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Locomotion: Control from the Periphery?

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Studies of the neural control of locomotion have tended to focus on the modulation of motoneuron firing by premotor neurons; new work indicates that the regulation of synaptic transmission at the neuromuscular junction can also be important, revealing an inverse relationship between input resistance and synaptic output in motoneurons.

Vertebrate locomotion relies on the coordinated activation of motoneurons in the spinal cord that enables the patterned contraction of muscle fibers at the periphery. Motoneurons form a pool of cells that are recruited according to the size principle [1]: while small, highly resistive motoneurons are recruited for low levels of excitation and typically lead to low amplitude movements at low speed, larger motoneurons with low input resistance require more excitation to be recruited to drive large amplitude movements at high speed. As the timing of spiking in motoneurons is set by descending inputs from the brain and from premotor interneurons in the spinal cord, the investigation of motor circuits controlling locomotion in vertebrates has largely focused on the dissection of upstream pathways onto motoneurons [2,3]. Consequently, the potential contribution of the periphery to locomotion, especially the synaptic strength and plasticity at the neuromuscular junction, has tended to be overlooked.

Recent studies [4–6] have shown that motoneurons have more complex properties than previously thought and that, together with glutamatergic premotor interneurons, they are components of dedicated microcircuits organized according to locomotor speed. In zebrafish larvae, spinal neurons can be easily targeted for recording, which led to the initial observations that motoneurons, as well as glutamatergic premotor V2a interneurons, are recruited in a topographic manner, according to their input resistance [7,8]. Furthermore, motoneurons receive selective inputs from identified subsets of glutamatergic premotor V2a interneurons, forming microcircuits recruited as a function of the locomotor speed [5,6,9]. As reported recently in *Current Biology*, Wang and Brehm [10] took advantage of a semi-intact preparation for accessing both the motor pool and body musculature in zebrafish larvae to demonstrate novel properties and organization of motoneurons at the level of the neuromuscular junction. The authors were able to show that motoneurons organized from slow to fast exhibit a gradient of synaptic properties, in terms of both strength and short-term plasticity. Synaptic currents induced by fast motoneurons with low input resistance onto muscle fibers are large and strongly depress, while those of motoneurons with high input resistance recruited at low speed are small and strongly potentiate.

The new study [10] builds on the earlier establishment of an innovative preparation for blocking muscle contractibility and recording motoneuron activity, while effectively voltage-clamping muscle fibers that are small and resistive in zebrafish larvae [11,12]. The voltage-clamp of muscle fibers enables low noise recordings in which all synaptic currents, even unitary ones, can be resolved. The *tour de force* of Wang and Brehm [10] lies in making double patch clamp recordings between motoneurons across the motor pool and muscle fibers. By performing this extensive analysis on neuromuscular junctions, the authors made the unexpected discovery that motoneurons segregate in terms of synaptic strength and short-term plasticity as a function of their input resistance, a property that directly relates to their recruitment pattern during fast or slow locomotion. While motoneurons

belonging to the fast circuit induce robust, large and depressing synaptic currents in connected muscle fibers, motoneurons belonging to slow circuits induce weak and potentiating synaptic currents. By eliciting spikes in motoneurons of non-paralyzed animals, Wang and Brehm [10] further show that this plasticity observed by patch clamp recording at the neuromuscular junction matches the actual muscle contraction *in vivo*.

Wang and Brehm's [10] work unravels an important mechanism that makes possible peripheral control of locomotion. This study indicates that the concept of speed-controlling spinal microcircuits characterized by selective connectivity between premotor and motoneurons may be extended to the neuromuscular junction. In the future, it will be critical to establish the full connectome from motoneurons onto muscle fibers, a task that will be challenging to achieve in mammals and that is amenable in the zebrafish larva. It will also be interesting to investigate how the observed gradient of synaptic strength and plasticity from slow to fast motoneurons could impact the maintenance of muscle fiber contraction over time in a speed-dependent manner. The large synaptic strength observed within the fast circuit may enable large amplitude movements necessary at the beginning of escapes or during burst swimming. Such synaptic release and subsequent muscle contraction demands a large amount of energy. The strong short-term depression of the synapses formed by low input resistance motoneurons may stop the fast large amplitude movements from being maintained for excessive periods. Such a mechanism could act in concert with the observed inhibition of slow motoneurons observed when fast motoneurons are recruited [13]. However, the role of the potentiation of weak neuromuscular junction synapses within the slow swimming circuit is less intuitive. Such potentiation may be relevant for building up the recruitment of slow fibers following fast swimming during long locomotor events. Alternatively the strengthening of synapses in the slow swimming circuit may contribute to maintaining slow swimming in response to long-lasting stimuli, such as the innate response of swimming against the flow, when sensory stimulation undergoes adaptation.

Interestingly, a similar distinction between synapses of the fast and the slow circuits has recently been observed in the circuits formed by GABAergic sensory neurons in the spinal cord [14,15]. Synaptic strengths from GABAergic sensory neurons onto targets of the fast circuit are large and strongly depress upon repetitive stimulations [15], while synaptic strengths from the same cell type onto targets of the slow circuit are small and potentiate [14]. Further experiments mapping the synapses formed by glutamatergic premotor interneurons onto motoneurons should reveal whether a gradient in synapse amplitude and short-term plasticity also occurs as a function of the recruitment of these microcircuits with locomotor speed.

Multiple studies have shown a topographical recruitment of motoneurons and interneurons in the spinal cord [7,8] and hindbrain [16,17]. Thanks to the systematic characterization of motoneuron input resistance, synaptic strength and plasticity, the study of Wang and Brehm [10] will enable to build, in the close future, computational models explaining the dynamic recruitment of motoneurons and the subsequent pattern of muscle contractions over time and across speed during movements. Furthermore, the new study establishes a fundamental basis for genetic studies modeling disease of the neuromuscular junction. Combined with the power of CRISPR-Cas9 technology to induce knock-out and/or knock-in, this work will open new opportunities to dissect the physiological consequences of lethal mutations identified in humans on synaptic physiology and plasticity at the neuromuscular junction.

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