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DIFFERENCES IN STRUCTURE-FUNCTION RELATIONS BETWEEN NONMAMMALIAN AND MAMMALIAN GONADOTROPIN-RELEASING HORMONE AND GONADOTROPIN RECEPTORS.

Mammalian gonadotropin-releasing hormone receptors (GnRH-R) differ from other G protein-coupled receptors in lacking the intracellular C-terminal tail and showing an exchange of otherwise highly conserved Asp and Asn residues in transmembrane domains (TM) 2 and 7, respectively. However, the first GnRH-R characterized from a nonmammalian vertebrate, the African catfish, contains an intracellular C-terminus, and has two Asp residues in TM 2 and 7. The roles of these Asp/Asn residues as well as the C-terminal tail in receptor functioning will be discussed. Moreover, the presumed interaction of residues in TM 2 and 3 that keeps the receptor in the active state has been studied with molecular modelling and site-directed mutagenesis. Studies on the spatio-temporal mRNA expression of this receptor and a second type of catfish GnRH-R, in combination with the mRNA expression profile of the two endogenous ligands, indicates functional co-expression of ligand-receptor pairs in the same or nearby tissues.

Mammalian gonadotropin receptors (luteinizing hormone receptor, LH-R, and follicle-stimulating receptor, FSH-R) display ligand selectivity. However, the African catfish FSH-R displays promiscuous hormone binding. The African catfish LH-R on the other hand, while binding LH fairly specifically, seems to be constitutively active. Comparative studies, involving domain-swapping and site-directed mutagenesis, on the N-terminal, extracellular ligand-binding domain of nonmammalian and mammalian gonadotropin receptors revealed that, in the mammalian context, only a few amino acid residues may determine ligand selectivity. These findings may provide new leads to the design of small, gonadotropin receptor-specific ligands.

Date: Thursday, 17 October 2002

Time: 4 PM

Venue: LT 31, Blk S16

Host: Dr Philippa Melamed

All are welcome

