Recent advances in understanding gonadotropin signaling

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Abstract

Gonadotropins are glycoprotein sex hormones regulating development and reproduction and bind to specific G protein–coupled receptors expressed in the gonads. Their effects on multiple signaling cascades and intracellular events have recently been characterized using novel technological and scientific tools. The impact of allosteric modulators on gonadotropin signaling, the role of sugars linked to the hormone backbone, the detection of endosomal compartments supporting signaling modules, and the dissection of different effects mediated by these molecules are areas that have advanced significantly in the last decade. The classic view providing the exclusive activation of the cAMP/protein kinase A (PKA) and the steroidogenic pathway by these hormones has been expanded with the addition of novel signaling cascades as determined by high-resolution imaging techniques. These new findings provided new potential therapeutic applications. Despite these improvements, unanswered issues of gonadotropin physiology, such as the intrinsic pro-apoptotic potential to these hormones, the existence of receptors assembled as heteromers, and their expression in extragonadal tissues, remain to be studied. Elucidating these issues is a challenge for future research.

Keywords

LH, FSH, hCG, gonadotropin, FSHR, LHCGR, reproduction, endosome, signaling, allosteric modulator

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Introduction

Gonadotropins are glycoprotein hormones regulating development and reproduction via targeting gonadal cells expressing specific G protein–coupled receptors. Gonadotropins are dimers having structural similarities and an identical common alpha subunit, and the beta subunit conserves about 70 to 80% of amino acid sequence identity in humans[1]. Receptor specificity is due to unique beta subunits encoded by follicle-stimulating hormone beta-subunit gene (*FSHB*) and luteinizing hormone beta-subunit gene (*LHB*), expressed in the pituitary. Choriogonadotropin beta-subunit genes (*CGBs*) are expressed in trophoblast cells and placenta[2,3].

During the fertile age, the action of gonadotropins is sex-specific and its secretion is regulated by a feedback mechanism depending on levels of sex steroid hormone. In the male, FSH binds its receptor (FSHR) expressed in Sertoli cells, where the hormone exerts trophic functions fundamental for sustaining gamete production and maturation. In contrast, LH binding to its receptor (LHCGR) stimulates the synthesis of testosterone by Leydig cells[4]. In the female, FSHR expression in granulosa cells is a requisite for sustaining the monthly ovarian follicle recruitment and subsequent FSH-mediated events, such as oocyte maturation, selection, and estrogen synthesis[5]. LH modulates proliferative and anti-apoptotic signals in granulosa cells, accompanied by androgen production in theca cells, and culminates in the induction of the dominant follicle ovulation and progesterone production by luteal cells[6]. During the first trimester of pregnancy, human chorionic gonadotropin (hCG) replaces the luteotrophic role of LH in sustaining the demand for increasing levels of progesterone. Chorionic gonadotropin is encoded by a cluster of six genes, embedding two pseudogenes[7], resulting in several slightly different isoforms and glycosylation variants acting through the LHCGR[8]. Although hCG glycoforms have different potencies in activating LHCGR-mediated signaling pathways[9], the specific physiological functions of these variants, if any, are uncertain. It was hypothesized that they evolved in humans to optimize fetal brain development[10].

The physiological functions of gonadotropins are exerted via multiple signaling cascades simultaneously activated in the target cells. A limited number of these pathways were known for decades, but an increasing body of knowledge emerging from recent literature is uncovering a more complex and complete view of the action of these hormones. Therefore, we provide an update on the classic view of gonadotropin physiology, reviewing recent advancements as well as unanswered questions.

Update on gonadotropin physiology

The "classic" pathway

One of the best-known intracellular signaling cascades activated by gonadotropins is the $G_{\alpha s}$ protein/adenylyl cyclase-dependent cAMP/protein kinase A (PKA) pathway. Historically, this pathway was studied using immunoassays to quantify cAMP accumulation in target cells thanks to the use of specific inhibitors and activators[11]. It was discovered that this pathway is fundamental for regulating steroidogenic events in gonadal cells[12], as

already known for the functionally similar steroidogenic cells of the adrenal gland[13]. An exception is provided by adult Sertoli cells, which cannot synthesize sex steroid hormones, and the cAMP/PKA pathway activated therein results in FSH-dependent trophic signals, sustaining cell metabolism and viability[14]. However, the activation of this intracellular signaling pathway may be triggered by all gonadotropins in target cells, where the intracellular cAMP increase is linked to other events such as trophic effects, mitotic functions, and sometimes apoptosis[14]. Downstream PKA, the cascade of kinase activations results in the extracellular-regulated kinase 1 and 2 (ERK1/2). The cAMP-responsive element-binding protein (CREB) phosphorylation is activated as well, inducing transcription of target genes, such as the steroidogenic acute regulatory protein StAR[15]. These common pathways modulating the steroidogenic signals are regulated in a cell- and developmental stage-dependent manner, and many newly discovered molecules and pathways were found to support steroid synthesis. For instance, protein kinase C (PKC) may amplify the cAMP-dependent steroidogenesis in both granulosa and Leydig tumor cells[16], but another research documented the opposite effects of PKA and PKC on progesterone synthesis in ovarian steroidogenic cells[17]. Interestingly, a recent study found that, in granulosa cells, lisosphingolipids may induce cAMP-independent CREB phosphorylation, which, however, is not linked to the activation of steroid synthesis[18]. These data suggest that steroidogenesis is strictly under the control of gonadotropins and that the phosphorylation of a transcription factor per se is not enough to trigger the transcription of key enzyme-encoding genes. Moreover, it was recently demonstrated that the FSH-dependent activation of steroidogenic signals and folliculogenesis might be impinged by salt-induced kinases, indicating the relevance of these enzymes in regulating ovarian functions[19]. On the other hand, in luteal cells, progestational signals specifically regulated by LH via activation of the cAMP/PKA pathway involve the Wingless and Int-1 (Wnt) pathway components glycogen synthase kinase-3β and β-catenin and increase the acute progesterone synthesis in response to gonadotropin stimulation[20]. These data are representative of cell-dependent, complex signaling networks interacting with the classic cAMP/PKA pathway for supporting the synthesis of steroid hormones. New insights into the modulation of the steroidogenic pathways were provided by experiments performed using Leydig cell lines, treated with recently developed allosteric modulators of gonadotropin receptors. This experimental setting revealed that β-arrestin 2, known to be involved in G protein–coupled receptor (GPCR) internalization and sustained signal transduction[21], may act as a negative modulator of testosterone synthesis[22]. Interestingly, steroidogenic signals can be induced by cAMP-independent mechanisms, at least in Leydig cells, where the LH-dependent phosphorylation of ERK1/2 and CREB may occur via activation of the Rous sarcoma oncogene-encoded protein (SRC)[23] and epidermal growth factor receptor[24].

Differences between the FSH- and LH-mediated signals

The two gonadotropin receptors have common signaling pathways. Besides triggering the aforementioned cAMP/PKA pathway, both membrane receptors are known to trigger the

activation of p38 mitogen-activated protein kinase (MAPK) pathway, an intracellular calcium ion (Ca^{2+}) increase, and the recruitment of the adaptor protein "APPL1"[25–31]. The overlapping of FSHR- and LHCGR-dependent intracellular signaling pathways would be due to structural similarities between the two receptors as an inheritance persisting during the evolution of an encoding gene from an ancient common ancestor sequence[32]. Interestingly, mutations conferring constitutive activity to the FSHR may even support sex steroid–independent spermatogenesis[33,34], suggesting that certain gonadal functions may be supported by the activation of overlapping pathways.

Although FSHR- and LHCGR-mediated signaling cascades are very similar, a number of receptor-specific pathways and target genes, which impact steroidogenesis, cell proliferation, and death, have been described. First of all, although both receptors are described as being capable of activating the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway[35,36], concerns about the reliability of data supporting FSH-induced pAKT activation were expressed[37]. FSHR-induced AKT phosphorylation would require the co-activation of insulin growth factor signaling cascades[38,39]. Moreover, FSH specifically regulates the histone H3 phosphorylation via a PKA-dependent mechanism[40], an effect fundamental for activating the LHCGR-encoding gene transcription[41]. In turn, in granulosa cells, some FSH-dependent metabolic functions, such as the upregulation of glucose uptake and glycogen synthesis, are inversely related to LHCGR expression levels and may be impaired under LH-related ovarian pathological conditions[42]. Moreover, the production of epiregulin and amphiregulin occurs predominantly together with progesterone increase upon granulosa cell treatment with LH rather than FSH[43]. In addition, the steroidogenic effect of these hormones depends on their different capacity to activate aromatase expression[44]. These features would underlie hormone-specific physiological effects in the ovary, consisting of the androgenic and progestational actions mediated by LH and the stimulation of estradiol synthesis by FSH[45]. Finally, the two gonadotropin receptors differently modulate and impact cell death signals in ovarian cells. In a β-arrestin 1- and 2-depleted granulosa cell line, FSH administration enhanced the basal FSHR pro-apoptotic activity whereas LH treatment did not produce any effect[46]. This result was reproduced by FSHR but not LHCGR overexpression, suggesting that the control of life and death signals is due to structural features intrinsic to FSHR and LHCGR, which might underlie physiological events such as follicle recruitment, growth, and selection[46]. These functions might be the consequence of ancient duplications of genes encoding gonadotropin-like hormones and their receptors and would consist of evolutionary mechanisms optimizing the neuroendocrine control of human reproduction[47,48]. In light of these considerations, gonadotropin-specific intracellular signals and physiology rely on the structural diversity between the two receptors[49], which achieves the maximal complexity in humans. Thus, although the FSHR and LHCGR induce partially overlapping signal transduction pathways, the two receptors mediate different and irreplaceable physiological effects.

Recent advances
Role of gonadotropin glycosylation

It was previously suggested that the incorporation of oligosaccharides in the structure of gonadotropins impacts intracellular signaling cascades activated by the hormones[50,51]. Gonadotropins can be naturally glycosylated to produce variants with physiological relevance as well as artificial compounds, synthesized for clinical purposes, with different glycosylations and pharmacological impact. The alpha subunit carries two carbohydrate chains joined to asparagine residues (N-linked glycosylation), and one and two are linked to the LHβ and FSHβ, respectively. Two N-linked glycosylation sites are also present in the hCGβ, which, in addition, has four glycosylated serine/threonine residues (O-glycosylation)[50,52]. This classic view has been revisited, especially in the last decade, thanks to studies deepening our understanding of the glycosylation on the function of FSH[53], LH[54], hCG[55], and even of the related glycoprotein thyroid-stimulating hormone (TSH)[56]. For instance, the existence of several hCG glycoforms is well known, was reviewed in 2016, and was considered to have a pathophysiological sense[57]. It was proposed that carbohydrate chains on hCG may be used to predict pregnancy outcomes as a marker of pathologies and infertility treatment[58–62]. During the first trimester of pregnancy, the quantitative and qualitative production of hCG glycoforms is exceptionally variable, starting with hyperglycosylated forms (H-hCG) of trophoblastic origin, followed by less glycosylated isoforms[63]. Moreover, H-hCGs were found in the serum of patients affected by certain tumors[64]. Given these observations, it was supposed that H-hCG, rather than being an activator of progesterone synthesis[65], would play a key role in inducing proliferative signals regulating trophoblast invasion and angiogenesis during the first two weeks of pregnancy as well as tumor growth[66]. This action would be exerted via cross-interaction between the hormone and the tumor growth factor beta (TGF-β) receptor[67]. However, this issue is controversial since another study found no TGF-β receptor activation by hCG and, instead, suggested the presence of growth factor contamination in the gonadotropin preparations[68]. Less glycosylated, "classic" hCG molecules have a shorter half-life than H-hCG[8] and higher potency for LHCGR activation[9]. These features characterize hCG as a hormone optimized for inducing maternal and fetal steroidogenesis, which is fundamental for supporting massive progesterone production by the corpus luteum and the placenta, for estrogen production, and for triggering the masculinization of the male fetus[69]. hCG does also exert a TSH-like action, inducing the production of thyroid hormones acting on the TSH receptor (TSHR)[70]. Although the TSH-like actions of hCG require further research, a 2009 study suggested a link between thyroid autoimmunity and miscarriage[71]. However, conflicting data raise concerns about this hypothesis[72]. Finally, gestational hyperthyroidism has been linked to the expression of *TSHR* gene variants with hCG hypersensitivity[73].

Although the debate over the pathophysiological impact of hCG glycoforms is far from being fully clarified, findings *in vitro* demonstrated that the glycosylation pattern of these

molecules might modulate the intracellular signaling and gene expression[9]. Similarly, changes in the glycosylation and composition of glycans attached to FSH and LH, related to the stage of the menstrual cycle, were found in the serum of women of fertile age[74,75]. Thus, it cannot be excluded that glycoform-specific intracellular signals can be activated[76]. For instance, poorly glycosylated FSH molecules are more active *in vitro* than those fully glycosylated[77] and this observation was repeatedly confirmed both *in vitro*[76,78,79] and in mouse models[80–82]. Together with FSH glycoforms, di- and tri-glycosylated LH molecules were supposed to contribute differently to the regulation of natural ovarian cycles[54] but these data need to be confirmed. To conclude, steps forward have been taken to elucidate molecular aspects related to gonadotropin glycobiology and the issue nourishes increasing interest of scientists and clinicians using these hormones as drugs for infertility treatment[83]. However, a clear-cut demonstration of its real impact on human physiology remains to be determined. Actually, the data available indicate that these glycoforms modulate short-term intracellular effects *in vitro*[76,79,84–86], which are flattened in the long term[85,86] and are extremely difficult to evaluate in humans without performing clinical trials with very large sample sizes[87].

Biased signaling and allosteric modulation of gonadotropin receptors

All GPCRs are activated upon hormone binding to their orthosteric site, which, in the case of gonadotropin receptors, is located in a wide horseshoe-shaped extracellular domain with leucine-rich repeats (LRRs)[88]. The binding of the ligand triggers a two-step activation mechanism, including the reshaping of the hormone conformation after contacting the LRR domain[89]. These events are followed by the interaction of the alpha and beta subunits with a sulfated tyrosine residue within the hinge region[90]. This process leads to the stabilization of ligand–receptor complexes and the inhibition of the agonistic activity of the hinge region[50]. As described above, these events are needed for triggering the $G_{\alpha s}$ protein coupling to the gonadotropin receptor and activation of the downstream cAMP/PKA pathway, which are preceded by conformational rearrangements of the transmembrane regions[91]. However, receptors may exist in multiple active conformations, leading to several signaling cascades simultaneously activated by coupling to other G proteins and intracellular interactors, triggering a network of simultaneous intracellular pathways[92]. Thus, particular signaling patterns may be induced by ligands displaying agonist, antagonist, or inverse agonist activities (or a combination of these) at the same GPCR, depending on the downstream endpoint evaluated, via induction of specific spatial conformations of the receptor molecule[93].

Although these features may be due to the aforementioned hormone glycosylation variants, another mechanism that may alter GPCR signaling may be provided by single-nucleotide polymorphisms (SNPs) at the receptor level. This is the case of the common nucleotide change at position 2039 of the *FSHR* gene (2039A>G), leading to the amino acid change

of asparagine to serine at position 680 at the intracellular portion of the protein (pN680S; rs6166). This SNP modulates the kinetics of cAMP activation, ERK1/2 and CREB phosphorylation, and synthesis of sex steroids[94] and is associated with the gonadal response to FSH in males and females[95,96].

Beta-arrestins are scaffold proteins that directly interact with the gonadotropin receptors[97] and modulate desensitization, internalization, and recycling. They also counteract $G_{\alpha s}$ protein coupling to the receptor[98] and upregulate ERK1/2 and AKT phosphorylation[99]. Moreover, the action of β-arrestins is susceptible to the phosphorylation pattern of the intracellular carboxyl-terminal end of GPCR, which differentially contributes to the recruitment of the scaffold protein, trafficking, and specific intracellular localization[100] of ERK1/2 activation[101,102]. These data may explain why overexpression of β-arrestins is linked to attenuation of intracellular cAMP increase[103] and may be associated with cell proliferation[46]. In particular, given the positive impact of β-arrestin functioning on tumorigenesis and cancer cell growth[104], they have been suggested as a therapeutic target[105,106] and promoted the development of *in vitro* systems for studying their functions[107]. Notably, β-arrestin–induced pERK1/2 activation occurs later but is more sustained than that triggered by the $G_{\alpha s}$ protein[108], revealing that intracellular kinase cascades may be targeted via distinct pathways and kinetics, a molecular mechanism likely modulating specific cell metabolic events. However, β-arrestins and G proteins may also cooperate via the formation of complexes linked to the receptor, leading to temporally sustained cAMP signaling activated from internalized cellular compartments[21]. These molecular assemblies may also mediate the inhibition of G protein signaling, depending on the spatial conformation of the GPCR–β-arrestin complexes[109]. Therefore, elucidating the mechanisms biasing gonadotropin receptor signaling is of crucial relevance for developing new therapeutic approaches to certain diseases.

In the last decade, small-molecule chemical compounds able to bind and modulate FSHR-mediated signaling have been developed[110]. Increasing interest arose around allosteric ligands, which bind the receptor in a site different from the hormone-binding site[111]. According to the mode of action, these molecules are grouped into classes defined as neutral, negative (NAMs), or positive (PAMs) allosteric modulators. All of these molecules require gonadotropin binding to the receptor for exerting their action[111] and modulate receptor-mediated signaling in the presence of the natural ligand. Interestingly, compounds acting via modulation of gonadotropin receptor assembly as homo/heteromers also have been described[112]. Among allosteric agonists, thiazolidinones are known to bind the FSHR transmembrane domain inducing the activation of $G_{\alpha s}$ protein-dependent pathways, similarly to FSH. However, compounds with preferential $G_{\alpha i}$ protein stimulatory activity also have been described[113,114]. Benzamides and dihydropyridines are known to have PAM activity at nanomolar concentrations for both the LHCGR and FSHR, activating cAMP in the presence of the bound ligand[115,116]. Tetrahydroquinolines belong

to the NAM group for both gonadotropin receptors inhibiting cAMP and progesterone, but not estradiol, production and maturation of the ovarian follicle *in vivo*[22,117–119]. Finally, compounds with antagonistic activity for FSHR were found to block FSH-induced steroid synthesis[120,121], similarly to what was recently found for the LHCGR[122]. Taken together, novel molecules with agonistic activity and able to differentially activate intracellular signaling are promising tools to be potentially used for optimizing or personalizing treatments of human infertility. Instead, molecules with NAM activity at the gonadotropin receptor, inhibiting the follicle growth without impairing steroid production, could become an option for contraceptive purposes.

New and exciting insights were provided by antibodies modulating selective activation of GPCRs via stabilization of particular hormone or hormone receptor conformations[91]. For instance, antibodies binding the FSHβ subunit were found to prevent the binding to the receptor and have protective effects against bone loss in ovariectomized mice[123]. Antibodies targeting a placental bovine hCG-like LH (equine chorionic gonadotropin), with both FSH and LH activity in other mammals, would be responsible for forming hormone–antibody complexes with increased β-arrestin–dependent signaling and activity *in vivo*[124,125]. New monoclonal and polyclonal compounds with agonistic activity for gonadotropin receptors and targeting the hinge region are currently under study[126–128] and may represent an alternative approach to allosteric chemicals for modulating gonadal functions. Among these immunoglobulins, nanobodies against the FSHR, with small molecular weight and low predicted immunogenicity in humans, can inhibit cAMP production[129]. In conclusion, immunoglobulins are promising compounds for future therapeutic purposes, such as infertility[130,131] and cancer[132] treatment.

Endosomal signaling and its physiological role

Mechanistic models explaining GPCR pathways of desensitization and recycling have greatly progressed in recent years. These functions have been known for decades[133], and the elucidation of their physiological significance was addressed recently[134] but remains mostly unclear. The current knowledge of gonadotropin receptor post-endocytotic processing indicates that these molecules are internalized and either recycled or directed to degradation after ligand binding and G protein activation. The activated receptor then is phosphorylated by GPCR kinases (GRKs) and recruits β-arrestins, leading to G protein uncoupling, desensitization, and internalization via the formation of clathrin-coated pits[135]. Recent studies have found that β-arrestin–mediated GPCRs internalization may also occur without uncoupling to G proteins, forming a molecular super-complex mediating sustained signaling[21,109,136]. Interestingly, most of these discoveries were provided by functional studies using *in vitro* transfected models, overexpressing the human FSHR and LHCGR, or rodent receptors, revealing that the internalization of human molecules is slower than that of murine receptors and is due to species-specific amino acids in the intracellular loop of the transmembrane region and the carboxyl-terminal tail[108,137].

GPCR internalization is followed by the activation of a recycling pathway mediated by different endosomes or by the degradation via lysosomes[138]. Therefore, the endocytotic pathways may sort the fate of receptors impacting their density at the cell surface and the spatial and temporal regulation of intracellular signaling[139]. One of the most studied pathways involves the formation of early endosomes (EEs). These structures are characterized by the presence of the Ras-related protein 5 Rab-5 (RAB5) and consist of fusion vesicles routing from the plasma membrane and the trans-Golgi network[140]. The embedding of GPCRs in EEs is the first step of a process directing receptors to two possible fates; the first one is the degradative pathway, which is triggered by the replacement of RAB5 with RAB7, thus trafficking these units to form multi-vesicular bodies preceding protein degradation in the lysosomes. This is the pathway controlling receptor desensitization, which occurs after persistent stimulation of the GPCRs[139]. Trafficking-defective receptors due to mutations causing protein misfolding are known and may provoke reproductive dysfunctions falling within a wide range of phenotypes[138]. Interestingly, defects of genes involved precisely in EE functioning were recently associated with dysregulation of GPCR signaling and linked to pathological conditions, such as polycystic ovary syndrome. For instance, perturbation of RAB5- or the clathrin-binding protein (DENND1A)-encoding gene expression in theca cells may result in over-activation of androgen synthesis and subsequent increased susceptibility to the disease[141]. Another pathway regulating the fate of receptors involves the ubiquitin or RAB4 protein, rerouting EEs to degradation or to recycling endosomes, respectively. The latter route depends mostly on a so-called "PDZ ligand" binding sequence at the carboxyl-terminal tail of LHCGR[142], and FSHR recycling may also occur via alternative pathways[133]. In this case, a crucial role is played by a palmitoylated cysteine at the C-tail, which is required for maintaining proper FSHR recycling, preventing excessive degradation and, likely, impairment of the cell signaling[143].

A gonadotropin receptor recycling pathway involves a novel intracellular compartment, the very-early endosome (VEE), where LHCGR is routed through the interaction of the so-called "$G_{\alpha i}$-interacting protein C-terminus" (GIPC) with the PDZ protein binding domain[100]. VEE differs from the EE in that the former lacks RAB5 and is smaller, but *in vitro* removal of the PDZ domain from LHCGR re-routes the receptor to the EE[100], inducing sustained ERK1/2 phosphorylation and revealing that these recycling pathways are interconnected. Interestingly, a similar behavior was observed for FSHR *in vitro*, using GIPC knockout without the PDZ domain, demonstrating the involvement of APPL1 in the receptor recycling through VEEs[26,144,145]. Indeed, APPL1 may interact with GIPC[146] and sustains FSHR-mediated ERK1/2 phosphorylation, as well as AKT activation and recruitment of the 14-3-3τ adapter protein[26,144,145,147], through a subpopulation of VEEs positive for APPL1. Interestingly, this molecule is recruited upon cAMP/PKA activation occurring via the FSHR and LHCGR itself[148] and depletion of VEE formation results in cAMP inhibition, as demonstrated for other GPCRs[149]. However, PKA (and VEE) blockade by a specific inhibitor did not evoke similar

effects, at least for LHCGR, which can induce sustained cAMP signaling, indicating a dual, receptor-specific effect of APPL1[25]. These data may be relevant for elucidating the whole functions exerted by gonadotropin receptors and their physiological impact. For instance, sustained LHCGR-mediated cAMP signaling would be required to unlock the oocyte from meiotic blockade[150], demonstrating its effects on reproduction. In summary, gonadotropin receptor trafficking, being much more than a pathway for recycling these molecules to the cell surface, plays a crucial role in sustaining prolonged intracellular signaling (Figure 1).

Functional differences between LH and hCG
LH and hCG are distinct molecules that have different functions[7,10,151]. Despite this knowledge, the fact that the two gonadotropins act on the same receptor and the difficulties of dissecting these differences in clinical studies[152] support the common belief that they are two clinically equivalent hormones. Thus, commercial preparations consisting of FSH, which may be supplemented with LH or hCG or both, were developed[153] under the assumption that hCG would provide "LH activity"[154] during the follicular phase of the menstrual cycle in inducing oocyte maturation and ovulation[153]. In the last decade, several studies elucidating specific roles of LH and hCG were

published and reviewed[3,155–157], pinpointing the differences between the two gonadotropins.

LHβ and hCGβ have a common evolutionary origin since *CGB* genes originated in primates likely by loss of the original stop codon and repeated duplication from an ancestral *LHB* gene[158,159]. More generally, CG molecules exist first in primates[160] but are missing in other mammals traditionally used to evaluate the action of hCG, such as mice[161–163]. Indeed, historically, LH action was typically studied using hCG in rodents. This is indicative of hCG binding capability to non-primate receptors that are structurally similar to primate LH/CG receptors[164]. Thus, it appears that in humans the complexity of the LHβ/hCGβ-encoding gene cluster is greater than that of other primates. It was suggested that this complexity might serve for supporting a more complex mechanism of placentation and highly energy-demanding brain development in humans[10] but this remains an unproven claim. In any case, this complexity indicates a specialization occurring uniquely in the LHCGR, which, in contrast to FSHR, discriminates between two ligand-specific signals and physiological functions. This exclusive feature would rely mostly on the region encoded by the *LHCGR* gene exon 10, which may recognize and distinguish the molecular interaction between LH and hCG,
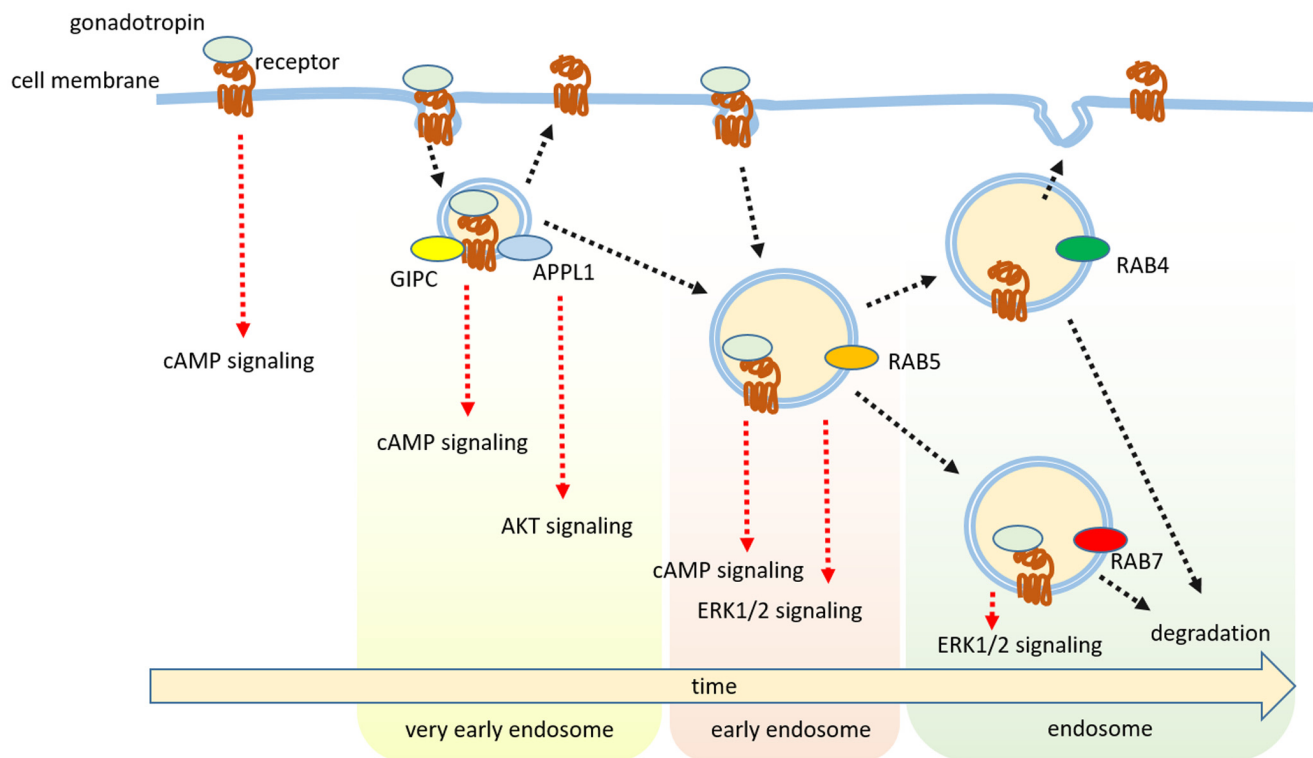
Figure 1. Endosomal signaling of gonadotropin receptors. Receptor bound to the hormone is internalized via different kinds of endosomal compartments, sustaining prolonged signaling, receptor degradation, or recycling on the cell surface. AKT, protein kinase B; ERK1/2, extracellular-regulated kinase 1 and 2; GIPC, "G$_{\alpha i}$-interacting protein C-terminus"; RAB4, Ras-related protein Rab-4; RAB5, Ras-related protein Rab-5; RAB7, Ras-related protein Rab-7.

modulating different hormone receptor conformations and intracellular signaling[165,166]. The role of the exon 10–encoded receptor domain was highlighted by a clinical case describing a boy with impaired development of secondary sexual characteristics due to a naturally occurring deletion of the *LHCGR* exon 10[151]. Although the phenotype at birth was clearly male, this patient presented with primary hypogonadism, which could be rescued by treatment with hCG, suggesting a possible action of the maternal choriogonadotropin inducing fetal sex determination but a lack of function of the high LH levels after birth. These data were corroborated by the discovery that the LH receptor sequence of the New World monkey *Callithrix jacchus* naturally lacks the exon 10–encoded domain. In this primate species, the pituitary produces an hCG-like molecule and not LH, thereby replacing the role of LH[167,168] in other species in which exon 10 is present.

Evolutionary issues suggest that LH and hCG exert different roles, a concept confirmed by the nature of their physiological functions. Although both *in vitro* and clinical data indicate that these hormones could be equivalent in inducing testosterone synthesis and spermatogenesis[169,170], reflecting the primary androgenic role of Leydig cells, different results were found in *in vitro* models of ovarian cells[171,172]. The two molecules display different intracellular signaling (Figure 2), indicating that hCG has a higher steroidogenic potential than LH and the latter induces preferentially proliferative and

anti-apoptotic signals[171–174]. Moreover, they display biased agonism at the LHCGR, differentially activating cAMP production and recruitment of β-arrestin 2, likely explaining the partial agonism of LH on progesterone production[175]. Because H-hCG activates the receptor with lower activity than hCG and retains a highly proliferative potential[9], it could be assumed that the hyperglycosylated gonadotropin modulates LH-like intracellular signaling patterns. Interestingly, the mouse receptor (Lhr) cannot discriminate qualitatively between the two human ligands[170]. This discrepancy between human and mouse receptor functioning should be due to LHCGR key residues involved in hCG/LH discrimination[165,166], which are missing in the Lhr[176]. In any case, data from human cells support the different physiological roles of the two hormones, which would consist of potent progestational effects mediated by hCG and a fine-tuned regulation of life signals required for ovarian follicle growth and maturation for LH[3]. Moreover, clinical hormone-specific effects may be evaluated by meta-analyses of studies analyzing large datasets, oppositely to what other studies performed in a clinical[177] or *in vitro*[84,86] context. A proper sample size is required for dissecting the effects of the two hormones *in vivo*, which indeed turn out to be different. Although the addition of hCG to FSH treatment for assisted reproduction may optimize the number of oocytes retrieved, suggesting an effect positively modulated by steroids, LH could be beneficial for the pregnancy rate as an indirect measure of better oocyte quality[152]. These data may provide
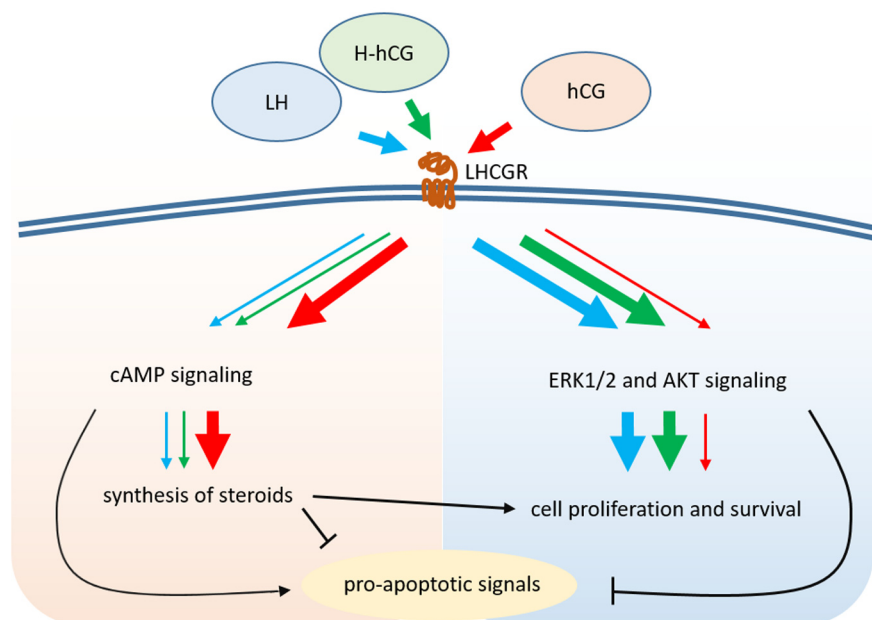
Figure 2. LH- and hCG-specific signals. LH and hCG induce different intracellular signaling. Whereas LH is more potent than hCG in activating proliferative and survival signals via EK1/2 and AKT phosphorylation, the choriogonadotropin acts preferentially as a progestational, inducing a more potent cAMP response. H-hCG has a relatively high proliferative potential and lower activity than hCG in activating the receptor. AKT, protein kinase B; ERK1/2, extracellular-regulated kinase 1 and 2; hCG, human chorionic gonadotropin; H-hCG, hyperglycosylated human chorionic gonadotropin; LH, luteinizing hormone; LHCGR, luteinizing hormone/chorionic gonadotropin receptor.

helpful insights for developing personalized protocols for assisted reproduction in specific categories of patients. For instance, poor-responder women[178] or those requiring luteal support[179,180] might benefit from the addition of LH and hCG, respectively, during the management of an assisted reproductive cycle[154,179]. On the other hand, gonadotropin-releasing hormone (GnRH) agonists are now the alternative option to hCG to prime ovulation and reduce the risk of ovarian hyperstimulation syndrome[181,182], but there are no clinical data comparing the effects of LH and hCG in men.

Pharmacogenomic use of FSH

More than two decades of studies focusing on polymorphisms of gonadotropins and their receptors revealed the existence of allelic variants linked to specific reproductive phenotypes or increased risk of developing related pathologies. In contrast to mutations[183,184], polymorphic allelic variants are commonly widespread among the human population, achieving allele frequencies greater than 1%[185]. To date, these variants may be identified by genetic screening at relatively low costs; in some instances, they are becoming relevant for developing individualized clinical treatments.

Genetic variants of *FSHB* and *FSHR* genes are promising candidates to be characterized for pharmacogenomic approaches since they impact the ovarian response to hormone stimulation[186]. Among the roughly 20 SNPs found within the *FSHB* gene, the only one demonstrated to have physiological significance and clinical impact so far is the guanidine (G) to thymidine (T) variation 211 nucleotides upstream of the start codon (c.-221G>T, rs10835638)[47]. In men, the T homozygosity is associated with lower serum FSH levels and testicular volume than other haplotypes[187] and decreased sperm quality[188]. However, similar findings were not always replicated by other studies evaluating spermatogenic potential and Sertoli cell number[189]. Even the opposite results were found in women[190], suggesting possible sex-specific effects of this SNP. In females, the T allele decreases the risk of developing endometriosis, delayed age of menopause, and longer menstrual cycles than the G allele[191]. At the same time, other studies found an association between the T allele and the FSH and LH levels, idiopathic infertility, and worst clinical assisted reproduction outcome[192,193]. These data indicate a lower transcriptional activity of the T allele of the *FSHB* promoter SNP[194], which would modulate the circulating levels of the hormone, thus impacting ovarian response.

A number of activating and inactivating *FSHR* mutations have been described within the receptor regions encoded by exons 7 and 10[184]. Loss-of-function *FSHR* mutations may lead to pathological conditions, such as amenorrhea, in women[186] and may be linked to infertile or subfertile phenotypes in men[131,195,196]. *FSHR* mutations overall are rare, and several *FSHR* SNPs may have been characterized and analyzed for their associations with the gonadal response. Among the best-known common

FSHR variants, the rs1394205 (c.-29G>A) in the *FSHR* promoter, as well as the two exon 10 SNPs rs6165 (c.919G>A) and rs6166 (c.2039G>A) usually in linkage disequilibrium, have been associated with the gonadal response to FSH. In particular, the rs6166 variant is linked to the asparagine-to-serine amino acid change at position 680 of the protein chain (p.N680S) and is located in the C-terminal region of the receptor. This substitution adds a potential phosphorylation site, increases early intracellular signaling, and impacts the kinetics of steroid synthesis[94]. In practice, homozygous individuals carrying the amino acid serine are less "sensitive" to FSH and show higher serum FSH levels and longer menstrual cycles than pN680S N homozygous women[197]. A role for FSHR SNP in male fertility has also been proposed[198]. Cases of idiopathic infertility related to this SNP were described in men[199]. However, these findings were obtained after analysis of the cumulative effects of the FSHR p.N680S SNP and other SNPs, revealing the overall mild but detectable impact of the polymorphism on male reproduction[196,199]. In men, the impact of the SNP rs6166 in modulating the action of FSH was eventually characterized by a pharmacogenetic study where sperm DNA fragmentation of idiopathic infertile patients improved after prolonged treatment with the gonadotropin[96]. Therefore, the p.N680S phenotype may be a marker of sperm quality.

Studies analyzing the allele frequencies of *FSHR* exon 10 SNPs should take into account the expression level of the receptor protein given that the polymorphism c.-29G>A modulates the transcriptional activity of the gene[200] and is linked to genotype-specific gonadal functions in both males[201,202] and females[203–205]. In particular, associations between reproductive parameters and the c.-29G>A SNP were found when analyzed together with the p.N680S FSHR polymorphism[201], revealing the cumulative effects of these hot spots. However, the opposite results, which likely indicate a weak clinical impact of the SNP per se, have also been reported[206–208]. Further studies using larger datasets are required to highlight the impact of this genetic variant on fertility. Therefore, the combined evaluations of several *FSHR* and *FSHB* SNPs are determinant to indicate how the whole haplotype is linked to specific endocrine phenotypes.

Although each FSHR SNP was linked to particular endocrine phenotypes in some studies, the combined analysis of several alleles revealed the real impact of specific haplotypes in increasing the risk of infertility[197,199]. These analyses should account for limitations intrinsic to each study. Different results due to ethnicity-related[201,209] or sample size[210] issues may occur, leading to the requirement of independent confirmation of the findings. Other limitations may be linked to the study design since weak selection criteria and different or unspecified primary endpoints provided non-comparable results[199]. Extensive interventional studies are needed to more deeply explore the therapeutic benefit of a pharmacogenomic approach to gonadotropin treatment. Nevertheless, after about two decades of

small studies on markers of the gonadal response, scientific support for the development of a pharmacogenetic approach to personalized hormonal treatments is now available. Given the dramatic cost reduction for genetic testing in recent years[211], conditions are now favorable for SNP analysis before clinical treatments of infertility.

Unanswered questions

Gonadotropin-driven cell death

Although steps forward have been made in the elucidation of gonadotropin physiology over the last three decades, several unknown aspects of their function remain. One of the most underrated issues related to gonadotropin signaling is the activation of pro-apoptotic signals[14]. Gonadotropins are classically linked to proliferative and survival signals, reflecting their roles in supporting gametogenesis. On the other hand, these molecules upregulate the phosphorylation of mitogenic/anti-apoptotic signals induced via ERK1/2 and AKT and through activation of several different intracellular pathways, including the positive impact on steroid hormone production, supportive of reproduction. In fact, convincing data confirmed that FSH and LH mediate signals required for sperm and somatic cell life in the male gonad[212]. Interestingly, the textbook knowledge of ovarian physiology is that follicular dominance is a process regulated by pro-apoptotic stimuli occurring after the decrease in serum FSH levels. This event would be responsible for declining proliferative signals occurring in individual follicles, which become atretic. The proliferative effect of gonadotropins is widely described in the scientific literature, where a number of studies describe how FSHR and LHCGR may activate life signaling pathways and, in certain cases, have even a tumorigenic potential[5]. However, pro-apoptotic stimuli delivered by gonadotropins via cAMP-related pathways were also described[213–215]. These effects would be triggered by relatively high intracellular levels of the second messenger, likely resulting in p38 MAPK and p53 activation[216,217] together with steroidogenic signals[218] and inducing cell death. From this point of view, the pro-apoptotic potential of gonadotropins would rely on the capacity to increase cAMP, a property previously demonstrated for FSH and hCG in certain experimental conditions *in vitro*[46,172]. In particular, persistently high FSHR expression levels and the lack of steroid hormones could be linked to insufficient inhibition of death signals[172], a possible explanation for the lack of consistent human ovarian steroidogenic cell lines expressing this receptor[46]. This condition is hardly obtainable *in vivo* in the ovary, where the FSH-induced signals are translated to estrogen production and FSHR is transitorily expressed in the follicles. On the other hand, steroids activate anti-apoptotic signals[172,219], as obligatory regulators of folliculogenesis[220], even inducing multi-follicular maturation during assisted reproduction[221,222], where relatively high gonadotropin doses are administered. However, death signals delivered through FSH may play an essential role in the ovary. They could be involved in the selection of the dominant follicle, inducing steroidogenesis and atresia of those follicles

expressing relatively high levels of FSHR[215]. The activation of cAMP is due to the preferential coupling to the G_s protein when FSHR is maximally expressed[215,223] in granulosa cells at the early/mid-antral stage of the menstrual cycle. Interestingly, oocyte maturation might depend on the capability of the membrane G protein–coupled estrogen receptor (GPER) to reprogram cAMP/death signals, linked to FSHR, into proliferative stimuli. The anti-apoptotic role of GPER in the ovary is exerted through the physical interaction with the FSHR, leading to the formation of heteromers activating the AKT pathway upon FSH binding[215]. These data indicate that the temporary succession of pro- and anti-apoptotic signals is orchestrated, at least in part, by interacting gonadotropin and steroid hormone membrane receptors, playing an essential role in female reproduction. Further studies are required to understand how these molecules act in concert to regulate folliculogenesis. Membrane receptor heteromers might be markers of ovarian cell proliferation[104,215] to be targeted by drugs for infertility and cancer treatment.

Receptor heteromers *in vivo*

Several GPCRs are known to form homo- and hetero-meric functional units consisting of the molecular association between the same or different but structurally similar receptors[224]. It is reasonable that GPCRs interact with molecules having an overall similar structure, as previously demonstrated for receptors of other pituitary[225] and non-pituitary[226] hormones. In particular, FSHR–LHCGR heteromers were demonstrated *in vitro*[227,228], where they are classically overexpressed in transfected cell lines and analyzed using imaging methods[229,230]. Recently, the GPER has been indicated as a novel interacting partner of both FSHR and LHCGR in ovarian cells[215]. The physiological implications of these heteromers are not fully understood. It was proposed that they mediate GPCR functional diversity, highly relevant for human physiology[231]. In particular, they should be involved in the development of competent oocytes during the normal menstrual cycle, reprogramming gonadotropin receptor–mediated death signals in proliferative stimuli[215,232]. Impairment of hormone-dependent signaling due to FSHR–LHCGR heteromer formation was reported in the transiently transfected human embryonic kidney (HEK293) cell line[233], further providing the rationale for the assembly of heteromers. However, the existence of naturally formed gonadotropin receptor heteromers, as a general feature of GPCRs, is not widely accepted[226]. In fact, this concept may be weakened by the difficulties in demonstrating heteromers in primary cell cultures, unspecific signals, or elevated background noise due to biosensor-tagged receptor overexpression obtained in an artificial system *in vitro* as well as the doubt that agonist-induced signals can be generated by heteromers or conformational changes within preassembled groups of receptors[234]. Therefore, the fact that gonadotropin receptor heteromers may occur *in vivo* is under debate. A step forward was taken by obtaining data in genetically modified mice coexpressing binding-deficient and signaling-deficient LH receptors[235]. These experiments were

based on a concept previously developed and demonstrated *in vitro*; binding-deficient receptors triggered cAMP activation through the interaction with a receptor, defective in signal generation, bound to hCG[236]. Even in mice, LH was able to trigger the activation of the cAMP/PKA intracellular signaling cascade via intermolecular cooperation between the two receptors[235]. This is a mechanistic proof of gonadotropin receptor interaction *in vivo*, which presumably occurs even in the human granulosa cells. In the ovary, LH-like signals could be induced via FSH binding to FSHR during the window of receptor coexpression[232]. However, results concerning the existence of FSHR–LHCGR transactivation were also provided, although stably transfected HEK293 cells used in this study were not a physiological model[237]. This issue merits further studies, and alternative experimental approaches may be essential in demonstrating gonadotropin receptor heteromers and complementarity in a physiological context. For instance, bivalent ligands able to bind receptor dimers or super-resolution imaging analysis could be extremely helpful[238].

Extragonadal gonadotropin receptors

By definition, gonadotropins act in the gonads by binding to receptors specifically expressed therein as a requisite for maintaining endocrine signal specificity and proper metabolic functions. This classic view was recently challenged by several studies describing the expression of functional ectopic gonadotropin receptors, mainly FSHR, supposed to play a significant role in non-reproductive processes. These effects include bone loss, obesity, and cardiovascular and cancer risk, which could be triggered by extragonadal FSHR activated by high FSH levels[239], such as those occurring after menopause. Lhr expression was found in the mouse adrenal cortex[240], reflecting previous data demonstrating the presence of LHCGR expression in adrenal glands of postmenopausal women[241]. Aberrant LHCGR expression in the adrenal gland would be linked to cortisol synthesis and Cushing's syndrome[242,243]. Functional LH receptors were also found in uterine tissues of human[244] and farm animal models under physiological conditions[245,246]. Surprisingly, immunoreactivity to LHCGR was found even in human brain microglial cells and was positively correlated to an increased risk of developing Alzheimer's disease[247]. More recently, the presence of LHCGR was suggested in the retina, where LH and hCG would have vascular endothelial growth factor–like functions[248].

Functional FSHRs were found in endometriotic lesions, where FSH may induce *CYP19A1* expression and estrogen production[249]. This is not the only study describing ectopic expression of this receptor; in this regard, an increasing amount of data from human and animal models has been published in the last two decades. Genetically modified or antibody-treated mouse models elegantly suggested that FSH-induced signals modulate bone mass and adipose tissue[123,250]. Around these issues,

several studies described a link between FSH, osteoporosis, and increased fat mass that occurs after menopause[251–258]. Similar conclusions were achieved by *in vitro* studies using human cells[259,260], although the existence of direct causality between gonadotropin receptor and the physiological effect was questioned[261]. Relatively low levels of FSH were associated with increased cardiometabolic risk and cardiovascular diseases in the Chinese population[262], and the rationale of this issue is provided by the angiogenetic support exerted by FSH via the PI3K/AKT pathway[263]. Finally, it was demonstrated that FSHR is expressed in tumor vessel cells upregulated by FSH[264–266]. These accumulating experimental data seem to clearly debunk the classic view of gonadotropin physiology, potentially leading to new diagnostic, therapeutic, and prognostic opportunities. For instance, the use of anti-FSH antibodies for bone- and fat-specific targeting was proposed for clinical testing[267]. However, the issue is highly debated, and several objections, including the low reliability of the antibodies used for investigating FSHRs in non-canonical tissues[268], firmly oppose the existence of extragonadal FSHRs and LHCGRs[269]. These data would rely on the discrepancy between mRNA and protein level detected in the analyzed samples, suggesting that they could be an artifact due to suboptimal antibody binding[270] and challenging Western blotting[271]. Missing control experiments of target mRNAs by DNA sequencing[263] put further concerns on the reliability of the detection. Together with the aforementioned experimental issues, the opposite results were also found. For instance, a decrease in body fat was not found in mice and humans maintained under gonadotropin production blockade by GnRH agonist/antagonist[272–274]. Finally, studies revisiting previous experimental conditions used for detecting extragonadal FSHRs in the human umbilical vein endothelial cells failed in replicating results[275], and several technical concerns arose when ectopic gonadotropin receptors were evaluated in other tissues[269]. In conclusion, the concept of extragonadal FSHRs remains highly controversial. Genetically modified mice may not be the best tools for assessing this issue. Interventional studies in humans will be the only way to demonstrate direct causality between gonadotropin receptors and the abovementioned effects.

Conclusions

Significant steps forward in the elucidation of gonadotropin signaling and regulation have been made in recent years. The current knowledge addressed most of the questions of the past, revealing novel aspects of FSH, LH, and hCG physiology and providing the potential for new therapeutic applications. Despite these advances, many unanswered questions remain, and the full potential of gonadotropin action, the presence of FSHR–LHCGR heteromers *in vivo*, and the role of extragonadal receptors warrant further research. Studying these aspects is vital for further scientific and clinical progress that could benefit human reproductive health.

Faculty Opinions

References

1. Costagliola S, Urizar E, Mendive F, *et al.*: **Specificity and promiscuity of gonadotropin receptors.** *Reproduction.* 2005; **130**(3): 275–81.
   PubMed Abstract | **Publisher Full Text**

2. Simoni M, Gromoll J, Nieschlag E: **The follicle-stimulating hormone receptor: Biochemistry, molecular biology, physiology, and pathophysiology.** *Endocr Rev.* 1997; **18**(6): 739–73.
   PubMed Abstract | **Publisher Full Text**

3. Casarini L, Santi D, Brigante G, *et al.*: **Two Hormones for One Receptor: Evolution, Biochemistry, Actions, and Pathophysiology of LH and hCG.** *Endocr Rev.* 2018; **39**(5): 549–92.
   PubMed Abstract | **Publisher Full Text**

4. Ramaswamy S, Weinbauer GF: **Endocrine control of spermatogenesis: Role of FSH and LH/ testosterone.** *Spermatogenesis.* 2015; **4**(2): e996025.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

5. Riccetti L, Sperduti S, Lazzaretti C, *et al.*: **The cAMP/PKA pathway: Steroidogenesis of the antral follicular stage.** *Minerva Ginecol.* 2018; **70**(5): 516–24.
   PubMed Abstract | **Publisher Full Text**

6. Hillier SG: **Gonadotropic control of ovarian follicular growth and development.** *Mol Cell Endocrinol.* 2001; **179**(1–2): 39–46.
   PubMed Abstract | **Publisher Full Text**

7. Nagirnaja L, Rull K, Uusküla L, *et al.*: **Genomics and genetics of gonadotropin beta-subunit genes: Unique *FSHB* and duplicated *LHB*/*CGB* loci.** *Mol Cell Endocrinol.* 2010; **329**(1–2): 4–16.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

8. Cole LA: **hCG, the wonder of today's science.** *Reprod Biol Endocrinol.* 2012; **10**: 24.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Koistinen H, Koel M, Peters M, *et al.*: **Hyperglycosylated hCG activates LH/hCG-receptor with lower activity than hCG.** *Mol Cell Endocrinol.* 2019; **479**: 103–9.
   PubMed Abstract | **Publisher Full Text** | **Faculty Opinions Recommendation**

10. Henke A, Gromoll J: **New insights into the evolution of chorionic gonadotrophin.** *Mol Cell Endocrinol.* 2008; **291**(1–2): 11–9.
    PubMed Abstract | **Publisher Full Text**

11. Chin EC, Abayasekara DRE: **Progesterone secretion by luteinizing human granulosa cells: A possible cAMP-dependent but PKA-independent mechanism involved in its regulation.** *J Endocrinol.* 2004; **183**(1): 51–60.
    PubMed Abstract | **Publisher Full Text**

12. Azhar S, Clark MR, Menon KM: **Regulation of cyclic adenosine 3', 5' -mono-phosphate dependent protein kinase of rat ovarian cells by luteinizing hormone and human chorionic gonadotropin.** *Endocr Res Commun.* 1976; **3**(2): 93–104.
    PubMed Abstract | **Publisher Full Text**

13. Roos BA: **Effect of ACTH and camp on human adrenocortical growth and function *in vitro*.** *Endocrinology.* 1974; **94**(3): 685–90.
    PubMed Abstract | **Publisher Full Text**

14. Casarini L, Crépieux P: **Molecular Mechanisms of Action of FSH.** *Front Endocrinol (Lausanne).* 2019; **10**: 305.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

15. Miller WL, Strauss 3rd JF: **Molecular pathology and mechanism of action of the steroidogenic acute regulatory protein, StAR.** *J Steroid Biochem Mol Biol.* 1999; **69**(1–6): 131–41.
    PubMed Abstract | **Publisher Full Text**

16. Manna PR, Huhtaniemi IT, Stocco DM: **Mechanisms of protein kinase C signaling in the modulation of 3',5'-cyclic adenosine monophosphate-mediated steroidogenesis in mouse gonadal cells.** *Endocrinology.* 2009; **150**(7): 3308–17.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

17. Nemer A, Azab AN, Rimon G, *et al.*: **Different roles of cAMP/PKA and PKC signaling in regulating progesterone and PGE$_2$ levels in immortalized rat granulosa cell cultures.** *Gen Comp Endocrinol.* 2018; **269**: 88–95.
    PubMed Abstract | **Publisher Full Text**

18. Paradiso E, Lazzaretti C, Sperduti S, *et al.*: **Sphingosine-1 phosphate induces cAMP/PKA-independent phosphorylation of the cAMP response element-binding protein (CREB) in granulosa cells.** *Mol Cell Endocrinol.* 2021; **520**: 111082.
    PubMed Abstract | **Publisher Full Text**

19. Armouti M, Winston N, Hatano O, *et al.*: **Salt-inducible Kinases Are Critical Determinants of Female Fertility.** *Endocrinology.* 2020; **161**(7): bqaa069.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

20. Roy L, McDonald CA, Jiang C, *et al.*: **Convergence of 3',5'-cyclic adenosine 5'-monophosphate/protein kinase A and glycogen synthase kinase-3beta/beta-catenin signaling in corpus luteum progesterone synthesis.** *Endocrinology.* 2009; **150**(11): 5036–45.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Faculty Opinions Recommended

21. Thomsen ARB, Plouffe B, Cahill TJ, *et al.*: **GPCR-G Protein-β-Arrestin Super-Complex Mediates Sustained G Protein Signaling.** *Cell.* 2016; **166**(4): 907–19.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

22. Ayoub MA, Yvinec R, Jégot G, *et al.*: **Profiling of FSHR negative allosteric modulators on LH/CGR reveals biased antagonism with implications in steroidogenesis.** *Mol Cell Endocrinol.* 2016; **436**: 10–22.
    PubMed Abstract | **Publisher Full Text**

23. Wayne CM, Fan HY, Cheng X, *et al.*: **Follicle-stimulating hormone induces multiple signaling cascades: evidence that activation of Rous sarcoma oncogene, RAS, and the epidermal growth factor receptor are critical for granulosa cell differentiation.** *Mol Endocrinol.* 2007; **21**(8): 1940–57.
    PubMed Abstract | **Publisher Full Text**

24. Manna PR, Chandrala SP, Jo Y, *et al.*: **cAMP-independent signaling regulates steroidogenesis in mouse Leydig cells in the absence of StAR phosphorylation.** *J Mol Endocrinol.* 2006; **37**(1): 81–95.
    PubMed Abstract | **Publisher Full Text**

25. Sposini S, Jean-Alphonse FG, Ayoub MA, *et al.*: **Integration of GPCR Signaling and Sorting from Very Early Endosomes via Opposing APPL1 Mechanisms.** *Cell Rep.* 2017; **21**(10): 2855–67.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

26. Nechamen CA, Thomas RM, Cohen BD, *et al.*: **Human follicle-stimulating hormone (FSH) receptor interacts with the adaptor protein APPL1 in HEK 293 cells: Potential involvement of the PI3K pathway in FSH signaling.** *Biol Reprod.* 2004; **71**(2): 629–36.
    PubMed Abstract | **Publisher Full Text**

27. Lee PSN, Buchan AMJ, Hsueh AJW, *et al.*: **Intracellular calcium mobilization in response to the activation of human wild-type and chimeric gonadotropin receptors.** *Endocrinology.* 2002; **143**(5): 1732–40.
    PubMed Abstract | **Publisher Full Text**

28. Conti M: **Specificity of the cyclic adenosine 3',5'-monophosphate signal in granulosa cell function.** *Biol Reprod.* 2002; **67**(6): 1653–61.
    PubMed Abstract | **Publisher Full Text**

29. Gonzalez-Robayna IJ, Falender AE, Ochsner S, *et al.*: **Follicle-Stimulating hormone (FSH) stimulates phosphorylation and activation of protein kinase B (PKB/Akt) and serum and glucocorticoid-Induced kinase (Sgk): Evidence for A kinase-independent signaling by FSH in granulosa cells.** *Mol Endocrinol.* 2000; **14**(8): 1283–300.
    PubMed Abstract | **Publisher Full Text**

30. Maizels ET, Cottom J, Jones JC, *et al.*: **Follicle stimulating hormone (FSH) activates the p38 mitogen-activated protein kinase pathway, inducing small heat shock protein phosphorylation and cell rounding in immature rat ovarian granulosa cells.** *Endocrinology.* 1998; **139**(7): 3353–6.
    PubMed Abstract | **Publisher Full Text**

31. Meng XL, Rennert OM, Chan WY: **Human chorionic gonadotropin induces neuronal differentiation of PC12 cells through activation of stably expressed lutropin/choriogonadotropin receptor.** *Endocrinology.* 2007; **148**(12): 5865–73.
    PubMed Abstract | **Publisher Full Text**

32. Szkudlinski MW: **New Frontier in Glycoprotein Hormones and Their Receptors Structure-Function.** *Front Endocrinol (Lausanne).* 2015; **6**: 155.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

33. Oduwole OO, Peltoketo H, Poliandri A, *et al.*: **Constitutively active follicle-stimulating hormone receptor enables androgen-independent spermatogenesis.** *J Clin Invest.* 2018; **128**(5): 1787–92.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

34. Gromoll J, Simoni M, Nieschlag E: **An activating mutation of the follicle-stimulating hormone receptor autonomously sustains spermatogenesis in a hypophysectomized man.** *J Clin Endocrinol Metab.* 1996; **81**(4): 1367–70.
    PubMed Abstract | **Publisher Full Text**

35. Tai P, Shiraishi K, Ascoli M: **Activation of the lutropin/choriogonadotropin receptor inhibits apoptosis of immature Leydig cells in primary culture.** *Endocrinology.* 2009; **150**(8): 3766–73.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

36. Law NC, Hunzicker-Dunn ME: **Insulin Receptor Substrate 1, the Hub Linking Follicle-stimulating Hormone to Phosphatidylinositol 3-Kinase Activation.** *J Biol Chem.* 2016; **291**(9): 4547–60.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

37. Stocco C: **Follicle-stimulating Hormone (FSH) Phosphorylation of Protein Kinase B (AKT) Remains Controversial.** *J Biol Chem.* 2016; **291**(27): 14385.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

38. Baumgarten SC, Convissar SM, Fierro MA, *et al.*: **IGF1R signaling is necessary for FSH-induced activation of AKT and differentiation of human Cumulus granulosa cells.** *J Clin Endocrinol Metab.* 2014; **99**(8): 2995–3004.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

39. Zhou P, Baumgarten SC, Wu Y, *et al.*: **IGF-I signaling is essential for FSH stimulation of AKT and steroidogenic genes in granulosa cells.** *Mol Endocrinol.* 2013; **27**(3): 511–23.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

40. Salvador LM, Park Y, Cottom J, *et al.*: **Follicle-stimulating hormone stimulates protein kinase A-mediated histone H3 phosphorylation and acetylation leading to select gene activation in ovarian granulosa cells.** *J Biol Chem.* 2001; **276**(43): 40146–55.
PubMed Abstract | Publisher Full Text

41. Zhang Y, Fatima N, Dufau ML: **Coordinated changes in DNA methylation and histone modifications regulate silencing/derepression of luteinizing hormone receptor gene transcription.** *Mol Cell Biol.* 2005; **25**(18): 7929–39.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Chahal N, Geethadevi A, Kaur S, *et al.*: **Direct impact of gonadotropins on glucose uptake and storage in preovulatory granulosa cells: Implications in the pathogenesis of polycystic ovary syndrome.** *Metab Clin Exp.* 2021; **115**: 154458.
PubMed Abstract | Publisher Full Text | Faculty Opinions Recommendation

43. Freimann S, Ben-Ami I, Dantes A, *et al.*: **EGF-like factor epiregulin and amphiregulin expression is regulated by gonadotropins/cAMP in human ovarian follicular cells.** *Biochem Biophys Res Commun.* 2004; **324**(2): 829–34.
PubMed Abstract | Publisher Full Text

44. Donadeu FX, Ascoli M: **The differential effects of the gonadotropin receptors on aromatase expression in primary cultures of immature rat granulosa cells are highly dependent on the density of receptors expressed and the activation of the inositol phosphate cascade.** *Endocrinology.* 2005; **146**(9): 3907–16.
PubMed Abstract | Publisher Full Text | Free Full Text

45. Bebia Z, Somers JP, Liu G, *et al.*: **Adenovirus-directed expression of functional luteinizing hormone (LH) receptors in undifferentiated rat granulosa cells: Evidence for differential signaling through follicle-stimulating hormone and LH receptors.** *Endocrinology.* 2001; **142**(6): 2252–9.
PubMed Abstract | Publisher Full Text

46. Casarini L, Reiter E, Simoni M: **β-arrestins regulate gonadotropin receptor-mediated cell proliferation and apoptosis by controlling different FSHR or LHCGR intracellular signaling in the hGL5 cell line.** *Mol Cell Endocrinol.* 2016; **437**: 11–21.
PubMed Abstract | Publisher Full Text

47. Casarini L, Santi D, Marino M: **Impact of gene polymorphisms of gonadotropins and their receptors on human reproductive success.** *Reproduction.* 2015; **150**(6): R175–84.
PubMed Abstract | Publisher Full Text

48. Dufour S, Quérat B, Tostivint H, *et al.*: **Origin and Evolution of the Neuroendocrine Control of Reproduction in Vertebrates, With Special Focus on Genome and Gene Duplications.** *Physiol Rev.* 2020; **100**(2): 869–943.
PubMed Abstract | Publisher Full Text | Faculty Opinions Recommendation

49. Smits G, Campillo M, Govaerts C, *et al.*: **Glycoprotein hormone receptors: Determinants in leucine-rich repeats responsible for ligand specificity.** *EMBO J.* 2003; **22**(11): 2692–703.
PubMed Abstract | Publisher Full Text | Free Full Text

50. Jiang X, Dias JA, He X: **Structural biology of glycoprotein hormones and their receptors: Insights to signaling.** *Mol Cell Endocrinol.* 2014; **382**(1): 424–51.
PubMed Abstract | Publisher Full Text

51. Ulloa-Aguirre A, Midgley AR Jr, Beitins IZ, *et al.*: **Follicle-stimulating isohormones: Characterization and physiological relevance.** *Endocr Rev.* 1995; **16**(6): 765–87.
PubMed Abstract | Publisher Full Text

52. Esteves SC, Alviggi C: **The role of LH in controlled ovarian stimulation**. In: *Principles and Practice of Controlled Ovarian Stimulation in ART.* Springer India; 2015 [cited 2020 Sep 16]; 171–96.
Publisher Full Text

53. Bousfield GR, May JV, Davis JS, *et al.*: ***In Vivo* and *In Vitro* Impact of Carbohydrate Variation on Human Follicle-Stimulating Hormone Function.** *Front Endocrinol (Lausanne).* 2018; **9**: 216.
PubMed Abstract | Publisher Full Text | Free Full Text

54. Wide L, Eriksson K: **Low-glycosylated forms of both FSH and LH play major roles in the natural ovarian stimulation.** *Ups J Med Sci.* 2018; **123**(2): 100–8.
PubMed Abstract | Publisher Full Text | Free Full Text

55. Fournier T, Guibourdenche J, Evain-Brion D: **Review: HCGs: different sources of production, different glycoforms and functions.** *Placenta.* 2015; **36 Suppl 1**: S60–5.
PubMed Abstract | Publisher Full Text

56. Wide L, Eriksson K: **Molecular size and charge as dimensions to identify and characterize circulating glycoforms of human FSH, LH and TSH.** *Ups J Med Sci.* 2017; **122**(4): 217–23.
PubMed Abstract | Publisher Full Text | Free Full Text

57. Fournier T: **Human chorionic gonadotropin: Different glycoforms and biological activity depending on its source of production.** *Ann Endocrinol (Paris).* 2016; **77**(2): 75–81.
PubMed Abstract | Publisher Full Text

58. Butler SA, Luttoo J, Freire MOT, *et al.*: **Human chorionic gonadotropin (hCG) in the secretome of cultured embryos: Hyperglycosylated hCG and hCG-free beta subunit are potential markers for infertility management and treatment.** *Reprod Sci.* 2013; **20**(9): 1038–45.
PubMed Abstract | Publisher Full Text

59. Brennan MC, Wolfe MD, Murray-Krezan CM, *et al.*: **First-trimester hyperglycosylated human chorionic gonadotropin and development of hypertension.** *Prenat Diagn.* 2013; **33**(11): 1075–9.
PubMed Abstract | Publisher Full Text

60. Keikkala E, Koskinen S, Vuorela P, *et al.*: **First trimester serum placental growth factor and hyperglycosylated human chorionic gonadotropin are associated with pre-eclampsia: A case control study.** *BMC Pregnancy Childbirth.* 2016; **16**(1): 378.
PubMed Abstract | Publisher Full Text | Free Full Text

61. Cole LA: **Proportion hyperglycosylated hCG: A new test for discriminating gestational trophoblastic diseases.** *Int J Gynecol Cancer.* 2014; **24**(9): 1709–14.
PubMed Abstract | Publisher Full Text

62. Chuan S, Homer M, Pandian R, *et al.*: **Hyperglycosylated human chorionic gonadotropin as an early predictor of pregnancy outcomes after *in vitro* fertilization.** *Fertil Steril.* 2014; **101**(2): 392–8.
PubMed Abstract | Publisher Full Text | Free Full Text

63. Kovalevskaya G, Kakuma T, Schlatterer J, *et al.*: **Hyperglycosylated HCG expression in pregnancy: Cellular origin and clinical applications.** *Mol Cell Endocrinol.* 2007; **260–262**: 237–43.
PubMed Abstract | Publisher Full Text

64. Kelly LS, Birken S, Puett D: **Determination of hyperglycosylated human chorionic gonadotropin produced by malignant gestational trophoblastic neoplasias and male germ cell tumors using a lectin-based immunoassay and surface plasmon resonance.** *Mol Cell Endocrinol.* 2007; **260–262**: 33–9.
PubMed Abstract | Publisher Full Text | Free Full Text

65. Crochet JR, Shah AA, Schomberg DW, *et al.*: **Hyperglycosylated human chorionic gonadotropin does not increase progesterone production by luteinized granulosa cells.** *J Clin Endocrinol Metab.* 2012; **97**(9): E1741–4.
PubMed Abstract | Publisher Full Text

66. Cole LA: **HCG variants, the growth factors which drive human malignancies.** *Am J Cancer Res.* 2012; **2**(1): 22–35.
PubMed Abstract | Free Full Text

67. Berndt S, Blacher S, Munaut C, *et al.*: **Hyperglycosylated human chorionic gonadotropin stimulates angiogenesis through TGF-β receptor activation.** *FASEB J.* 2013; **27**(4): 1309–21.
PubMed Abstract | Publisher Full Text

68. Koistinen H, Hautala L, Koli K, *et al.*: **Absence of TGF-β Receptor Activation by Highly Purified hCG Preparations.** *Mol Endocrinol.* 2015; **29**(12): 1787–91.
PubMed Abstract | Publisher Full Text | Free Full Text

69. O'Shaughnessy PJ, Antignac JP, Le Bizec B, *et al.*: **Alternative (backdoor) androgen production and masculinization in the human fetus.** *PLoS Biol.* 2019; **17**(2): e3000002.
PubMed Abstract | Publisher Full Text | Free Full Text

70. Hoermann R, Broecker M, Grossmann M, *et al.*: **Interaction of human chorionic gonadotropin (hCG) and asialo-hCG with recombinant human thyrotropin receptor.** *J Clin Endocrinol Metab.* 1994; **78**(4): 933–8.
PubMed Abstract | Publisher Full Text

71. Toulis KA, Goulis DG, Venetis CA, *et al.*: **Thyroid autoimmunity and miscarriages: The corpus luteum hypothesis.** *Med Hypotheses.* 2009; **73**(6): 1060–2.
PubMed Abstract | Publisher Full Text

72. Toulis KA, Goulis DG, Tsolakidou K, *et al.*: **Thyrotropin receptor autoantibodies and early miscarriages in patients with Hashimoto thyroiditis: A case-control study.** *Gynecol Endocrinol.* 2013; **29**(8): 793–6.
PubMed Abstract | Publisher Full Text

73. Caron P, Broussaud S, Galano-Frutos JJ, *et al.*: **New variant (Val597Ile) in transmembrane region of the TSH receptor with human chorionic gonadotropin hypersensitivity in familial gestational hyperthyroidism.** *Clin Endocrinol (Oxf).* 2020; **93**(3): 339–345.
PubMed Abstract | Publisher Full Text

74. Wide L, Eriksson K: **Dynamic changes in glycosylation and glycan composition of serum FSH and LH during natural ovarian stimulation.** *Ups J Med Sci.* 2013; **118**(3): 153–64.
PubMed Abstract | Publisher Full Text | Free Full Text

75. Walton WJ, Nguyen VT, Butnev VY, *et al.*: **Characterization of human FSH isoforms reveals a nonglycosylated beta-subunit in addition to the conventional glycosylated beta-subunit.** *J Clin Endocrinol Metab.* 2001; **86**(8): 3675–85.
PubMed Abstract | Publisher Full Text

76. Zariñán T, Butnev VY, Gutiérrez-Sagal R, *et al.*: **In Vitro Impact of FSH Glycosylation Variants on FSH Receptor-stimulated Signal Transduction and Functional Selectivity.** *J Endocr Soc.* 2020; **4**(5): bvaa019.
PubMed Abstract | Publisher Full Text | Free Full Text

77. Bousfield GR, Butnev VY, Butnev VY, *et al.*: **Hypo-glycosylated human follicle-stimulating hormone (hFSH(21/18)) is much more active *in vitro* than fully-glycosylated hFSH (hFSH(24)).** *Mol Cell Endocrinol.* 2014; **382**(2): 989–97.
PubMed Abstract | Publisher Full Text | Free Full Text

78. Jiang C, Hou X, Wang C, *et al.*: **Hypoglycosylated hFSH Has Greater Bioactivity Than Fully Glycosylated Recombinant hFSH in Human Granulosa Cells.** *J Clin Endocrinol Metab.* 2015; **100**(6): E852–60.
PubMed Abstract | Publisher Full Text | Free Full Text

79. Liang A, Plewes MR, Hua G, *et al.*: **Bioactivity of recombinant hFSH glycosylation variants in primary cultures of porcine granulosa cells.** *Mol Cell Endocrinol.* 2020; **514**: 110911.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

80. Wang H, Butnev V, Bousfield GR, *et al.*: **A human *FSHB* transgene encoding the double N-glycosylation mutant (Asn(7Δ) Asn(24Δ)) FSHβ subunit fails to rescue *Fshb* null mice.** *Mol Cell Endocrinol.* 2016; **426**: 113–24.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

81. Simon LE, Liu Z, Bousfield GR, *et al.*: **Recombinant FSH glycoforms are bioactive in mouse preantral ovarian follicles.** *Reproduction.* 2019; **158**(6): 517–527.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

82. Wang H, May J, Butnev V, *et al.*: **Evaluation of *in vivo* bioactivities of recombinant hypo- (FSH ²¹/¹⁸) and fully- (FSH ²⁴) glycosylated human FSH glycoforms in *Fshb* null mice.** *Mol Cell Endocrinol.* 2016; **437**: 224–236.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

83. Lombardi A, Andreozzi C, Pavone V, *et al.*: **Evaluation of the oligosaccharide composition of commercial follicle stimulating hormone preparations.** *Electrophoresis.* 2013; **34**(16): 2394–406.
PubMed Abstract | **Publisher Full Text**

84. Casarini L, Riccetti L, Paradiso E, *et al.*: **Two human menopausal gonadotropin (hMG) preparations display different early signaling *in vitro*.** *Mol Hum Reprod.* 2020; **26**(12): 894–905.
PubMed Abstract | **Publisher Full Text**

85. Riccetti L, Sperduti S, Lazzaretti C, *et al.*: **Glycosylation Pattern and *in vitro* Bioactivity of Reference Follitropin alfa and Biosimilars.** *Front Endocrinol (Lausanne).* 2019; **10**: 503.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

86. Riccetti L, Klett D, Ayoub MA, *et al.*: **Heterogeneous hCG and hMG commercial preparations result in different intracellular signalling but induce a similar long-term progesterone response *in vitro*.** *Mol Hum Reprod.* 2017; **23**(10): 685–697.
PubMed Abstract | **Publisher Full Text**

87. Casarini L, Brigante G, Simoni M, *et al.*: **Clinical Applications of Gonadotropins in the Female: Assisted Reproduction and Beyond.** *Prog Mol Biol Transl Sci.* 2016; **143**: 85–119.
PubMed Abstract | **Publisher Full Text**

88. Fan QR, Hendrickson WA: **Structural Biology of Glycoprotein Hormones and their Receptors.** *Endocrine.* 2005; **26**(3): 179–88.
PubMed Abstract | **Publisher Full Text**

89. Jiang X, Liu H, Chen X, *et al.*: **Structure of follicle-stimulating hormone in complex with the entire ectodomain of its receptor.** *Proc Natl Acad Sci U S A.* 2012; **109**(31): 12491–6.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

90. Costagliola S, Panneels V, Bonomi M, *et al.*: **Tyrosine sulfation is required for agonist recognition by glycoprotein hormone receptors.** *EMBO J.* 2002; **21**(4): 504–13.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

91. Ulloa-Aguirre A, Crépieux P, Poupon A, *et al.*: **Novel pathways in gonadotropin receptor signaling and biased agonism.** *Rev Endocr Metab Disord.* 2011; **12**(4): 259–74.
PubMed Abstract | **Publisher Full Text**

92. Gloaguen P, Crépieux P, Heitzler D, *et al.*: **Mapping the follicle-stimulating hormone-induced signaling networks.** *Front Endocrinol (Lausanne).* 2011; **2**: 45.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

93. Landomiel F, de Pascali F, Raynaud P, *et al.*: **Biased Signaling and Allosteric Modulation at the FSHR.** *Front Endocrinol (Lausanne).* 2019; **10**: 148.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

94. Casarini L, Moriondo V, Marino M, *et al.*: **FSHR polymorphism p.N680S mediates different responses to FSH *in vitro*.** *Mol Cell Endocrinol.* 2014; **393**(1–2): 83–91.
PubMed Abstract | **Publisher Full Text**

95. Wunsch A, Sonntag B, Simoni M: **Polymorphism of the FSH receptor and ovarian response to FSH.** *Ann Endocrinol (Paris).* 2007; **68**(2–3): 160–6.
PubMed Abstract | **Publisher Full Text**

96. Simoni M, Santi D, Negri L, *et al.*: **Treatment with human, recombinant FSH improves sperm DNA fragmentation in idiopathic infertile men depending on the FSH receptor polymorphism p.N680S: A pharmacogenetic study.** *Hum Reprod.* 2016; **31**(9): 1960–9.
PubMed Abstract | **Publisher Full Text**

97. Ayoub MA, Landomiel F, Gallay N, *et al.*: **Assessing Gonadotropin Receptor Function by Resonance Energy Transfer-Based Assays.** *Front Endocrinol (Lausanne).* 2015; **6**: 130.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

98. Troispoux C, Guillou F, Elalouf JM, *et al.*: **Involvement of G protein-coupled receptor kinases and arrestins in desensitization to follicle-stimulating hormone action.** *Mol Endocrinol.* 1999; **13**(9): 1599–614.
PubMed Abstract | **Publisher Full Text**

99. Lefkowitz RJ, Shenoy SK: **Transduction of receptor signals by beta-arrestins.** *Science.* 2005; **308**(5721): 512–7.
PubMed Abstract | **Publisher Full Text**

100. Jean-Alphonse F, Bowersox S, Chen S, *et al.*: **Spatially restricted G

protein-coupled receptor activity via divergent endocytic compartments.** *J Biol Chem.* 2014; **289**(7): 3960–77.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

101. Dwivedi-Agnihotri H, Chaturvedi M, Baidya M, *et al.*: **Distinct phosphorylation sites in a prototypical GPCR differently orchestrate β-arrestin interaction, trafficking, and signaling.** *Sci Adv.* 2020; **6**(37): eabb8368.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

102. Reiter E, Ayoub MA, Pellissier LP, *et al.*: **β-arrestin signalling and bias in hormone-responsive GPCRs.** *Mol Cell Endocrinol.* 2017; **449**: 28–41.
PubMed Abstract | **Publisher Full Text**

103. Marion S, Robert F, Crepieux P, *et al.*: **G protein-coupled receptor kinases and beta arrestins are relocalized and attenuate cyclic 3',5'-adenosine monophosphate response to follicle-stimulating hormone in rat primary Sertoli cells.** *Biol Reprod.* 2002; **66**(1): 70–6.
PubMed Abstract | **Publisher Full Text**

104. Czogalla B, Partenheimer A, Jeschke U, *et al.*: **β-arrestin 2 Is a Prognostic Factor for Survival of Ovarian Cancer Patients Upregulating Cell Proliferation.** *Front Endocrinol (Lausanne).* 2020; **11**: 554733.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

105. Rosanò L, Bagnato A: **New insights into the regulation of the actin cytoskeleton dynamics by GPCR/β-arrestin in cancer invasion and metastasis.** *Int Rev Cell Mol Biol.* 2019; **346**: 129–55.
PubMed Abstract

106. Shukla AK, Dwivedi-Agnihotri H: **Structure and function of β-arrestins, their emerging role in breast cancer, and potential opportunities for therapeutic manipulation.** *Adv Cancer Res.* 2020; **145**: 139–56.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

107. Baidya M, Kumari P, Dwivedi-Agnihotri H, *et al.*: **Genetically encoded intrabody sensors report the interaction and trafficking of β-arrestin 1 upon activation of G-protein-coupled receptors.** *J Biol Chem.* 2020; **295**(30): 10153–67.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

108. Kara E, Crépieux P, Gauthier C, *et al.*: **A phosphorylation cluster of five serine and threonine residues in the C-terminus of the follicle-stimulating hormone receptor is important for desensitization but not for beta-arrestin-mediated ERK activation.** *Mol Endocrinol.* 2006; **20**(11): 3014–26.
PubMed Abstract | **Publisher Full Text**

109. Cahill 3rd TJ, Thomsen ARB, Tarrasch JT, *et al.*: **Distinct conformations of GPCR-β-arrestin complexes mediate desensitization, signaling, and endocytosis.** *Proc Natl Acad Sci U S A.* 2017; **114**(10): 2562–7.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

110. Anderson RC, Newton CL, Millar RP: **Small Molecule Follicle-Stimulating Hormone Receptor Agonists and Antagonists.** *Front Endocrinol (Lausanne).* 2019; **9**: 757.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

111. Christopoulos A, Changeux JP, Catterall WA, *et al.*: **International Union of Basic and Clinical Pharmacology. XC. multisite pharmacology: Recommendations for the nomenclature of receptor allosterism and allosteric ligands.** *Pharmacol Rev.* 2014; **66**(4): 918–47.
PubMed Abstract | **Publisher Full Text**

112. Nataraja S, Sriraman V, Palmer S: **Allosteric Regulation of the Follicle-Stimulating Hormone Receptor.** *Endocrinology.* 2018; **159**(7): 2704–16.
PubMed Abstract | **Publisher Full Text**

113. Arey BJ, Yanofsky SD, Pérez MC, *et al.*: **Differing pharmacological activities of thiazolidinone analogs at the FSH receptor.** *Biochem Biophys Res Commun.* 2008; **368**(3): 723–8.
PubMed Abstract | **Publisher Full Text**

114. Sriraman V, Denis D, de Matos D, *et al.*: **Investigation of a thiazolidinone derivative as an allosteric modulator of follicle stimulating hormone receptor: Evidence for its ability to support follicular development and ovulation.** *Biochem Pharmacol.* 2014; **89**(2): 266–75.
PubMed Abstract | **Publisher Full Text**

115. van Koppen CJ, Verbost PM, van de Lagemaat R, *et al.*: **Signaling of an allosteric, nanomolar potent, low molecular weight agonist for the follicle-stimulating hormone receptor.** *Biochem Pharmacol.* 2013; **85**(8): 1162–70.
PubMed Abstract | **Publisher Full Text**

116. Yu HN, Richardson TE, Nataraja S, *et al.*: **Discovery of substituted benzamides as follicle stimulating hormone receptor allosteric modulators.** *Bioorg Med Chem Lett.* 2014; **24**(9): 2168–72.
PubMed Abstract | **Publisher Full Text**

117. van Straten NCR, van Berkel THJ, Demont DR, *et al.*: **Identification of substituted 6-amino-4-phenyltetrahydroquinoline derivatives: Potent antagonists for the follicle-stimulating hormone receptor.** *J Med Chem.* 2005; **48**(6): 1697–700.
PubMed Abstract | **Publisher Full Text**

118. Dias JA, Bonnet B, Weaver BA, *et al.*: **A negative allosteric modulator demonstrates biased antagonism of the follicle stimulating hormone receptor.** *Mol Cell Endocrinol.* 2011; **333**(2): 143–50.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

119. Dias JA, Campo B, Weaver BA, *et al.*: **Inhibition of follicle-stimulating hormone-induced preovulatory follicles in rats treated with a nonsteroidal negative allosteric modulator of follicle-stimulating hormone receptor.** *Biol Reprod.* 2014; **90**(1): 19.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

120. Danesi R, La Rocca RV, Cooper MR, *et al.*: **Clinical and experimental evidence of inhibition of testosterone production by suramin.** *J Clin Endocrinol Metab.* 1996; **81**(6): 2238–46.
PubMed Abstract | **Publisher Full Text**

121. Arey BJ, Deecher DC, Shen ES, *et al.*: **Identification and characterization of a selective, nonpeptide follicle-stimulating hormone receptor antagonist.** *Endocrinology.* 2002; **143**(10): 3822–9.
PubMed Abstract | **Publisher Full Text**

122. Wang Y, Dong Y, Wu S, *et al.*: **Acephate interferes with androgen synthesis in rat immature Leydig cells.** *Chemosphere.* 2020; **245**: 125597.
PubMed Abstract | **Publisher Full Text** | **Faculty Opinions Recommendation**

123. Ji Y, Liu P, Yuen T, *et al.*: **Epitope-specific monoclonal antibodies to FSHβ increase bone mass.** *Proc Natl Acad Sci U S A.* 2018; **115**(9): 2192–7.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

124. Wehbi V, Decourtye J, Piketty V, *et al.*: **Selective modulation of follicle-stimulating hormone signaling pathways with enhancing equine chorionic gonadotropin/antibody immune complexes.** *Endocrinology.* 2010; **151**(6): 2788–99.
PubMed Abstract | **Publisher Full Text**

125. Hervé V, Roy F, Bertin J, *et al.*: **Antiequine chorionic gonadotropin (eCG) antibodies generated in goats treated with eCG for the induction of ovulation modulate the luteinizing hormone and follicle-stimulating hormone bioactivities of eCG differently.** *Endocrinology.* 2004; **145**(1): 294–303.
PubMed Abstract | **Publisher Full Text**

126. Agrawal G, Dighe RR: **Critical involvement of the hinge region of the follicle-stimulating hormone receptor in the activation of the receptor.** *J Biol Chem.* 2009; **284**(5): 2636–47.
PubMed Abstract | **Publisher Full Text**

127. Dhar N, Mohan A, Thakur C, *et al.*: **Dissecting the structural and functional features of the Luteinizing hormone receptor using receptor specific single chain fragment variables.** *Mol Cell Endocrinol.* 2016; **427**: 1–12.
PubMed Abstract | **Publisher Full Text**

128. Majumdar R, Railkar R, Dighe RR: **Insights into differential modulation of receptor function by hinge region using novel agonistic lutropin receptor and inverse agonistic thyrotropin receptor antibodies.** *FEBS Lett.* 2012; **586**(6): 810–7.
PubMed Abstract | **Publisher Full Text**

129. Crepin R, Veggiani G, Djender S, *et al.*: **Whole-cell biopanning with a synthetic phage display library of nanobodies enabled the recovery of follicle-stimulating hormone receptor inhibitors.** *Biochem Biophys Res Commun.* 2017; **493**(4): 1567–72.
PubMed Abstract | **Publisher Full Text**

130. Ghosalkar JD, Dharma SJ, Nandedkar TD, *et al.*: **Identification of the region 285-309 of follicle stimulating hormone receptor as a bioneutralizing epitope.** *J Reprod Immunol.* 2007; **74**(1–2): 24–33.
PubMed Abstract | **Publisher Full Text**

131. Casarini L, Crépieux P, Reiter E, *et al.*: **FSH for the Treatment of Male Infertility.** *Int J Mol Sci.* 2020; **21**(7): 2270.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

132. Gera S, Kumar SS, Swamy SN, *et al.*: **Follicle-Stimulating Hormone Is an Autocrine Regulator of the Ovarian Cancer Metastatic Niche Through Notch Signaling.** *J Endocr Soc.* 2018; **3**(2): 340–57.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

133. Krishnamurthy H, Kishi H, Shi M, *et al.*: **Postendocytotic trafficking of the follicle-stimulating hormone (FSH)-FSH receptor complex.** *Mol Endocrinol.* 2003; **17**(11): 2162–76.
PubMed Abstract | **Publisher Full Text**

134. Sayers N, Hanyaloglu AC: **Intracellular Follicle-Stimulating Hormone Receptor Trafficking and Signaling.** *Front Endocrinol (Lausanne).* 2018; **9**: 653.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

135. Kanamarlapudi V, Thompson A, Kelly E, *et al.*: **ARF6 activated by the LHCG receptor through the cytohesin family of guanine nucleotide exchange factors mediates the receptor internalization and signaling.** *J Biol Chem.* 2012; **287**(24): 20443–55.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

136. Shukla AK, Westfield GH, Xiao K, *et al.*: **Visualization of arrestin recruitment by a G-protein-coupled receptor.** *Nature.* 2014; **512**(7513): 218–22.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

137. Kishi H, Ascoli M: **Multiple distant amino acid residues present in the serpentine region of the follitropin receptor modulate the rate of agonist-induced internalization.** *J Biol Chem.* 2000; **275**(40): 31030–7.
PubMed Abstract | **Publisher Full Text**

138. Ulloa-Aguirre A, Zariñán T, Gutiérrez-Sagal R, *et al.*: **Intracellular Trafficking of Gonadotropin Receptors in Health and Disease.** *Handb Exp Pharmacol.* 2018; **245**: 1–39.
PubMed Abstract | **Publisher Full Text**

139. Hanyaloglu AC: **Advances in Membrane Trafficking and Endosomal Signaling of G Protein-Coupled Receptors.** *Int Rev Cell Mol Biol.* 2018; **339**: 93–131.
PubMed Abstract | **Publisher Full Text**

140. Nagano M, Toshima JY, Siekhaus DE, *et al.*: **Rab5-mediated endosome formation is regulated at the *trans*-Golgi network.** *Commun Biol.* 2019; **2**: 419.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

141. Kulkarni R, Teves ME, Han AX, *et al.*: **Colocalization of Polycystic Ovary Syndrome Candidate Gene Products in Theca Cells Suggests Novel Signaling Pathways.** *J Endocr Soc.* 2019; **3**(12): 2204–23.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

142. Hirakawa T, Galet C, Kishi M, *et al.*: **GIPC binds to the human lutropin receptor (hLHR) through an unusual PDZ domain binding motif, and it regulates the sorting of the internalized human choriogonadotropin and the density of cell surface hLHR.** *J Biol Chem.* 2003; **278**(49): 49348–57.
PubMed Abstract | **Publisher Full Text**

143. Uribe A, Zariñán T, Pérez-Solis MA, *et al.*: **Functional and structural roles of conserved cysteine residues in the carboxyl-terminal domain of the follicle-stimulating hormone receptor in human embryonic kidney 293 cells.** *Biol Reprod.* 2008; **78**(5): 869–82.
PubMed Abstract | **Publisher Full Text**

144. Nechamen CA, Thomas RM, Dias JA: **APPL1, APPL2, Akt2 and FOXO1a interact with FSHR in a potential signaling complex.** *Mol Cell Endocrinol.* 2007; **260–262**: 93–9.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

145. Thomas RM, Nechamen CA, Mazurkiewicz JE, *et al.*: **The adapter protein APPL1 links FSH receptor to inositol 1,4,5-trisphosphate production and is implicated in intracellular Ca$^{(2+)}$ mobilization.** *Endocrinology.* 2011; **152**(4): 1691–701.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

146. Lin DC, Quevedo C, Brewer NE, *et al.*: **APPL1 associates with TrkA and GIPC1 and is required for nerve growth factor-mediated signal transduction.** *Mol Cell Biol.* 2006; **26**(23): 8928–41.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

147. Dias JA, Mahale SD, Nechamen CA, *et al.*: **Emerging roles for the FSH receptor adapter protein APPL1 and overlap of a putative 14-3-3τ interaction domain with a canonical G-protein interaction site.** *Mol Cell Endocrinol.* 2010; **329**(1–2): 17–25.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

148. Sposini S, Hanyaloglu AC: **Spatial encryption of G protein-coupled receptor signaling in endosomes; Mechanisms and applications.** *Biochem Pharmacol.* 2017; **143**: 1–9.
PubMed Abstract | **Publisher Full Text**

149. Irannejad R, Tomshine JC, Tomshine JR, *et al.*: **Conformational biosensors reveal GPCR signalling from endosomes.** *Nature.* 2013; **495**(7442): 534–8.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

150. Lyga S, Volpe S, Werthmann RC, *et al.*: **Persistent cAMP Signaling by Internalized LH Receptors in Ovarian Follicles.** *Endocrinology.* 2016; **157**(4): 1613–21.
PubMed Abstract | **Publisher Full Text**

151. Müller T, Gromoll J, Simoni M: **Absence of exon 10 of the human luteinizing hormone (LH) receptor impairs LH, but not human chorionic gonadotropin action.** *J Clin Endocrinol Metab.* 2003; **88**(5): 2242–9.
PubMed Abstract | **Publisher Full Text**

152. Santi D, Casarini L, Alviggi C, *et al.*: **Efficacy of Follicle-Stimulating Hormone (FSH) Alone, FSH + Luteinizing Hormone, Human Menopausal Gonadotropin or FSH + Human Chorionic Gonadotropin on Assisted Reproductive Technology Outcomes in the "Personalized" Medicine Era: A Meta-analysis.** *Front Endocrinol (Lausanne).* 2017; **8**: 114.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

153. Lunenfeld B, Bilger W, Longobardi S, *et al.*: **The Development of Gonadotropins for Clinical Use in the Treatment of Infertility.** *Front Endocrinol (Lausanne).* 2019; **10**: 429.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

154. Hugues JN: **Impact of 'LH activity' supplementation on serum progesterone levels during controlled ovarian stimulation: A systematic review.** *Hum Reprod.* 2012; **27**(1): 232–43.
PubMed Abstract | **Publisher Full Text**

155. Choi J, Smitz J: **Luteinizing hormone and human chorionic gonadotropin: A review of their varied clinical applications in assisted reproductive technology.** *Expert Rev Endocrinol Metab.* 2015; **10**(1): 87–100.
PubMed Abstract | **Publisher Full Text**

156. Choi J, Smitz J: **Luteinizing hormone and human chorionic gonadotropin: Distinguishing unique physiologic roles.** *Gynecol Endocrinol.* 2014; **30**(3): 174–81.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

157. Choi J, Smitz J: **Luteinizing hormone and human chorionic gonadotropin: Origins of difference.** *Mol Cell Endocrinol.* 2014; **383**(1–2): 203–13.
PubMed Abstract | **Publisher Full Text**

158. Hallast P, Nagirnaja L, Margus T, *et al.*: **Segmental duplications and gene conversion: Human luteinizing hormone/chorionic gonadotropin beta gene cluster.** *Genome Res.* 2005; **15**(11): 1535–46.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

159. Hallast P, Rull K, Laan M: **The evolution and genomic landscape of *CGB1* and**

CGB2 genes. *Mol Cell Endocrinol.* 2007; **260–262**(9): 2–11.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

160. Hallast P, Saarela J, Palotie A, *et al.*: **High divergence in primate-specific duplicated regions: Human and chimpanzee *chorionic gonadotropin beta* genes.** *BMC Evol Biol.* 2008; **8**: 195.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

161. Takehara I, Igarashi H, Kawagoe J, *et al.*: **Impact of endoplasmic reticulum stress on oocyte aging mechanisms.** *Mol Hum Reprod.* 2020; **26**(8): 567–75.
PubMed Abstract | **Publisher Full Text**

162. Lee-Thacker S, Jeon H, Choi Y, *et al.*: **Core Binding Factors are essential for ovulation, luteinization, and female fertility in mice.** *Sci Rep.* 2020; **10**(1): 9921.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

163. Hasegawa A, Mochida K, Matoba S, *et al.*: **Development of assisted reproductive technologies for *Mus spretus*.** *Biol Reprod.* 2021; **104**(1): 234–43.
PubMed Abstract | **Publisher Full Text**

164. Gu X, Wang Y, Gu J: **Age distribution of human gene families shows significant roles of both large- and small-scale duplications in vertebrate evolution.** *Nat Genet.* 2002; **31**(2): 205–9.
PubMed Abstract | **Publisher Full Text** | **Faculty Opinions Recommendation**

165. Grzesik P, Kreuchwig A, Rutz C, *et al.*: **Differences in Signal Activation by LH and hCG are Mediated by the LH/CG Receptor's Extracellular Hinge Region.** *Front Endocrinol (Lausanne).* 2015; **6**: 140.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

166. Grzesik P, Teichmann A, Furkert J, *et al.*: **Differences between lutropin-mediated and choriogonadotropin-mediated receptor activation.** *FEBS J.* 2014; **281**(5): 1479–92.
PubMed Abstract | **Publisher Full Text**

167. Troppmann B, Kleinau G, Krause G, *et al.*: **Structural and functional plasticity of the luteinizing hormone/choriogonadotrophin receptor.** *Hum Reprod Update.* 2013; **19**(5): 583–602.
PubMed Abstract | **Publisher Full Text**

168. Gromoll J, Wistuba J, Terwort N, *et al.*: **A new subclass of the luteinizing hormone/chorionic gonadotropin receptor lacking exon 10 messenger RNA in the New World monkey (*Platyrrhini*) lineage.** *Biol Reprod.* 2003; **69**(1): 75–80.
PubMed Abstract | **Publisher Full Text**

169. Santi D, Spaggiari G, Casarini L, *et al.*: **Central hypogonadism due to a giant, "silent" FSH-secreting, atypical pituitary adenoma: Effects of adenoma dissection and short-term Leydig cell stimulation by luteinizing hormone (LH) and human chorionic gonadotropin (hCG).** *Aging Male.* 2017; **20**(2): 96–101.
PubMed Abstract | **Publisher Full Text**

170. Riccetti L, De Pascali F, Gilioli L, *et al.*: **Human LH and hCG stimulate differently the early signalling pathways but result in equal testosterone synthesis in mouse Leydig cells in vitro.** *Reprod Biol Endocrinol.* 2017; **15**(1): 2.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

171. Casarini L, Lispi M, Longobardi S, *et al.*: **LH and hCG action on the same receptor results in quantitatively and qualitatively different intracellular signalling.** *PLoS One.* 2012; **7**(10): e46682.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

172. Casarini L, Riccetti L, De Pascali F, *et al.*: **Estrogen Modulates Specific Life and Death Signals Induced by LH and hCG in Human Primary Granulosa Cells In Vitro.** *Int J Mol Sci.* 2017; **18**(5): 926.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

173. Gupta C, Chapekar T, Chhabra Y, *et al.*: **Differential response to sustained stimulation by hCG & LH on goat ovarian granulosa cells.** *Indian J Med Res.* 2012; **135**(3): 331–40.
PubMed Abstract | **Free Full Text**

174. Gomez-León VE, Andrade JP, Kirkpatrick BW, *et al.*: **Selection of fewer dominant follicles in Trio carriers given GnRH antagonist and luteinizing hormone action replaced by nonpulsatile human chorionic gonadotropin†.** *Biol Reprod.* 2020; **103**(6): 1217–28.
PubMed Abstract | **Publisher Full Text**

175. Riccetti L, Yvinec R, Klett D, *et al.*: **Human Luteinizing Hormone and Chorionic Gonadotropin Display Biased Agonism at the LH and LH/CG Receptors.** *Sci Rep.* 2017; **7**(1): 940.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

176. Lazzaretti C, Secco V, Paradiso E, *et al.*: **Identification of Key Receptor Residues Discriminating Human Chorionic Gonadotropin (hCG)- and Luteinizing Hormone (LH)-Specific Signaling.** *Int J Mol Sci.* 2020; **22**(1): 151.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

177. Hill MJ, Levy G, Levens ED: **Does exogenous LH in ovarian stimulation improve assisted reproduction success? An appraisal of the literature.** *Reprod Biomed Online.* 2012; **24**(3): 261–71.
PubMed Abstract | **Publisher Full Text**

178. Marchiani S, Tamburrino L, Benini F, *et al.*: **LH supplementation of ovarian stimulation protocols influences follicular fluid steroid composition contributing to the improvement of ovarian response in poor responder women.** *Sci Rep.* 2020; **10**(1): 12907.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

179. Kol S, Segal L: **GnRH agonist triggering followed by 1500 IU of HCG 48 h after**

oocyte retrieval for luteal phase support. *Reprod Biomed Online.* 2020; **41**(5): 854–8.
PubMed Abstract | **Publisher Full Text**

180. Bildik G, Akin N, Esmaeilian Y, *et al.*: **hCG Improves Luteal Function and Promotes Progesterone Output through the Activation of JNK Pathway in the Luteal Granulosa Cells of the Stimulated IVF Cycles†.** *Biol Reprod.* 2020; **102**(6): 1270–80.
PubMed Abstract | **Publisher Full Text**

181. Castillo JC, Haahr T, Martínez-Moya M, *et al.*: **Gonadotropin-releasing hormone agonist ovulation trigger-beyond OHSS prevention.** *Ups J Med Sci.* 2020; **125**(2): 138–43.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

182. Castillo JC, Humaidan P, Bernabéu R: **Pharmaceutical options for triggering of final oocyte maturation in ART.** *Biomed Res Int.* 2014; **2014**: 580171.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

183. Huhtaniemi IT, Themmen APN: **Mutations in Human Gonadotropin and Gonadotropin-Receptor Genes.** *Endocrine.* 2005; **26**(3): 207–17.
PubMed Abstract | **Publisher Full Text**

184. Desai SS, Roy BS, Mahale SD: **Mutations and polymorphisms in FSH receptor: Functional implications in human reproduction.** *Reproduction.* 2013; **146**(6): R235–48.
PubMed Abstract | **Publisher Full Text**

185. Casarini L, Pignatti E, Simoni M: **Effects of polymorphisms in gonadotropin and gonadotropin receptor genes on reproductive function.** *Rev Endocr Metab Disord.* 2011; **12**(4): 303–21.
PubMed Abstract | **Publisher Full Text**

186. Conforti A, Vaiarelli A, Cimadomo D, *et al.*: **Pharmacogenetics of FSH Action in the Female.** *Front Endocrinol (Lausanne).* 2019; **10**: 398.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

187. Grigorova M, Punab M, Ausmees K, *et al.*: ***FSHB* promoter polymorphism within evolutionary conserved element is associated with serum FSH level in men.** *Hum Reprod.* 2008; **23**(9): 2160–6.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

188. Busch AS, Tüttelmann F, Cremers JF, *et al.*: ***FSHB* -211 G>T Polymorphism as Predictor for TESE Success in Patients With Unexplained Azoospermia.** *J Clin Endocrinol Metab.* 2019; **104**(6): 2315–24.
PubMed Abstract | **Publisher Full Text** | **Faculty Opinions Recommendation**

189. Schubert M, Kaldewey S, Lanuza LP, *et al.*: **Does the *FSHB* c.-211G>T polymorphism impact Sertoli cell number and the spermatogenic potential in infertile patients?** *Andrology.* 2020; **8**(5): 1030–7.
PubMed Abstract | **Publisher Full Text** | **Faculty Opinions Recommendation**

190. Schüring AN, Busch AS, Bogdanova N, *et al.*: **Effects of the FSH-β-subunit promoter polymorphism -211G->T on the hypothalamic-pituitary-ovarian axis in normally cycling women indicate a gender-specific regulation of gonadotropin secretion.** *J Clin Endocrinol Metab.* 2013; **98**(1): E82–6.
PubMed Abstract | **Publisher Full Text**

191. Ruth KS, Beaumont RN, Tyrrell J, *et al.*: **Genetic evidence that lower circulating FSH levels lengthen menstrual cycle, increase age at menopause and impact female reproductive health.** *Hum Reprod.* 2016; **31**(2): 473–81.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

192. Rull K, Grigorova M, Ehrenberg A, *et al.*: ***FSHB* -211 G>T is a major genetic modulator of reproductive physiology and health in childbearing age women.** *Hum Reprod.* 2018; **33**(5): 954–66.
PubMed Abstract | **Publisher Full Text**

193. Trevisan CM, de Oliveira R, Christofolini DM, *et al.*: **Effects of a Polymorphism in the Promoter Region of the Follicle-Stimulating Hormone Subunit Beta (*FSHB*) Gene on Female Reproductive Outcomes.** *Genet Test Mol Biomarkers.* 2019; **23**(1): 39–44.
PubMed Abstract | **Publisher Full Text**

194. Hoogendoorn B, Coleman SL, Guy CA, *et al.*: **Functional analysis of human promoter polymorphisms.** *Hum Mol Genet.* 2003; **12**(18): 2249–54.
PubMed Abstract | **Publisher Full Text** | **Faculty Opinions Recommendation**

195. Santi D, Crépieux P, Reiter E, *et al.*: **Follicle-stimulating Hormone (FSH) Action on Spermatogenesis: A Focus on Physiological and Therapeutic Roles.** *J Clin Med.* 2020; **9**(4): 1014.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

196. Simoni M, Brigante G, Rochira V, *et al.*: **Prospects for FSH Treatment of Male Infertility.** *J Clin Endocrinol Metab.* 2020; **105**(7): dgaa243.
PubMed Abstract | **Publisher Full Text**

197. Simoni M, Casarini L: **Mechanisms in endocrinology: Genetics of FSH action: a 2014-and-beyond view.** *Eur J Endocrinol.* 2014; **170**(3): R91–107.
PubMed Abstract | **Publisher Full Text**

198. Ahda Y, Gromoll J, Wunsch A, *et al.*: **Follicle-stimulating hormone receptor gene haplotype distribution in normozoospermic and azoospermic men.** *J Androl.* 2005; **26**(4): 494–9.
PubMed Abstract | **Publisher Full Text**

199. Schubert M, Lanuza LP, Gromoll J: **Pharmacogenetics of FSH Action in the Male.** *Front Endocrinol (Lausanne).* 2019; **10**: 47.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

200. Wunsch A, Ahda Y, Banaz-Yaşar F, et al.: **Single-nucleotide polymorphisms in the promoter region influence the expression of the human follicle-stimulating hormone receptor.** *Fertil Steril.* 2005; **84**(2): 446–53.
PubMed Abstract | **Publisher Full Text**

201. Wu Q, Zhang J, Zhu P, et al.: **The susceptibility of** *FSHB* **-211G > T and** *FSHR* **G-29A, 919A > G, 2039A > G polymorphisms to men infertility: an association study and meta-analysis.** *BMC Med Genet.* 2017; **18**(1): 81.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

202. Lend AK, Belousova A, Haller-Kikkatalo K, et al.: **Follicle-stimulating hormone receptor gene haplotypes and male infertility in estonian population and meta-analysis.** *Syst Biol Reprod Med.* 2010; **56**(1): 84–90.
PubMed Abstract | **Publisher Full Text**

203. Paschalidou C, Anagnostou E, Mavrogianni D, et al.: **The effects of follicle-stimulating hormone receptor (FSHR) -29 and Ser680Asn polymorphisms in IVF/ICSI.** *Horm Mol Biol Clin Investig.* 2020; **41**(2).
PubMed Abstract | **Publisher Full Text**

204. Desai SS, Achrekar SK, Paranjape SR, et al.: **Association of allelic combinations of FSHR gene polymorphisms with ovarian response.** *Reprod Biomed Online.* 2013; **27**(4): 400–6.
PubMed Abstract | **Publisher Full Text**

205. Achrekar SK, Modi DN, Meherji PK, et al.: **Follicle stimulating hormone receptor gene variants in women with primary and secondary amenorrhea.** *J Assist Reprod Genet.* 2010; **27**(6): 317–26.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

206. Zamaniara T, Taheripanah R, Ghaderian SMH, et al.: **Polymorphism FSHR (-29G/A) as a genetic agent together with ESRI (XbaIG/A) in women with poor response to controlled ovarian hyperstimulation.** *Hum Antibodies.* 2017; **26**(3): 143–7.
PubMed Abstract | **Publisher Full Text**

207. Tohlob D, Abo Hashem E, Ghareeb N, et al.: **Association of a promoter polymorphism in FSHR with ovarian reserve and response to ovarian stimulation in women undergoing assisted reproductive treatment.** *Reprod Biomed Online.* 2016; **33**(3): 391–7.
PubMed Abstract | **Publisher Full Text**

208. García-Jiménez G, Zariñán T, Rodríguez-Valentín R, et al.: **Frequency of the T307A, N680S, and -29GA single-nucleotide polymorphisms in the follicle-stimulating hormone receptor in Mexican subjects of Hispanic ancestry.** *Reprod Biol Endocrinol.* 2018; **16**(1): 100.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

209. Cannarella R, Musso N, Condorelli RA, et al.: **Combined Effects of the** *FSHR* **2039 A/G and** *FSHR* **-29 G/A Polymorphisms on Male Reproductive Parameters.** *World J Mens Health.* 2020.
PubMed Abstract | **Publisher Full Text**

210. Tsitlakidis D, Katopodi T, Goulis DG, et al.: **Association of follicle-stimulating hormone receptor single nucleotide polymorphisms with fertility in Greek men.** *J Endocrinol Invest.* 2017; **40**(7): 721–6.
PubMed Abstract | **Publisher Full Text**

211. Capalbo A, Poli M, Riera-Escamilla A, et al.: **Preconception genome medicine: Current state and future perspectives to improve infertility diagnosis and reproductive and health outcomes based on individual genomic data.** *Hum Reprod Update.* 2021; **27**(2): 254–79.
PubMed Abstract | **Publisher Full Text**

212. Oduwole OO, Peltoketo H, Huhtaniemi IT: **Role of Follicle-Stimulating Hormone in Spermatogenesis.** *Front Endocrinol (Lausanne).* 2018; **9**: 763.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

213. Amsterdam A, Keren-Tal I, Aharoni D, et al.: **Steroidogenesis and apoptosis in the mammalian ovary.** *Steroids.* 2003; **68**(10–13): 861–7.
PubMed Abstract | **Publisher Full Text**

214. Amsterdam A, Keren-Tal I, Aharoni D: **Cross-talk between cAMP and p53-generated signals in induction of differentiation and apoptosis in steroidogenic granulosa cells.** *Steroids.* 1996; **61**(4): 252–6.
PubMed Abstract | **Publisher Full Text**

215. Casarini L, Lazzaretti C, Paradiso E, et al.: **Membrane Estrogen Receptor (GPER) and Follicle-Stimulating Hormone Receptor (FSHR) Heteromeric Complexes Promote Human Ovarian Follicle Survival.** *iScience.* 2020; **23**(12): 101812.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

216. Chen MJ, Chou CH, Shun CT, et al.: **Iron suppresses ovarian granulosa cell proliferation and arrests cell cycle through regulating p38 mitogen-activated protein kinase/p53/p21 pathway.** *Biol Reprod.* 2017; **97**(3): 438–48.
PubMed Abstract | **Publisher Full Text**

217. Shiota M, Sugai N, Tamura M, et al.: **Correlation of mitogen-activated protein kinase activities with cell survival and apoptosis in porcine granulosa cells.** *Zoolog Sci.* 2003; **20**(2): 193–201.
PubMed Abstract | **Publisher Full Text**

218. Inagaki K, Otsuka F, Miyoshi T, et al.: **p38-Mitogen-activated protein kinase stimulated steroidogenesis in granulosa cell-oocyte cocultures: role of bone morphogenetic proteins 2 and 4.** *Endocrinology.* 2009; **150**(4): 1921–30.
PubMed Abstract | **Publisher Full Text**

219. Pasapera AM, Jiménez-Aguilera MdP, Chauchereau A, et al.: **Effects of FSH and 17beta-estradiol on the transactivation of estrogen-regulated promoters and cell proliferation in L cells.** *J Steroid Biochem Mol Biol.* 2005; **94**(4): 289–302.
PubMed Abstract | **Publisher Full Text**

220. Drummond AE, Findlay JK: **The role of estrogen in folliculogenesis.** *Mol Cell Endocrinol.* 1999; **151**(1–2): 57–64.
PubMed Abstract | **Publisher Full Text**

221. Baerwald AR, Adams GP, Pierson RA: **Ovarian antral folliculogenesis during the human menstrual cycle: A review.** *Hum Reprod Update.* 2012; **18**(1): 73–91.
PubMed Abstract | **Publisher Full Text**

222. Sobotka V, Streda R, Mardesic T, et al.: **Steroids pretreatment in assisted reproduction cycles.** *J Steroid Biochem Mol Biol.* 2014; **139**: 114–21.
PubMed Abstract | **Publisher Full Text**

223. Tranchant T, Durand G, Gauthier C, et al.: **Preferential β-arrestin signalling at low receptor density revealed by functional characterization of the human FSH receptor A189 V mutation.** *Mol Cell Endocrinol.* 2011; **331**(1): 109–18.
PubMed Abstract | **Publisher Full Text**

224. Agwuegbo UC, Jonas KC: **Molecular and functional insights into gonadotropin hormone receptor dimerization and oligomerization.** *Minerva Ginecol.* 2018; **70**(5): 539–48.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

225. Liu Y, Zhang Y, Jiang J, et al.: **GHR/PRLR Heteromultimer Is Composed of GHR Homodimers and PRLR Homodimers.** *Mol Endocrinol.* 2016; **30**(5): 504–17.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

226. Sleno R, Hébert TE: **Shaky ground - The nature of metastable GPCR signalling complexes.** *Neuropharmacology.* 2019; **152**: 4–14.
PubMed Abstract | **Publisher Full Text**

227. Ji I, Lee C, Jeoung M, et al.: *Trans*-activation of mutant follicle-stimulating hormone receptors selectively generates only one of two hormone signals. *Mol Endocrinol.* 2004; **18**(4): 968–78.
PubMed Abstract | **Publisher Full Text**

228. Song YS, Ji I, Beauchamp J, et al.: **Hormone interactions to Leu-rich repeats in the gonadotropin receptors. I. Analysis of Leu-rich repeats of human luteinizing hormone/chorionic gonadotropin receptor and follicle-stimulating hormone receptor.** *J Biol Chem.* 2001; **276**(5): 3426–35.
PubMed Abstract | **Publisher Full Text**

229. Kroeger KM, Eidne KA: **Study of G-protein-coupled receptor-protein interactions by bioluminescence resonance energy transfer.** *Methods Mol Biol.* 2004; **259**: 323–33.
PubMed Abstract | **Publisher Full Text**

230. Jonas KC, Chen S, Virta M, et al.: **Temporal reprogramming of calcium signalling via crosstalk of gonadotrophin receptors that associate as functionally asymmetric heteromers.** *Sci Rep.* 2018; **8**(1): 2239.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

231. Jonas KC, Hanyaloglu AC: **Impact of G protein-coupled receptor heteromers in endocrine systems.** *Mol Cell Endocrinol.* 2017; **449**: 21–27.
PubMed Abstract | **Publisher Full Text**

232. Casarini L, Santi D, Simoni M, et al.: **'Spare' Luteinizing Hormone Receptors: Facts and Fiction.** *Trends Endocrinol Metab.* 2018; **29**(4): 208–217.
PubMed Abstract | **Publisher Full Text**

233. Feng X, Zhang M, Guan R, et al.: **Heterodimerization between the lutropin and follitropin receptors is associated with an attenuation of hormone-dependent signaling.** *Endocrinology.* 2013; **154**(10): 3925–30.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

234. Jockers R: **Comment on "The Use of BRET to Study Receptor-Protein Interactions".** *Front Endocrinol (Lausanne).* 2014; **5**: 3.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

235. Rivero-Müller A, Chou YY, Ji I, et al.: **Rescue of defective G protein-coupled receptor function in vivo by intermolecular cooperation.** *Proc Natl Acad Sci U S A.* 2010; **107**(5): 2319–24.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

236. Ji I, Lee C, Song Y, et al.: *Cis*- and *trans*-activation of hormone receptors: The LH receptor. *Mol Endocrinol.* 2002; **16**(6): 1299–308.
PubMed Abstract | **Publisher Full Text**

237. Zhang M, Guan R, Segaloff DL: **Revisiting and questioning functional rescue between dimerized LH receptor mutants.** *Mol Endocrinol.* 2012; **26**(4): 655–68.
PubMed Abstract | **Publisher Full Text**

238. Huang B, St Onge CM, Ma H, et al.: **Design of bivalent ligands targeting putative GPCR dimers.** *Drug Discov Today.* 2021; **26**(1): 189–199.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

239. Lizneva D, Rahimova A, Kim SM, et al.: **FSH Beyond Fertility.** *Front Endocrinol (Lausanne).* 2019; **10**: 136.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **Faculty Opinions Recommendation**

240. Kero J, Poutanen M, Zhang FP, et al.: **Elevated luteinizing hormone induces expression of its receptor and promotes steroidogenesis in the adrenal cortex.** *J Clin Invest.* 2000; **105**(5): 633–41.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

241. Pabon JE, Li X, Lei ZM, et al.: **Novel presence of luteinizing hormone/chorionic gonadotropin receptors in human adrenal glands.** *J Clin Endocrinol Metab.* 1996; **81**(6): 2397–400.
PubMed Abstract | **Publisher Full Text**

242. Plöckinger U, Chrusciel M, Doroszko M, et al.: **Functional Implications of LH/hCG**

Receptors in Pregnancy-Induced Cushing Syndrome. *J Endocr Soc.* 2017; **1**(1): 57–71.
PubMed Abstract | Publisher Full Text | Free Full Text

243. Li S, Yang C, Fan J, *et al.*: **Pregnancy-induced Cushing's syndrome with an adrenocortical adenoma overexpressing LH/hCG receptors: A case report.** *BMC Endocr Disord.* 2020; **20**(1): 62.
PubMed Abstract | Publisher Full Text | Free Full Text

244. Perrier d'Hauterive S, Berndt S, Tsampalas M, *et al.*: **Dialogue between blastocyst hCG and endometrial LH/hCG receptor: Which role in implantation?** *Gynecol Obstet Invest.* 2007; **64**(3): 156–60.
PubMed Abstract | Publisher Full Text

245. Ziecik AJ: **Luteinizing hormone/human chorionic gonadotropin receptors in myometrium and their role in uterine motility.** *Arch Immunol Ther Exp (Warsz).* 1990; **38**(1–2): 141–4.
PubMed Abstract

246. Ziecik AJ, Kaczmarek MM, Blitek A, *et al.*: **Novel biological and possible applicable roles of LH/hCG receptor.** *Mol Cell Endocrinol.* 2007; **269**(1–2): 51–60.
PubMed Abstract | Publisher Full Text

247. Bukovsky A, Indrapichate K, Fujiwara H, *et al.*: **Multiple luteinizing hormone receptor (LHR) protein variants, interspecies reactivity of anti-LHR mAb clone 3B5, subcellular localization of LHR in human placenta, pelvic floor and brain, and possible role for LHR in the development of abnormal pregnancy, pelvic floor disorders and Alzheimer's disease.** *Reprod Biol Endocrinol.* 2003; **1**: 46.
PubMed Abstract | Publisher Full Text | Free Full Text

248. Movsas TZ, Muthusamy A: **The potential effect of human chorionic gonadotropin on vasoproliferative disorders of the immature retina.** *Neuroreport.* 2018; **29**(18): 1525–1529.
PubMed Abstract | Publisher Full Text | Free Full Text

249. Ponikwicka-Tyszko D, Chrusciel M, Stelmaszewska J, *et al.*: **Functional Expression of FSH Receptor in Endometriotic Lesions.** *J Clin Endocrinol Metab.* 2016; **101**(7): 2905–14.
PubMed Abstract | Publisher Full Text

250. Sun L, Peng Y, Sharrow AC, *et al.*: **FSH directly regulates bone mass.** *Cell.* 2006; **125**(2): 247–60.
PubMed Abstract | Publisher Full Text | Faculty Opinions Recommendation

251. Zaidi M, Blair HC, Iqbal J, *et al.*: **Proresorptive actions of FSH and bone loss.** *Ann N Y Acad Sci.* 2007; **1116**: 376–82.
PubMed Abstract | Publisher Full Text

252. Zaidi M, Blair HC, Iqbal J, *et al.*: **New insights: Elevated follicle-stimulating hormone and bone loss during the menopausal transition.** *Curr Rheumatol Rep.* 2009; **11**(3): 191–5.
PubMed Abstract | Publisher Full Text

253. Iqbal J, Sun L, Zaidi M: **Commentary-FSH and bone 2010: Evolving evidence.** *Eur J Endocrinol.* 2010; **163**(1): 173–6.
PubMed Abstract | Publisher Full Text

254. Agrawal M, Zhu G, Sun L, *et al.*: **The role of FSH and TSH in bone loss and its clinical relevance.** *Curr Osteoporos Rep.* 2010; **8**(4): 205–11.
PubMed Abstract | Publisher Full Text

255. Zaidi M, Sun L, Liu P, *et al.*: **Pituitary-bone connection in skeletal regulation.** *Horm Mol Biol Clin Investig.* 2016; **28**(2): 85–94.
PubMed Abstract | Publisher Full Text

256. Zaidi M, New MI, Blair HC, *et al.*: **Actions of pituitary hormones beyond traditional targets.** *J Endocrinol.* 2018; **237**(3): R83–R98.
PubMed Abstract | Publisher Full Text | Free Full Text

257. Zaidi M, Lizneva D, Kim SM, *et al.*: **FSH, Bone Mass, Body Fat, and Biological Aging.** *Endocrinology.* 2018; **159**(10): 3503–14.
PubMed Abstract | Publisher Full Text | Free Full Text

258. Taneja C, Gera S, Kim SM, *et al.*: **FSH-metabolic circuitry and menopause.** *J Mol Endocrinol.* 2019; **63**(3): R73–R80.
PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

259. Wang J, Zhang W, Yu C, *et al.*: **Follicle-Stimulating Hormone Increases the Risk of Postmenopausal Osteoporosis by Stimulating Osteoclast Differentiation.** *PLoS One.* 2015; **10**(8): e0134986.
PubMed Abstract | Publisher Full Text | Free Full Text

260. Robinson LJ, Tourkova I, Wang Y, *et al.*: **FSH-receptor isoforms and**

FSH-dependent gene transcription in human monocytes and osteoclasts. *Biochem Biophys Res Commun.* 2010; **394**(1): 12–7.
PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

261. Khosla S: **Estrogen Versus FSH Effects on Bone Metabolism: Evidence From Interventional Human Studies.** *Endocrinology.* 2020; **161**(8): bqaa111.
PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

262. Wang N, Shao H, Chen Y, *et al.*: **Follicle-Stimulating Hormone, Its Association with Cardiometabolic Risk Factors, and 10-Year Risk of Cardiovascular Disease in Postmenopausal Women.** *J Am Heart Assoc.* 2017; **6**(9): e005918.
PubMed Abstract | Publisher Full Text | Free Full Text

263. Stilley JA, Guan R, Duffy DM, *et al.*: **Signaling through FSH receptors on human umbilical vein endothelial cells promotes angiogenesis.** *J Clin Endocrinol Metab.* 2014; **99**(5): E813–20.
PubMed Abstract | Publisher Full Text | Free Full Text

264. Planeix F, Siraj MA, Bidard FC, *et al.*: **Endothelial follicle-stimulating hormone receptor expression in invasive breast cancer and vascular remodeling at tumor periphery.** *J Exp Clin Cancer Res.* 2015; **34**(1): 12.
PubMed Abstract | Publisher Full Text | Free Full Text

265. Siraj MA, Pichon C, Radu A, *et al.*: **Endothelial follicle stimulating hormone receptor in primary kidney cancer correlates with subsequent response to sunitinib.** *J Cell Mol Med.* 2012; **16**(9): 2010–6.
PubMed Abstract | Publisher Full Text | Free Full Text

266. Radu A, Pichon C, Camparo P, *et al.*: **Expression of follicle-stimulating hormone receptor in tumor blood vessels.** *N Engl J Med.* 2010; **363**(17): 1621–30.
PubMed Abstract | Publisher Full Text | Faculty Opinions Recommendation

267. Gera S, Sant D, Haider S, *et al.*: **First-in-class humanized FSH blocking antibody targets bone and fat.** *Proc Natl Acad Sci U S A.* 2020; **117**(46): 28971–9.
PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

268. Bonci EA, Buiga R, Badan M, *et al.*: **Follicle-stimulating hormone receptors: A comparison of commercially-available monoclonal and polyclonal antibodies as immunohistochemical markers for cancer research.** *J BUON.* 2018; **23**(6): 1912–21.
PubMed Abstract

269. Chrusciel M, Ponikwicka-Tyszko D, Wolczynski S, *et al.*: **Extragonadal FSHR Expression and Function-Is It Real?** *Front Endocrinol (Lausanne).* 2019; **10**: 32.
PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

270. Moeker N, Peters S, Rauchenberger R, *et al.*: **Antibody Selection for Cancer Target Validation of FSH-Receptor in Immunohistochemical Settings.** *Antibodies (Basel).* 2017; **6**(4): 15.
PubMed Abstract | Publisher Full Text | Free Full Text

271. Karakaya C, Guzeloglu-Kayisli O, Hobbs RJ, *et al.*: **Follicle-stimulating hormone receptor (*FSHR*) alternative skipping of exon 2 or 3 affects ovarian response to FSH.** *Mol Hum Reprod.* 2014; **20**(7): 630–43.
PubMed Abstract | Publisher Full Text | Free Full Text

272. Doroszko M, Chrusciel M, Stelmaszewska J, *et al.*: **GnRH antagonist treatment of malignant adrenocortical tumors.** *Endocr Relat Cancer.* 2019; **26**(1): 103–17.
PubMed Abstract | Publisher Full Text | Free Full Text

273. Vuorenoja S, Mohanty BP, Arola J, *et al.*: **Hecate-CGbeta conjugate and gonadotropin suppression shows two distinct mechanisms of action in the treatment of adrenocortical tumors in transgenic mice expressing Simian Virus 40 T antigen under inhibin-alpha promoter.** *Endocr Relat Cancer.* 2009; **16**(2): 549–64.
PubMed Abstract | Publisher Full Text

274. Finkelstein JS, Lee H, Burnett-Bowie SAM, *et al.*: **Gonadal steroids and body composition, strength, and sexual function in men.** *N Engl J Med.* 2013; **369**(11): 1011–22.
PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

275. Stelmaszewska J, Chrusciel M, Doroszko M, *et al.*: **Revisiting the expression and function of follicle-stimulation hormone receptor in human umbilical vein endothelial cells.** *Sci Rep.* 2016; **6**: 37095.
PubMed Abstract | Publisher Full Text | Free Full Text