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Review Article

There is no turning back on the paradigm shift on the actions of human chorionic gonadotropin and luteinizing hormone

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ARTICLE INFO

Article history:
Received 1 July 2015
Accepted 2 July 2015
Available online 10 July 2015

Keywords:
Human chorionic gonadotropin
Luteinizing hormone
hCG/LH receptors
Nongonadal receptors
hCG therapies

ABSTRACT

Investigators from around the world, working for more than 25 years, have contributed to the progress on the paradigm shift on the actions of human chorionic gonadotropin (hCG) and luteinizing hormone (LH). Although many knowledge gaps remain, the paradigm shift has already provided a better understanding of many normal phenomena, several human diseases, and offered many potential new therapies. As all the previous paradigm shifts, this too faced uphill battles. Nevertheless, it is now here to stay and there is no turning back.

1. Introduction

hCG and LH are two of the gonadotropins that are critical to female and male reproductive competence.[1] While hCG is primarily secreted by placental syncytiotrophoblasts, LH is secreted by gonadotropes in anterior pituitary gland.[1] Both are heterodimeric glycoprotein hormones, consisting of non-covalently bound α and β subunits.[1] While the common α subunit is transcribed by a single gene, β subunit of hCG is encoded by a six-gene cluster, which consists of both active and pseudogenes.[2] The cluster has likely evolved, via gene duplication, and mutations, which shifted transcription start site and c-terminus extension of the LH-β subunit gene.[2] hCG is more glycosylated than LH, which increases its circulatory half life.[1] In addition, hCG can bind to the receptors with higher affinity than LH.[3] These two features make hCG more active in vivo than LH.[1,3,4] While hCG is present only in humans and subhuman primates, LH is present in all species.[4,5] Because of structural and functional similarity, hCG can bind to the same G-protein coupled cell surface receptors as LH; thus, they are often called as hCG/LH receptors.[6,7] The receptor is encoded by a single copy gene.[6,7] hCG is commonly used ligand to study the receptor functions in all the species. The hCG and LH-like molecules have been found in lower organisms, which suggests that these molecules, performing different functions, have been conserved during the evolution.[8–12]

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http://dx.doi.org/10.1016/j.jrhm.2015.07.001

2. Old paradigm

As gonadotropins, hCG and LH were believed to act only on female and male gonads. hCG is a pregnancy hormone and its actions are thought to regulate only corpus luteum, fetal gonads, and adrenals.[4,13] The regulation of corpus luteum involves its rescue from regression in a fertile cycle and maintains its progesterone secretion, until shift in its synthesis to placenta is completed by about the 9th week of pregnancy. After the shift, hCG was presumed to be a vestigial hormone, even though it is known that low levels are present during the remainder of pregnancy and hCG is believed to contribute to an increased relaxin levels during the second and third trimesters of pregnancy by stimulating its secretion by corpus luteum.[14–16] These findings alone should have alerted us to question whether hCG has functions beyond early pregnancy. The paradigm shift provided an ample evidence to suggest that hCG indeed has actions throughout pregnancy.

3. Paradigm shift

Contrary to the previous belief, hCG/LH receptors have been found to be widely distributed in the body.[17–20] The receptor positive tissues include reproductive as well as non-reproductive tissues in both genders.[17–23] The latter consist of tissues and cells that are generally either responsive to sex steroid hormones and/or can synthesize them.[17–23] There are more data on receptor characterization and functional relevance in some tissues than in the others.[17–23] The nongonadal receptors are not only found in humans but also in many other animal species.[17–23]

There is a selectivity in the nongonadal hCG/LH receptor distribution in adults. For example, adult liver, lungs, kidney, spleen, and skeletal smooth muscle do not contain them.[17–20] This selectivity does not seem to exist in human fetus. For example, human fetal liver, lungs, kidneys, and small and large intestines contain the receptors.[24] This could be an indication that hCG may regulate the growth and differentiation of fetal tissues. In fact, it has been shown that hCG induces the proliferation and differentiation of human embryonic stem cells into neuroectodermal rosettes, through an upregulation of progesterone synthesis.[25] Once the differentiation process is complete, then the adult receptor expression pattern may set in. This possibility has implications for nongonadal cancers. For example, while cancer cells may be receptor positive, the normal counterparts could be receptor negative, implying that the cellular dedifferentiation could recapitulate the receptor expression. Interestingly, many cancers can produce small amounts of non-glycosylated hCG, which are rapidly eliminated from the body.[9,26] As a result, the hCG levels are barely detectable in the circulation. The hCG produced by cancers probably serve as an autocrine growth factor through an activation of its cancer cell receptors. There is already direct evidence in support of this possibility for lung cancers, which produce small amounts of hCG, as well as for gestational trophoblastic neoplasms, which produce prodigious amounts of hCG.[27–30]

Follicles stimulating hormone (FSH) also had a paradigm shift on its actions.[31–33] But the data are not as extensive as that on hCG/LH. The nongonadal FSH receptor distribution parallels that of hCG/LH receptors, which suggests that these two gonadotropins may regulate different functions in the same tissues, as they do in the gonads.

From the data on the hormones like prolactin, oxytocin, relaxin, gonadotropin releasing hormone, etc., which can regulate many more tissues than originally believed, it should not have been difficult to accept the paradigm shift on the hCG/LH actions.[34,35] Yet there was a considerable initial resistance as all the other previous paradigm shifts have faced. This initial resistance mostly melted away by the mounting scientific evidence. There are still many naysayers. The inability to accept a new normal is not new.

4. The paradigm shift provided potential explanations for many normal phenomena

These explanations came from the demonstrations of functional hCG/LH receptor presence in nongonadal cells and tissues and evidence-based extrapolations of the findings to various normal contexts. Additional research is needed to further validate and extend these extrapolations.

a. hCG and its receptors are coexpresssed in unfertilized oocytes (unpublished data). After fertilization, their polarity changes and the amount increases (unpublished data). hCG, together with LH, may play a role in gametes (male and female) transport, maturation, and fertilization in female reproductive tract, promote early embryonic growth and development, and its timely transport for implantation in the uterus.[17–20] Upon arrival, hCG may also play a role in the implantation process and serves as a communication molecule between endometrium and blastocyst.[36–41]

   These findings opened the possibility that intrauterine hCG infusion prior to embryo transfer in assisted reproductive technologies might improve the implantation and clinical pregnancy rates. In fact, three studies reported a success[42–44] and one reported a failure.[45]

   Another possibility is hCG treatment of cocultures of embryos with autologous reproductive tract epithelial cells, before embryo transfer, could further improve pregnancy chances beyond that obtained by coculturing alone, in a subset of women who repeatedly fail to become pregnant by in vitro fertilization/embryo transfer procedures.[46–51]

b. Once implanted, hCG contributes to myometrial quiescence, dampens the maternal immune response to prevent fetal rejection and promotes scores of other changes that favor pregnancy continuation.[52–55]

c. hCG could increase feto-placental perfusion by dilating uterine blood vessels.[56,57] The increased uterine blood flow can not only meet the nutritional demands of the growing fetus, but also may help in removing fetal waste products.

d. Fetal hCG may play a role in growth and differentiation of human fetal tissues.[24,25]

e. The hCG actions in placenta could explain cytotrophoblasts differentiation into syncytiotrophoblasts, pregnancy hCG profile, and invasion of intermediate cytotrophoblasts