which was shown to send input to reticulospinal neurons and to elicit locomotion in cats (173). In zebrafish, neurons of the medial longitudinal fasciculus (nMLF) also play an important role in locomotor initiation, speed, and bout duration, through direct projections to spinal locomotor circuits (174).

Reticulospinal Neurons: Vertebrate Equivalent of Invertebrate "Command Neurons"?

The spinal CPGs receive powerful inputs from reticulospinal cells, and since the early studies of Orlovsky and his group (175, 176) it has been recognized that these supraspinal neurons play a crucial role in the descending control of locomotion. Lamprey reticulospinal cells are functionally heterogeneous, including excitatory and inhibitory neurons (177). Since the early studies by Carl Rovainen on the physiology of lamprey reticulospinal neurons (178, 179), major advances have been made in understanding the contribution of these neurons to the descending control of locomotion. Reticulospinal neurons resemble command neurons described in invertebrates (180,

181). They project directly to locomotor CPG neurons in the spinal cord and in turn receive inputs from several sensory modalities to adapt their activity in response to conditions prevailing in the external and internal environments (Ref. 182 in lamprey, Ref. 174 in zebrafish). Specific populations of lamprey reticulospinal cells initiate, maintain, or stop locomotion (126, 183–185). Other reticulospinal populations control locomotor speed, adjust posture, or produce forward versus backward swimming (186–189). Studies on the mammalian reticulospinal system have recently established the presence and role of genetically defined excitatory and inhibitory reticulospinal cells (124, 190, 191).

In recent years, the role of reticular glutamatergic V2a neurons has been examined in zebrafish and mice. In the zebrafish, glutamatergic V2a neurons in the hindbrain were identified by their expression of the transcription factor Chx10 (192). They project to the spinal cord, and their optogenetic activation elicits locomotion, whereas their inactivation stops it (192). Recordings of these neurons revealed that they are rhythmically active during swimming (192). In contrast, in mice the group of Ole Kiehn showed that V2a neurons located at the ponto-medullary border acted as stop neurons. They halt locomotion when optogenetically activated on both sides, whereas they decrease the occurrence of spontaneous stopping when their synaptic output is blocked (193). Activation of some brainstem V2a neurons was observed during stops in vivo by calcium imaging in mice (194). Unilateral activation of V2a neurons induces ipsilateral turns in vivo in mice (195, 196). Virus injections in mice revealed that V2a reticulospinal neurons projecting to the cervical and lumbar segments differentially control head turns or decrease in locomotor speed, respectively (196). The activity of brainstem V2a neurons that control turning maneuvers is controlled by direct inputs from superior colliculus (195). Whether similar V2a reticular neurons were recorded in zebrafish and mice is not fully resolved. In zebrafish, V2a reticular neurons receive input from the MLR (125). In mice, some V2a neurons receive inputs from the MLR according to calcium imaging experiments, and they express the early response gene c-fos after a long bout of locomotor activity (122). However, a monosynaptic tracing study showed that V2a reticular neurons do not receive input from the MLR in mice, so the extent to which the MLR controls V2a neurons in mammals is not fully resolved (195).

In lamprey, three different populations of reticulospinal 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 (185). The activity pattern of the latter cell group was present not only when locomotion was elicited by MLR stimulation but also during sensory-evoked or spontaneous locomotion (185). Pharmacological activation of these cells was shown to stop ongoing locomotion, whereas their inactivation impaired the termination process (185). Like what was reported in mice, the lamprey stop cells are predominantly located in an area homologous to the caudal pons of mammals. Interestingly, in lamprey these stop cells receive input from the MLR, confirming that the MLR has direct access to a stopping mechanism (183, 184).

Inhibitory reticulospinal cells have also been shown to stop ongoing locomotion in the *Xenopus* tadpole (197) and in mice (124). In *Xenopus*, these cells are activated by sensory inputs (197). In mice, optogenetic activation of inhibitory neurons in various reticular nuclei of the caudal brain stem stops movement (124).

A study in lamprey has shown that reticulospinal neurons not only play a role in activating the spinal neurons responsible for generating locomotion but also activate interneurons involved in phase-dependent modulation of reflexes or reflex reversal. These observations demonstrate that descending inputs from the brain stem also control the flux of sensory information reaching spinal interneurons involved in generating locomotion (198).

CONTROLLING THE SPEED OF LOCOMOTION: SPINAL AND SUPRASPINAL CONTRIBUTIONS

Speed-Dependent Networks

In vertebrate swimmers, the neural mechanisms responsible for controlling locomotor speed involve both supraspinal and spinal structures. The MLR has been shown to act like a gas pedal by controlling the power of locomotor output (Ref. 199; for review see Ref. 161). In every animal species where the MLR was identified, increasing the stimulation strength of this region linearly increased the locomotor output, indicating that the MLR controls the speed of locomotion by modulating the excitatory drive onto reticulospinal neurons that in turn directly activate spinal CPG neurons (e.g., lamprey: Ref. 126, salamander: Refs. 24, 123, mouse: Refs. 124, 130–132, 134, 155, 190, 191, zebrafish: Ref. 125, reviewed in Refs. 20, 22, 23).

The spinal mechanisms underlying locomotor speed control were also recently investigated. A first series of studies in larval zebrafish revealed that different layers of motoneurons and interneurons neurons are recruited as a function of swimming speed (29, 200) (Fig. 2*D*). In adult zebrafish, double patch-clamp experiments during locomotor activity revealed that separate classes of ipsilaterally projecting glutamatergic V2a interneurons selectively activate slow, intermediate, and fast motoneuronal pools (31, 201). Interestingly, speed-dependent activity was also observed in commissural excitatory $V0_V$ interneurons in adult zebrafish (202). In adult zebrafish, inhibitory commissural interneurons were also shown to be recruited in a speed-dependent manner (203). Axial motoneurons themselves contribute to the generation of the swimming rhythm by acting on premotor CPG interneurons through electrical coupling (Ref. 204; see however Ref. 205 in lamprey). These separate neural modules allow for the increase of swimming speed by sequentially adding slow, intermediate, and fast microcircuits likely through the activation of descending inputs from the brain stem motor command centers. Although the organization of the descending excitatory drive to these different subclasses of neurons remains unknown, reticulospinal cells receiving a direct input from the MLR are good candidates. In adult zebrafish, brain stem glutamatergic neurons with axons in the medial longitudinal fasciculus were found to be important in the control of speed-related spinal modules (174).

In tetrapods, a modular reciprocal organization of premotor inhibitory and excitatory networks has been suggested for the hindlimb CPG in the neonatal mouse (32, 206). Whether the modules can be further subdivided into specific subunits driving slow, intermediate, and fast motoneuron pools (as indicated above) remains to be determined. An additional complexity is the high variability in the motor unit composition between limb muscles in the adult stage (207).

Asymmetric Control of Stance and Swing Phases and Forelimb-Hindlimb CPG Differences

In adult tetrapods, a change in stepping speed is accomplished by varying the duration of the stance phase, while the swing phase remains relatively invariant (reviewed in Ref. 76). This extensor/flexor asymmetry is an inbuilt property of the limb CPG as shown by electrophysiological recordings in decerebrate/spinal cats and optogenetics in in vitro isolated spinal cords of neonatal mice (54, 208). This suggests that the bursting capabilities of rhythm-generating flexor circuits are stronger than those of the rhythm-generating extensor circuits (cf. Refs. 93, 209). Simulations of the mammalian CPG revealed that the flexor burst can be kept constant, whereas the duration of the extensor burst could vary by 10-fold when the excitatory drive to the extensor part of the network was changed (95). However, descending signals from the brain stem (e.g., indirect inputs from the MLR) and proprioceptive signals can contribute to produce the different modes of phase-cycle period changes observed during locomotion (208, 210).

Quadrupeds commonly switch between gaits or between locomotor modes as they change their speed of locomotion (211). For example, in salamanders ground locomotor speed increases by switching from walking to trotting (i.e., change in gait) and in water by switching from trotting to swimming (i.e., change in locomotor mode) (212–215). Studies using selective ablation of genetically identified commissural interneurons in neonate rodents suggest a gait-dependent organization of the commissural neuron population at the pelvic girdle (see Ref. 67 for review). Data in neonatal mice suggest that a group of inhibitory interneurons ensures hindlimb alternation during slow walking frequencies, whereas a distinct group of excitatory interneurons is recruited at higher frequencies to maintain left-right hindlimb alternation (32).

It is likely that forelimb and hindlimb CPGs are organized differently. An early study suggested that the commissural connections between forelimb CPGs are less flexible than those between hindlimb CPGs. The coordination pattern between forelimb CPGs is always a left-right alternation during spontaneous fictive locomotion in the cat (216). In contrast, several fictive coordination patterns between hindlimb CPGs have been reported, each one corresponding to a specific gait (walk, trot, or gallop) (6, 56, 216, 217). Furthermore, forelimb-axial coupling appears to be stronger than the hindlimb-axial coupling during fictive locomotion in salamanders (215). Differences between the intrinsic frequencies of the forelimb and hindlimb CPGs have also been reported (Refs. 55, 80, 217; see Ref. 61, however). Taken together, these functional differences between the cervical and pelvic girdle CPGs are likely related to the observation that the hindlimbs are more involved in gait changes than the forelimbs (218).

Switches in Coordination during Fictive Locomotion: What Do They Tell Us?

Spontaneous abrupt switches between fictive gaits have been observed in thalamic, decerebrate, and high spinal-paralyzed cats, thus revealing that spinal motor circuits are sufficient to govern gait changes (216, 217, 219). Switches between rostrocaudal waves and caudorostral waves were also reported during fictive locomotion in lampreys (39, 40) and salamanders (215, 220). The central pathways and the mechanisms underlying fictive gait switches are not fully understood. Simulations of the lamprey locomotor circuitry showed that switches in coordination between rostro-caudal and caudo-rostral waves can easily be accounted for (267). The mechanism proposed is the trailing oscillator hypothesis, according to which the oscillator of higher excitability leads the oscillator chain (39, 40). The rostral oscillator leads the chain during rostrocaudal traveling waves (forward swimming), and the caudal oscillator leads the chain during caudorostral traveling waves (backward swimming) (39, 40, 267). Similarly, in a modeling study of the salamander locomotor circuitry (221) local uncontrolled fluctuations of the tonic pharmacological drive evoked by glutamatergic agonists in the bath could play a role in the status of saturation of forelimb versus hindlimb oscillatory centers, and this would in turn influence the propagation direction of the traveling wave in the axial circuit. Several findings suggest that propriospinal neurons connecting the lumbar and cervical enlargements could also be involved, but the relative strength of ascending and descending influences seems to depend on the preparation used (55, 58, 59, 80, 216). A study using genetic tools has revealed a complex functional organization of the propriospinal pathways in mice (222). The ascending tracts (e.g., the ventral spinocerebellar tract) that give off collaterals at more rostral spinal segmental levels and exhibit rhythmic activity during fictive locomotion could contribute to intergirdle coordination (76). It is likely that the central interactions between the forelimb and hindlimb networks are functionally separated, in accordance with the different functional modules described within each limb CPG (223). This modular design increases the dynamics of the interlimb coordinating network by increasing its number of degrees of freedom. A model of interlimb coordination considering part of this modular organization replicates the speed-dependent expression of locomotor gaits and transitions between them as observed in vivo (224).

The switch between two hindlimb fictive gaits is always complete within one or two cycles (216). This supports the view that switch from one fictive hindlimb gait to another results from a transition from one motor program to another (225). However, other mechanisms can be involved during real locomotion. Indeed, several observations in vertebrates suggest that the movement-related inputs from the limbs can couple or decouple the fore- and hindlimbs during real locomotion (225–232). In line with this, spinal cats can walk forward or backward depending on the direction of the treadmill (233). Inputs from supraspinal structures also likely

play a critical role in intergirdle coordination switches during real locomotion (234–237). This could explain why both gradual and abrupt switches between gaits are observed in intact animals (238), whereas only abrupt switches are observed during fictive locomotion (216, 219).

In conclusion, the central coordination of the four limbs can be viewed as resulting from the interactions between forelimb and hindlimb CPGs with several different preferred modes of coupling. However, the forelimb and hindlimb CPGs sometimes may be uncoupled and run freely in various fictive preparations (59, 80, 217) and in split-belt experiments in cats (239). This emphasizes the important role of the movement-related afferent feedback in interlimb coordination.

Coordination between Limb and Axial CPGs during Locomotion

It should be stressed here that in searching for the central mechanisms underlying interlimb coordination it is necessary to include the network controlling the body axis. During locomotion in cats and humans, there are two bursts of EMG activity in lower back muscles for each step cycle (Refs. 240–242; for review Ref. 243). During alternate stepping in high decerebrate cats the back muscles have two bursts of activity per step cycle, but during gallop the back muscle activity is a single burst of ~200-ms duration that starts some 75 ms before the onset of activity in the quadriceps (242).

Interestingly, during pharmacologically induced fictive locomotion in the high spinal cat (lesion at the upper cervical level) the muscle nerves innervating the lumbar back muscles display a variety of rhythmic patterns corresponding to the different gaits observed in freely moving animals (219). Systematic investigations of the different motor patterns produced by in vitro isolated spinal cords of several lower vertebrates have revealed a high degree of flexibility in the intersegmental coordination pattern, i.e., in the operating mode of the CPG controlling the body axis (39, 40, 215, 244). Intersegmental phase lags range from positive values (i.e., backward-propagating motor waves) to negative values (i.e., forward-propagating motor waves). Importantly, each fictive axial motor pattern is characterized by a distinct combination of intersegmental phase lags and cycle durations (215, 244). The flexibility in the fictive axial motor pattern has been related to the diversity of locomotor modes observed in vivo (Refs. 39, 40, 215, 221, 244; see also Ref. 245).

The mechanisms of axial motor pattern selection (i.e., switch between locomotor modes) remain to be identified. Studies in lower vertebrates have demonstrated that some spinal neurons (multifunctional neurons) are shared by several rhythmic axial motor patterns whereas others (specialized neurons) are dedicated to a specific pattern (Ref. 246; for review see Ref. 247). As an example, a core of neurons producing left-right alternation is used during forward and backward swimming in larval zebrafish, whereas separate groups of neurons are recruited to produce the intersegmental coordination pattern specific of each swimming mode (248).

Some findings in lamprey, larval zebrafish, and *Xenopus* tadpole further suggest that tonic inputs from distinct brain stem nuclei and sensory inputs from specific areas of the body (e.g., head/tail) play a critical role in switching between axial locomotor modes (249–251). This suggests that each type of sensory or descending input activates a specialized spinal network dedicated to producing just one behavior. An alternative view is that a single spinal network is sufficient to produce multiple rhythmic motor patterns through its reconfiguration induced by descending and afferent inputs (252).

Modeling and robotics experiments suggest that in salamanders a single spinal network controlling the axial musculature generates traveling waves during swimming but is made to generate standing waves when under the influence of limb controllers during walking (253). One possible mechanism for locomotor mode transition might be a gating process by which the MLR drive would not be transmitted from reticulospinal neurons to the limb controllers when it exceeds a certain threshold. Another possibility would be a spinal mechanism by which the limb oscillators, but not the axial ones, would have a limited capability to oscillate at high frequency ("saturation") (253).

The intrinsic frequency of the limb CPGs is lower than that of the axial CPG in adult salamanders (253), *Xenopus* at metamorphic climax ("froglet", Ref. 254) and newborn rats (Ref. 255; see Ref. 256, however). The difference in the intrinsic frequencies of limb and axial oscillators in salamanders provides an explanation for the abrupt increase of frequency during the switch from stepping to swimming when limb oscillators saturate (253). A similar mechanism might explain the abrupt transition between slow and fast swimming in zebrafish (257, 258). In froglet, the coupling of the axial and the hindlimb CPGs for swimming appears to be under aminergic control to set the swimming mode ("tail based" or "limb based") to the demands of the animal (254).

A neurobiological study in salamander suggests that the central coupling between the limbs and the axial CPGs is mainly local, i.e., it involves a coupling of limb oscillators to the nearest axial oscillators, as opposed to a coupling to large parts of the axial CPG (215). A numerical simulation has suggested that this configuration of the locomotor network is able to generate several of the various locomotor modes and gaits (swimming, forward and backward land stepping, forward aquatic stepping) expressed by salamanders, as well as transition between them, when under control of only two drives, which can be provided by the brain stem or by sensory feedback (259). Further experiments are needed to elucidate the mechanisms involved.

CONCLUSIONS

Studies in different animal models have yielded important advances in our understanding of the control of locomotion. Whereas mammalian studies have traditionally provided important information at the system level, studies in lamprey and *Xenopus* tadpole, with their simpler nervous systems, have additionally elucidated many of the cellular and synaptic mechanisms underlying locomotion thanks to electrophysiological, anatomical, and imaging experiments. More recently, optogenetic techniques used in zebrafish and in mice now pave the way for characterizing the role of genetically identified neurons. With a powerful set of genetic tools in development, the salamander is now becoming an

attractive model to understand the development of limb controllers and their interaction with axial networks, as well as their control by the brain and sensory feedback, before and after regeneration of the nervous system (260). From a historical perspective, the complementary approaches from all these preparations undoubtedly contribute to increase the speed at which neuroscientists can reach a better understanding of the neural control of locomotion. Although not explored here, muscle anatomy, muscle dynamics, and sensory feedback also contribute in addition to the CPGs to the production of different gaits (261–263). Because of the complexity of the interactions between these components, a global approach combining neurosciences, modeling, and genetics is needed to understand locomotion (260, 264, 265).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.R. prepared figures; R.D. and J.-M.C. drafted manuscript; R.D., J.-M.C., and D.R. edited and revised manuscript; R.D. and D.R. approved final version of manuscript.

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