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 (LHCRG). LHCRG belongs to a family of seven-trans membrane spanning G-protein coupled receptors (McFarland et al., 1989; Ascoliet 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 LHCRG 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 gene
togenesis (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., 1996a; Apaja et al. 2005),
cervix (Lin et al., 2003), fetal tissues (Abdallah 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 (Ebelen 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 func-
tions, which have led to the development of widely used LH/hCG
therapy to stimulate final follicular and oocyte maturation and ovu-
lation induction (Filicori 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 effec-
tiveness (Tesarik and Mendoza, 2002; De Placido et al., 2005), whereas other studies, on the contrary, showed no evidence of
increasing effectiveness (Nyboeandersen 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 (Alviggi 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 meno-
pausal gonadotrophin) 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 con-
ception 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 endo-
metrial morphological changes and cytokines production (Filicori
et al., 2005).

hCG has been shown to possess a number of tropic actions in the
reproductive tract and fetoplacental unit and plays an immunosuppres-
sive 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 Mg 2+
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 rel-
enance 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 popu-
lations 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 Obstetri-
cians 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 lympho-
cyes to virus negative lymphocytes (Pollioti et al., 2002). In a trans-
genic 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 LH/CGR (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 LH/CGR 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 LH/CGR 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-amyloid 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 et al., 2000) which has been attributed to differences in the degree of differentiation in the breast (Russo et al., 1992). This protective 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, d; 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 LH/CGR in the reproductive tract of wild-type mice has been analyzed (Zhang et al., 2001b). LH/CGR mRNA expression has been shown in stromal cells of the wild-type murine 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 LH/CGR 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 LH/CGR have been suggested to be physiologically redundant on the basis of a LH/CGR 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 LH/CGR 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 LHHRKO model was created by targeted deletion of the proximal part of the LHR promoter and exon 1 (Lei et al., 2001), and the LuRKO 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 LHGR action (Chudgar et al., 2005; Pakarainen et al., 2005). LHR null mice with transplanted wild-type ovaries in LuRKO (Pakarainen et al., 2005) mice could become pregnant, but not in LHHRKO (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 LuRKO 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, angionstimulation by recombinant hCG was abrogated completely by deletion of LHGR, i.e. as in LuRKO 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 LHGR 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 gonadectomized inhibit null mice (inh/–/–) (Matzuk et al., 1992; Matzuk et al., 1994) and transgenic mice under the inhx promoter fused with SV40 T antigen oncogene (inhx/Tag) express adrenocortical LHCGR and have a distinct adrenal phenotype emphasizing the nongonadal LHGR effects. Gonadectomized inhx/–/– and inhx/Tag develop adrenocortical tumors in 100% pene-trance, demonstrating that inhibit is also a tumor suppressor for the adrenal gland. The appearance and growth of adrenal tumors in inhx/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., 2007). 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). Inhx/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, polycystic ovaries, and ovarian tumors (Risma et al., 1995). Intact TG βLHβ-CTP females with enhanced ovarian estrogen synthesis have been shown to be involved in increased secretion of prolactin (PRL), which consequently elevated the LHR expression of female mice with chronically elevated LH (Kero et al., 2000). LuRKO 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 significance of LH/hCG and LHGR.

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, compared 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 macroadenomas, 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 abolished 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 LHGR 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 observed in hCGβ+ mice. The overexpression models may not be highly useful in deciphering the information on the importance on 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 selectively 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 LuRKO 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 circulating bioactive LH/hCG, are so pathologically high (either 30-fold or more than 1000-fold) levels of hCG there were no nongonadal phenotypes in mice caused by nongonadal LHGR. The overexpression models may not be highly useful in deciphering the information on the importance on 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 selectively down-regulated resulting in abrogation of response. 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 1).

### 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
diagnosis and treatment, cancer remains a major concern and cause of morbidity and mortality. Majority of the available anti-neoplastic therapies have severe side effects, where tumor cells often develop drug resistance. We have developed a receptor-based therapy (LHCR), using lytic peptides, as they appear to selectively kill cancer cells due to change of their membrane potential, where most tumor cells possess a negatively charged outer layer which directs the action of lytic peptides towards the tumor cells and kills them, but spares the healthy ones even with LHCR (Leuschner and Hansel, 2004). Hecate CGβ conjugate (Leuschner et al., 2001) is a fusion polypeptide of 23-amino acid hecate, an amphipathic lytic peptide, synthetic analog of mellitin, the principal toxic component of natural honeybee venom, which was tethered with a 15 amino acid (81–95) fragment of hCG β chain possesses high receptor affinity towards LH receptors and hecate CGβ conjugate selectively destroys cells expressing the LHCR (Leuschner et al., 2001; Bodek et al., 2003; Bodek et al., 2005a, b). The cytotoxic activity of the conjugate induces plasma membrane disruption in a short period of time (Bodek et al., 2005b). The efficacy of hecate CGβ conjugate has been investigated with significantly successful results with no detectable side effects in prostate cancer (Hansel et al., 2001; Leuschner et al., 2001, 2003b; Bodek et al., 2005a), mammary tumors (Bodek et al., 2003; Leuschner et al., 2003a) as well as in ovarian cancer (Gawronska et al., 2002; Bodek et al., 2005b), testicular tumors (Bodek et al., 2005b), and finally adrenal tumors (Vuorenoja et al., 2008), all of which possesses LHCR. Hecate-CGβ conjugate induced a rapid and cell-specific membrane permeabilization of LHCR expressing cells in vitro, suggesting a necrotic mode of cell death, without activation of apoptosis (Bodek et al., 2005b). The necrotic mode of cell death was also apparent in prostate cancer cells (Bodek et al., 2005a). Clinical studies will be able to provide more evidence on their effectiveness and limitations on human endocrine cancers expressing LHCR (Pabon et al., 1996b; Lojun et al., 1997; Meduri et al., 1997; Tao et al., 1997a).

### Table I Murine transgenic models providing evidence for or against extragondal 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 nongondosal effects of LHCR—organ specificity (ref)</th>
<th>Gonadectomy required in order to express the LHCR</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 (inha/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-CTP)</td>
<td>(Rima 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>(Rull et al., 2002, 2003)</td>
<td>Against—pituitary, mammary gland, bone, adrenals (Rull et al., 2003, 2002; Yarram et al., 2003)</td>
<td>NO</td>
</tr>
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</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 LHCR 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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