# APP/APLP1/APLP2 in the brain

https://neurodegenerationresearch.eu/survey/app-aplp1-aplp2-in-the-brain/

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**Country**

USA

**Title of project or programme**

APP/APLP1/APLP2 in the brain

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 2,040,787.16

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15/12/2001

**Total duration of award in years**

2

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

Alzheimer's disease & other dementias

**Keywords**

Amyloid beta-Protein Precursor, Protein Family, Brain, presenilin, Cerebral cortex

**Research Abstract**

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common cause of dementia, and is characterized neuropathologically by the loss of synapses and neurons as well as the presence of amyloid plaques and neurofibrillary tangles. Mutations in the amyloid precursor protein (APP) and presenilins (PS) have been linked to familial forms of AD. ß-Amyloid peptides, major components of amyloid plaques, are derived from proteolytic

processing of APP. Despite the importance of APP in AD pathogenesis, its normal physiological role in the brain remains unclear due to the presence of APP functional homologues, APLP1 and APLP2, which likely compensate functionally for the loss of APP in APP single germline knockout (KO) mice, and to the broad expression pattern of these proteins. Although single, double and triple APP/APLP1/APLP2 KO mice have been generated, the pleiotropic phenotypes exhibited by APP single KO mice and the early lethality and neurodevelopmental phenotypes associated with double (APP/APLP2, APLP1/APLP2) and triple KO mice made it difficult to ascertain the normal physiological role of APP family in mature neurons and synapses. Although impaired synaptic function is widely thought to play a causal role in the pathogenesis of AD, the synaptic function of APP family remains to be elucidated. Therefore, it is of central importance to create cell type-specific APP/APLP1/APLP2 conditional KO (cKO) mice lacking one, two or all three APP family members specifically in mature neurons and synapses in order to uncover their normal functions in the adult brain. In the current application, we propose three Specific Aims to test our hypothesis that APP plays essential roles in mature neurons and synapses of the adult cerebral cortex. In order to uncover fully its normal function, we will need to generate cell type-specific conditional null mutants lacking all APP family members to avoid functional redundancy among APP, APLP1 and APLP2, and to circumvent perinatal lethality of triple germline KO mice. Thus, we will develop postnatal forebrain-restricted APP/APLP1/APLP2 single, double and triple cKO mice and characterize these mice molecularly with Southern, PCR followed by sequencing, Northern, Western, in situ hybridization and immunohistochemical analyses (Aim 1). We will then perform histological, behavioral and electrophysiological analyses to define the role of APP family in the adult cerebral cortex (Aim 2). We will further dissect the role of APP family in the synapse by generation and analysis of hippocampal CA1- and CA3-restricted APP/APLP1/APLP2 single, double and triple cKO mice to dissect their presynaptic and postsynaptic roles (Aim 3). Completion of the proposed study will provide the much-needed insight into APP biology and may shed light into the pathogenesis of Alzheimer’s disease.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is the most common neurodegenerative disorder, and mutations in the amyloid precursor protein (APP) and the presenilins are linked to inherited forms of the disease. Our previous genetic studies elucidated the roles of presenilins in the developing and adult brain; however, the normal physiological role of APP remained elusive due to genetic redundancies and the lack of appropriate conditional mutant mice. We propose to uncover normal physiological roles of APP in mature neurons and synapses through the generation of cell type-specific conditional null mutant mice lacking all three members of the APP family.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

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

**Years:**

2016

**Database Categories:**
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