PKR and danger molecules in Alzheimer's disease

Principal Investigators

HUGON Jacques

Institution

Biocanvas Paris

Contact information of lead PI
Country

France

Title of project or programme

PKR and "danger molecules" in Alzheimer's disease

Source of funding information

ANR

Total sum awarded (Euro)

€ 787,910

Start date of award

01/01/2013

Total duration of award in years

4.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract
Alzheimer's disease (AD) is a neurodegenerative disease leading to cognitive deficits which is becoming a major public health issue because of population aging and the lack of effective treatment. Neuropathological lesions include senile plaques made of accumulated ß-amyloid (Aß) peptide, neurofibrillary tangles containing hyperphosphorylated tau protein, and synaptic and neuronal losses. The amyloid cascade hypothesis implies that the Aß peptide is neurotoxic

and could be responsible for neuronal degeneration in AD brains. Formation of the Aß peptide results from the cleavage of the amyloid precursor protein (APP) at specific sites. The enzymes involved are the ß-site APP-cleaving enzyme 1 (BACE1) and ?-secretases. BACE1 levels are increased in the brains of AD patients, providing a possible explanation for Aß accumulation. PKR (double stranded RNA-dependent protein kinase) is a pro-apoptotic, neurotoxic and pro-inflammatory kinase initially identified in the context of antiviral responses. It blocks protein synthesis by phosphorylating eukaryotic initiation factor 2a (eIF2a). We have discovered that PKR is activated in degenerating neurons of AD brains and in response to Aß in cells in culture. In addition, we have shown that PKR can contol tau phosphorylation and the levels of BACE1.PKR can thus exert multiple neurotoxic effects. PKR activation can be triggered by a number of metabolic or inflammatory stresses that are known to favor the occurrence of AD. Danger molecules (like S100a8,S100a9 or biglycan) are released by activated macrophages or lesioned tissues and can activate innate immunity and PKR. We propose that PKR activation and danger molcules may contribute significantly to the pathogenesis of AD by amplifying the production of Aß and initiating and/or potentiating neurotoxic events. Thus activated PKR may be a useful early biomarker of the disease as well as a promising novel therapeutic target. The general aim of this project is to test these hypotheses and assess the role of PKR in AD. The proposed tasks are to: – Determine if the neurotixicity of PKR in cultures can be mediated by danger molecules released by activated microglial cells . – Examine whether deficit in PKR slows down the evolution of toxic and genetic mouse models of AD using neuropathological and cognitive/behavioral readouts. Evaluate the interest of PKR and danger molecules as early biomarkers in MCI od AD

patients. This project will be carried out in 4 laboratories each with an established expertise in complementary fields. It combines clinical and basic research, including in vitro experiments in neurons in culture, experiments in several genetic mouse

models, and study of human brain samples and of blood and cerebrospinal fluid (CSF) samples from AD and MCI (mild cognitive impairment) patients and controls. The expected output is a better understanding of AD pathogenesis, an evaluation of potential novel early biomarkers, and the possible identification of a novel target for pharmacological treatment of AD.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
France

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A