Mechanisms of Central Synaptic Dysfunction in SMA

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Country

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Title of project or programme

Mechanisms of Central Synaptic Dysfunction in SMA

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,581,591.74

Start date of award

01/04/2012

Total duration of award in years

1

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, Motor Neurons, Synapses, Complement 1q, Functional disorder

Research Abstract
DESCRIPTION (provided by applicant): Spinal muscular atrophy (SMA) is an inherited neurodegenerative disease characterized by motor neuron loss and skeletal muscle atrophy. SMA is the most common genetic cause of death in infancy, but no effective treatment is

currently available. While much is known about the genetic causes of the disease, less information is available on the physiological alterations that explain the severity of motor symptoms displayed by affected individuals. Dysfunction of specific, vulnerable neuronal populations may precipitate secondary changes in neural circuits that could exacerbate neuronal dysfunction. In the spinal cord, motor neurons receive direct synaptic inputs from local interneurons, descending pathways from the brain, and sensory neurons. In a previous study we reported that the strength of monosynaptic connections between sensory primary afferents and motor neurons in SMA mice is greatly reduced early in the course of the disease, before substantial motor neuron cell loss can be detected. This loss of function is mediated in part by the loss of primary afferent boutons on motor neurons in SMA mice. The goals of this study is to identify which inputs or parts of the motor circuit are particularly affected by the disease and whether this is due to motor neuron dysfunction or intrinsic to SMN deficiency in these neuronal circuits. In Aim 1, we will analyze the functional effects of a neuronal population that makes direct synapses on the somata and dendrites of spinal motor neurons in SMA mice. In addition we will correlate functional and structural defects by mapping and quantifying the synaptic density on motor neurons in SMA mice. These studies will extend longitudinally to determine the time course of the defects in the course of the disease. In Aim 2, we will use novel mice taking advantage of the Cre-lox technology to study the effects of regulation of SMN protein in reversing the severe phenotype of the disease. We will employ behavioral, physiological and morphological assays to determine efficacy of these approaches. Laser capture microdissection will also be employed to isolate selected, disease-relevant neuronal types from control and SMA mice for RNA analysis. These will include motor neurons in the ventral horns of the lumbar spinal cord and several other neuronal and non-neuronal populations. In Aim 3, we will investigate mechanisms involved in synaptic loss in the motor circuits affected in SMA. We will employ immunohistochemical markers to identify the origin of the synapses affected at different stages of the disease by comparing SMA and wild type spinal cords. Collectively, these experiments have the potential to elucidate the importance of synaptic defects in the progression of the disease in SMA mice.

Lay Summary
SMA is an incurable motor neuron disease and the leading genetic cause of death in infancy. We will establish whether central synaptic defects are causally involved in the severe phenotype in a mouse model of SMA, employing behavioral, physiological and morphological assays. Different mechanisms of synaptic elimination will be investigated by utilizing novel transgenic mouse models and determine their potential beneficiary effects in reversing the SMA phenotype.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Spinal muscular atrophy (SMA)

Years:
2016

Database Categories:

N/A

Database Tags:
N/A