# Hippocampal Synaptic Structure

https://neurodegenerationresearch.eu/survey/hippocampal-synaptic-structure/

**Principal Investigators**

LANDFIELD, PHILIP W.

**Institution**

UNIVERSITY OF KENTUCKY

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

USA

**Title of project or programme**

Hippocampal Synaptic Structure

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 2,362,697.25

**Start date of award**

01/01/1998

**Total duration of award in years**

27

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

Alzheimer's disease & other dementias

**Keywords**

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Behavioral and Social Science... Brain Disorders... Dementia... Endocrine System... Neurodegenerative... Neurosciences

**Research Abstract**
FK506-Binding Protein 12.6/1b (FKBP1b) stabilizes intracellular calcium release in heart cells but its role in brain neurons has been unknown. During the preceding phase of this project, we conducted systematic tests of our working hypothesis that an aging-related decline in FKBP1b

underlies many calcium-mediated aspects of unhealthy brain aging. These studies showed that reproducing the proposed pathogenic decline with FKBP1b knockdown in the hippocampus recapitulated the calcium dysregulation brain aging syndrome in young rats. Conversely, counteracting the aging-related hippocampal FKBP1b decline by using virally- mediated FKBP1b overexpression fully reversed calcium dysregulation and cognitive impairment in aged rats (Gant et al, 2011; 2014; 2015), thereby providing strong support for this novel hypothesis on the molecular basis of unhealthy brain aging. Subsequent long term studies using behavioral and gene expression assessment revealed that cognitive rescue was similarly effective after 7 months and after 2 months of FKBP1b overexpression. Further, cognitive aging changes and rescue by FKBP1b correlated with age related changes in calpain gene and protein expression and with cytoskeletal gene expression (Gant et al, in prep.). Based on these findings, we propose the following specific aims for the next phase of research: Aim 1. Corticosterone and vitamin D are steroid hormones that regulate calcium related biomarkers of hippocampal aging in opposite directions. Therefore, we will test the hypothesis that these two naturally occurring hormonal factors act on brain aging processes by modulating FKBP1b. Aim 2. Based on findings in the preceding phase, we will test the hypothesis that downstream negative effects of declining FKBP1b are mediated in part by the calpain pathway. Aim 3. We will use rodent models to test aspects of the intriguing hypothesis that aging related changes in hippocampal and entorhinal FKBP1b expression link normal brain aging to increased risk of Alzheimer’s disease.

**Lay Summary**
RELEVANCE (See instructions): The increasing aging population in the U.S. (20% of the population will be >65 years of age by the year 2030) often has cognitive decline, that can significantly affect quality of life and profoundly add to health care burden. Our results indicate that a specific pathway (FKBP-Ca2+) plays a critical role in brain aging and cognitive decline; thus the goal of this project is to use gene therapy techniques to determine whether such interventions can prevent or slow the onset of age-related brain decline. The outcomes may have substantial

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Alzheimer's disease & other dementias

**Years:**
2016

**Database Categories:**
N/A

**Database Tags:**
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