Enhanced respiratory plasticity in models of respiratory motor neuron death

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USA

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Enhanced respiratory plasticity in models of respiratory motor neuron death

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NIH (NINDS)

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2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Motor Neurons, neuron loss, Cholera Toxin, respiratory, Amyotrophic Lateral Sclerosis

Research Abstract

Project Summary/Abstract Candidate and Environment: The immediate and long-term goals of the candidate are to gain knowledge and experience necessary to become a successful

academic researcher with an independent laboratory focused on the neural control of breathing. UW-Madison has many world-renowned respiratory physiologists that meet weekly for a respiratory neurobiology seminar series and journal club series making it a unique research environment in which the candidate can thrive. Thus, remaining at UW-Madison [will enable the candidate to be mentored by top-notch researchers in neuroplasticity and respiratory neurobiology (one of very few places studying this combination) and attain the required knowledge and experience to transition to independence.] Research: ALS is a devastating disease leading to progressive motor neuron degeneration and compromised breathing which ultimately leads to death. Despite its fundamental importance, respiratory insufficiency has seldom been studied in any ALS model. Thus, strategies to preserve adequate ventilatory function are needed to preserve life. The fundamental goal of this proposal is to identify compensatory mechanisms that trigger enhanced respiratory plasticity (intermittent hypoxia induced phrenic long-term facilitation; pLTF). Enhanced plasticity may allow us to restore phrenic motor output in models of respiratory motor neuron death, thereby preserving ventilatory capacity. We propose to study pLTF in rat models of respiratory motor neuron death including the progressive disease encountered in a genetic model of ALS (SOD1G93A rats) and a stable, inducible model (cholera toxin B conjugated to saporin; CTB-SAP). We propose to use a multidisciplinary approach including: 1) inducing respiratory motor neuron death using CTB-SAP; 2) phrenic nerve recordings to directly assess motor output; 3) RNAi in vivo to assess cellular mechanisms of AIH-induced pLTF in CTB-SAP rats; and 4) immunohistochemical methods to determine phrenic motor neuron survival and their expression of key molecules. [Three] specific aims are proposed: 1) increased SOD1G93A expression triggers compensatory increases in NADPH oxidase expression, thereby preserving ROS levels sufficient to express pLTF; [2) induced respiratory motor neuron death enhances pLTF; and 3) induced respiratory motor neuron death enhances pLTF by a mechanism distinct from that in SOD1G93A rats.] Since most ALS patients develop respiratory insufficiency, leading to ventilator dependence or death, our long-range goal is to develop new strategies to delay respiratory motor neuron death and enhance the functional capacity of spared motor neurons. Here we will harness mechanisms that increase function of surviving motor neurons (AIH-induced plasticity). These novel strategies, if successful, may guide future, translational studies in patients suffering from respiratory motor neuron death, including ALS patients. The present studies may have wide reaching benefits for non-respiratory motor pools in ALS, and other neurodegenerative diseases.

Lay Summary
Project Narrative-Relevance ALS is a devastating disease, leading to paralysis and death from ventilatory failure. Our goal is to restore respiratory function in a rat ALS model (SOD1G93A rats) by inducing a known form of spinal respiratory plasticity. By inducing respiratory plasticity with intermittent hypoxia, we will enhance the contributions from spared motor neurons, thereby preserving ventilatory capacity. This project may lead to novel therapies to extend and improve life for ALS patients by preserving breathing; these approaches may also work in other neurological disorders.

Further information available at:

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Investments > €500k

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United States of America

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