Evolution of gonadotropin receptor genes

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Homologs of all of the five major GPCR families arose before nematodes diverged from the chordate lineage, and two rounds of genome duplications yielded paralogous copies of the ancestral chordate genes. A sub-branch of one of the four main groups of the large rhodopsin family accommodates the so-called leucine-rich repeat-containing GPCRs (LGRs). LGRs, among which are the glycoprotein hormone receptors (GpHRs: LHR, FSHR and TSHR), show these repeats in their extracellular, hormone-binding domains. The phylogeny of glycoprotein hormone (GpH: LH-, FSH- and TSH-) subunit and GpHR genes could be traced to invertebrate orthologs by comparing their primary sequences.

In mammals, the physiological roles of gonadotropins are in general well differentiated: FSH regulates proliferation as well as adult functioning of FSHR-expressing cell types (Sertoli/granulosa cells) derived from the coelomic epithelium. These cells provide structural germ cell support and produce paracrine factors influencing gametogenesis. LH regulates steroid production in LHR-expressing cell types. The interaction between gonadotropins and their receptors is highly specific, because the receptors display a low sequence identity in their hormone-binding domain. It was therefore postulated that GpH-GpHR pairs underwent co-evolution, resulting in a high binding specificity that prevents promiscuous cross-activation between the different GpH-GpHR endocrine systems.

In sub-mammalian vertebrates (*e.g.* in teleost fish), however, the bioactivities of gonadotropins seem to be less specific. For example, African catfish LH can efficiently activate both catfish FSHR and LHR, while catfish FSH solely activates catfish FSHR. Remarkably, FSH effectively stimulates testicular androgen production both *in vitro* and *in vivo*, with a similar potency as LH. While the mechanism by which this action is exerted is unknown, the most direct explanation was assuming FSHR expression by Leydig cells, which we tested by laser microdissection-qPCR analysis of interstitial *vs.* intratubular tissue fractions and by *in situ* hybridisation. Our studies revealed that in African catfish, like in mammals, intratubular Sertoli cells exclusively express FSHR, whereas Leydig cells express both LHR and FSHR. This observation allowed us to explain the strong steroidogenic potency of FSH by its direct action on FSHR-expressing Leydig cells. LH activation of the FSHR, on the other hand, may support steroidogenesis, modulate spermiogenesis and/or play a role in recruiting a new batch of immature germ cells during spawning, when blood LH levels are high.

In conclusion, the requirement for specific *vs.* promiscuous gonadotropin bioactivities may be related to distinct reproductive strategies (*e.g.* viviparity *vs.* oviparity, respectively) as a consequence of different evolutionary histories of mammalian *vs.* non-mammalian species, respectively.

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