



Dynamics and plasticity of spinal locomotor circuits

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Spinal circuits generate coordinated locomotor movements. These hardwired circuits are supplemented with neuromodulation that provide the necessary flexibility for animals to move smoothly through their environment. This review will highlight some recent insights gained in understanding the functional dynamics and plasticity of the locomotor circuits. First the mechanisms governing the modulation of the speed of locomotion will be discussed. Second, advantages of the modular organization of the locomotor networks with multiple circuits engaged in a task-dependent manner will be examined. Finally, the neuromodulation and the resulting plasticity of the locomotor circuits will be summarized with an emphasis on endocannabinoids and nitric oxide. The intention is to extract general principles of organization and discuss some ontogenetic and phylogenetic divergences.

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Introduction

Most of the processing in the nervous system is translated into motor actions to enable continuous interactions with the external environment. Motor behavior emerges from the coordinated activity of neural circuits that control the sequential pattern of muscle activation [1–3]. They are under a continuous modulatory tone from biogenic amines, peptides and retrograde messengers that results in a dynamic regulation of these circuits to accommodate contextual demands and hence generate behavior with the optimal parameters [4–6]. An understanding of how motor behavior is generated necessitates an integrative view of the processing at all levels of interaction.

Locomotor circuits are tractable for an integrative analysis to directly link the mechanisms of circuit assembly, function and modulation to their encoded behavior

[2,3,7*,8–10,11**,12]. The overall organization of these circuits has been revealed in lamprey and *Xenopus* [2,10,13]. These studies are being expanded using genetically amenable model systems (*e.g.* zebrafish and mouse) to integrate knowledge on the molecular diversity of neuronal components and their functional roles [2,7*,9]. The molecular mechanisms of development of locomotor circuits are comparable across vertebrate species, arguing for a conserved organization and function [2,9,14**,15].

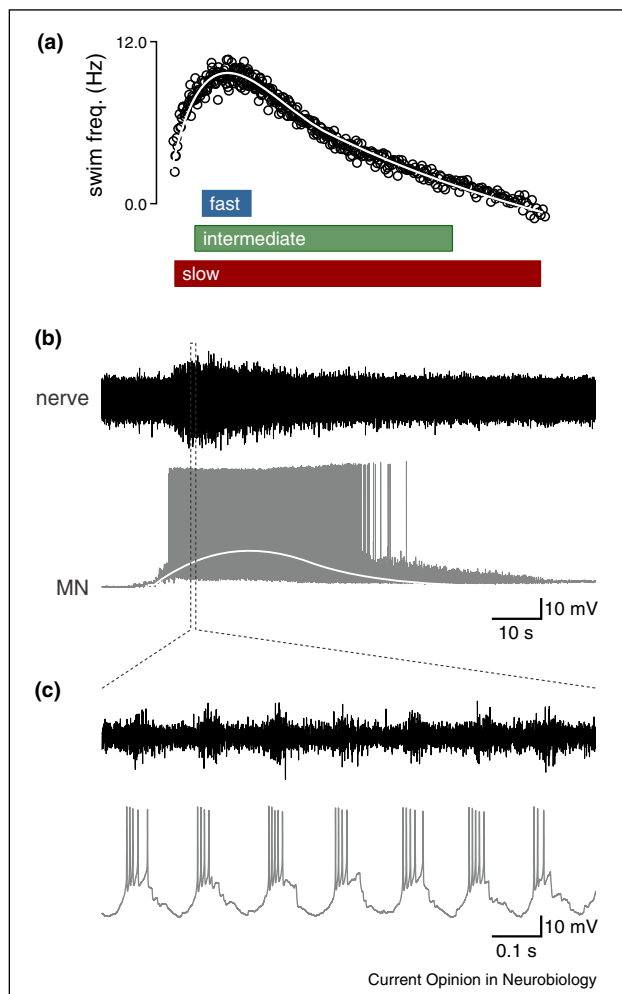
Locomotion is not a static motor behavior, but it is highly flexible. From fish to mammals, the locomotor output varies in speed, force, and coordination to allow animals to move efficiently through their environment. This is ultimately mediated by complex interactions within built-in hardwired circuits that are supplemented with prominent modulatory systems [4–6,16,17*].

This review will highlight some of the recent insights gained in understanding the functional organization and flexibility of the locomotor circuits. The focus will be on the modulation of the speed of locomotion and the activity of different classes of motoneurons and interneurons. In addition, the modulation of the locomotor pattern and gait by engaging specific microcircuits in a task-dependent manner will be discussed. Finally, the neuromodulation and the resulting plasticity of the locomotor circuits will be summarized. The intention is to extract general principles of organization, dynamics and plasticity of the locomotor circuits.

Modulation of the speed of locomotion – regulation of motoneuron activity

Motoneurons represent the final stage of neuronal processing and hence need to be activated in an orderly fashion to produce a smooth change in speed. Recent studies in zebrafish have characterized the rules governing the graded activation of motoneurons. They reveal a developmental reorganization of motor pools and the mechanisms underlying their activation as significant differences emerge between larval and adult stages. In adult zebrafish all muscle types (slow, intermediate and fast) are fully acquired and swimming consists of continuous bouts [18]. Only the late-developed secondary motoneurons are active during swimming, while the early-developed fast primary motoneurons are exclusively active during escape [19*] (Figure 1). Secondary motoneurons are segregated into three pools innervating slow, intermediate and fast muscles [19*]. These motoneuron pools form discrete modules and are successively activated at a precise frequency threshold during swimming with increasing speed (Figure 2).

Figure 1



Modulation of the speed of locomotion. **(a)** Swimming activity with varying frequencies can be induced in the adult zebrafish preparation. During a typical swimming bout different motoneurons from slow (red), to intermediate (green) and fast (blue) pools are activated. **(b)** The activity can be recorded extracellularly from motor nerves and intracellularly from identified motoneurons. Motoneurons receive large tonic excitation (white curve) that can enable them to fire action potentials. **(c)** Expanded time scale recordings from the region indicated with the dashed line in (b) showing that the recorded motoneuron receives phasic excitatory drive allowing it to fire action potentials in phase with the motor bursts recorded in the peripheral nerve.

The order of recruitment of secondary motoneurons does not simply obey the ‘size principle’. Instead, it is governed by a combined computation of synaptic input and biophysical properties, which makes up a higher level of integration than the input resistance rule, which underlies the size principle, can accommodate [20]. Remarkably, the first recruited pool (the slow secondary motoneurons) receives large excitatory synaptic drive, display low spike thresholds and fire in bursts with post-inhibitory rebound (Figure 2). In contrast, the last recruited pool (the fast secondary motoneurons) receives weak excitatory input,

require a large depolarizing current to reach the firing threshold and display a strong adaptation [20]. The synaptic drive and membrane properties of the intermediate secondary motoneuron pool bridge between those of slow and fast pools. Thus, in adult zebrafish the synaptic and biophysical properties of motoneurons are designed to confine their recruitment to the type of muscle they innervate and hence result in an incremental activation from slow to intermediate and fast during swimming (Figure 2).

In larval zebrafish, the motor column organization, the activation pattern of motoneurons and the underlying mechanisms are relatively ‘simpler’ than in the adult [21,22]. At this early developmental stage, swimming consists of fast locomotor bursts occurring episodically to produce a beat-and-glide motor pattern mediated by the fast primary and fast secondary motoneurons [23–25]. The morphological and physiological properties of these fast motoneurons lie in a continuum without any clear segregation into distinct pools [22]. All motoneurons seem to receive equal synaptic drive and their recruitment pattern is primarily dictated by the ‘size principle’ [21].

The development of zebrafish from larval towards adult stages involves a refinement of the principles governing motoneuron recruitment to accommodate developmental changes in the biomechanical apparatus, the pattern and speed of swimming. A reorganization of motoneuron innervation of muscles and the locomotor activity also occurs in *Xenopus* tadpoles, resulting in a more selective and flexible control of the muscles and swimming activity [26]. Similarly, humans and rodents do not have a mature neural control of locomotion at birth, and they walk only several days or months later. The stepping pattern becomes more complex as they develop from neonate to adult stages [27,28]. Thus, the development of locomotor patterns requires progressively tuning of cellular and synaptic properties [29,30].

Modulation of the excitatory drive within the locomotor circuit

The modulation of the speed of locomotion is mediated by changes in the excitatory drive within the locomotor circuits [2,10,13,31]. In zebrafish, selective ablation and optogenetic studies revealed that V2a interneurons represent the excitation source that is necessary and sufficient for driving locomotion [32]. When only a part of this population was ablated, higher stimulation intensities were required to elicit a swimming bout that was always briefer than control and with a significant decrease in burst frequency [32]. The decrease in the swimming burst frequency caused by ablating V2a interneurons was always much more pronounced in preparations where the activity was induced by stimulating descending inputs than pharmacologically with NMDA. Optogenetic

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