The 5-HT4 receptor networks: bodyguards of ADAM10 and APP trafficking

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Country

France

Title of project or programme

The 5-HT4 receptor networks: bodyguards of ADAM10 and APP trafficking

Source of funding information

ANR

Total sum awarded (Euro)

€ 405,100

Start date of award

01/03/2013

Total duration of award in years

4

Keywords
Research Abstract
Bodygards to protect against Alzheimer’s disease
This project aims to identify proteins that will protect the actors involved in Alzheimer’s disease pathogenesis. By controlling the cellular trip of theses VIP, bodyguards will impair senile plaque formation.
Reduce toxic amyloid peptide production
Alzheimer’s disease (AD) is the most common form of dementia affecting 35 million individuals worldwide and over 800 000 in France.
During the course of this pathology, disequilibrium arises that induces Aß peptide over-

production by the cells, and in particular by neurons. The accumulation of this peptide is toxic for the cells and leads to the formation of amyloid plaques and neurodegeneration.
We demonstrated that the presence of a serotonin receptor at the cell membrane promotes the reduction of amyloid peptide production. This bodyguard and partners modify the traffic of the amyloid protein precursor and of the alpha-secretase ADAM10 inside the cell.
This project will identify the protein partners of the serotonin receptor and explain how they control the intracellular trip of the actors involved in Alzheimer's disease pathogenesis.
The final objective is to propose innovative strategies aiming to reduce amyloid peptide production in order to slow down, or maybe to stop, the progression of Alzheimer's disease.
Mass spectrometry and functional characterisation of protein partners
The characterization of the protein networks associated with the serotonin type 4 receptor and ADAM10 is carried out by mass spectrometry. This technology enables to accurately determine the protein composition of a biologic sample. This unbiased approach provides an exhaustive list of network partners, within which we focus our attention on the proteins likely having a role in intracellular trafficking. We over-express or suppress these relevant proteins in the cells to analyse the impact on amyloid peptide production. Then, we try to decipher the action mechanisms of the more efficient candidates and to propose innovative strategies that may have an application in vivo. Finally, our hypotheses are validated with the help of transgenic animal models of Alzheimer's disease.
Moreover, in cellular models and in vivo, we study the effect of the serotonin receptor activation by chemicals, drug candidates.

Further information available at:

Types:
Investments < €500k

Member States:
France

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A