How to make an FSH receptor into an LH receptor? (“Just blink twice”)

Bogerd J
Dept of Endocrinology, Utrecht University, Utrecht

Glycoprotein hormones (GpHs) and glycoprotein hormone receptors (GpHRs) constitute an interesting example of co-evolution. Glycoprotein hormones (LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; hCG, choriogonadotropin) are heterodimers consisting of a common α-subunit and a receptor-specific β-subunit. GpHRs are G protein-coupled receptors characterized by a large N-terminal, extracellular domain (ECD) responsible for the specific recognition and binding of the hormones. LH and hCG bind to the same LH/hCG receptor (LHR), whereas TSH and FSH bind to the TSH receptor (TSHR) and the FSH receptor (FSHR), respectively. The ECD of a particular GpHR contains the molecular determinants to bind and select the ‘correct’ GpH from the bouquet of potential GpHs present in the circulation in order to elicit the correct physiological response.
Functional characterization of fish gonadotropin receptors revealed that their FSHRs displayed promiscuous gonadotropin-signaling behaviour (*i.e.* binding both FSH and LH), whereas mammalian GpHRs bind GpHs with high selectivity (*i.e.* virtually no cross-reactivity between GpHs and the heterologous GpHRs).
The observed difference in gonadotropin selectivity allowed us to design a gain-of-function strategy in order to identify the LH/hCG-selective determinants for the human gonadotropin receptors. Domain-exchange experiments, followed by single amino acid substitutions, for various LHR-ECD domains using the FSHR as ‘host’ receptor revealed that only two amino acids function as LH/hCG-selective determinants (*i.e.* Asn^{104}, a positive, LHR-derived determinant, and Lys^{179}, a negative, FSHR-derived determinant), apart from numerous low-impact, common GpH contact sites.
Recent data on FSH-selective determinants will also be discussed.
The results obtained will be molded into a general model for GpH binding and selection, may provide clues whether polymorphisms of GpHR genes could constitute risk factors and yield a better understanding of the etiology of pathological states known for some GpH-GpHR pairs.

Jan Bogerd, Department of Endocrinology, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, t 030 2534177, e-mail j.bogerd@bio.uu.nl

session 16