Gonadotropin

Gonadotropins are decorated with glycans that regulate several functions of the protein including folding, heterodimerization, stability, transport, conformational maturation, efficiency of heterodimer secretion, metabolic fate, interaction with their cognate receptor, and selective activation of signaling pathways.

From: *Progress in Molecular Biology and Translational Science*, 2016

Related terms:

Diethylstilbestrol, Protein, Chorionic Gonadotropin, Follitropin, Gonadorelin-, Luteinizing Hormone, Testosterone, Progesterone

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Female Reproduction

T. Rajendra Kumar, in *Encyclopedia of Reproduction (Second Edition)*, 2018

Clinical Applications of Gonadotropins

Human gonadotropin preparations purified from pituitary and urine sources were used for clinical research in the past. However, recombinant gonadotropins expressed in mammalian cell expression systems replaced the earlier preparations and have now been in use for various human in vitro fertilization protocols at the clinic. These recombinant gonadotropins are routinely used for ovarian follicle induction in vivo and follicle maturation in vitro. These preparations are pathogen-free and thus safe for human use. Elegant molecular cloning techniques have also allowed expressing improved versions of gonadotropins such as single chain gonadotropin analogs in which the two gonadotropins subunits are genetically fused in tandem. A long-acting FSH analog with enhanced serum half-life of FSH was also generated by genetically fusing the DNA sequence encoding the carboxy terminus of hCG to 3′-end of DNA sequence encoding the human FSH subunit. This FSH analog is currently approved for use in human IVF protocols in some countries. Although the primary goal of recombinant human gonadotropins is to benefit human reproductive healthcare, recombinant homologous hormones are equally efficacious in many veterinary/agricultural livestock species.
Gonadotropins

In *Meyler's Side Effects of Drugs (Sixteenth Edition)*, 2016

Immunologic

Gonadotropins of natural origin contain various allergens, which can give rise to hypersensitivity reactions. This was a serious problem with the “PMS” gonadotropin formulations formerly made from the serum of pregnant mares but now apparently obsolete; it was also described in the past with an FSH formulation of porcine origin. However hypersensitivity reactions can also occur to extracts of human material.

- A generalized allergic reaction to human menopausal gonadotropin (Pergonal) has been described during controlled ovarian hyperstimulation [63]. In this case a desensitization protocol allowed the patient to complete her treatment cycle without further problems. Subsequently recombinant follicle stimulating hormone was used successfully and uneventfully.

On occasion, there have even been such reactions to highly purified human products, notably FSH; they can be managed by changing the treatment to intramuscular recombinant follicle stimulating hormone [64].

There have been reports of systemic hypersensitivity reactions to goserelin and leuprolide.

- An 8-year-old girl developed anaphylaxis after a goserelin acetate implant [65]. Her symptoms continued for 4 days after the implant was removed. Less severe symptoms recurred 6 weeks later. She had had a systemic allergic reaction to leuprolide acetate 3 years before.

The long half-lives of these agents in tissues requires clinicians to be aware of the possibility of continued and recurrent anaphylaxis.

Volume II

Estradiol

The administration of estradiol to women or other female mammals is followed by an initial suppression of plasma LH and FSH, but both gonadotropins, particularly LH, are subsequently increased. The time course of this biphasic action depends on the species and the dose of estradiol used. In women, the inhibitory effects persist for 2 to 3 days and are followed by augmentation of LH secretion—“positive feedback.” With the use of exogenous GnRH, both the inhibitory and the stimulatory effects of estradiol were shown to be exerted on the gonadotrope cell. In women, LH responses to GnRH are suppressed during the first 36 hours but are augmented after 48 hours, and the enhanced responses persist for several days. The temporal relationships in sheep, together with the pituitary site of estradiol action, are shown in Figure 116-4. Estradiol initially inhibits LH release to pulsatile GnRH, but responses are then augmented and mean plasma LH increases. This positive action of estradiol accounts in part for variations in LH responsiveness to GnRH during the menstrual cycle. LH responses are augmented during the late follicular and midluteal phases of the cycle, when plasma estradiol is elevated. Humans appear to be unique with the pituitary being the primary site of estradiol positive feedback.

In other mammalian species, including nonhuman primates, the site of positive estradiol feedback on gonadotropin secretion is at both the hypothalamic and pituitary levels. In vitro studies in rat pituitary cells show that LH responses to GnRH are augmented after 12 hours of exposure to estradiol. The mechanisms of estradiol action include enhanced GnRHR upregulation by GnRH, and increasing both the amount of LH released by each cell and the number of cells releasing LH. However, in vivo data in the rat show that estradiol also stimulates GnRH secretion by increasing POA norepinephrine release on the afternoon of proestrus.

In contrast to its action on LH, estradiol inhibits FSH release. The differential effects of estradiol on pituitary LH and FSH secretion are seen in studies in which GnRH pulses are administered to women with isolated GnRH deficiency (Kallmann’s syndrome). Pretreatment with estradiol abolishes FSH responses to GnRH, but LH responsiveness is maintained. As shown in Figure 116-5, the inhibitory effect of estradiol on FSH release is evident when endogenous plasma estradiol >50 to 75 pg/mL, and FSH release is abolished by the addition of exogenous estradiol. In vitro studies using pituitary cells have shown that estradiol inhibition of FSH secretion involves reducing FSH synthesis after 6 to 8 hours’ exposure to steroid.

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Comparative Reproduction
GnIH was discovered in Japanese quail as the first inhibitory hypothalamic neuropeptide of gonadotropin release (Tsutsui et al., 2000). GnIH peptide was isolated and identified in various mammalian species including hamsters, monkeys and humans (Ubuka et al., 2016). GnIH is also named RFamide-related peptide in mammals, because GnIH peptides have LPXRFamide (X = L or Q) amino acid sequence at their C-termini. GnIH neuronal cell bodies exist in the dorsomedial hypothalamic area (DMH) in mammals and terminate on GnRH and kisspeptin neurons that express GnIH receptors (Fig. 1). Expression of GnIH peptide and GnIH neuronal activities are regulated by natural and social environmental cues and stress. Therefore, one of the important roles of GnIH is to convey favorable and unfavorable environmental and social information to the HPG axis (Ubuka et al., 2016).

Gonadotropin-Inhibitory Hormone
Kazuyoshi Tsutsui, Takayoshi Ubuka, in Handbook of Hormones, 2016

Abstract
Gonadotropin-inhibitory hormone (GnIH) was originally identified in birds, and subsequently in mammals and other vertebrates. GnIH acts on the pituitary and on gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus via GPR147, a G protein-coupled receptor. GnIH decreases gonadotropin synthesis and release, inhibiting gonadal development and maintenance. Such a downregulation of the hypothalamo-pituitary–gonadal (HPG) axis may be conserved across vertebrates. GnIH also inhibits reproductive behaviors, such as sexual and aggressive behaviors. GnIH may operate at the level of the gonads as an autocrine/paracrine regulator of steroidogenesis and gametogenesis. GnIH acts in the HPG axis to appropriately regulate reproductive activity across the seasons and during times of stress.
Gonadotropins: from Bench Side to Bedside

T. Rajendra Kumar, in Progress in Molecular Biology and Translational Science, 2016

Abstract

Gonadotropins play fundamental roles in reproduction. More than 30 years ago, Cga transgenic mice were generated, and more than 20 years ago, the phenotypes of Cga null mice were reported. Since then, numerous mouse strains have been generated and characterized to address several questions in reproductive biology involving gonadotropin synthesis, secretion, and action. More recently, extragonadal expression, and in some cases, functions of gonadotropins in nongonadal tissues have been identified. Several genomic and proteomic approaches including novel mouse genome editing tools are available now. It is anticipated that these and other emerging technologies will be useful to build an integrated network of gonadotropin signaling pathways in various tissues. Undoubtedly, research on gonadotropins will continue to provide new knowledge and allow us transcend from benchside to the bedside.

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Gonadotropins: from Bench Side to Bedside

L. Casarini, ... D. Santi, in Progress in Molecular Biology and Translational Science, 2016

Abstract

Gonadotropins (LH, FSH, and hCG) act in concert in the regulation of female reproductive system. Exploiting this influence, they are part of the assisted reproductive technique protocols. In this review we analyze the effectiveness of the different available gonadotropin formulations and the consequent adverse events. Moreover, different protocols for poor-responders and polycystic ovary syndrome affected women are explored. All these clinical different approaches have specific molecular bases, covered in this review starting from evolution and population genetics, getting to in vitro studies of gonadotropins action. Beyond their application in assisted reproductive technique, gonadotropins have also been largely studied for their intertwined network of interactions with other hormones, which all together contribute to the
functioning of the reproductive system and other hormonal axes. In particular, there is both clinical and molecular evidence of interaction between thyroid hormones and insulin growth factors with gonadotropins. Finally, gonadotropins are widely studied for their role in the maintenance of the proper balance between cell proliferation and differentiation, and therefore in cancer.

> Read full chapter

**Neuroendocrine Control of the Menstrual Cycle**

Janet E. Hall, in *Yen & Jaffe's Reproductive Endocrinology (Seventh Edition)*, 2014

**Gonadotropin Inhibitory Hormone**

Gonadotropin inhibitory hormone (GnIH) is a hypothalamic neuropeptide that inhibits GnRH secretion. First discovered in the quail, there is now evidence that it is present in other avian species as well as in mammals, including the human.\(^{25,26}\) GnIH is secreted into the pituitary portal system\(^{27}\) and its receptor, G-protein coupled receptor 147 (GPR147) is present on both GnRH and gonadotrope cells, raising the distinct possibility that it functions at both the hypothalamic and pituitary level to regulate secretion of LH and FSH. Importantly, there is also evidence that GnIH increases food intake in sheep without reducing energy expenditure,\(^{28}\) raising the possibility that GnIH may be a factor that mediates the inverse relationship between LH and body mass index in women.

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**Anterior Pituitary**

Mark E. Molitch, in *Goldman's Cecil Medicine (Twenty Fourth Edition)*, 2012

**Clinical Manifestations**

Gonadotropin-producing tumors are somewhat more common in men than women and increase in prevalence with age. FSH- and LH-producing tumors do not usually cause a characteristic hormone excess syndrome. The tumors, typically large macroadenomas, present as clinically nonfunctioning tumors with symptoms and signs related to local mass effects. Visual field loss is found in more than 70% of patients. Many are detected incidentally by CT and MRI performed for unrelated
indications. Symptoms of hypogonadism with loss of libido are also common. Men with predominantly FSH-secreting tumors may present with testicular enlargement from hypertrophy of the seminiferous tubules but may also be hypogonadal due to low levels of testosterone. These patients must be distinguished from those with primary hypogonadism due to testicular dysfunction. Tumors that primarily secrete LH are rare but can cause increased testosterone levels. Premenopausal women with gonadotropin-producing tumors may experience menstrual irregularity or secondary hypogonadism. Postmenopausal women often show reduced gonadotropin levels because the mass effects of the gonadotropin-producing tumors cause stalk compression, impairing GnRH stimulation of gonadotropins from normal pituitary cells.

> Read full chapter

**Female Infertility**

Robert L. Barbieri, in *Yen & Jaffe's Reproductive Endocrinology (Sixth Edition)*, 2009

**GONADOTROPIN INJECTIONS AND GONADOTROPIN INJECTIONS PLUS INTRAUTERINE INSEMINATION**

Both gonadotropin injections alone and gonadotropin injections plus IUI increase fecundability in women with unexplained infertility. Gonadotropin injections plus IUI also appears to increase fecundability in infertile women with stage I or II endometriosis and in infertile men with semen abnormalities (Fig. 21-18). In one study, 932 infertile couples with unexplained infertility or stage I or II endometriosis were randomized to one of four treatment groups: ICI, IUI, FSH injections plus ICI, or FSH injections plus IUI. The pregnancy rate in the control, the ICI group, was 2% per cycle. In the FSH-plus-ICI and the FSH-plus-IUI groups, the pregnancy rate per cycle was 4% and 9%, respectively. The main complication of the use of FSH injections in the treatment of infertility in women with unexplained infertility is an increase in the rate of multiple gestations and ovarian hyperstimulation. Of the ongoing pregnancies in this study, 3% were quadruplets, 5% were triplets, and 20% were twins. In another study of gonadotropin injections with or without IUI, Serhal randomized 62 couples with unexplained infertility to receive IUI alone, gonadotropin injections alone, or gonadotropin injections plus IUI. The per-cycle pregnancy rate was 2.2% for IUI alone, 6.1% for gonadotropin injections alone, and 26% for gonadotropin injections plus IUI. Similar results have been reported by other investigators.
Although there is evidence for the efficacy of gonadotropin with or without IUI for the treatment of unexplained infertility, many authorities highlight the increased risk of multiple gestation with these therapies, and advise that the use of gonadotropin-IUI should be very limited. In addition, if good prognosis couples with unexplained infertility can be counseled to continue to try to get pregnant on their own, and not pursue gonadotropin therapy, many will become pregnant spontaneously.

In a recent trial comparing the three-step sequential treatment protocol (clomiphene-IUI, followed by gonadotropin-IUI, followed by IVF) versus a two-step sequential treatment protocol (clomiphene-IUI, followed by IVF), the clinical utility of the gonadotropin-IUI was poor. In this study, the per-cycle pregnancy rate for clomiphene-IUI was 7.6%, gonadotropin-IUI 9.8%, and IVF 31%. Because gonadotropin-IUI is expensive, and much less effective than IVF, the most cost-efficient approach was the two-step sequential treatment plan of clomiphene-IUI followed by IVF. The two-step approach was approximately 15% less expensive per live birth than the traditional three-step approach.

In IVF cycles, the addition of a GnRH agonist analogue to the gonadotropin injection regimen is known to improve pregnancy rates. However, the addition of a GnRH agonist analogue to a regimen of gonadotropin injections plus IUI does not appear to increase the pregnancy rate in couples with unexplained infertility. In one study, 91 couples with unexplained infertility were randomized to receive treatment with gonadotropin injections and IUI or GnRH agonist analogue treatment plus gonadotropin injections and IUI. The pregnancy rate per cycle was 11% and 13%, respectively.

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