Glycoprotein hormone receptor structure and function

» Prof. Dr. Ralf Paschke

The research group focuses on gaining insights into the fundamentals of signal generation and transduction between the extracellular ligand binding (LB) domain of glycoprotein hormone receptors (GPHRs) and the transmembrane (TM) domain common to all G-protein-coupled receptors (GPCRs) with the main focus on the complex of the thyroid-stimulating hormone (TSH) with its receptor (TSHR).

A key part of the LB domain is the enigmatic C-terminal hinge region, which is involved in transmitting the signal to the TM domain. The group has previously identified several binding and signaling sensitive residues within this region of the TSHR (Mueller et al. 2009/2011) and demonstrated that despite its low conservation, the hinge region appears to have a common function within GPHRs (Jaeschke et al. 2011).

In order to gain structurally supported insights the researchers pursue a strategy combining (i) molecular modelling (in cooperation with Jens Meiler from Vanderbilt University, Nashville TN), (ii) experimental determination of structural parameters with mass-spectrometry based methods like chemical crosslinking, disulfide-pattern analysis, and H/D-exchange (in cooperation with Stefan Kalkhof from UFZ, Leipzig) and (iii) detailed functional characterization of receptor and ligand variants generated by site-directed mutagenesis. In an iterative feedback loop the modelling results will be used to guide the experiments and the experimental result will in turn be used to refine the models of a full length GPHR in its free and ligand-bound form. This approach will also lead to the identification of (i) antagonistic, (ii) inverse agonistic and (iii) agonistic TSH variants.

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The hinge region of the TSH receptor stabilizes ligand binding and determines different signaling profiles of human and bovine TSH. Endocrinology 152 (2011), 3986 – 3996.


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The hinge region: an important receptor component for GPHR function. Trends in Endocrinology & Metabolism 21 (2010), 111 – 122.

The supragonistic activity of bovine thyroid-stimulating hormone (TSH) and the human TR1401 TSH analog is determined by specific amino acids in the hinge region of the human TSH receptor. J Biol Chem 284 (2009), 16317 – 16324.

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