Summary

In this thesis, novel aspects of TPH have been described for these different species:

- **Drosophila melanogaster**

An independent gene encoding tryptophan hydroxylase (CG9122; DmTPH) was cloned as a third gene for aromatic amino acid hydroxylases (AAAH) in Drosophila melanogaster in addition to tyrosine hydroxylase (TH) and phenylalanine hydroxylase (PAH or Henna). Before it was thought that Henna has both activities, PAH and TPH. The enzymatic activity of DmTPH to hydroxylate Trp to 5OHTrp was higher than the one of Henna and Trp was a more suitable substrate for DmTPH than for Henna.

- **Mouse**

The TPH2 gene was targeted in ES cells to generate knockout mice, but the ES cells produced only chimeric mice without germ line transmission probably due to an important role of TPH2 in the spermatogenesis process. Accordingly the expression of TPH2, but not TPH1, was discovered in the testis of mice, rats, and humans.

- **Zebrafish**

Three isoforms of TPH were cloned in zebrafish in contrast to two isoforms in other vertebrates confirming the hypothesis of a whole genome duplication during the evolution of fish and assuming the loss of the fourth TPH gene. 5HT was found in early stages of zebrafish embryos in prenervous stages (8-cell-, blastula, gastrula, and 1dpf stages) indicating a developmental role of 5HT during embryogenesis. In later stages 5HT was found in the hatching gland, olfactory bulb and in the raphe nucleus correlating with TPH2- and 5HTT expression. 5HT in the pineal gland was correlated with TPHD1- and surprisingly also with TPH2 expression. 5HT was also found in cells, which were termed 5HT single cells, in intestine, dorsal root ganglia, pharyngeal arches and skin. Neural crest cells were identified as the origin of those single cells, since Sox10 regulates 5HT single cells in the skin and Foxd3 regulates the cells in the intestine, dorsal root ganglia, and pharyngeal arches. Also the 5HT2B receptor of zebrafish was cloned for the first time, and its expression was found in the heart and pharyngeal arches similar as in mouse.

TPH2 deficient fish were generated by injection of morpholino antisense oligonucleotides and exhibited many developmental defects in neural crest derived tissues like pharyngeal arches, peripheral and enteric nervous system, and heart. The specification of neural crest cells was not affected in TPH2 morphants as shown by the expression of different early markers. 5HT single cells in the skin and in the pharyngeal arches were not detectable in TPH2 morphants which lack also the endodermal pouches.

Pharmacological and genetic loss of function tests for 5HT2B receptors induced defects in the function of the heart and in development the pharyngeal arches correlating with its expression pattern in both tissues.