



The intrinsic operation of the networks that make us locomote

Sten Grillner and Abdeljabbar El Manira

The spinal cord of all vertebrates contains the networks that coordinate the locomotor movements. In lamprey, zebrafish and amphibian tadpoles these networks generate the swimming movements and depend primarily on ipsilateral excitatory premotor interneurons of the V2a type (zebrafish) generate the segmental burst pattern. In zebrafish they can be further subdivided into three subclasses activating slow, intermediate and fast muscle fibers. Inhibitory commissural neurons are responsible for the alternating pattern between the two sides of the body. Stretch receptor neurons sense the movements and provide sensory feedback. In mammals the locomotor pattern in each limb comprises four different phases including flexor – extensor alternation. Also in this case local ipsilateral excitatory V2 interneurons can drive rhythmic burst activity in individual muscle groups. The coordination between the two hind limbs appears to be controlled by separate sets of commissural interneurons (V0) most likely engaged in walk, trot and gallop respectively.

Addresses

Department of Neuroscience, Karolinska Institute, SE-17177 Stockholm, Sweden

Corresponding authors: Grillner, Sten (sten.grillner@ki.se) and Manira, Abdeljabbar El (abdel.elmanira@ki.se)

Current Opinion in Neurobiology 2015, **31**:244–249

This review comes from a themed issue on **Brain rhythms and dynamic coordination**

Edited by **György Buzsáki** and **Walter Freeman**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 17th January 2015

<http://dx.doi.org/10.1016/j.conb.2015.01.003>

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Introduction

Many brain functions are encoded by rhythmic activity of individual or ensembles of neurons. The resulting rhythm serves as feature binding information transfer or generation of motor behavior. The ubiquity of rhythmic activity in the CNS argues that the underlying cellular and synaptic mechanisms may be shared between the different networks [1]. Hence understanding their generation, maintenance and modulation in one region can be transferred to another one. Circuits in the brainstem and spinal cord are attractive for their accessibility and their

measurable output that can be directly linked to for instance locomotor behavior. Indeed the role of identified neuronal populations and specific cellular and synaptic properties can be directly associated with specific features of the rhythmic motor output.

In vertebrates from lamprey to primates the locomotor system is dependent on central networks located in the spinal cord that by themselves can coordinate the sequential activation of the different muscles contributing to the locomotor cycle. These networks are turned on from the brainstem, and they are under the influence of a multitude of feedback circuits that help adapt the movements to the external environment and correct for perturbations. The feedback is due to a set of specific sensory circuits (from proprioceptors and cutaneous receptors) that form an integral part of the locomotor control system [2–5]. In addition compensatory signals from the brainstem and cortical level impinge on the spinal networks related to postural adjustments or the accurate placement of the feet (via vestibulo-spinal, cortico-spinal or reticulospinal neurons) [6]. The spinal central pattern generator networks (CPGs) should thus be viewed as flexible modules, continuously bombarded with signals from a number of different actors at segmental and suprasegmental level that they respond to in a behaviorally meaningful way.

A further flexibility is required by the need to change the forms of locomotion as when walking forward, backward or sideways. This requires rearrangements of the coordination between different muscle groups. Similarly in fish, the direction of swimming can be changed by reversing the direction of the undulatory wave transmitted from head to tail in forwards swimming to instead producing backwards swimming. These CPG networks are thus designed to be flexible and responsive to rapid adaptations, and composed of modules that can be recombined. This review will summarize some of the neuronal and circuit features the neural networks underlying locomotion in vertebrates.

General design features of rhythmic networks of the motor system

The burst generation in rhythmic networks including the different locomotor CPGs, the preBötzinger complex in respiratory pattern generation and the networks underlying chewing, all appear to depend on a core of interacting excitatory interneurons. In each case rhythmic activity can be produced after a pharmacological blockade of inhibitory synaptic transmission. The burst generation

in each module depends on synaptic interaction and the intrinsic properties (blend of ion channels) of the different groups of neurons involved.

The coordination between different burst generating modules relies on synaptic interaction, and in the case of alternating activity, this depends on reciprocal inhibition and conversely involves synchronous rhythmic activity can depend on mutual excitation between two modules. More complex patterns can also be generated by weighting the inhibitory and excitatory interaction and the inherent frequency of each burst generating module [7]. The fact that rhythmic bursting can be generated without inhibition at a given frequency, however, does not exclude that inhibitory processes can influence for instance the amplitude of the burst activity, as may occur in the respiratory preBötzinger module [8**].

Origin of excitation underlying locomotor rhythm

The transmitter phenotype and projection pattern of spinal interneurons driving locomotor activity was already determined from studies in lamprey and *Xenopus* tadpoles [7,9,10]. However, the molecular identity of these interneurons and the effects of their activation or silencing on the generation of the locomotor rhythm have been missing. Thus far, the best experimental evidence for the necessity and sufficiency of a defined class of excitatory interneurons driving the locomotor rhythm is from studies in zebrafish. V2a interneurons are a class of excitatory interneurons defined by the expression of the transcription factor *Chx10* and that share transmitter and axonal projection phenotypes with those of lamprey and *Xenopus* tadpoles. In zebrafish, ablation of a proportion of V2a interneurons dramatically impaired the generation of the locomotor rhythm [11]. In addition, selective activation of V2a interneurons using optogenetics was sufficient to drive a coordinated locomotor rhythm in zebrafish [12*]. These interneurons seem to form an interconnected excitatory circuit that converts commands from the brainstem into a well-defined rhythmic pattern underlying locomotion. Such an organization is reminiscent of that shown in lamprey and *Xenopus* tadpoles and could apply to mammalian locomotor networks.

Similarly, in mouse a sub-class of V2 interneurons has been implicated in the generation of the basic rhythm underlying locomotion. These interneurons express the transcription factor *Chx2*, and interfering with their release of glutamate by genetic deletion of *vglut2* resulted in a decrease in the frequency of the locomotor rhythm. This is compatible with the role of *Chx2* expressing interneurons in contributing part of the excitation setting the baseline rhythm frequency [13*,14].

Overall, studies across vertebrate species have demonstrated that the locomotor rhythm is driven by a network

of excitatory interneurons that seem to have similar molecular origin.

Scaling synaptic current and input resistance to set the firing threshold

A salient feature of locomotor movements is the versatility of their speed, which requires a gradual increase in the activity of the excitatory interneurons driving locomotion [15,16]. The mechanisms encoding the recruitment of these interneurons have been revealed in zebrafish with the focus on V2a interneurons [17,18]. These interneurons form a functionally heterogeneous class that can be segregated into three distinct subclasses. The recruitment order of the different subclasses of V2a interneurons is determined by an appropriate scaling of the excitatory synaptic currents with their input resistance combined with their spike threshold [19**]. Accordingly, the slow V2a interneurons receive the highest excitatory drive during locomotion and have the lowest spike threshold allowing them to be recruited first, whereas the fast V2a interneurons receive the weakest drive and their spike threshold is the highest while the intermediate ones bridge between the slow and fast subclasses.

Circuit architecture encoding locomotor speed

The locomotor networks have been considered to consist of a uniform functional unit conveying equal and homogeneous excitatory drive to all motoneurons with the increase in the locomotor speed being the consequence of increased overall activity [3,7,20,21]. Recent findings show that the locomotor network is not uniform but instead it consists of three separate microcircuit modules with distinct excitatory V2a interneuron subclasses driving selectively slow, intermediate or fast motoneurons [19**]. Each module is engaged at a specific frequency to increase the speed of locomotion. Indeed, this modular design reflects the contractile properties of muscle fibers and ensures smooth changes in locomotor speed by selectively engaging microcircuit layers from slow to intermediate and fast [22].

Coordination of rhythmic activity

The left-right alternation of locomotor activity is ensured by commissural interneurons that have been shown in vertebrates to be either inhibitory or excitatory [23–25]. In *Xenopus* tadpoles, optogenetic inhibition of one side of the spinal cord blocked the rhythmic activity on the other side, suggesting that commissural interneurons can contribute to the generation of the fast locomotor rhythm in stage 37 [26]. In other species the isolated hemicord can generate the motor pattern without crossed inhibition [27].

In mouse V0 interneurons represent an important class of commissural interneurons and contains both ventral (V0v) excitatory and dorsal (V0d) inhibitory subpopulations

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