UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2023-2024

Laboratory/Institute: Grenoble Institut des Neurosciences - GIN **Director:** E. Barbier
Team: Neuropathologies et Dysfonctionnements synaptiques **Head of the team:** Alain Buisson

Name and status of the scientist in charge of the project: Fabien Lanté **HDR: yes**
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Program of the Master's degree in Biology: Neurosciences and Neurobiology

Title of the project:

How Alzheimer disease Amyloid-β peptide (Aβ) modulates the K+/Cl- cotransporter (KCC2) expression and function in hippocampal glutamatergic neurotransmission

Objectives (up to 3 lines):

The aim of the project will be to study the link between changes in KCC2 expression and alterations in glutamatergic transmission, loss of density and morphological changes of dendritic spines induced by Aβ

Abstract (up to 10 lines):

KCC2 does not appear to be specific to GABAergic synapses; it can also be found at dendritic spines, close to glutamate receptors. The role of KCC2 in the function of excitatory synapses was demonstrated by reducing expression of the transporter using RNA interference. Under these experimental conditions, it has been revealed a decrease in the expression of AMPA receptors containing the GluR1 subunit, as well as an alteration in the plasticity potential of glutamatergic synapses. These disturbances in glutamatergic signaling are also associated with a reduction in the activity of cofilin, a protein capable of destabilizing actin filaments. Loss of cofilin activity leads to increased polymerization of the actin cytoskeleton at the postsynaptic level, and an increase in the diameter of dendritic spine heads. Recently we observed a reduction in KCC2 expression within the hippocampus of Alzheimer's disease mouse model and after perfusion of Aβ on hippocampal slices. We will investigate whether the reduction in KCC2 expression induced by Aβ modifies cofilin activity and disrupt glutamatergic neurotransmission through a perturbation of actin cytoskeleton.

Methods (up to 3 lines):

Western Blot and immune fluorescence will be used to assess KCC2 expression, cofilin phosphorylation and actin dynamics. We will use different electrophysiological techniques to measure glutamatergic transmission as well as synaptic plasticity phenomenon (Long term potentiation) in the hippocampus. Experiments will be performed on primary cultures of hippocampal neurons and hippocampal slices.

Up to 3 relevant publications of the team:

Rolland M et al; Effect of Aβ oligomers on neuronal APP triggers a vicious cycle leading to the propagation of synaptic plasticity alterations to healthy neurons. Journal of Neuroscience 2020 Jul 1;40(27):5161-5176.

Rush T et al; Synaptotoxicity in alzheimer's disease involved a dysregulation of actin cytoskeleton

dynamics through cofilin 1 phosphorylation. Journal of Neuroscience 2018 38:10349–10361.

Frandemiche ML et al ; Activity-dependent tau protein translocation to excitatory synapse is disrupted by exposure to amyloid-beta oligomers. J Neuroscience. 2014 Apr 23;34(17):6084-97

Requested domains of expertise (up to 5 keywords):

Electrophysiology, Confocal microscopy, Molecular Biology, Immunofluorescence.