# The PPAR-delta pathway in neural function and Huntingtons disease neuropathology

https://neurodegenerationresearch.eu/survey/the-ppar-delta-pathway-in-neural-function-and-huntingtons-disease-neuropathology/

**Principal Investigators**

LA SPADA, ALBERT R

**Institution**

UNIVERSITY OF CALIFORNIA SAN DIEGO

**Contact information of lead PI**
**Country**

USA

**Title of project or programme**

The PPAR-delta pathway in neural function and Huntingtons disease neuropathology

**Source of funding information**

NIH (NINDS)

**Total sum awarded (Euro)**

€ 2,068,686.24

**Start date of award**

01/02/2010

**Total duration of award in years**

5

**The project/programme is most relevant to:**

Huntington's disease

**Keywords**

PPAR delta, Neurophysiology - biologic function, Peroxisome Proliferator-Activated Receptors, Huntington Disease, neuropathology

**Research Abstract**

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a relentlessly

progressive autosomal dominant neurodegenerative disorder characterized by involuntary movements and cognitive decline. HD results from a CAG trinucleotide repeat expansion in the coding region of the huntingtin (htt) gene, and pathogenesis stems from production of htt protein with an expanded polyglutamine tract. We found that the mitochondrial dysfunction and metabolic deficits in HD result from transcriptional dysregulation of peroxisome proliferator-activated receptor [PPAR] gamma coactivator-1 alpha (PGC-????To determine the basis for PGC ???transcription interference in HD, we performed an unbiased screen for htt-interacting protins, and identified PPARs as candidate interactors. When we evaluated the different PPARs, we documented a physical interaction between PPAR? and htt in the cortex of BAC-HD97 transgenic mice, and confirmed that PPAR? is highly expressed in neurons. Mutant htt repressed PPAR? transactivation in neurons from BAC-HD97 mice, but could be rescued by PPAR? agonist treatment or over-expression. These findings formed the basis for our initial R01 project where we proposed to determine the role of the PPAR?-PGC-1? pathway in HD pathogenesis, define the function of PPAR? in the CNS, and test if PPAR? agonist therapy might be a viable treatment paradigm for HD and related disorders. In the last funding cycle, we confirmed the importance of the PPAR?-PGC-1? pathway in HD by documenting that htt physically interacts with PPAR? and represses PPAR? transactivation function to yield mitochondrial dysfunction and neurotoxicity, and determined that transgenic mice expressing dominant-negative PPAR? in the striatum recapitulate HD-like phenotypes. Furthermore, we observed neurological disease phenotypes in mice expressing dominant-negative PPAR?, thereby identifying neurons as a cell type where PPAR? function is essential for homeostasis. Finally, we validated a selective and potent PPAR? agonist, KD3010, as capable of rescuing htt neurotoxicity, and performed a preclinical trial of KD3010 in HD mice, where we documented significant improvements in motor function, neurodegeneration, and survival. In this renewal proposal, we will determine how PPAR? promotes neuroprotection by examining the effects of PPAR? on bioenergetics function, autophagy, and mitochondrial quality control. We will determine how PPAR? counters htt neurotoxicity by defining the cistrome and active regulome of PPAR? in normal neurons and HD neurons, and we will seek the basis for PPAR? neuroprotection by transcriptome analysis of HD mice treated with PPAR? agonist to identify genes and pathways required for PPAR? neuroprotection. To evaluate the contribution of such genes and pathways to PPAR? neuroprotection, we will test if expression modulation of target genes is sufficient to produce rescue in BAC-HD and HD patient neurons, or is capable of preventing rescue by PPAR? agonists.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: In the last funding cycle, we set out to determine the role of the PPAR?-PGC-1? pathway in HD, to define the function of PPAR? in the CNS, and to test if PPAR? agonist therapy might be a viable treatment for HD and related disorders; we found that huntingtin (htt) protein physically interacts with PPAR? and represses PPAR? transactivation function to yield mitochondrial dysfunction and neurotoxicity, and determined that transgenic mice expressing dominant-negative PPAR? in the striatum recapitulate HD-like phenotypes. We observed neurological disease phenotypes in mice expressing dominant-negative PPAR?, thereby identifying neurons as a cell type where PPAR? function is essential for homeostasis, validated a selective and potent PPAR? agonist, KD3010, as capable of rescuing htt neurotoxicity, and documented significant improvements in motor function, neurodegeneration, and survival in HD mice treated with KD3010 agonist. In this renewal proposal, we will determine how PPAR? promotes neuroprotection by examining the effects of PPAR? on

bioenergetics function, autophagy, and mitochondrial quality control, by defining the cistrome and active regulome of PPAR? in normal neurons and HD neurons, by performing transcriptome analysis of HD mice treated with PPAR? agonist, and by validating identified PPAR? target genes and pathways in directed experiments in HD primary neurons cultured from BAC transgenic mice or derived from HD patient stem cells.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Huntington's disease

**Years:**
2016

**Database Categories:**
N/A

**Database Tags:**
N/A