Best Practice & Research Clinical Endocrinology & Metabolism xxx (2018) 1–12

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Pharmacogenetics of GPCR variants: FSH receptor and infertility treatment

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
FSH
FSH receptor
single nucleotide polymorphism
infertility

Infertility treatment may represent a paradigmatic example of precision medicine. Follicle-stimulating hormone (FSH) has been proposed as a valuable therapeutic option both in males and in females, even if a standardized approach is far to be established. To date, several genetic mutations as well as polymorphisms have been demonstrated to significantly affect the pathophysiology of FSH-FSH receptor (FSHR) interaction, although the underlying molecular mechanisms remain unclear. This review aims to highlight possible aspects of FSH therapy that could benefit from a pharmacogenetic approach, providing an up-to-date overview of the variability of the response to FSH treatment in both sexes. Specific sections are dedicated to the clinical use of FSH in infertility and how FSHR polymorphisms may affect the therapeutic endpoints.

Introduction

The treatment of infertility is a modern example of personalized medicine, in which the use of follicle-stimulating hormone (FSH) is largely proposed in both sexes, although solid, scientific evidence determining the best approach does not exist so far. It is well known that FSH acts in concert with

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https://doi.org/10.1016/j.beem.2018.01.001
1521-690X/

luteinising hormone (LH) regulating gamete production and reproduction in both males and females [1]. However, an accepted, efficient therapeutic approach has not been standardized and once the infertility diagnosis is established, FSH is prescribed and used depending mainly on the experience of the physician. In this context, the clinician may choose among several urinary and recombinant FSH compounds, dosages and regimens, however precluding a personalized treatment, which could benefit from a pharmacogenetic approach based on patients' genotype. Nevertheless, the role of FSH and its receptor (FSHR) is widely considered in the setting of infertility and it may be relevant for impacting on ethnicity-related human reproductive success [2]. Indeed, studies evaluating the role of *FSHR* single nucleotide polymorphisms (SNPs) on reproductive function found a marker predictive of the ovarian response falling within the receptor's gene [3]. Moreover, cumulative effects modulating the cell response to FSH may occur depending on the haplotype provided by *FSHR* and the FSH beta subunit encoding gene (*FSHB*) variants [4]. The FSH-FSHR complex initiates a cascade of molecular events in the gonads, from the increase of intracellular cyclic adenosine monophosphate (cAMP) to the transcription of mRNA products encoding for enzymes modulating the synthesis of steroid hormones [5–7]. In this way, FSH stimulates folliculogenesis and steroidogenesis in the ovary [8] and testicular development and spermatogenesis in the testis [9]. FSH administration for male or female infertility aims at inducing these gonadal activities and gametogenesis to achieve the pregnancy of the female partner.

In this review, we analyze how a phamacogenetic approach could influence the therapeutic efficacy of FSH in both males and females. To this purpose, both mutations and SNPs of the *FSHR* gene have been considered.

Interaction between the FSH beta subunit and its receptor

FSH is a dimer having an alpha subunit, shared with other glycoprotein hormones, and a beta subunit (FSHβ) providing specificity for the receptor binding. The human FSHβ is encoded by the *FSHB* gene located on the chromosome 11p.21 [10] and heterogeneous variants are known, differing mainly for glycosylation, which occur as post-translational modifications of the nascent protein enriched by asparagine-linked N-glycan chains. Glycosylation is a determinant factor for dimer assembling, secretion rate, half -life and modulation of the signal transduction [11]. Several studies suggested so far that different glycosylation of artificially produced FSH may impact on clinical outcomes of assisted reproduction techniques (ART) [12,13].

The FSHR is a 76 kDa G protein-coupled receptor, consisting of 695 amino acids and belonging to the rhodopsin-like receptor subfamily [14]. The *FSHR* gene is located at chromosome 2.p21, spans more than 190 Kbases and embeds 10 exons and 9 introns. Exons 1–9 encode for the extracellular domain deputed to ligand binding, while the large exon 10 for part of the so-called “hinge region”, for the seven transmembrane-spanning domains and for the intracellular C-terminal tail. FSHR is expressed mainly in granulosa and Sertoli cells, in which it mediates steroid synthesis and gametogenesis. Upon ligand binding, the receptor undergoes a conformational change, leading to the simultaneous activation of multiple signaling pathways at the intracellular level [15]. The activation of Gαs protein is a well-known early event resulting in subsequent adenosine triphosphate (ATP) conversion to cAMP increase by the enzyme adenylyl cyclase, protein kinase A (PKA) recruitment, extracellular-regulated kinase (ERK1/2) and cAMP-responsive element binding-protein (CREB) phosphorylation. CREB is a transcription factor mediating the expression of genes encoding for enzymes modulating steroidogenesis and life/death signals, such as the steroid acute regulatory protein (StAR) and aromatase, cyclins and p53. On the other side, ERK1/2 is involved in the regulation of steroidogenic signals, receptor desensitization and proliferative events, and is activated by PKA within about 5 min after receptor binding and by β-arrestins within about 10 min. These latter mediate the internalization of desensitized GPCRs, downregulating the pro-apoptotic stimuli [16]. Besides cAMP/PKA and ERK pathways, a number of other intracellular events occur, such as intracellular Ca^{2+} increase and activation of protein kinase B (AKT)-, epidermal growth factor receptor (EGFR)- and mammalian target of rapamycin (mTOR)-pathways, resulting in a complex balance between steroidogenic, pro- and anti-apoptotic signals [17].

The genomic region embedding the *FSHR* gene is a hot spot for ovarian response to gonadotropins. Indeed, SNPs falling within this region may modulate receptor expression and signaling [18,19], and are reasonably linked to endocrine dysfunction such as polycystic ovary syndrome [20].

Please cite this article in press as: Santi D, et al., Pharmacogenetics of GPCR variants: FSH receptor and infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.01.001