Cortical Pathophysiology in Mouse Models of Huntingtons Disease

https://www.neurodegenerationresearch.eu/survey/cortical-pathophysiology-in-mouse-models-of-huntingtons-disease/

Principal Investigators

LEVINE, MICHAEL S

Institution

UNIVERSITY OF CALIFORNIA LOS ANGELES

Contact information of lead PI
Country

USA

Title of project or programme

Cortical Pathophysiology in Mouse Models of Huntingtons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

491041.2844

Start date of award

15/07/2016

Total duration of award in years

1

Keywords
Research Abstract

? DESCRIPTION (provided by applicant): The fatal mutation in Huntington’s disease (HD) leads to an expanded glutamine repeat within the huntingtin protein which causes neuronal dysfunction typically followed by selective neurodegeneration especially within the striatum and cortex. These dysfunctions in neurons and circuits occur during the development of the disease phenotype, well before there is significant cell loss. Recent studies in animal models have emphasized that synaptic cell-cell interactions play a role in the pathophysiology of this disease. For example, removing mutant huntingtin from the cerebral cortex ameliorates some HD symptoms. The experiments in this application are designed to understand the functional

changes that occur in specific populations of cortical neurons during the progression of the HD phenotype and to uncover new targets and approaches for therapies. However, little is known about functional changes in cortical neurons, although these neurons also degenerate in HD. Before motor symptoms become apparent, sensory, cognitive and emotional disturbances occur and these seem to depend on aberrant communication in the cortex that probably involves thalamocortical pathways. These pathways have never been examined in HD. Our overarching hypothesis is that sensory and motor cortical areas are differentially and asynchronously affected during HD progression. We propose that sensory thalamocortical pathways are downregulated early leading to faulty integration and interpretation of sensory signals. In turn, the motor cortex becomes upregulated and disorganized, leading to altered corticostriatal communication and motor symptoms. In this grant proposal we will use state-of-the-art techniques in three different laboratories at UCLA. Aim 1 uses optogenetics and slice electrophysiology to examine mechanistically altered synaptic communication between thalamic sensory and motor nuclei and their corresponding cortical projection areas. Aim 2 uses high-density silicon microprobes to record firing of hundreds of neurons simultaneously in sensory and motor cortical areas as well as thalamic nuclei. Aim 3 uses genetically encoded calcium indicators to visualize neuronal activity in sensory and motor cortical areas. Together, the studies will provide new and important mechanistic insights into the understudied cortical dysfunction and will provide the basis for novel and rational treatments for HD by delineating more restricted targets spatially and temporally. These studies also will be relevant for understanding other CAG triplet repeat diseases and neurodegenerative disorders.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A