Role of the purinergic receptor P2X7 in Alzheimer’s disease

https://neurodegenerationresearch.eu/survey/role-of-the-purinergic-receptor-p2x7-in-alzheimer%c2%92s-disease/

Principal Investigators

FONTAINE Bertrand

Institution

ICM Paris

Contact information of lead PI
Country

France

Title of project or programme

Role of the purinergic receptor P2X7 in Alzheimer’s disease

Source of funding information

ANR

Total sum awarded (Euro)

€ 533,261

Start date of award

01/02/2013

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 the most common form of dementia, with an increasing prevalence due to an aging population. AD is a fatal brain disease and currentlyly, there is no cure or treatment which delays or stops the progression of AD. This neurodegenerative disease is characterized by two main lesions: senile plaques and neurofibrillary tangles. The exact processes that cause the disease are still poorly understood. Senile plaques are composed of

extracellular aggregates of amyloid ß (Aß) peptides and might act as an essential trigger in the disease to initiate a cascade of lesions leading to clinical dementia (Gandy 2005). The Aß peptides are generated by the sequential cleavage of the amyloid precursor protein (APP) by ß and gamma secretases (amyloidogenic pathway). We have recently demonstrated that the purinergic receptor P2X7 (P2X7R), an ATP-gated cationic channel, is involved in the non-amyloidogenic processing of APP (Delarasse, Auger et al. 2011). In this pathway, an a secretase cleaves APP within the Aß peptide sequence, precluding the formation of neurotoxic Aß peptides, and produces a soluble fragment, sAPPa, endowed with neurotrophic and neuroprotective properties (Mattson 1997). P2X7R is upregulated in activated microglia and astrocytes around senile plaques in animal models of AD and in patients with AD (Parvathenani, Tertyshnikova et al. 2003; McLarnon, Ryu et al. 2006). In addition, P2X7R plays a role in the non-cytolytic release of inflammatory cytokines, such as IL-1ß, IL-6 and TNF-a from activated macrophages and microglia (Ferrari, Pizzirani et al. 2006). Notably, P2X7R is involved in Aß-triggered release of IL-1ß from microglia cells (Rampe, Wang et al. 2004; Sanz, Chiozzi et al. 2009). These pleiotropic actions of P2X7R lead us to hypothesize that P2X7R stimulation may have a dual effect in AD depending upon the stage of the disease. P2X7R could first sense ATP as a danger signal and in response trigger the non amyloidogenic pathway which is neuroprotective. Then, at more advanced stages of the disease, overactivated microglial cells might release excessive pro-inflammatory cytokines.
To test our hypothesis, we will 1) determine the effects of inhibiting this receptor in a mouse model of AD using two different but complementary strategies by a pharmacological strategy and a total or cell specific gene invalidation, 2) use multidisciplinary and transversal approaches such as behavioural analysis, immune cell profiling, histological and biochemical experiments to evaluate the impact of a lack of P2X7Rfunction in a mouse transgenic model of AD and 3) evaluate P2X7R pathway implication in AD genetic susceptibility. If some gene interactions within the P2X7R pathway are highlighted, it would reinforce the hypothesis of the implication of P2X7R and its partners in AD.
In summary, the goal of this project is to evaluate the role of P2X7R in AD, in vivo, using animal model of the disease and in AD patients by determining its implication in AD genetic susceptibility. In term of translational research, we will explore the role of inflammation and of the non-amyloidogenic pathway in disease progression because identification of key components in these pathways may pave the way to develop alternative therapeutic strategies to treat AD (Bandyopadhyay, Goldstein et al. 2007; El Khoury and Luster 2008; Endres and Fahrenholz 2010). It is our assumption that P2X7R, through its role in both inflammation and non-amyloidogenic pathways, is a newly-identified potential target for AD treatment.

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