Creating new Drosophila models to study Tau loss and gain-off functions

https://neurodegenerationresearch.eu/survey/creating-new-drosophila-models-to-study-tau-loss-and-gain-off-functions/

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Country

USA

Title of project or programme

Creating new Drosophila models to study Tau loss and gain-off functions

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

388532.1101

Start date of award

01/03/2016

Total duration of award in years

2

Keywords

tau Proteins, gain of function, Drosophila genus, Tauopathies, Microtubules

Research Abstract
? DESCRIPTION (provided by applicant): The microtubule-associated protein Tau is a key component of the intracellular inclusions that are found in Alzheimer's disease (AD) and a variety of other neurodegenerative diseases, together referred to as Tauopathies. However, the mechanisms of pathology in these diseases are still unclear. A long standing debate is whether disease-associated changes in Tau are pathogenic because they induce a loss of its normal function, induce a novel toxic gain-of function, or a combination of both. In addition, the differet

disease- associated mutations and modifications of Tau may have different pathogenic mechanisms. Whereas gain-of functions have been investigated in several models, loss of functions have been less well studied and most of the studies addressing such functions have been done in vitro. Furthermore, the majority of gain-of function studies are based on expression system that cause overexpression or ectopic expression, which can cause phenotypes even with normal wild type Tau. To address the hypothesis that the mechanism of pathogenesis are due to combinations of loss-of and gain-of functions and that the degree of their contributions may vary in different Tauopathies, it is proposed to create novel Drosophila models that expressing human Tau instead of fly Tau. Due to their short generation time, the unique genetic means available in this model, and the small size of their brain which allows time lapse imaging of intact brains (to measure microtubule-associated axonal transport), Drosophila provides a uniquely suitable model to analyze these lines in a relatively short time frame. These studies will also take advantage of the recent characterization of flies lacking endogenous fly Tau (dTau), which show age-related neurodegeneration and various microtubules defects. These defined phenotypes will therefore allow an analysis to what degree a mutant Tau has lost its normal function. Creating flies carrying a disease-associated and a wild type form (or a copy of dTau) can be used to study gain-of function effects and the expression by the endogenous fly Tau promoter should prevent overexpression phenotypes. The results obtained in this exploratory proposal can then provide the basis to identify genetic and pharmacological means that interfere with the pathology or its consequences and they can be used to address specific pathogenic mechanisms in the mouse model. Public Heath Relevance: A roadblock in understanding and developing treatment strategies for Tauopathies is that the mechanisms of pathology are still unclear. Identifying loss-of functions versus gain-of functions of disease-associated Tau is critical to develop such treatment strategies. Whereas Tauopathies that are mainly caused by Tau gain-of functions could be ameliorated by reducing Tau, loss-of function phenotypes would be aggravated by such strategies. Similarly, treatment strategies based on stabilizing microtubules would be a promising approach in cases where a mutation causes a loss of the microtubule function but not in cases where they lead to a novel, microtubule independent, gain-of function.

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