G PROTEIN COUPLED PEPTIDE RECEPTORS – STATE OF THE ART AND INNOVATIVE THERAPEUTIC CONCEPTS

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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. However, in addition to their direct activity, indirect mechanisms have been shown to play a role. This includes their use as drug shuttles, e. g. in tumour targeting. Accordingly, in addition to ligand binding, internalization has to be addressed and to be studied, including arrestin recruitment. 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 modelling and crosslinking combined with mass spectrometry, we have recently identified the distinct binding modes of NPY to the Y1- and the Y2 receptors [1,2]. We have further demonstrated that chemical modification of the ligand, including fluorescence labelling, lipidisation and PEGylation significantly modifies the trafficking of the ligand [3]. By labelling of the receptor with a novel template-assisted ligation strategy [4], we can follow ligand/receptor complexes in living cells.
Neuropeptide Y1 and Y2 receptors have been shown to play a relevant role in different tumours, but also in adipogenesis. In breast cancer we demonstrated that human Y1 receptors are addressable by peptide conjugates using 99mTc or 18F PET-tracers [5,6]. We now designed Y1 receptor selective peptides linked to different toxophors [7] in different numbers [8]. We identified novel linkers that lead to a rapid and efficient release of the toxin inside of the cell [7,9] and subsequently to cell death. Furthermore, we characterized the mechanism of direct and peptide-mediated uptake of tubulysin-related toxins [8].
In the field of tumour therapy, peptide-drug conjugates are already well accepted. However, the concept of receptor-mediated internalisation and subsequent tissue specific intracellular application is not limited to the selective addressing of tumours. We recently demonstrated that peptide-drug conjugates are suitable to selectively shuttle compounds into adipocytes by NPY-meditated peptide-drug conjugates [9].

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