Active zone loss cause dying back neuropathy in amyotrophic lateral sclerosis

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Contact information of lead PI
Country

USA

Title of project or programme

Active zone loss cause dying back neuropathy in amyotrophic lateral sclerosis

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NIH (NINDS)

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1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Neuromuscular Junction, Neuropathy, Amyotrophic Lateral Sclerosis, Denervation, Back

Research Abstract
DESCRIPTION (provided by applicant): The object of this proposal is to reveal the presynaptic defects of neuromuscular junctions (NMJs) and synapses between upper and lower motor

neurons (corticospinal synapses) prior to the onset of amyotrophic lateral sclerosis (ALS) and to test the causality of active zone loss in NMJ denervation. Motor neuron degeneration in patients and animal models is preceded by NMJ denervation, which suggests that ALS is a dying back neuropathy. The mechanisms of NMJ denervation and the reasons for the preferential death of motor neurons in ALS remain unknown; therefore, effective treatments for ALS are lacking. Thus, our long-term goal is to elucidate the molecular mechanisms underlying denervation in ALS to identify new therapeutic targets. Here, we hypothesize that denervation in ALS is caused by an impairment of presynaptic active zones. This hypothesis has been formulated on the basis of (1) patients showing reduced active zone size in synapses on lower motor neurons; (2) our data showing a loss of NMJ active zones in ALS mouse and rat models; (3) NMJ denervation observed in humans and mice exhibiting active zone loss; and (4) our studies showing NMJ active zone organization via interactions between an active zone-organizer, a receptor for the organizer (presynaptic voltage dependent calcium channels, VDCC), and active zone proteins. The uniqueness of this hypothesis is that the NMJ active zone loss and its putative causal role in denervation represent a novel concept in ALS research. The specific aims for testing this hypothesis are as follows: (1) analyze the integrity of active zones and presynaptic proteins in NMJs of ALS mouse model prior to disease onset and evaluate the expression level of the active zone organizers; (2) test the causality of active zone loss in NMJ denervation; and (3) analyze the integrity of active zones and presynaptic proteins in corticospinal synapses. In the first aim, NMJ structural and functional defects prior to disease onset will be elucidated. In the second aim, the causality of active zone loss in NMJ denervation will be tested by (a) our mouse model that has a reduced number of active zones and (b) by exercise that increases the life span of SOD1G93A mice. Electrophysiology will be used to detect the functional alteration of VDCCs due to the lack of active zone proteins. In the third aim, the presynaptic defects of corticospinal synapses will be investigated. The role of the newly identified active zone organizer will be tested in these synapses using knockout mice. The proposed research is innovative because it is based on a novel, untested concept, namely the relationship between active zone integrity and NMJ denervation, and is thus distinct from current ALS research approaches. The second innovative aspect is the testing of the role of new organizers, which are attenuated in the TDP-43- depleted mouse brain, in active zone organization at corticospinal synapses. The contribution will be significant because the project represents the first step toward revealing the mechanisms of one of the earliest ALS symptoms (denervation), and the results will aid in the identification of new therapeutic targets.

Lay Summary

The project is relevant for human health because the discovery of the molecular mechanisms of presymptomatic denervation in ALS will provide novel and mechanism-based target(s) to treat ALS patients. Thus, the proposed research is relevant to NINDS’s mission to support the development of fundamental knowledge that will help reduce the burden of neurological disease.

Further information available at:

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Investments > €500k

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United States of America

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