Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Neurobiology

Origin and circuitry of spinal locomotor interneurons generating different speeds

Henrik Boije and Klas Kullander

The spinal circuitry governing the undulatory movements of swimming vertebrates consist of excitatory and commissural inhibitory interneurons and motor neurons. This locomotor network generates the rhythmic output, coordinate left/right alternation, and permit communication across segments. Through evolution, more complex movement patterns have emerged, made possible by sub-specialization of neural populations within the spinal cord. Walking tetrapods use a similar basic circuitry, but have added layers of complexity for the coordination of intralimbic flexor and extensor muscles as well as interlimbic coordination between the body halves and fore/hindlimbs. Although the basics of these circuits are known there is a gap in our knowledge regarding how different speeds and gaits are coordinated. Analysing subpopulations among described neuronal populations may bring insight into how changes in locomotor output are orchestrated by a hard-wired network.

Address
Department of Neuroscience, Uppsala University, Box 593, 751
24 Uppsala, Sweden

Corresponding authors: Boije, Henrik (henrik.boije@neuro.uu.se),
Kullander, Klas (klas.kullander@neuro.uu.se)

Current Opinion in Neurobiology 2018, **53**:16–21

This review comes from a themed issue on **Developmental neuroscience**

Edited by **Alex Kolodkin** and **Guillermina López-Bendito**

https://doi.org/10.1016/j.conb.2018.04.024

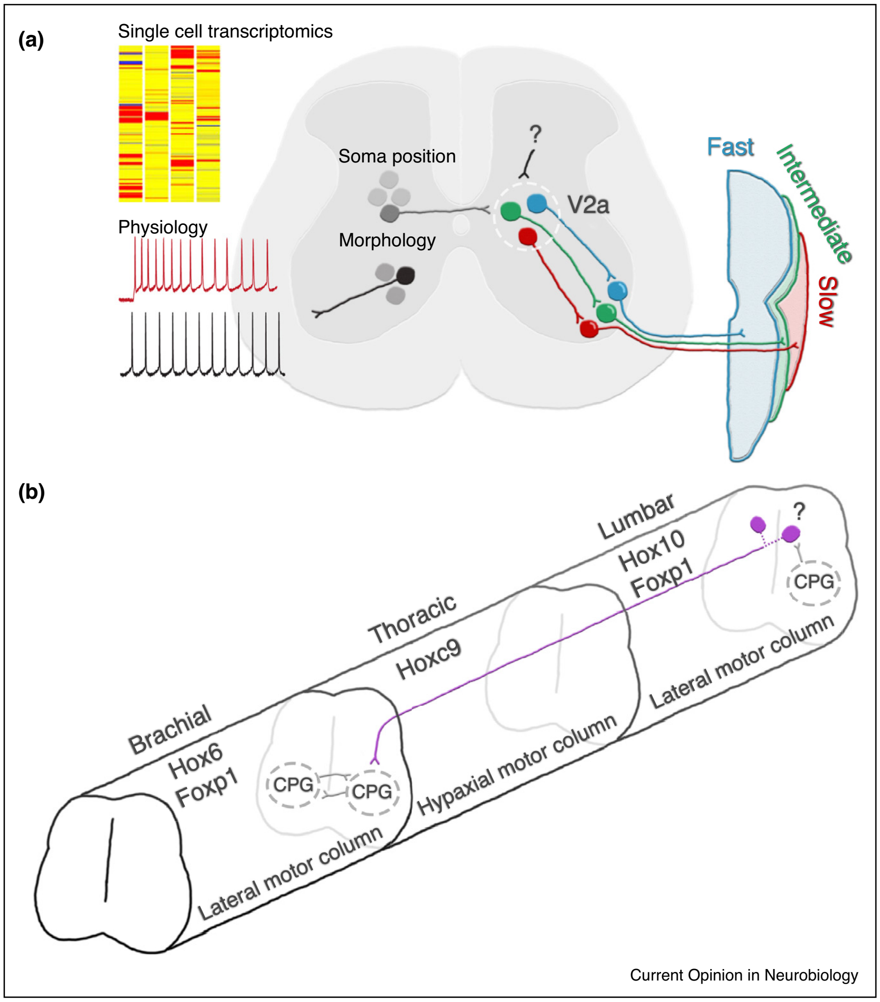
Introduction

The earliest characterization of neurons was based on soma position, morphology of dendrites, and axonal projections. Whereas these parameters are still crucial today, our ambition of understanding sub-specialization force us to include several more such as electrophysiological properties, connectivity, and transcriptional profiles (Figure 1a). Recent studies combining these parameters have made breakthroughs regarding categorizing neural subpopulations within the spinal cord, helping us to disentangle how regulation of different movement patterns may be organized by hard-wired neuronal circuits [1,2].

The specification of neurons in the spinal cord is highly dependent on their position along the dorsoventral and rostrocaudal axis. Antiparallel dorsoventral gradients of BMP and Shh during development are translated into various transcriptional networks conveying the competence to form particular sets of neurons [3–5]. Some years ago, Alaynick and colleagues published a summary of the molecular diversity within the spinal cord known at the time; twelve progenitor domains, which differentiate into 23 neuronal subtypes [6,7]. Sub-specialization along the rostrocaudal axis has primarily been focused on motor neurons where the evolution of movable appendixes has, through Hox-genes, generated specialized segments innervating fins, wings and legs (Figure 1b) [8•]. Hox6 and Hox10 defines the brachial and lumbar motor neurons, respectively, while Hoxc9 defines the thoracical segments by suppressing Foxp1 at non-limb levels [8•]. Lateral motor neurons in mice express Lhx1 and direct their axons via induction of EphA4 to dorsal extensor muscles, while medially located motor neurons express Isl1 and target flexor muscles by activation of EphB1 guiding the axons [9]. Of note, several axon guidance signals are integrated, where Netrin-1, which was shown to attract laterolateral motor columns while repelling mediolateral motor columns, coordinate its actions with A-class and B-class ephrin ligands [10]. In skates, a cartilaginous fish that perform pelvic fin walking, the motor neurons innervating pectoral and pelvic fins were also segregated into medial Isl1, EphB1 positive and lateral Lhx1, EphA4 positive pools [11•]. This suggests a common molecular program for segregating fin-innervating and limb-innervating motor neurons that existed before vertebrates sat foot on land. Furthermore, a variant Hox-gene pattern, along with an inability to produce or respond to retinoic acid, underlies motor neuron specification for digit innervation [12].

Movement in our evolutionary ancestors relied on a basic spinal network governing the frequency output, left-right alternation, and coordinating activity between segments. The formation of fins and limbs, flexor and extensor muscles, and digits, are all examples of evolutionary steps increasing the ability to move at the cost of more complex regulation. These advances have spurred the divergence of neuronal populations and new techniques, combined with ambitious undertakings, have recently revealed a much richer heterogeneity than previously described

Figure 1



Sub-specialization of neural populations. **(a)** V2a interneurons, motor neurons, and muscles form three distinct speed modules in the zebrafish spinal cord. Evolutionary conserved programs guide the innervation of limbs while motor neuron soma position regulates sensory input. **(b)** Hox-genes encode sub-specialization along the rostrocaudal axis where limb innervating regions display an increased diversification. Identifying interneuron populations coordinating intrasegmental output is critical for our understanding of how speed and gaits are orchestrated.

within the spinal cord. Correlating animal behaviour with network activity and cellular characterization should provide a better understanding of how the locomotor network is formed and how it operates. This review will discuss how and why different gait and speed modules may have evolved and put them in context regarding recent progress in the categorization of new neuronal subpopulations within the spinal cord.

Moving at different speeds

Evolutionary adaptation to the environment has given rise to considerable variation in modes of animal locomotion. Different strategies for locomotion include undulation in snakes and fish, two-legged locomotion in primates and kangaroos, and four-legged locomotion in a variety of tetrapods. Each strategy poses its own challenges to provide a range of speeds suitable for foraging, long-distance travel, escape and hunting. Here we will mainly focus on different swim speeds in zebrafish and trot/gallop in four-legged animals with the purpose of discussing emerging concepts in how interneurons participate in locomotor pattern formation and gait adjustment upon speed change.

In the zebrafish, undulating movements starts within the first day of development as a rhythmic coiling behaviour. Four to five day old larvae swim in a ‘burst and glide fashion’, regulating their speed by altering the length of the active swim burst period and the inactive interburst period [13]. At first glance, this regulation seems straightforward and could provide a variety of speeds. However, kinematic analysis in 6 and 7 day old larvae revealed