CBH Graduate School
Université Grenoble Alpes

Involvement of the astrocytic TRPA1 channel in the pathogenesis of Alzheimer's disease

PhD supervisor: Mireille Albrieux (mireille.albrieux@univ-grenoble-alpes.fr)

Host laboratory: Grenoble Institut Neurosvciences - Team Neuropathology and Synaptic Dysfunction - Chemin Fortuné Ferrini - 38700 La Tronche

The sequential progression of cellular dysfunctions in preclinical Alzheimer's disease must be elucidated to develop new therapeutic routes. Hippocampal neuronal hyperactivity is one of the earliest events occurring during the preclinical stages of Alzheimer's disease in both humans and mouse models. The most acknowledged hypothesis describes amyloid β accumulation as the triggering factor of the disease but the effects of such accumulation and the cascade of events leading to cognitive decline remain undetermined. In mice, we previously showed that amyloid β-dependent activation of TRPA1 channel (transient receptor potential ankyrin 1 channel) triggers hippocampal astrocyte hyperactivity, subsequently inducing hyperactivity in nearby neurons. We confirmed in a transgenic mouse model of Alzheimer's disease that the aberrant hippocampal astrocyte activity is the first observable disruptions in the hippocampus and that it triggers pyramidal neuron hyperactivity at the onset of the amyloid pathology. Targeting TRPA1, we then investigated the potential protection induced by an early chronic pharmacological inhibition the TRPA1 channel on Alzheimer's disease progression. We showed that TRPA1 blockade normalizes the astrocytic calcium activity, prevents neuronal dysfunction, preserves structural synaptic integrity and strengthens the glial plaque barrier. Interestingly, these protective effects preserved spatial working-memory in this Alzheimer's disease mouse model (Paumier et al., Brain, 2022).

TRPA1 channel is also expressed in glial cells of the enteric nervous system. Like astrocytes in the brain, these glial cells participate in the maintenance of the homeostasis of the intestinal tissue. The Aβ peptide can accumulate in the intestine and constitutes an aggravating factor of the neurodegeneration. Glial cells could participate in the Aβ clearance and this function could be regulated by the TRPA1 channel. The toxic effect of Aβ on astrocytes/glial cells triggered by TRPA1 channel activation seems thus to be crucial in Alzheimer's disease progression. TRPA1 blockade prevent irreversible neuronal dysfunction, confirming this channel as a potential therapeutic target to promote early neuroprotection.

In order to fully validate TRPA1 as a therapeutic target, it is still needed to decipher the molecular mechanisms of TRPA1 activation by Aβ and subsequent processes leading to neuronal hyperactivity. The purpose is to better understand the establishment of early toxicity of the Aβ peptide and to allow an optimization of future therapeutic strategies.

The objective of this project is therefore to understand how the Aβ peptide activates the TRPA1 channel, whether it interacts with the channel directly or indirectly and how we can modulate or prevent this activation to block deleterious cascade of events leading to pathogenesis. In parallel, we will characterize the mechanisms linking astrocytic TRPA1 activation to neuronal hyperactivity by studying, in particular, the gliotransmitter release and re-uptake. We will also study the role of TRPA1 in the clearance and elimination of toxic forms of Aβ in the brain but also in the intestine.

Main methodology:

- Heterologous expression and functional characterization of ion channels in Xenopus oocyte
- Electrophysiology and calcium imaging on acute mouse brain slices
- Cryo-electronic microscopy

- Animal experimentation
- Immunohistochemistry
- Molecular biology
- Biochemistry

Relevant publications:

- Paumier A., Boisseau S., Jacquier-Sarlin M., Pernet-Gallay K., Buisson A. and Albrieux M. (2022). Astrocyte-neuron interplay is critical for Alzheimer's disease pathogenesis and is rescued by TRPA1 channel blockade. *Brain* 145 (1).

- Bosson, A., Paumier, A., Boisseau, S., Jacquier-Sarlin, M., Buisson, A.and Albrieux, M. (2017). TRPA1 channels promote astrocytic Ca2+ hyperactivity and synaptic dysfunction mediated by oligomeric forms of amyloid-β peptide. *Molecular Neurodegeneration* 12 (1) : 53.

- García-Fernández MD, Chatelain FC, Nury H, Moroni A, Moreau CJ. (2021) Distinct classes of potassium channels fused to GPCRs as electrical signaling biosensors. *Cell Reports Methods*. Ahead of print.

- Lemel L, Nieścierowicz K, García-Fernández MD, Darré L, Durroux T, Busnelli M, Pezet M, Rébeillé F, Jouhet J, Mouillac B, Domene C, Chini B, Cherezov V, Moreau CJ. (2021) The ligand-bound state of a G protein-coupled receptor stabilizes the interaction of functional cholesterol molecules. *J. Lipid Res*. 62:100059.