Identifying synaptic molecular components that contribute to motor nerve terminals vulnerability in a mouse model of Spinal Muscular Atrophy

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Spinal Muscular Atrophy (SMA) is an autosomal recessive neurodegenerative disease characterized by loss of spinal cord motoneurons, muscle weakness, and paralysis. It is caused by defects in the Survival of Motoneuron 1 gene (*SMN1*). In SMA mouse models, neurotransmitter release is severely impaired, but its cause is unknown. We investigated the molecular mechanisms potentially responsible for this functional deficit, and the molecular basis of the selective muscle vulnerability observed in SMA.

We combined electrophysiological experiments with confocal microscopy to investigate the calcium dependence of neurotransmitter release and the expression of distinct synaptic proteins that play a key role in neurotransmission. These experiments were done in control and SMA (SMNΔ7) muscles affected in different degree.

Our results show that SMNΔ7 terminals present a reduction in P/Q-type voltage-dependent Ca^{2+} channels density, without alteration in the Ca^{2+} cooperativity and sensitivity of the secretory machinery. Besides this, SMN-deficient terminals present a low release probability (p_r), and are unable to normally increase the number of functional release sites (n) upon high frequency stimulation, even when vesicles were available. Additionally, we found that highly vulnerable muscles show a large reduction of synaptotagmin-2 (Syt2) and synaptic vesicle protein 2 (SV2) B, while other synaptic proteins, such as syntaxin-1B and synaptotagmin-7, were not decreased. The results also show that synaptotagmin-1 (Syt1) undergoes a process of physiological downregulation during the postnatal synaptic maturation period. This process occurs earlier in more vulnerable muscles.

In conclusion, we propose that the reduction of Syt2 and SV2B are key factors for the synaptic dysfunction in SMA and that the rate at which the physiological downregulation of Syt1 occurs is important to muscle vulnerability in the disease.

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