Mechanisms Underlying Excitability Regulation of Motoneuron Types in ALS

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USA

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Mechanisms Underlying Excitability Regulation of Motoneuron Types in ALS

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, Motor Neurons, Spinal, Regulation, Riluzole

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is an incurable, fatal disease characterized by selective death of fast- twitch spinal motoneurons (F-MNs) before

slow-twitch spinal motoneurons (S-MNs), a degeneration differential which suggests that S-MNs are less vulnerable to ALS than F-MNs. Riluzole, the only ALS treatment, extends life by only 3 months; thus, understanding the mechanisms that prolong life in S-MNs or hasten death in F-MNs could provide targets for more effective treatments. Our previous work has shown that S- and F-MNs differ in their intrinsic expression of SK channels. As SK current contributes to MN excitability regulation, this could potentially explain the vulnerability differential between S- ad F-MNs in ALS. Understanding MN excitability dysregulation in ALS is challenging because ongoing disease and compensatory changes have opposing pro- and anti-excitability effects that maintain a pseudo-normal net excitability which masks disease progression. Because multiple changes take place concurrently, and because some changes cannot be directly measured in experiments, experimental methods require the support of computer simulations that are accurate enough to analyze the effects of individual cellular changes on overall MN excitability. Therefore, to study mechanisms underlying the vulnerability differential between S- and F-MNs in ALS, we will develop high-fidelity computational models based on in-vitro animal data. These models will be used to examine the impact of differing SK channel expression levels between S- and F-MNs. While computational models are useful, their predictions are theories which require challenge and validation by experimental tools. Therefore, we will use immunohistochemistry and electrophysiology experiments to test model predictions in transgenic mice. The data from these experiments will be used to update the computational models, in an iterative cycle, to produce a “”next generation”” of computational models with even more accurate predictions. Resulting predictions will be used to plan additional experiments to rigorously test hypotheses on the contribution of SK channels to overall disease progression in S- vs. F-MNs.

Lay Summary
PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) is an incurable, fatal disease characterized by weakness and paralysis, culminating in respiratory failure and death 1-3 years after symptoms appear. This proposal focuses on examining the mechanisms that underlie the differential degeneration of motoneuron types in ALS. The premise is that motoneuron types have differences in their intrinsic properties that may contribute to the disease process.

Further information available at:

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Investments > €500k

Member States:
United States of America

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