Modeling Synaptic Vulnerability of a Brainstem Sensorimotor Circuit in a Mouse Model for Amyotrophic Lateral Sclerosis

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Modeling Synaptic Vulnerability of a Brainstem Sensorimotor Circuit in a Mouse Model for Amyotrophic Lateral Sclerosis

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Trigeminal System, Jaw, Amyotrophic Lateral Sclerosis, Brain Stem, Motor Neurons

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic Lateral Sclerosis (ALS) is an invariably fatal neuromuscular disease underlying degeneration of motoneurons (MN) throughout the brain and spinal cord. Excitability of MNs is a crucial endogenous mechanism of neuroprotection and

modulating excitability early in the disease process can recruit neuroprotective mechanisms in ALS. However, it is not fully understood how pre- symptomatic excitability is modulated during disease progression. Our long-term goals are to delineate mechanisms underlying MN excitability and establish targets that can promote survival and preserve function resulting in delayed disease onset and progression. In this application, we seek to investigate early differential alterations in synaptic properties of brainstem MNs that are selectively vulnerable to ALS in comparison to MNs that are relatively resistant to degeneration. A key component of the proposed study is to compare synaptic excitability changes in disease vulnerable trigeminal motor neurons (TMNs) versus resistant oculomotor neurons (OMNs) at an early developmental stage (P8-P12) in the well-characterized SOD1G93A mouse model for ALS. We will further capitalize on our recently proposed clustering approach to classify MNs into their respective motor unit types as fast fatigable, fast fatigue resistant and slow, to assess differential alterations in fast fatigable motor units that are preferentially vulnerable to degeneration. In th current study, we will utilize this classification strategy and assess changes in synaptic excitability and the underlying ionic basis using in vitro patch-clamp electrophysiological and molecular approaches. Additionally, we will leverage a unique brainstem sensorimotor circuit involving vulnerable TMNs and the closely located sensory mesencephalic V (Mes V) neurons that provide monosynaptic proprioceptive inputs from jaw closer muscle spindles and form the only primary sensory cells within the central nervous system. By comparing alterations in synaptic properties of jaw closer (JC) trigeminal MNs that receive Mes V inputs with identified jaw opener (JO) trigeminal MNs that lack spindle inputs, we will be able to make novel claims on selective synaptic vulnerability within functionally distinct motor pools. Within the scope of proposed work, we will examine inhibitory glycine and GABAergic (Aim 1) and excitatory glutamatergic (Aim 2) synaptic currents to JC and JO TMNs as well as to OMNs, further distinguishing these results between motor unit types. Finally, we will develop a dynamic model of jaw stretch reflex circuit and a simplified central pattern generator driving rhythmic activity n TMNs such as during rhythmic chewing to test the functional outcome of synaptic alterations (Aim 3). Recently, using a computer-based model of the jaw closer motor pool, we demonstrated a functional outcome of the alterations in trigeminal motor unit excitability in the SOD1 ALS mouse. Here we will incorporate those intrinsic excitability changes in addition to the observed synaptic changes together paving the way for a novel circuitry-based hypothesis for disease vulnerability and progression in ALS. Synaptic failure is evident in other neurodegenerative diseases including Alzheimer’s, Huntington’s and Parkinson’s, and, therefore our proposed studies will be crucial in providing novel research directions in the basic understanding of disease development in ALS.

Further information available at:

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