SMA

Spinal Muscular Atrophy (SMA) is a genetic disease which severity depends on the amount of SMN protein, the product of the genes SMN1 and SMN2. Symptomatology goes from severe neuromuscular impairment leading to early death in infants to slow progressing motor deficits during adulthood. Our laboratory works with several mouse model of different forms of SMA (SMND7, SMN1 A2G, SMARD). Our aim is to understand the disease mechanisms from a functional and structural point of view, and from this knowledge to test possible therapeutic drugs for SMA. We combine electrophysiological methods (from electromyography to intracellular recording), and IHC techniques to explore the function impairment of the motor nerve terminals regarding neurotransmitter release, organization of presynaptic organelles (synaptic vesicles, mitochondria, active zones), and cytoskeleton. We found that in mouse SMA deficient motor terminals the kinetics of the postsynaptic end-plate potentials are slowed and evoked neurotransmitter release is decreased by 55% in most affected muscles. http://www.ncbi.nlm.nih.gov/pubmed/21307238 In addition, low SMN levels results in an anomalous increase in asynchronous neurotransmitter release, suggesting an alteration on intraterminal calcium buffering at motor nerve terminals. http://www.ncbi.nlm.nih.gov/pubmed/21307238 Clustering of synaptic vesicles and active zones, reduction in the size of the readily releasable pool (RRP), and the recycling pool (RP) of synaptic vesicles, decrease in active mitochondria and limiting of neurofilament and microtubule maturation are characteristics of SMN-deficient motor nerve terminals. http://www.ncbi.nlm.nih.gov/pubmed/22022549 Actin conte motor nerve terminals is decreased in SMN-deficient mouse models. However, overexpression of plastin-3 (PLS-3), a F-actin bundling protein, increases actin in these mice, together with synaptic vesicle content and active zone amount. http://www.ncbi.nlm.nih.gov/pubmed/23263861 Synaptotagmin-2 and -1 levels are linked to neurotransmission impairment and muscle vulnerability. The summed level of the two proteins is significantly reduced in SMA. Nerve terminals in highly vulnerable muscles (TVA, OIA) express less Syt than in less vulnerable (diaphragm, LAL) muscles. https://academic.oup.com/hmg/article-abstract/25/21/4703/2525902/Synaptotagmin-2-and-1-linked-to-neurotransmission?redirectedFrom=fulltext.