Muscle activation in health and disease: The importance of ClC-1 regulation for muscle excitability and function

Ole Bækgaard

The function of skeletal muscle requires that they can respond to activating action potentials from the central nervous system when these arrive at the neuromuscular junction. At the junction, the action potentials are conveyed to the muscle fibres by the release of acetylcholine from the pre-synaptic membrane of the motor neuron. Acetylcholine then binds to receptors in the muscle membrane causing them to open with ensuing inflow of excitatory sodium current. This in turn activates nearby voltage gated sodium channels whereby an action potential is initiated that propagates along the length of the muscle fiber signaling muscle contraction.

In general, the initiation and propagation of muscle fiber action potentials requires that the excitatory sodium current is sufficient to depolarize the nearby membrane to beyond its voltage threshold for action potential generation. At rest, muscles have a high safety factor for the neuromuscular signal transmission and action potential propagation. During activity, however, the safety factor is for several reasons decreased and continued function of the muscles therefore dependents on acute regulation of their excitability. Several recent studies from our laboratory have demonstrated that a key component in this regulation is the muscle specific ClC-1 chloride channels. These channels belong to a large gene family of Cl^- selective channels and Cl^-/H^+ exchangers sharing similar protein structure and common regions of highly conserved key residues for Cl^- coordination and selectivity.

In the seminar I will show results from our studies on ClC-1 regulation and discuss its relevance for maintenance of muscle excitability and function during work in health and disease.