Chapter 1: Introduction

1.3. Outline of the thesis

The main focus of this thesis is the study of the roles of two subclasses of the tyrosine kinase receptor family during central nervous system development in *Drosophila*. Both subclasses, the Rors and Ryks, comprise Wnt5 receptors (Yoshikawa, McKinnon et al. 2003; Wouda, Bansraj et al. 2008) (Oishi, Suzuki et al. 2003) and are essential in non-canonical Wnt signaling pathways (Oishi, Suzuki et al. 2003; Yoshikawa, McKinnon et al. 2003; Wouda, Bansraj et al. 2008; Jensen, Hoerndli et al. 2012). In this thesis, we present novel data that further the understanding of the molecular mechanisms by which these pathways operate and the biological processes they mediate during development.

In the first section of **Chapter 1,** a comprehensive review is presented on the roles of the Ror receptors in Wnt signaling in the nervous system in a variety of organisms. Vital functions of the Rors in neurogenesis, axon guidance, neuronal survival and synaptic homeostasis are discussed. In 1.2. a general introduction on the use of *Drosophila melanogaster* as a model for neurobiological studies is presented and in 1.3. the outline of this thesis.

Chapter 2 describes the construction of a *Drosophila Ror* mutant generated via an imprecise P-element deletion. The *Ror* mutant flies display distinct phenotypes during development of the central nervous system and the neuromuscular junction. In the embryo, we observed defects in the organization and extension of axon fascicles and the migration and orientation of the longitudinal glia that support them. Later during development at the larval neuromuscular junction, we observe abnormalities in the branching pattern of the synapse. Moreover, the *ror* mutant exhibits decreased quantal content suggesting a reduction in neurotransmitter release upon stimulation.

In **Chapter 3**, several biochemical properties of the *Drosophila* RYK protein Drl as a Wnt5 receptor, are described. We show that Drl can form homodimers, but also heterodimers with the other two *Drosophila* Ryk receptors, Drl-2 and Dnt. Moreover, this dimerization is increased upon binding of its ligand Wnt5. Our study also deciphers the biochemical properties of the interaction between Drl and its downstream effector Src64B. The exact domains responsible for the interaction between Drl and Src64B are identified, as well as their functional relevance *in vivo* for axon repulsion during the formation of the commissural pathways in the embryonic ventral nerve cord.

In **Chapter 4** we show that in the olfactory system, the antennal lobe is patterned by secreted Wnt5 during pupal development. Wnt5 is expressed as a gradient emanating from a set of guidepost cells, neurons located at the dorsolateral pole of the antennal lobe, and Drl is expressed in a dorsal to ventral gradient on the projection neuron dendrites. We propose that Wnt5 acts as a repulsive cue for these dendrites and that Drl acts cell-autonomously on the dendrites to antagonize Wnt5 signaling. The Wnt5 gradient thus provides positional information along the dorsal-ventral axis to allow the projection neurons, expressing different levels of Drl, to terminate onto their appropriate targets.

Chapter 5 describes data supporting a model for the mechanisms through which Drl and Wnt5 regulate/mediate axon branching during development of the adult *Drosophila* mushroom body, structures involved in learning and memory. Specifically, we show that

Drl acts as an anchor to bind Wnt5, thus presenting it to the growth cone of a neighboring set of migrating axons that express Drl-2, one of the other two Ryks in *Drosophila*. This Ryk protein acts as the repulsive guidance, i.e. signaling receptor of Wnt5 in this cellular context.

In **Chapter 6** we summarize and discuss the results presented in this thesis and reflect on future studies that follow from this work.

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