Gonadotropins beyond ART

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Abstract

Gonadotropins (LH, FSH and hCG) play a central role in controlling steroidogenesis and gametogenesis. For this reason, they are largely used in the treatment of infertility, especially in the setting of assisted reproductive technique. Beyond their important action in the regulation of reproduction, gonadotropins are also involved in other hormonal processes, closely interacting with other endocrine axes. Among them, the interaction between gonadal and thyroid axes is widely studied in the literature. There is evidence of an undeniable structural similarity of both hormones and receptors, maybe due to a common ancient origin. Indeed, altered levels of thyroid hormones could lead to different disorders of gonadal development and function throughout entire life, especially before and during pregnancy. Moreover, a complex interplay between insulin-like growth factors and gonadotropins has been described both at central and peripheral level. Finally, several tumors are able to produce gonadotropins or are regulated by them in their own growth. The role of gonadotropins in the regulation of cellular growth and apoptosis is evident by now, but still not fully understood.

KEY WORDS:: gonadotropins, hormones interaction, thyroid axis, glycoprotein hormones, cancer.

Introduction

The hypothalamic-pituitary-gonadal (HPG) axis is the main actor in the control of reproductive function in humans. In particular, the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from hypothalamus regulates synthesis and rhytmic release of gonadotropins by the pituitary gland (1). In turn, the gonadotropins follicle stimulating hormone (FSH), luteinizing hormone (LH) and chorionic gonadotropin (hCG) exert their effects by binding to their specific receptors and mediating several complex intracellular signalling cascades in the target cells. Interestingly, gonadotropins are characterized by similar molecular structures: glycoprotein heterodimers, composed of a common α-subunit non-convalently linked to a unique β-subunit (1) (Figure 1). Whereas the β-subunit is encoded by specific genes and differs among hormones, providing biological specificity and receptor selectivity, the α-chain, encoded by the unique CGA gene, is shared with other glycoprotein hormones, such as the thyroid stimulating hormone (TSH) (2) (Figure 1).
In clinical practice, several gonadotropin preparations are commercially available and can be used in the treatment of specific clinical conditions. In particular, given their relevant effect on gameto-

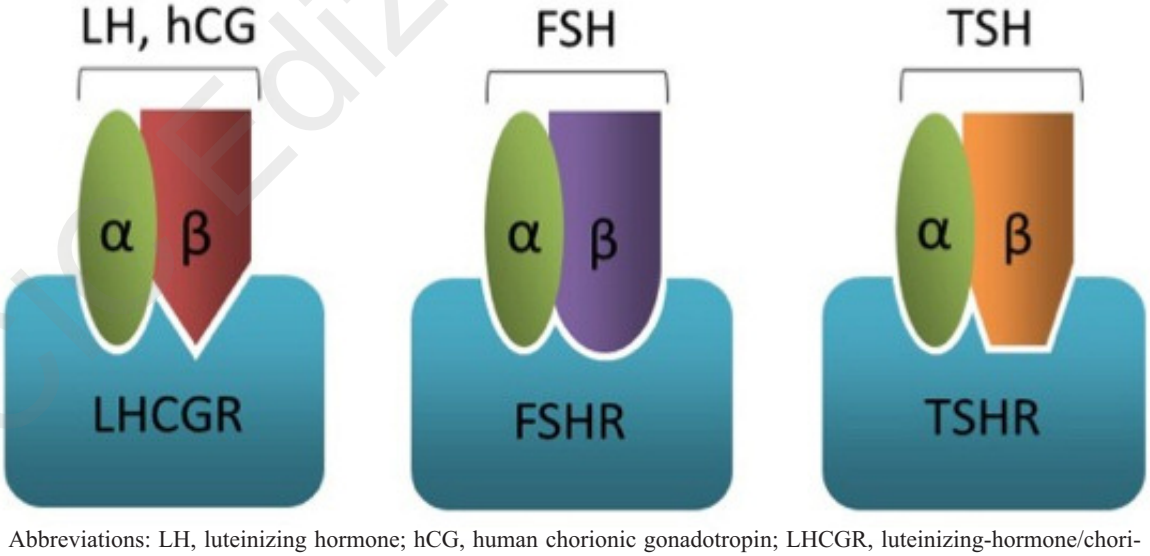
genesis, these drugs represent a valid therapeutic option for infertility of both genders, especially in the setting of assisted reproductive technique (ART) (3). Currently, since a gold standard approach to ART is lacking, there is high heterogeneity in the use of gonadotropins in ART schemes mainly empirical and unstandardized. For this reason, in spite of the wide use in infertility context, the real effectiveness of gonadotropin treatment is still uncertain and data about outcomes in ART are highly controversial in the literature (4-7).

Nevertheless, the biological action of gonadotropins is not limited to reproductive function control. These hormones are deeply involved in other endocrine processes, having a close interplay with other molecules at different levels in intracellular signalling cascades. In this context, many aspects of gonadotropins signalling are still to be elucidated and represent a thrilling topic for scientific research. Thus, an increasing number of studies has been performed to investigate the complex molecular interaction between gonadotropins and other hormones at the cellular level.

Gonadotropins and thyroid axis

TSH is a glycoprotein hormone, composed of a common α-subunit and a specific β-subunit, that shows structural similarity to LH, FSH and hCG (Figure 1). It is produced by the anterior pituitary gland under the stimulus of the hypothalamic thyrotropin-releasing hormone (TRH) and in turn induces the thyroidal follicle cells to synthesize thyroid hormones (THs). Thyroxine (T4) and triiodothyronine (T3) are the precursor and the biologically active form of THs, respectively. In target tissues, specific transporter proteins, like monocarboxylate transporter 8, can transfer THs across membrane into cells (8). Once inside the cell, T3 can exert its action by binding to nuclear receptors, thyroid hormone receptor (TR)-α and TR-β, with the final effect of regulating the transcription of target genes or by activating αVβ3 integrin on the cell surface (9, 10).

The gonadotropins-thyroid interplay is evident throughout entire life both in males and females, since the early stages of embryo development as explained in the subsequent paragraph (Table 1). At pubertal age, when the pulsatile release of GnRH leads to pituitary-gonadal axis activation, the multilevel interactions between the thyroid and the gonadal axes are strictly interlinked. Generally, thyroid volume and function implementation occurs, together with an increased conversion of T4 to bioactive T3, in response to body and sexual development (11). As evidence, a delay in sexual maturation is often observed in children with hypothyroidism; surprisingly, pre-



Abbreviations: LH, luteinizing hormone; hCG, human chorionic gonadotropin; LHCGR, luteinizing-hormone/choriogonadotropin receptor; FSH, follicle-stimulating hormone; FSHR, follicle-stimulating hormone receptor; TSH, thyroid stimulating hormone; TSHR, thyroid-stimulating hormone receptor.

Figure 1 - Structural similarity among glycoprotein hormones and their own receptors. They all are glycoprotein heterodimers, composed of a common α-subunit non-convalently linked to a unique β-subunit.

Table 1 - Thyroid hormones and gonadotropins interactions throughout entire life and their consequent clinical effects.

Stage of life	THs - gonadotropin interactions	Clinical effects
Embryo	Modulation of sex-determining genes expression and androgen synthesis	• Sexual differentiation • Gonadal and neuronal development
Puberty	TRH-induced prolactin increase and consequent alteration of gonadotropin secretion Cross-interaction of TSH with FSHR	• If hypothyroidism: delay in sexual maturation • If extreme hypothyroidism: precocious puberty • If hyperthyroidism: delayed puberty
Male fertile life	Changes in sexual hormone-binding globulin and sex steroids	• Alteration in seminal parameters (sperm motility in thyrotoxicosis, sperm morphology in hypothyroidism) • Erectile dysfunction
Female fertile life	Altered pulsatility of LH secretion Pre-ovulatory follicle maturation	• Menstrual irregularities • Polycystic ovaries and endometriosis • If hypothyroidism with positive anti-thyroid autoantibodies: reduced fertility
	During ovarian stimulation, estrogen-related increase of TBG	• Significant increase of TSH
Pregnancy	Thyrotropic activity of hCG through: • binding to TSHR • modulation of sodium-iodide symporter	• Increase of THs and decrease of TSH for implantation and early stage of embryogenesis • If hypothyroidism with positive anti-thyroid autoantibodies: increased rate of pregnancy complications

Abbreviations: THs, thyroid hormones; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; FSHR, follicle-stimulating hormone receptor; LH, luteinizing hormone; TBG, thyroxine binding globulin; hCG, human chorionic gonadotropin.

cocious puberty has been described in case of extreme hypothyroidism too (11, 12). Several hypotheses have been elaborated in order to explain how altered thyroid function leads to pubertal disorders. First, since TRH induces the simultaneous stimulation of both prolactin (PRL) and TSH, elevated levels of TRH, due to the lack of negative feedback by TH, cause hyperprolactinemia. As a consequence, hyperprolactinemia alters GnRH pulsatile secretion, finally resulting in delayed puberty (2, 11). Secondly, because of the structural similarity of FSH and TSH receptors, a cross-interaction between elevated serum TSH with FSH receptor (FSHR) expressed in gonads could be responsible for gonadal activation, leading to a precocious puberty onset (11). On the other hand, the effect of hyperthyroidism on sexual development is still uncertain, even if a possible association with delayed puberty and secondary amenorrhea has been described (12).

During fertile life, normal thyroid function is important to preserve reproduction in both genders. This issue is of increasing interest in the literature and, in the last decade, many studies have been published regarding the relation between thyroid and infertility or pregnancy. Changes in sexual hormone-binding globulin and sex steroids are associated with thyroid disorders, affecting reproductive function both in females and males (13). In the latter, several abnormalities in seminal parameters, mainly sperm motility, have been reported in the context of thyrotoxicosis, whereas sperm morphology is more affected in hypothyroidism (13). Again, many patients with erectile dysfunction present disthyroidism (13). The restoration of euthyroidism generally leads to an improvement of all these abnormalities, again suggesting an interaction between gonadotropin and thyroid axes (13).

Concerning female fertility, THs have great influence on menstrual cycles, through direct actions on the ovaries and indirectly by interacting with sex hormone binding proteins. In particular, hypothyroidism is associated with ovulatory disorders, menstrual irregularities and hirsutism, due to the altered pulsatility of LH secretion (14, 15).

In addition, it has been speculated that THs might be involved, in concert with gonadotropins, in pre-ovulatory follicle maturation. This hypothesis is supported by the finding of THs in human follicular fluid and the expression of THs receptors in cumulus cells, oocytes and granulosa cells (16, 17). Thus, thyroid dysfunction is more prone to be associated with the development of polycystic ovaries and endometriosis; in this context, the benefit from treatment with levothyroxine is a further evidence of the involvement of THs in the pathogenesis of these conditions (15).

Moreover, there is increasing evidence about reduced fertility in women with hypothyroidism, especially when positivity of anti-thyroid autoantibodies is present. Overt hypothyroidism has been associated not only with a lower possibility of achieving pregnancy, but also with an increased rate of complications, such as spontaneous abortion, premature delivery and/or low birth weight, fetal distress in labor (13). However, a screening of thyroid function extended to all women with desire of pregnancy is still matter of debate in clinical practice, whereas there is accordance in testing at least women with personal or familiar history of thyroid diseases.

Further evidence of the tight interplay between gonadotropins and thyroid axes are observable in ART procedures. In this context, one of the aim of controlled ovarian hyperstimulation is to reach elevated levels of estradiol, which may have adverse effect on thyroid homeostasis. In fact, both euthyroid and hypothyroid women display significant increase of TSH levels during treatment and up to three months after that (18, 19). This can be explained by the estrogen-related increase of thyroxine-binding globulin (TBG) and the consequent decrease in unbound serum THs, which in turn stimulates pituitary secretion of TSH. When autoimmune thyroid disease is present, the impact of controlled ovarian hyperstimulation may become even more severe, in the presence of preexisting thyroid abnormalities (13).

In recent years, more and more fascinating studies have been published to describe the tight connection between HPG and hypothalamic-pituitary-thyroid endocrine systems. From an evolutionist point of view, it has been proposed that gonadal and thyroid axes evolved from an ancestral endocrine axis that was able to regulate reproduction, metabolism, and development (20). Thus, fundamental interactions between THs and sex steroids in extant vertebrates may reflect the deep evolutionary history of overlapping functions of these two endocrine axes (20). Recently, another elegant study demonstrated the involvement of THs in seasonal reproduction in vertebrates with different pathways among birds, mammals and fishes (21). In particular, light information seems to induce TSH and THs secretion; then, through morphological changes in terminals of neurons that express GnRH, gonadotropin secretion from the pituitary gland is facilitated (21).

Together with gonadotropins and TSH, a novel member of the glycoprotein hormone family has been identified. This heterodimeric glycoprotein is the corticotroph-derived glycoprotein hormone (CHG), also known as thyrostimulin, due to its capability of activating TSHR *in vitro* and *in vivo*, but not FSH and LH receptors (22). The exact role in thyroid physiology is still unknown, since it does not seem to participate in the hypothalamic-pituitary-thyroid feedback (22). More likely, it has been supposed that thyrostimulin may play a paracrine role in the anterior part of pituitary gland and other tissues that express TSHR, such as brain, heart, adipose tissue and orbital fibroblasts (22). This heterodimer is curiously expressed in oocytes of mammalian ovary, where it can bind TSHR and activate intracellular signalling pathways (23). In contrast to the constitutive expression of thyrostimulin in ovary, the ovarian expression of TSHR is finely regulated by gonadotropins (23). This suggests that oocyte-derived thyrostimulin together with granulosa cell-expressed TSHR compose a paracrine system in the ovary, is under the control of gonadotropins (23).

Gonadotropins and THs during embryogenesis

The scenario becomes more complicated and thrilling during pregnancy, when increasing hCG levels occur thanks to the secretion by syncytiotrophoblast cells. hCG exerts a thyrotropic activity at different levels, with the final effect of ensuring adequate levels of THs that are necessary for implantation and early stage of embryogenesis (24). First, hCG is able to bind and activate the TSH receptor (TSHR) in thyroid. This effect results in an increase of serum T3 and T4 levels in concomitance with the peak of hCG and in a decrease in serum TSH levels (25). Moreover, hCG regulates iodide transport from maternal to fetal circulation, through the modulation of the

expression of the sodium-iodide symporter (26). At the same time, several peripheral changes in THs metabolism have been supposed. Among these, it has been reported an overexpression of the deiodinase enzyme type 3 in placenta, causing inactivation of THs; in response, this could lead to increased expression of THs transporters in placental cells (27).

Afterwards, there is strong evidence that THs play a key role in sexual differentiation and gonadal development in mammalian and non-mammalian species with complex mechanisms during embryogenesis (28). Among these, THs modulate the expression of sex-determining genes in favor of males and stimulate androgen synthesis and responsiveness through direct and indirect regulation of enzyme expression and activity (28). Furthermore, neuronal and gonadal development alterations have been extensively described in children with thyropatic mother during first phase of pregnancy, although the underlying molecular mechanisms have not been elucidated yet (29, 30).

In conclusion, there is evidence of the crucial role of THs in regulating reproductive development and function, suggesting a close interplay with HPG axis. However, in spite of the clinical evidence and some basic clues, many aspects of this complex network of signalling pathways remain to be elucidated in detail.

Gonadotropins and insulin-like growth factors

It is well known that the main action of somatotropic axis consists of controlling growth and development. In addition to this, emerging evidence suggested the influence of insulin-like growth factor (IGF) family members on gonadal axis. In this research stream, several studies, both *in vitro* and *in vivo*, with knockout mouse models for IGF family members, demonstrated the central role of IGFs as intraovarian regulator of follicle growth, cellular differentiation and steroidogenesis. For this reason, considering the synergistic actions with gonadotropins, IGFs have earned the appellation of 'co-gonadotropins'. Thus, in contrast with the classical conception of IGFs as peripheral elements in the somatotropic axis via its synthesis in the liver, it has been reported that IGF-1 is also synthesized at the central level, within neurons and glia (31). At this level, IGF-1 is involved in the regulation of neuroendocrine functions, including direct actions on GnRH neurons, that co-express IGF-1 and the its receptor (31). Another evidence of the central interaction between somatotropic and gonadotropic axes is represented by PRL; in fact, human growth hormone (GH) binds to both GH and PRL receptors, exerting both somatotrophic and lactotrophic effects (32). In particular, PRL-mediated actions are responsible for inhibition of gonadotropin secretion by the pituitary gland (32). Indeed, this could explain why clinical disorders characterized by excessive production of GH or GH resistance, acromegaly and Laron syndrome respectively, are associated with altered reproductive function (32). Similarly, it has been demonstrated that in IGF-1 gene-knockout mice the onset of puberty and/or fertility is altered (32).

Furthermore, data about a possible influence of IGFs on the gonadal axis at the ovarian level are reported too. In particular, the successful development of a healthy oocyte and appropriate granulosa cell differentiation depends on multiple factors, including a properly functioning IGF system (33, 34). On the other hand, also in the context of polycystic ovarian syndrome, a contribution of IGFs to the observed resistance to FSH action has been proposed (34).

Considering molecular basis, differently from what previously said about receptor cross-talk between gonadotropins and TSH, to our knowledge no direct molecular cross-interaction among IGF-1 and gonadotropin receptor has been described so far. It is possible to speculate on this, suggesting a predominant intracellular interplay, rather than at the receptor level, between IGFs and gonadotropins. Anyway, disruption of even one component of this system can lead to abnormal follicular development and function and compromised reproductive capacity.

Gonadotropins and cancer

Several genetic elements are involved in the control of cell proliferation, differentiation and apoptosis. Any changes in term of expression of these genes can be responsible for the break of this fragile balance, resulting in uncontrolled growth and, thus, tumor. Considering that hormones physiologically take part in cell cycle regulation, a possible role in cancer onset and progression is matter of increasing interest for scientific research. In

particular, the expression of glycoprotein hormones and their cognate receptors in various cancer tissues has been reported (35). The expression of hormones in tissues/cells, in which they are normally not expressed is surprising and interesting. It was suggested that tumor cells may create a new hormonal environment able to stimulate their own growth in an autocrine manner (35).
In the light of these considerations, FSH and LH, but also TSH, have been implicated in several processes of tumorigenesis. Different aspects should be considered in defining the possible role of gonadotropins in tumorigenesis. For example, the precise role of LH in Leydig cell proliferation is not clear and it has been suggested that the proliferative effect of LH on Leydig cell is strictly related to the phase of cell maturation. In particular, LH may only stimulate the proliferation of the progenitor Leydig cells (35). Again, in presence of a previous damage to DNA, like in the context of anticancer therapies, it has been surprisingly evidenced a possible protective effect of LH on oocytes, against apoptosis and preserving fertility (36). Also the different molecular isoforms seem to play a role in biological activity of gonadotropin: hypoglycosylated FSH has greater activity than fully glycosylated recombinant FSH in human granulosa cells, probably explaining different effects in tumorigenesis too (37). Finally, a recent study revealed for the first time some previously unrecognized features intrinsic to the two structurally similar gonadotropin receptors (FSHR and LHCGR), oppositely resulting in the regulation of life and death signals *in vitro* (2). In particular, a higher pro-apoptotic potential of FSHR compared to LHCGR in granulosa cell has been reported (2).
The role of hCG in cancerogenesis deserves a separate discussion. During pregnancy, it promotes trophoblast invasion and modulates immune cell system (38). For both features, hCG is a candidate for tumor pathogenesis control, although the mechanisms underlying pro- and anti-carcinogenic effects are not fully understood yet. A possible mechanism could be explained by the tumor production of hyperglycosylated hCG that, antagonizing the transforming growth factor receptor-β (TGFβR), leads to a final antiapoptotic and proliferative effect (38). However, the action of hCG on TGFβR may be due to growth factors contaminating the hCG preparations used *in vitro*, thus this issue should be further investigated (39). Anyway, hCG is used as a clinical marker of placental malignancies and germ cell tumor of the testis and the ovary. But also other tumors express hCG, such as bladder carcinoma, lung cancer, colorectal carcinoma, prostate cancer, gastric carcinomas and different gynecological cancers; however, the real significance in these contexts remains unclear (40).

Conclusion

There is evidence that THs and IGFs have a role in the regulation of gonadal development and reproductive function both in females and males. Viceversa, gonadotropins are able to influence other hormonal balances, in particular during pregnancy. The emblem of such inter-axes dialogue is represented by the complex signaling network in the ovaries, that regulates folliculogenesis and ovulation.
Finally, gonadotropins seem to play a role on cell growth regulation in several tissues, beyond gonads. This influence is finally adjusted and variable depending on the surrounding pathophysiological conditions. Obviously, it opens wide-ranging horizons for gonadotropin research, ranging from reproduction to oncology.

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