Recent progress in luteinizing hormone/human chorionic gonadotrophin hormone research

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ABSTRACT: The role of luteinizing hormone (LH) and human chorionic gonadotrophin hormone (hCG) in the regulation of normal reproductive functions in males and females is quite well established. Besides the use of hCG in the development of diagnostic immunoassays, it has been successfully used in the induction of final follicular maturation and ovulation in the assisted reproductive technologies. The basic and clinical research on the nongonadal actions of LH/hCG in the recent years has extended the potential of using these hormones in several clinical indications. Hereby we will analyze the advances in the LH/hCG research (briefly emphasizing the nongonadal research), which has the potential for multiple novel therapies in reproductive and the other areas of medicine.

Key words: luteinizing hormone / human chorionic gonadotrophin / luteinizing/human chorionic gonadotrophin receptor / gonadal and nongonadal effects

Introduction

Hypothalamic gonadotrophin-releasing hormone stimulated the secretion of luteinizing hormone (LH) by the anterior pituitary. Human chorionic gonadotrophin (hCG) is secreted by the placenta (Pierce and Parsons, 1981). Both LH and hCG are heterodimeric glycoprotein hormones belonging to cystine-knot growth factor families possessing the properties of cytokines and chemokines (Lapthorn et al., 1994). hCG is structurally related to LH and both hormones bind to the same LH/choriogonadotrophin receptor (LHCGR). LHCGR belongs to a family of seven-trans membrane spanning G-protein coupled receptors (McFarland et al., 1989; Ascoli et al., 2002). hCG is more potent than LH due to its higher receptor binding affinity and a longer circulatory half-life (Rao, 1979). Chorionic gonadotrophin is produced in primates, equines and in man, whereas LH is present in all species. hCG appears in the circulation around the time of implantation, increases to reach its peak about ninth week of pregnancy and then drops down to about one-tenth of the peak levels and remains there until the end of pregnancy. hCG is believed to be essential for the maintenance of the pregnancy by stimulating progesterone production by the corpus luteum gravidarum, although this concept was challenged by the discoveries of the multiple actions of hCG in nongonadal tissues throughout pregnancy and during labor (Lei and Rao, 2001a, b). hCG has been shown to stimulate testosterone production of fetal Leydig cells (Huhtaniemi and Pelliniemi, 1992; Huhtaniemi et al., 1977; Apaja et al., 2005). This review will concentrate on the LH/hCG in reproductive biology and general medicine with particular emphasis on nongonadal research.

The majority of the studies on nongonadal LH/hCG receptors were done on human rather than on other species (Rao and Lei, 2007). Although the studies on nongonadal LH/hCG actions led to a greater potential for novel therapeutic uses of hCG/LH than from the studies on the gonadal actions of LH/hCG (for a review, see Rao and Lei, 2007); few studies have been done in transgenic murine models, where physiologic significances of nongonadal LHR expression in reproductive function is questioned (Ahtiainen et al., 2007; Pakarainen et al., 2005, 2007). We will enclose a brief discussion on some recent studies based on transgenic murine models either overexpressing or showing disrupted genes, including analysis of the pros and cons of LH/hCG actions in nongonadal tissues.

The LH/hCG research on reproductive biology issues

Classical expression of the LHCGR has been well established in the testicular Leydig and ovarian theca, granulosa and luteal cells where...
LH has been shown to regulate steroid hormone synthesis and gametogenesis (Segaloff and Ascoli, 1993; Dufau, 1998). LHCGR has been found in many nongonadal tissues in human and rodents. For example, human and rat adrenal glands (Pabon et al., 1995a; Apaja et al. 2005), cervix (Lin et al., 2003), fetal tissues (Abdalallah et al., 2004), mammary gland (Tao et al., 1997b), oviduct (Lei et al., 1993b; Han et al., 1996; Zhang et al., 2001b), placenta (Reshef et al., 1990), uterus (Reshef et al. 1990; Han et al., 1997; Zhang et al., 2001b), sperm (Eblen et al., 2001) and many others.

**LH/hCG research in ovulation induction, assisted reproductive technologies, pregnancy and miscarriages**

The research on the chemistry of LH/hCG has led to the development of diagnostic immunoassays, which have been extensively used in reproductive medicine, such as intrauterine or ectopic pregnancy detection and reproductive cancer diagnostics (Davies et al., 2003). hCG is also very widely used for ovulation induction, where it is assumed that the beneficial effects come from its ovarian actions (Kafy and Tulandi, 2007; Rao and Lei, 2007). The actions of LH/hCG have been studied quite extensively in the control of ovarian functions, which have led to the development of widely used LH/hCG therapy to stimulate follicular and oocyte maturation and ovulation induction (Filocori et al., 2005; Kafy and Tulandi, 2007). There is still an ongoing discussion on the supplementation of recombinant LH to the recombinant FSH with daily doses during the second half of the follicular phase, where some studies showed increased effectiveness (Tesarik and Mendoza, 2002; De Placido et al., 2005), whereas other studies, on the contrary, showed no evidence of increasing effectiveness (Nygboeandersen et al., 2008) on the ongoing pregnancy rates in the general population. The similar debate also includes whether some subgroups of women (aged >35 years) might benefit from LH activity supplementation during ovarian stimulation (Alvigo et al., 2006). The use of hCG to correct the luteal phase defect is not very popular nowadays (Dawood, 1994). A recent cohort study has shown that a subgroup of patients with a high rate of oocyte immaturity during a cycle stimulated with only recombinant (rec) FSH, and addition of LH (hMG, human menopausal gonadotropin) in subsequent cycle increased significantly the number of mature oocytes and better quality embryos were obtained compared with only FSH cycles (Huddleston et al., 2009). The results of this study are quite convincing as the study design is done in a matched-pair design, where each patient serves as her own control (Huddleston et al., 2009). Further studies with bigger groups with similar criteria are needed in order to establish the appropriate clinical relevance for LH supplementation, which could increase the conception rate in assisted reproductive technologies. It has been shown that increased endometrial thickness and implantation rates could be achieved in the patients receiving hCG along with the GnRH analogs with estrogen/progesterone-supplemented oocyte recipients (Fujimoto et al., 2002; Tesarik et al., 2003). Another approach that might improve the implantation rates is the in vivo direct application of hCG to endometrium, which provokes endometrial morphological changes and cytokines production (Filocori et al., 2005).

hCG has been shown to possess a number of tropic actions in the reproductive tract and fetoplacental unit and plays an immunosuppressive role at the maternal–fetal interface (Lei and Rao, 2001a, b; Rao, 2001). hCG also has a relaxing effect on the uterine arteries, which increases the utero-placental perfusion (Toth et al., 2001). A single i.m. injection of hCG has been shown to decrease spontaneous as well as habitual miscarriage, as compared with Mg²⁺ treatment alone, and no maternal or fetal side effects could be observed (Toth et al., 2001).

**Prevention of prematurity with hCG**

Human myometrium contains LHCGR (Reshef et al., 1990; Han et al., 1997) and there exists also ample evidence on their functional relevance to an inhibition of contractions (Slattery et al., 2001; Belmonte et al., 2005; Phillips et al., 2005). Thus, it was hypothesized that hCG could also be a hormone contributing to myometrial quiescence in order to maintain the pregnancy. This putative tocolytic action of hCG was shown in a murine model (Kurtzman et al., 1999; Kurtzman et al., 2001). This tocolytic action was further demonstrated in women with preterm labor, although it was less effective in infection induced preterm labor cases (Than et al., 2003). It is likely that advanced infections reduce the efficacy of the hCG action, simply because the adverse changes have progressed too far for hCG to reverse or stop them. We believe that further cohort studies with larger populations are required before hCG can be recommended for routine use in prematurity prevention.

**Potential role of hCG in preventing HIV/AIDS infection**

Babies born to HIV-positive mothers are generally infected during the intrapartum period, when they are exposed to virus in maternal body fluids (Matheson et al., 1995). This observation prompted the basis for delivering babies of HIV-positive mothers after antiviral treatments by Cesarean sections, as instructed by the American College of Obstetricians and Gynecologists. It has been shown that the hCG suppressed HIV replication, reverse transcriptase, gene transcription and protein synthesis and prevents viral transmission from virus-positive lymphocytes to virus negative lymphocytes (Polliotti et al., 2002). In a transgenic HIV murine model, it was shown that hCG, but not the steroids, prevented the rapid progression of disease and premature demise of homozygous pups (De et al., 2002). These initial but quite promising results suggested that hCG could serve as a supportive drug for the potential treatment of HIV/AIDS along with the main antiviral drugs. Further studies are needed in order to establish the putative preventive role of hCG in HIV/AIDS.

**Potential use of LH/hCG in endometriosis and their involvement in endometrial carcinomas**

Endometriosis is characterized by the presence of endometrial tissue outside the uterus. This condition causes painful periods, chronic pelvic pain, subfertility and a profound reduction in quality of life, especially during women’s reproductive years (Huber et al., 2004). Until now only surgery has been proved to provide definitive cure. There is insufficient evidence for hormonal use to completely cure this disease (Giudice and Kao, 2004; Berkley et al., 2005). The potential
use of hCG in the treatment of endometriosis was based on the findings that its symptoms ameliorate and lesions regress during pregnancy and menopause (Huber et al., 2004), ectopic implants contain LHCGR (Lincoln et al., 1992; Huber et al., 2004), and their activation by gonadotrophins leads to an inhibition of implants (Huber et al., 2004). hCG treatment had been shown to lead to significant and clinically relevant reduction in pain intensity and to greatly improved quality of life in women with therapy-refractory endometriosis (Huber et al., 2004). The same group went on further to show that hCG treatment altered the gene expression profile of stromal cells obtained from endometriotic lesions (Huber et al., 2007). Most of the up-regulated genes encoded proteins turned out to be involved with cell adhesion, intercellular communication, extracellular matrix remodeling, apoptosis and inflammation (Huber et al., 2007). Further studies are needed to validate therapeutic benefit of hCG use in endometriosis.

LHCGR is up-regulated in the endometrial carcinoma, even in the precursor lesions as comparison with normal endometrium. This finding suggested a potential role of the LH/hCG in endometrial carcinoma (Lin et al., 1994; Konishi et al., 1997). LH has been shown to have anti-apoptotic actions in human endometrial carcinoma cell lines, and post-menopausal obese women with endometrial carcinoma showed elevated levels of serum LH compared with age-matched obese women without the disease (Nagamani et al., 1992; Davies et al., 2000; Dabizzi et al., 2003). It would be important to know the molecular mechanisms underlying the up-regulation of LHCGR expression in endometrial carcinoma, which could suggest a new modality of treatment for this disease.

The LH/hCG research on some overall medical issues

LH/hCG in Alzheimer disease research

Epidemiological studies showed a significant reduction in neurodegenerative disease among prostate cancer patients treated with GnRH analogs, which suggested a potential role for LH in Alzheimer disease (AD) (Casadesus et al., 2005; Barron et al., 2006). LH is known to cross the blood–brain barrier and a very high number of LHCGR are mostly concentrated in the hippocampus, the region most vulnerable to AD (Lei et al., 1993a). LH levels are also significantly elevated in both the serum and the pyramidal neurons of AD subjects compared with age-matched control subjects, which significantly correlated with the α-amloid protein processing (Bowen et al., 2004; Casadesus et al., 2005; Barron et al., 2007). Genetically altered mice with exaggerated LH signaling showed behavioral changes that are consistent with the role of LH in promoting AD (Bowen et al., 2004; Casadesus et al., 2005; Barron et al., 2007). These findings suggest that it is not necessarily the estrogen deficiency alone, but rather chronically elevated LH levels with the dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis at menopause is a physiologically relevant signal that could promote neurodegeneration and predispose some post-menopausal women to develop AD (Bowen et al., 2004; Casadesus et al., 2005; Barron et al., 2007). AD features such as cognitive loss and amyloid beta deposition could be diminished by GnRH analog treatment, where LH signaling seems to be a useful therapeutic strategy. Clinical trials are underway for the treatment of AD using GnRH analogs (Atwood et al., 2005; Meethal et al., 2005) (also M.A. Smith, personal communication), which should provide further insights into the LH connection in AD.

Preventive actions of hCG for breast cancer

Completing a full-term pregnancy before the 20 years of age has a protective effect against breast cancer development in later life (Lei and Rao, 2000) which has been attributed to differences in the degree of differentiation in the breast (Russo et al., 1992). This protection effect appears to be due to the anticancer actions of hCG inducing differentiation of proliferative type to secretory type breast epithelial cells (Lei and Rao, 2000). The relevance of this protective effect has been extensively assessed in a rat model (Russo et al., 1990a, c; Russo and Russo, 1993), It showed that hCG protects the mammary gland against carcinogenic initiation and progression, mimicking the physiological process of pregnancy (Russo et al., 1990b, c; Russo and Russo 1993; Lei and Rao, 2000). In a recent study, hCG has been shown to induce apoptosis in breast cancer cells which may have a great potential to facilitate chemotherapeutic intervention and improve patient outcomes (Lopez et al., 2008). In this study, direct intratumoral injection of hCG into human breast cancer xenografts grown in nude mice increased the apoptotic index (Lopez et al., 2008). These results were supported by the findings that exposure to purified hCG decreased cell viability in five different breast cancer cell lines (Lopez et al., 2008). In some of these cell lines, the effects of hCG in cell viability appear to correlate with activation/expression of the hCG/LH receptor (Lopez et al., 2008). The authors suggested that preoperative apoptotic induction by hCG may improve local control or work synergistically with neoadjuvant chemotherapy to improve complete pathologic response of locally advanced breast cancer (Lopez et al., 2008). In light of these above-mentioned studies, hCG may have potential as a preventive measure against carcinogenic initiation and progression as well as its pro-apoptotic action opening the possibility for hCG to facilitate chemotherapeutic initiatives.

Transgenic murine models on nongonadal actions of LH/hCG

The presence and localization of LHCGR in the reproductive tract of wild-type mice has been analyzed (Zhang et al., 2001b). LHCGR mRNA expression has been shown in stromal cells of the wild-type mouse endometrium and in the uterine serosa (Zhang et al., 2001b). Uterine smooth muscle cells had low levels of expression, and the endometrial epithelium was negative, whereas in the oviduct, high levels of LHCGR expression were noted on the serosa and in subepithelial cells (Zhang et al., 2001b). Oviduct smooth muscle had low expression, and the epithelium was negative (Zhang et al., 2001b). The nongonadal LHCGR have been suggested to be physiologically redundant on the basis of a LHCGR disrupted transgenic murine model, LuRKO, and said to come into play when pharmacological doses of hormones are administrated (Pakarainen et al., 2005). This speculation is not correct, as receptors in the nongonadal tissues, similarly in the gonads, have been activated by similar hormone concentrations (Kananen et al., 1997; Kiiveri et al., 1999; Kero et al., 2000; Rahman et al., 2004). Two independent groups reported two different LHCGR knock out murine models (LHRKO and LuRKO), with clear and rather similar phenotypes.
with completely eliminated functional LHR in the (−/−) mice (Lei et al.
2001; Zhang et al., 2001a). The LHRKO model was created by targeted
deletion of the proximal part of the LHR promoter and exon 1 (Lei et al.,
2001), and the LuRK0 model by targeted disruption of the long 11th
exon of LHR, encoding the transmembrane and intracellular domains
of the receptor (Zhang et al., 2001a). Discrepancies on phenotypic
interpretation between these models occur regarding the evidence for
or against the functional significance of nongonadal LHCGR action
(Chudgar et al., 2005; Pakarainen et al., 2005). LHR null mice with trans-
planted wild-type ovaries in LuRK0 (Pakarainen et al., 2005) mice could
become pregnant, but not in LuRK0 (Chudgar et al., 2005) mice. The
pregnancy failure in the latter case was predictable because of the
uterine genes involved in implantation are dependent on the uterine
LH/hCG actions. It is highly likely that the strategies used in receptor
silencing could be the reason for this discrepancy (Lei et al., 2001;
Zhang et al., 2001a). Actually LuRK0 mice has been used successfully
in another uterine study in order to prove the functionality of the
uterine LHCGR, where in mice aortic ring study, angiostimulation by
recombinant hCG was abrogated completely by deletion of LHCGR, i.e.
as in LuRK0 mice (Berndt et al., 2006). This study additionally
showed the angiogenic activity of hCG through LHCGR on endothelial
epithelial cells of the endometrium (Berndt et al., 2006).

Murine transgenic (TG) models have been very productive in
demonstrating the nongonadal adrenocortical LHCGR functionality.
LHR expression in the murine adrenal gland is an exception and not
found in wild-type (WT) animal (Kero et al., 2000; Rahman et al.,
2004). Prepubertally gonadectomyinhibin null mouse (inh−/−) (Matzuk et
al., 1992; Matzuk et al., 1994) and transgenic mice under the inh
promoter fused with SV40 T antigen oncogene (inhα/Tag) express adrenocortical LHCGR and have a distinct adrenal phenotype
emphasizing the nongonadal LHCGR effects. Goandectomized
inh−/− and inhα/Tag develop adrenocortical tumors in 100% pene-
trance, demonstrating that inhibin is also a tumor suppressor for the
adrenal gland. The appearance and growth of adrenal tumors in
inhα/Tag mice were found to be gonadotrophin dependent, since
they failed to appear after functional gonadectomy induced either by
administration of a GnRH antagonist or by cross-breeding the TG
mice into the hypogonadotropic hpg genetic background (Cattanach
et al., 1977; Kananen et al., 1997). The post-gonadectomy elevation
of LH levels apparently induced the ectopic LHCGR expression in the
adrenal cortex, which together with the potent oncogene Tag
co-expression triggered adrenocortical tumorigenesis (Rahman et al.,
2001, 2004). Inhα/Tag adrenocortical mice additionally have very
successfully been used to test the hypothesis that adrenocortical
tumors possessing LHCGR could be selectively destroyed by a
lytic peptide hecate, conjugated to CGβ subunit (Vuorenoja et al.,
2008; Vuorenoja et al., 2009). TG female mice-expressing LHβ-CTP
(a chimeric protein derived from the β-subunit of bovine LH and
a fragment of the β-subunit of hCG) exhibit elevated serum LH,
infertility, polyendocrine ovaries, and ovarian tumors (Risma et al.,
1995). Intact TG LHβ-CTP females with enhanced ovarian estrogen
synthesis have been shown to be involved in increased secretion of pro-
lactin (PRL), which consequently elevated the LHR expression of female mice with chronically elevated LH (Kero et al., 2000).
LuRK0 9- to 10-week-old female mice exhibited decreases in bone
histomorphometric parameters tested, indicating that the loss of LH
signaling results in a reduction in bone formation or an increase in
bone resorption (Yarram et al., 2003). All these above-mentioned
TG murine model reports strongly support the nongonadal signifi-
cance of LH/hCG and LHCGR.

TG mice overexpressing hCG (hCGβ and common α-subunits
under the human ubiquitin C promoter), producing 3–4-fold elevation
in males, 30-fold in females (hCGα or hCGβ) or drastically 1000-fold
elevated levels of circulating bioactive LH/hCG in hCGαβ mice, com-
pared with WT-littermates (Rulli et al., 2002, 2003). Clear nongonadal
phenotypes were also observed in these hCG overexpressing TG
mice: the females developed obesity, pituitary macrolactinomas,
mammary gland adenocarcinomas and elevated bone density in
hCGβ (Rulli et al., 2002, 2003; Yarram et al., 2003), or in hCGαβ+ mice:
germ cell tumors in females and prostate hyperplasia, lower
urinary tract obstruction and hydronephrosis and dilated urinary
bladder in males (Rulli et al., 2003; Pakarainen et al., 2007). However,
all the nongonadal phenotypes of hCGβ+ could be abol-
ished or prevented after gonadectomy, indicating abnormal gonadal
hormone production, rather than direct nongonadal hCG effects,
could be responsible for the nongonadal phenotypes observed in
hCGβ+ females or in hCGαβ+ mice (Rulli et al., 2002, 2003; Yarram et al.,
2003; Pakarainen et al., 2007). No adrenal gland
LHCGR expression has been reported in these hCG overexpressing
mice. These examples do not support the nongonadal actions of
LH/hCG and LHCGR, as they show even in the presence of very
(30-fold) or extremely high (1000-fold) levels of hCG there were no
nongonadal phenotypes of hCG in mice caused by nongonadal LHCGR.
The overexpression models may not be highly useful in deciphering the
information on the importance of nongonadal LH/hCG receptors.
This is simply because unusually high hCG/LH levels could indeed
bypass nongonadal targets as the receptors in them could be selec-
tively down-regulated resulting in abrogation of response.

Analyzing the evidence for and against nongonadal effects of LH/
hCG through LHCGR from transgenic mice research, we would
argue that the evidence for their importance is much stronger than
that against. For instance, the LuRK0 mice getting pregnant after
ovary transplants as explained above could be due to the different
receptor silencing methodology used. With regard to the uterine
issue, we believe that a uterine specific LHR knockout model should
be developed in order to prove the functionality of uterine LHCGR.
As for hCG overexpressing models, we believe that when the circulat-
ing bioactive LH/hCG, are so pathologically high (either 30-fold or
more than 1000-fold) as compared with WT littersmates, that they
could drive the gonads excessively masking nongonadal actions.
Moreover, very high hCG levels could be just as ineffective as very
low levels because they may down-regulate the receptors more
rapidly in nongonadal tissues than in gonadal tissues (Table I).

A novel therapeutic approach to
treat endocrine tumors through
their LHCGR by hecate chorionic
gonadotrophin β conjugate lytic peptide

Improvements in cancer research are a big challenge of medical
research. Despite the immense efforts made in the improvement of
Table 1  Murine transgenic models providing evidence for or against extragonadal actions of LH/hCG.

<table>
<thead>
<tr>
<th>Genetically targeted overexpressing/disrupted TG murine models (model name)</th>
<th>References</th>
<th>Evidence for/against the nongonadal effects of LHCGR—organ specificity (ref)</th>
<th>Gonadectomy required in order to express the LHCGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHR knockout mice (LuRKO)</td>
<td>(Zhang et al., 2001a, b).</td>
<td>Against—uterus (Pakarainen et al., 2005) For—uterus (Berndt et al., 2006); bones (Yarram et al., 2003)</td>
<td>NO</td>
</tr>
<tr>
<td>LHR knockout mice (LHRKO)</td>
<td>(Lei et al., 2001)</td>
<td>For—uterus (Chudgar et al., 2005; Lin et al., 2005a, b)</td>
<td>NO</td>
</tr>
<tr>
<td>Inhibin null mice (inh−/−)</td>
<td>(Matzuk et al., 1992)</td>
<td>For—adrenals (Matzuk et al., 1994)</td>
<td>YES</td>
</tr>
<tr>
<td>Inhibin α promoter SV40 T antigen mice (inhα/Tag)</td>
<td>(Kananen et al., 1996)</td>
<td>For—adrenals (Rahman et al., 2001, 2004; Vuorenoja et al., 2008, 2009)</td>
<td>YES</td>
</tr>
<tr>
<td>Mice expressing a chimeric protein derived from the β-subunit of bovine LH and a fragment of the β-subunit of hCG (LHβ-CTF)</td>
<td>(Rama et al., 1995)</td>
<td>For—adrenals (Kero et al., 2000)</td>
<td>NO</td>
</tr>
<tr>
<td>Mice overexpressing hCGβ and common α-subunits under the human ubiquitin C promoter (hCGβ+ and/or hCGαβ+)</td>
<td>(Rulli et al., 2002, 2003)</td>
<td>Against—pituitary, mammary gland, bone, adrenals (Rulli et al., 2003, 2002; Yarram et al., 2003)</td>
<td>NO</td>
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</tbody>
</table>

Conclusions and future directions

hCG, as a therapeutic drug is rather nontoxic with negligible side effects, if any. It is an inexpensive drug as compared with other drugs used for any of the above-mentioned medical conditions and with the advancement of DNA recombinant technology, the scaling up of hCG production became much easier. This extremely low toxicity, easy availability and extensive research makes hCG an important choice for treating or for prevention of several diseases, as mentioned in this review. Lytic peptide hecate CGβ conjugate, which kills selectively the LHCGR possessing cells, sparing the healthy normal cells also opens up a new possibility perhaps beginning as a supplement for synergistic or additive treatment effects with existing chemotherapeutic agents or with other forms of cancer treatment, rather than replacing them. In this regard, the cytotoxicity against the healthy cells could be reduced and lytic peptide mediated destabilization of cancer cells and may even confer chemosensitivity on cancer cells with multi-drug resistance phenotype. The discovery that hCG/LH can act on nongonadal tissues represents a paradigm shift. Although it is obvious that a lot more intensive research is still needed, the current state of knowledge reaffirms that the physiological actions of hCG and LH include nongonadal targets along with the gonadal targets. The studies on nongonadal LH/hCG actions lead to a greater potential for novel therapeutic LH/hCG uses than all the previous studies on the gonadal actions of LH/hCG.
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