NOVEL MECHANISMS OF NEURODEGENERATION IN HUMAN BRAIN UNCOVERED BY PATHOGENIC NEUROPEPTIDE MUTATIONS

https://neurodegenerationresearch.eu/survey/novel-mechanisms-of-neurodegeneration-in-human-brain-uncovered-by-pathogenic-neuropeptide-mutations/

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Title of project or programme

NOVEL MECHANISMS OF NEURODEGENERATION IN HUMAN BRAIN UNCOVERED BY PATHOGENIC NEUROPEPTIDE MUTATIONS

Source of funding information

Swedish Research Council

Total sum awarded (Euro)

€ 1,050,054

Start date of award

01-01-2014

Total duration of award in years

5

The project/programme is most relevant to:

Neurodegenerative disease in general

Keywords
Research Abstract

We focus on human neuropeptide mutations that CAUSE profound neurodegeneration in human brain (Bakalkin et al., 2010). Generalized pathological changes in patients carrying the mutations emphasize a fundamental role of neuropeptides in the brain, and propose that essential molecular mechanisms are affected. Mutations have been identified in the dynorphin opioid peptides that are also unique in their ability to produce excitatory pathogenic effects likely through a novel non-receptor voltage-dependent electric and Ca2+ signaling (manuscript in preparation). The mutations may enhance non-opioid pathogenic dynorphin activities, or cause neuronal dysfunction through elevated aggregation of prodynorphin protein in the endoplasmic reticulum (ER), ER stress and unfolded protein response (UPR). We are testing these hypotheses in cellular models and transgenic mice expressing human wild-type or mutant prodynorphin protein. We will define whether wt- and pathogenic mutant dynorphins disrupt synaptodendritic structure and induce neuronal death, and evaluate a potential of opioid and glutamate antagonists to protect against this damage. We will also examine whether wt- and pathogenic prodynorphin causes ER stress and UPR; and whether prodynorphin molecules are eliminated by the ER-Associated Protein Degradation. These mechanisms may selectively impair dynorphin neuronal networks in carriers of these mutations and also in addicted and depressed subjects with upregulated dynorphins.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
Sweden

Diseases:
Neurodegenerative disease in general

Years:
2016

Database Categories:
N/A

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