

We saw in the previous optogenetic experiment about 25% increase in the hippocampal interstitial fluid of A β ₄₂ level immediately following acute opsin light activation of the LEC. In this experiment which is a follow-up experiment, we want to show that tauopathy in the brain is aggravated by increased accumulation of APP fragments leading to an increase phosphorylation of tau and increased induction of neurofibrillary tangles (NFTs). Mature tau pathology in turn spreads and could aggravate A β -associated neuronal dysfunction and aberrant signaling, leading to a harmful feedback loop.

Aim

In optogenetically induced mice, assess the relationship between amyloid-beta accumulation and tau pathology and its propagation along neuronal circuits, in ISF and CSF.

For the research, we will use the Tg EC-Tau/hAPP mice, which overexpress a mutant amyloid precursor protein (hAPP) and entorhinal cortex (EC) tau pathology in the brain.

Initially we will have two groups of mice, one group injected with AAV-SSFO and the other group with AAV-EYFP (for details see last week experiment), these mice will be at least 9 months old. After some period of time following the injection, we will follow the same protocol used in last week experiment:

- Acute optogenetic stimulation of the LEC

We will optically stimulate neurons in the LEC for 2s every minute for 4 hr for 24 hours. ISF samples will be then collected and tau concentration will be measured using tau microdialysis [1]. In addition, we will sample CSF to measure CSF A β with A β microdialysis and CSF tau concentration using tau microdialysis technique. We will then measure relative ISF and CSF A β and tau levels every hour, starting 2 hours before the optical stimulation up to 4 hours after stimulation. These measurements will allow to investigate how ISF and CSF A β and tau levels are related by plotting % ISF and CSF levels every hour. First, to assess the robustness of our experiments, we will verify previous studies establishing ISF tau is 10-fold higher concentrated in brain interstitial fluid than in CSF, and how these concentrations change over time [1][2]. Then we will analyze potential correlations between ISF and CSF A β , ISF and CSF tau, ISF A β and tau, ISF A β and CSF tau, CSF A β and tau. We will repeat the same experiments with younger mice and draw conclusions which will show that A β and tau pathologies are age-dependent but also, we will study how they change comparatively with age.

Hippocampal and brain extracts will be collected so:

- We will perform Immunohistochemistry and morphometric analyses of A β depositions and quantification of A β burden
- And fractions of brain extracts will be used to be able to visual bands of tau and quantify tau aggregates

- Chronic optogenetic stimulation

Instead of applying an acute optical stimulation, we will stimulate the LEC of older mice once for 2 every 24 Hr for at least 5 months and we will run the same analyses detailed above.

We will use ECrtgTau mice for which tau propagation along the hippocampal perforant pathway from transgene-expressing neurons in the dentate gyrus (DG) has been previously observed in aged ECrtgTau mice.