ß-amyloid induces mGluR5 and calcium signaling dysregulation in cultured astrocytes

BIOLOGIE & SANTÉ 2011

AstroConAqua Real time molecular imaging of aquaporins and connexins in astrocytes interaction and water regulation

Neurosciences, neurologie et psychiatrie NEURO 2007

Christian Giaume (Coordinateur, CIRB Collége de France)
Jacob Kowalewski, Edwige Amigou
Antoine Triller (Partenaire, IBENS, ENS)
Amulya Nidhi Shrivastava, Marianne Renner

Context and objectives

Following recent publications from the laboratories of Dr C. Giaume (1) and Dr A. Trilller (2) we have investigated initial mechanisms of β-amyloid-oligomers (Aβo) binding on to the plasma membrane of cultured astrocytes. Then, we have studied the consequence of this binding on the membrane dynamics of metabotropic glutamate receptor 5 (mGluR5) using single particle tracking (SPT), quantitative immunofluorescence imaging and Ca^{2+} imaging. The Aβo (biotin-labelled and Alexa-555-labelled) used in these experiments were generated and provided in collaboration with Dr. Ronald Melki (LEBS, UPR 3082 CNRS, Gif-sur-Yvette).

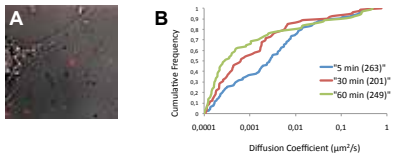
The objectives of this work were: i/ to determine how Aβo bind to astroglial membrane and interact with mGluR5, ii/ to investigate the role of Aβo/mGluR5 interaction in initiation of dys-regulation of astrocytes calcium signaling .

Introduction

As other neurodegenerative pathologies, Alzheimer's disease is characterized by a reactive gliosis that is associated to important phenotypic changes of astrocytes (3). The role played by such reactive astrocytes in the alterations of synaptic function (4) and in neuronal toxicity (5) associated with Aβ plaques has only started to be considered. Indeed, although the pathologic potential of astrocytes in dementia was initially suggested in 1910 by Alois Alzheimer (6), until now the exact role of astrocytes in AD is not well understood. Such reactive astrocytes are found close to neuritic plaques, even just at the outer edge of Aβ plaques (7,8) with processes infiltrating the core of the plaques.
Here, we report the effect of Aβo in two important properties of astrocytes, the dynamics of metabotropic glutamate receptor expression at the membrane and intracellular calcium oscillations.

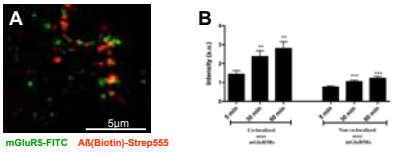
Results

1/ Aβ-oligomers bind rapidly onto the surface of astrocytes



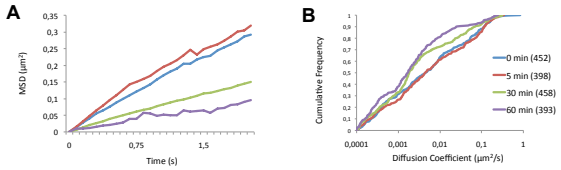
Aβ-oligomers bind to the surface of astrocytes (A) within minutes. SPT data shows a decreased mobility of bound oligomers over time (B).

2/ Aβ-oligomers are highly co-localized with mGluR5 clusters



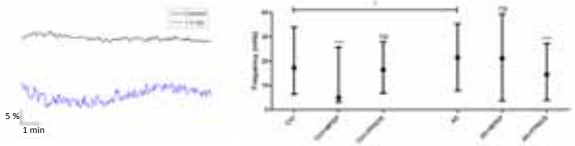
mGluR5 forms clusters that co-localize with Aβ-oligomers on the astrocyte surface (A). These clusters become more intense over time (B).

3/ Aβ-oligomers reduce mobility of mGluR5



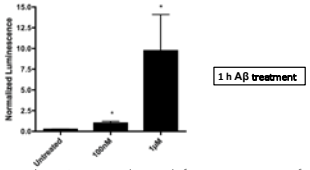
Following treatment by Aβ-oligomers diffusion of mGluR5 becomes highly confined (A). In parallel its diffusion coefficient is reduced (B).

4/ Aβ-oligomers alter calcium oscillations in astrocytes



Calcium oscillation frequency increases following Aβ-oligomer treatment (1 h, 100 nM). This frequency alternation was not abolished by the mGluR5 antagonist MPEP. ATP binding purinergic P2 receptor antagonists PPADS and MRS abolish the change in frequency indicating a possible ATP dependence.

5/ Aβ-oligomers induce immediate release of ATP



ATP release assay shows that ATP is released from astrocytes following Aβ-oligomer treatment in a concentration dependent manner.

Conclusions and perspectives

Altogether these results indicate that Aβ-oligomers bind rapidly into the cell surface of astrocytes and are slowed down over time. Interestingly, these oligomers are highly co-localizes with mGluR5 clusters. Aβ-treatment results in a decrease of mGluR5 mobility and triggers an imbalance in Ca^{2+}-oscillations in astrocytes. However, these changes in intracellular calcium signaling are not due to mGlu5Rs, but involve purinergic P2 receptors.
In order to understand the mechanisms underlying the partnership between mGluR5 and Aß-oligomers in astrocytes several points remain to be addressed such as: i/ to define the receptor type and the signaling pathway involved in the P2 receptor-induced decrease in Ca^{2+}-hyperactivity, ii/ to determine whether ATP is released during these treatments, and iii/ to investigate the recruitment of P2X and/or P2Y1 receptors in mGluR5/Aβ-clusters. Answering to these should contribute to identify the phenotypic changes occurring in reactive astrocytes at amyloid plaques and determine their contribution to neuronal damages.

(1) Orellana JA et al. (2011) J Neurosci. 31:4962-77. (2) Renner M et al. (2011). Neuron. 66:739-54. (3) Heneka MT et al. (2010 Brain Res Rev. 63:189-211. (4) Kuchibhotla,K.V.et al. (2008) Neuron 59: 214-225. (5) Meyer-Luehmann, M. et al. (2008) Nature 451: 720-724. (6) Alzheimer A. , Histologische und Histopathologische Arbeiten .....: Verlag von Gustav Fischer (1910) pp. 401–562. (7) Nagele, J.et al. (2004). Neurobiol Aging 25. 663-674. (8) Wisniewski, HM. & Wegiel, J. (1991) Neurobiol Aging 12: 593-600.

CONTACT :
christian.giaume@college-de-france.fr