University of Fribourg / Faculty of Science and Medicine / Department of Biology

Sleep, learning, and memory in *Drosophila melanogaster*

Ana Margarita Humbert Camps

Sleep, learning, and memory are interconnected processes regulated by dopamine, which are impaired by neurodegenerative disorders such as Alzheimer's disease. We used *Drosophila melanogaster* to study the molecular, genetic, and neuronal mechanisms of this complex network.

We established a fruit fly model of early-stage of Alzheimer's disease by expressing neurotoxic Amyloid-β (Aβ) peptides exclusively in the mushroom body, a brain region regulating sleep as well as associative olfactory learning and memory. We found an age-dependent disease progression (where young flies showed an increased rate of forgetting, and old flies had impaired memory) that was affected by the epilepsy drug Levetiracetam, neuronal excitability, and sleep. We also implemented a 2-photon live imaging protocol combined with a genetically encoded calcium indicator to study neuronal hyperactivity in the mushroom body. Taken together, our observations point to a mechanism linking Aβ to memory, forgetting, sleep, and neuronal excitability, and support the use of our model to study this relationship and to test potential pharmaceutical reagents in Alzheimer's disease.

Sleep deprivation has been shown to impair memory consolidation and cause the intraneuronal accumulation of Aβ peptides. We identified new sleep-regulating genes by using targeted DamID to profile gene expression after sleep deprivation in the mushroom body and then carrying out an RNAi knockdown sleep screen for the candidate genes identified by DamID. This study identifies sleep-regulated genes within a center that is a key regulator of complex behavior and sensory processing, offering a valuable starting point for future investigations. This approach provides a method for cell-type specific analysis of genes regulated by sleep loss in *Drosophila*.

In *Drosophila*, the action of dopamine is mediated by four receptors. We created specific antibodies for each dopamine receptor as well as transgenic conditional knockout lines for three of them. With these tools, we studied their localization and their individual roles in learning and memory. This work sheds some light on the mechanisms of a crucial neuromodulator involved in several essential brain processes, and the tools created can be used in many future studies.

Jury:

- **Prof. Simon Sprecher**, Thesis supervisor, University of Fribourg, Switzerland
- **Prof. Emi Nagoshi**, Co-examiner, University of Geneva, Switzerland
- **Dr. Boris Egger**, Co-examiner, University of Fribourg, Switzerland
- **Prof. Dominique Glauser**, President of the thesis committee, University of Fribourg, Switzerland