Molecular and Cellular Endocrinology 383 (2014) 203–213

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Luteinizing hormone and human chorionic gonadotropin: Origins of difference ☆

Janet Choi [a,*], Johan Smitz [b,1]

[a] The Center for Women's Reproductive Care at Columbia University, New York, NY, United States
[b] UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

ARTICLE INFO

Article history:
Received 25 September 2013
Received in revised form 6 December 2013
Accepted 12 December 2013
Available online 21 December 2013

Keywords:
Gonadotropin
Lutropin
Luteinizing hormone
Human chorionic gonadotropin
Luteinizing hormone/choriogonadotropin receptor
Luteinizing hormone receptor

ABSTRACT

Luteinizing hormone (LH) and human chorionic gonadotropin (hCG) are widely recognized for their roles in ovulation and the support of early pregnancy. Aside from the timing of expression, however, the differences between LH and hCG have largely been overlooked in the clinical realm because of their similar molecular structures and shared receptor. With technologic advancements, including the development of highly purified and recombinant gonadotropins, researchers now appreciate that these hormones are not as interchangeable as once believed. Although they bind to a common receptor, emerging evidence suggests that LH and hCG have disparate effects on downstream signaling cascades. Increased understanding of the inherent differences between LH and hCG will foster more effective diagnostic and prognostic assays for use in a variety of clinical contexts and support the individualization of treatment strategies for conditions such as infertility.

Contents

* Corresponding author. Address: The Center for Women's Reproductive Care at Columbia University, 1790 Broadway, 2nd Floor, New York, NY 10019, United States. Tel.: +1 646 756 8282; fax: +1 646 756 8280.
E-mail addresses: jmc30@columbia.edu (J. Choi), johan.smitz@uzbrussel.be (J. Smitz).
[1] Address: UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. Tel.: +32 2 477 50 52; fax: +32 2 477 50 60.

0303-7207/$ - see front matter © 2013 The Authors. Published by Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mce.2013.12.009

1. Introduction

It is well established that luteinizing hormone (LH) and human chorionic gonadotropin (hCG) play key roles in the reproductive cycle. Textbooks recognize the disparate endogenous functions of these hormones, underscoring the role of LH in follicular maturation and ovulation induction, while acknowledging the essential role of hCG in early pregnancy survival. During early pregnancy, hCG is vital to support secretion of progesterone by the corpus luteum, without which a pregnancy cannot persist (Fritz and Speroff, 2011; Mesiano, 2009). Nonetheless, LH and hCG are frequently depicted as interchangeable, with one contemporary text stating that the 'β subunits [of human LH (hLH) and hCG] confer identical biologic activities when associated with the α subunit' (Bulun, 2011).

Although similar in structure and function, LH and hCG are distinct molecular entities with divergent patterns of expression and physiologic functions. LH and hCG share a common receptor, yet each hormone triggers a unique cascade of events following receptor binding (Casarini et al., 2012; Gupta et al., 2012). Moreover, within the same hormone family, individual isoforms exhibit unique characteristics regarding half-life and biologic functions. Emerging data suggest that these differences between LH and hCG have functional significance. Identifying the unique roles of LH and hCG is key to understanding both normal physiologic processes (e.g., reproduction, placentation) and dysfunctional states (e.g., infertility, gestational and non-gestational neoplasms). Advances in gonadotropin purification and recombinant technology have helped to differentiate the varied actions of LH and hCG. In turn, this has improved the diagnosis and treatment of human disease, most significantly in the context of infertility.

2. Materials and methods

A comprehensive literature review of LH and hCG was conducted, focusing on differentiation in terms of hormone structure, expression, modification, receptor activation, and clinical use. Scientific literature was identified via interrogation of the MEDLINE database using relevant search terms, including but not limited to: 'gonadotropin', 'human chorionic gonadotropin', 'luteinizing hormone', 'luteinizing hormone/choriogonadotropin receptor', 'lutropin', and 'lutropin receptor'. Results were limited to articles published in English. Additional resources were extracted from clinical texts and review articles. Article inclusion was predicated on relevance to the topic without use of an objective set of criteria, given that the review is descriptive rather than systematic in nature.

3. Molecular structure

Both LH and chorionic gonadotropin (CG) are heterodimeric glycoproteins comprised of α and β subunits. Along with thyroid-stimulating hormone (TSH) and follicle-stimulating hormone (FSH), they share a common 92-amino acid α subunit, whose gene resides on chromosome 6q12–q21 in humans (Bulun, 2011; Naylor et al., 1983). The unique functions and receptor-binding capacity of each of these hormones stem from differences among the β subunits (Table 1). Transcription of the β-subunit is the rate-limiting step in LH and CG production (Nagirnaja et al., 2010). The genes for the LH and hCG β subunits are located within a cluster of seven similar sequences on human chromosome 19q13.32 (Boorstein et al., 1982; Jameson and Hollenberg, 1993). One of those sequences encodes the β-subunit of LH (*LHB*); four are hCG β-subunit coding genes (*CGB, CGB5, CGB7, and CGB8*), and the remaining two are pseudogenes (*CGB1, CGB2*).

Table 1
Characteristics of hLH[a] and hCG[b].

	hLH	hCG
Molecular weight (Da)	~30,000	~36,000[c]
α Subunit		
Gene location	6q12–q21	6q12–q21
Size of mature subunit (no. of amino acids)	92	92
β Subunit		
Gene location	19q13.32	19q13.32
Size of mature subunit (no. of amino acids)	121	145

hLH, human luteinizing hormone; hCG, human chorionic gonadotropin.
[a] Bulun (2011).
[b] Cole (2010).
[c] Molecular weight of hyperglycosylated form is 40,000–41,000 Da.

The high degree of sequence conservation among *CGB* genes, combined with the fact that CG is detected only in equine and primate species (whereas LH is found in all vertebrates) suggests that CG is a relatively recent evolutionary derivative of LH. The amino acid sequences of human LH (hLH) and hCG are highly conserved, sharing 82% homology (Bulun, 2011). hCG retains the full 145−amino-acid complement in its β-subunit. In contrast, the β-subunit of LH undergoes cleavage of its 24-amino acid leader sequence to generate its final 121-amino acid sequence.

As a result of structural differences and post-translational modifications, hCG is more stable and has a longer circulating half-life than LH. The half-lives of these molecules typically are expressed as a range (on the order of minutes for LH and hours for hCG), reflecting the heterogeneity of circulating isoforms. The shorter half-life of LH is physiologically important, as it allows for the production of LH pulses. The longer half-life of hCG and its greater receptor binding affinity make it more biologically active than hLH (Rahman and Rao, 2009; Rao, 1979).

3.1. Gonadotropin variants

In the endogenous state, LH and hCG consists of isohormone mixtures that result from (1) post-translational modification of the native proteins; (2) metabolism to form truncated or nicked intermediates; and (3) natural sequence variants (Bergendah and Veldhuis, 2001; Cole, 2009; Stanton et al., 1993). Post-translational modification chiefly consists of the addition of various carbohydrate side chains, including sialic and sulfonic acid moieties, thus creating a variety of isoforms (upwards of 30 for LH and 15 for hCG) that differ with respect to half-life, bioactivity, and signaling properties (Arey and Lopez, 2011; Bergendah and Veldhuis, 2001; Cole, 2009; Stanton et al., 1993). Obviously, the number of isoform classes for each hormone is determined by our capacity for analytical discrimination. Because glycosylation affects the size and conformation of the molecule as well as access to binding sites, differences in interactions with their cognate receptor are to be expected (Arey and Lopez, 2011).

Naturally occurring variants of both LH and hCG have been characterized. A variant of LH that has an additional glycosylation site compared with wild-type LH is relatively common within certain populations (Lamminen and Huhtaniemi, 2001; Nilsson et al., 1997). Data have been collected showing that variant LH differs from normal LH in its biological effects (Haavisto et al., 1995). This LH variant has been associated with unexplained infertility and subfertility due to ovulatory dysfunction in females, and with slowed pubertal progression in males (Raivio et al., 1996; Takahashi et al., 1998, 1999). Preliminary data also suggest that the variant LH is more prevalent among women who demonstrate resistance to ovarian stimulation with recombinant human FSH, compared