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Genetic, molecular and neuronal basis of memory in *Drosophila melanogaster*

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In this PhD thesis, different aspects of learning and memory were investigated. How animals acquire information about the environment and encode it in memories is a central question of neuroscience. The fruit fly *Drosophila melanogaster* is able to form olfactory memories, in which odors are associated with reinforcing stimuli, such as electric shock or food reward. Flies display the learned association as a selective approach or avoidance of the reinforced odor. Several different memory phases have been described, including long-term memory (LTM) that persists for several days. The ability to form memories, the enormous repertoire of genetic tools, and knowledge about the neuronal circuit make *Drosophila* a great model system to study the genetic, molecular, and neuronal mechanism of learning and memory.

In a first project (chapter 2), a transcriptomic approach was used to identify genes that regulate LTM. We profiled gene expression changes in the mushroom body (MB), a key brain area for olfactory learning, at distinct time intervals after training. This experiment revealed the transcriptional program during different phases of memory formation and maintenance. Moreover, 33 candidate genes were selected and tested for aberrant memory using RNAi knockdown. We identified 10 genes that showed decreased or increased LTM performance when inhibited in the MB. Two genes, *hacd1* and *vajk-1*, were characterized in more detail. Our results suggest that *hacd1* functions as negative regulator of LTM, while *vajk-1* is involved in the learning process.

In chapter 3, we investigated the transcription factor CrebB, which has a central role in LTM. We used CRISPR/Cas9, a powerful technique for specific genome editing, to create a *CrebB* conditional knockout allele. This generated fly line allows temporally controlled deletion of *CrebB* in specific cell types. At first, we validated the efficiency of the *CrebB* conditional knockout line with antibody staining and confirmed that CrebB is required for long-term, but dispensable for short-term memory. Next, we induced CrebB knockout in the MB, in a subset of MB output neurons (MBONs) and dopaminergic MB input neurons. Our results indicate that LTM formation requires CrebB in the MB and in MBON α3, but not in MB afferent dopamine neurons. The MB can be subdivided into three distinct anatomical classes called α/β, α′/β′ and γ neurons. Our findings suggest that LTM depends on activity of CrebB in MB α/β and MB α'/β' neurons.

Finally in chapter 4, we present a predictive plasticity rule as an alternative to Hebbian or correlation-based synaptic plasticity. Various olfactory conditioning experiments were designed and performed to test the predictive learning model and to compare it with other learning models. The simple predictive learning model could reproduce our behavioral experiments along with published trace conditioning experiments using identical parameter values. Furthermore, predictive plasticity was implemented in the MB circuit, in which dopamine neurons signal the prediction error and induce plasticity of the synapses to the MBONs. We propose that olfactory learning in *Drosophila* relies on predictive plasticity.

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