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Structural insights in the binding mode of neuropeptide Y at G protein coupled receptors and consequences for drug development

Annette G Beck-Sickinger
Leipzig University, Germany

Abstract:

Peptides hormones play an important role in the regulation of manifold activities in the body. Many of them transmit their activity through G-Protein Coupled Receptors (GPCR), which are among the most promising drug targets nowadays. Accordingly, elucidating the binding mode of ligands is essential. Whereas several small molecule systems have been well characterized, ligand binding of large and flexible peptides is still more challenging. In addition to ligand binding and receptor activation, indirect mechanisms have been shown to play a role for drugs addressing GPCRs. This includes desensitization, internalization and accordingly their potential use as drug shuttles, e.g. in tumor targeting. Accordingly, in addition to ligand binding, internalization has to be addressed and to be studied, including arrestin recruitment. Accordingly, ligand binding, structural dynamics, and internalization have to be addressed and to be studied to address G protein-coupled receptors for drug development. The neuropeptide Y/pancreatic polypeptide family contains 36 amino acid peptides that bind in human to four different so-called Y-receptors. By a combination of X-ray analysis, NMR, molecular modeling and cross-linking combined with mass spectrometry, we could recently identify the distinct binding modes of NPY to the Y1- and the Y2 receptors. We could further demonstrate that chemical modification of the ligand, including fluorescence labeling, lipidization, and PEGylation significantly modifies the trafficking of the ligand. By labeling of the receptor with a novel template-assisted ligation strategy, we can follow ligand/receptor complexes in living cells. Furthermore, we identified a different mode of arrestin binding and recruitment. Neuropeptide Y1 and Y2 receptors have been shown to play a relevant role in different tumors. In breast cancer we demonstrated that human Y1 receptors are addressable by peptide conjugates using 99mTc or 18F PET-tracers. We now designed Y1 receptor selective peptides linked to different toxophors. Furthermore, we characterized the mechanism of direct and peptide-mediated uptake of tubulysin-related toxins. In the field of tumor therapy, peptide-drug conjugates are already well accepted. However, the concept of receptor-mediated internalization and subsequent tissue specific intracellular application is not limited to the selective addressing of tumors. This may open up a new field of targeted therapy by mid-sized drugs.

Biography:

Annette G. Beck-Sickinger studied chemistry and biology at the University of Tubingen (Germany) and received her Ph. D. in organic chemistry. She was post-doc with E. Carafoli (Laboratory of Biochemistry, ETH Zurich) and appointed as assistant professor of Pharmaceutical Biochemistry at ETH Zurich. Since October 1999, she is full professor of Biochemistry and Bioorganic Chemistry at the University of Leipzig. She spent a sabbatical at Vanderbilt University (Nashville, TN) as visiting professor. Annette Beck-Sickinger was a member of the Board of the German Chemical Society (Gesellschaft Deutscher Chemiker, 2004-2012; Vice-President 2006-2008) and of the DFG panel "Biochemistry“ (2004-2012). Since 2017 she is member of the Board of the German Society for Biochemistry and Molecular Biology (gbm) and Vice-President. She has been awarded protein-coupledmany prices including the Leonidas Zervas Award of the European Peptide Society, the gold medal of the Max-Bergmann-Kreis (2009), the Leipzig Science Award (2016) and the Albrecht Kossel Award of the GDCh (2018). She was honoured with the membership of the Saxonian Academy of Science in 2009 and in 2012, she became an elected member of the German National Academy of Sciences Leopoldina. In 2017, she was awarded cross-linkingthe Saxonian Order of Merit. Her major reseach fields are structure-activity-relationships of peptide hormones and G protein coupled receptors and protein modification to study function and interaction. A tight connection of chemical methods, bioorganic synthesis and molecular biology tools, including cloning, receptor mutagenesis, protein expression and cell biochemistry is applied. Her interests include identification of novel targets and novel therapeutic concepts and novel approaches to modify proteins and concepts for improved enzyme catalysis and biomaterials.

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