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Human chorionic gonadotropin: Different glycoforms and biological activity depending on its source of production

L'hormone chorionique gonadotrope humaine : différentes glycoformes et activités biologiques en fonction de sa source de production

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Abstract

Human chorionic gonadotropin (hCG) is the first hormonal message from the placenta to the mother. It is detectable in maternal blood two days after implantation and behaves like a super LH agonist stimulating progesterone secretion by the *corpus luteum*. In addition to maintaining the production of progesterone until the placenta itself produces it, hCG also has a role in myometrial quiescence and local immune tolerance. Specific to humans, hCG is a complex glycoprotein composed of two highly glycosylated subunits. The α-subunit is identical to the pituitary gonadotropin hormones (LH, FSH, TSH), contains two N-glycosylation sites, and is encoded by a single gene (*CGA*). By contrast, the β-subunits are distinct for each hormones and confer both receptor and biological specificity, although LH and hCG bind to the same receptor (LH/CG-R). The hCG ß-subunit is encoded by a cluster of genes (*CGB*) and contains two sites of N-glycosylation and four sites of O-glycosylation. The hCG glycosylation state varies with the stage of pregnancy, its source of production and in the pathology. It is well established that hCG is mainly secreted into maternal blood, where it peaks at 8–10 weeks of gestation (WG), by the syncytiotrophoblast (ST), which represents the endocrine tissue of the human placenta. The invasive extravillous trophoblast (iEVT) also secretes hCG, and in particular hyperglycosylated forms of hCG (hCG-H) also produced by choriocarcinoma cells. In maternal blood, hCG-H is elevated during early first trimester corresponding to the trophoblastic cell invasion process and then decreases. In addition to its endocrine role, hCG has autocrine and paracrine roles. It promotes formation of the ST and angiogenesis through LH/CG-R but has no effect on trophoblast invasion in vitro. By contrast, hCG-H stimulates trophoblast invasion and angiogenesis by interacting with the TGFß receptor in a LH/CG-R independent signalling pathway. hCG is largely used in antenatal screening and hCG-H might represent a serum marker of implantation and early trophoblast invasion. In conclusion, hCG is the major pregnancy glycoprotein hormone, whose maternal concentration and glycan structure change all along pregnancy. Depending on its source of production, glycoforms of hCG display different biological activities and functions that are essential for pregnancy outcome.

Keywords: Glycoproteins; Glycosylation; Structure-function; Receptors; Syncytiotrophoblast; Extravillous trophoblast; Invasion

Résumé

L'hormone chorionique gonadotrope humaine (hCG) est le premier message hormonal produit par le placenta vers l'organisme maternel. L'hCG est détectable dans le sang maternel, deux jours après l'implantation et se comporte comme un super agoniste de la LH stimulant la sécrétion de progestérone par le corps jaune. En plus de maintenir la production de la progestérone jusqu'à ce que le placenta en produise, l'hCG intervient dans la quiescence du myomètre et la tolérance immunitaire locale. Spécifique à l'espèce humaine, l'hCG est une glycoprotéine complexe composée de deux sous-unités fortement glycosylées. La sous-unité α est identique aux hormones gonadotrophines hypophysaires (FSH, LH, TSH). Elle est codée par un gène unique (*CGA*) et contient deux sites de N-glycosylation. En revanche, les sous-unités β sont distinctes pour chacune des hormones et confèrent la spécificité biologique en se liant à leur récepteur respectif bien que LH et hCG reconnaissent le même récepteur (LH/CG-R). La sous-unité β de l'hCG est codée par un cluster de gènes (*CGB*) et contient deux sites de N-glycosylation et quatre sites de O-glycosylation. La glycosylation de l'hCG, dépend du stade de la grossesse, de sa source de production et de la pathologie. Il est bien établi que l'hCG est principalement sécrétée par le syncytiotrophoblaste (ST), qui représente le tissu endocrine et d'échanges du placenta humain. Sa concentration dans le sang maternel

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culmine à 8–10 semaines de gestation (WG). Le trophoblaste extravilleux invasif (iEVT) sécrète également de l'hCG et tout particulièrement des formes hyperglycosylées d'hCG (hCG-H) également produites par les cellules de choriocarcinome. Dans le sang maternel l'hCG-H est élevée au début du premier trimestre correspondant au processus physiologique d'invasion trophoblastique. Outre son rôle endocrine, l'hCG joue un rôle autocrine et paracrine. Il favorise la formation du ST et stimule l'angiogenèse par l'intermédiaire du LH/CG-R mais n'a aucun effet sur l'invasion trophoblastique in vitro. En revanche, l'hCG-H stimule l'invasion trophoblastique et l'angiogenèse en interagissant avec les récepteurs du TGFβ et indépendamment du LH/CG-R. L'hCG est largement utilisé dans le dépistage prénatal et l'hCG-H pourrait représenter un marqueur sérique de l'implantation et de l'invasion trophoblastique. En conclusion, l'hCG est l'hormone glycoprotéique majeure de la grossesse, dont la concentration sérique maternelle et la glycosylation évoluent tout au long de la grossesse. En fonction de sa source de production, les glycoformes de l'hCG présentent des activités biologiques et des fonctions différentes qui sont essentielles à l'issue de grossesse.

Mots clés : Glycoprotéine ; Glycosylation ; Structure-fonction ; Recepteur ; Syncytiotrophoblaste ; Trophoblaste extravilleux ; Invasion

1. Human placenta development

The placenta is a transitory organ necessary for pregnancy and foetal growth. The human placenta is characterized by extensive invasion of uterus wall by the trophoblast, allowing direct contact of cytotrophoblasts with maternal blood (hemochorial placenta), by considerable changes in the vasculature of the uterus and by the extent and specificity of its hormonal production [1]. The chorionic villus represents the structural and functional unit of the human placenta and is bathed in maternal blood within the intervillous space from the end of the first trimester of pregnancy when trophoblast plugs are removed and the uterine spiral arteries (usa) remodelled. After the initial phase of nidation, human cytotrophoblasts differentiate along either the villous or extravillous cytotrophoblast pathway (Fig. 1A and B) [2].

Extravillous cytotrophoblasts (EVT) are located at the tip of the anchoring chorionic villi contacting the uterine wall. They are involved in anchoring the placenta into the uterus and participate to immunotolerance and remodelling of uteroplacental vascularization. EVT proliferate to form multilayered columns of cells and then exit the cell cycle and invade the decidua up to the upper third of the myometrium. EVT also specifically migrate toward and invade the usa through endovascular and perivascular routes replacing the endothelial lining and most of the musculoelastic tissue, leading to low-resistance vessels that escape to vasomotor molecules. This invasion process and remodeling of the uterine arterioles are essential to provide an adequate supply of maternal blood necessary for foetal growth [1–4]. It is finely regulated during pregnancy (first trimester) and space (oriented towards the usa). Shallow trophoblast invasion and defective usa remodelling during first trimester are often associated with foetal growth restriction (FGR) and preeclampsia. Preeclampsia is a major and frequent complication of human pregnancy (about 3–7% corresponding to more than 16,000 pregnancies per year in France), with serious maternal and fetal (FGR) consequences. It has been identified as one of the first causes of severe prematurity. To date, there is neither curative nor preventive treatment for preeclampsia, except delivery of the placenta.

The mononucleated villous cytotrophoblasts (VCT) form an epithelium that covers the floating chorionic villi containing the foetal-placental vessels. VCT aggregate and fuse with the outerlayer – a multinucleated syncytiotrophoblast (ST) – which is renewed all along pregnancy and in direct contact with maternal blood within the intervillous space. This ST ensures exchanges of gases and nutrients between maternal and foetal blood. The ST represents also the endocrine tissue of the placenta, secreting large amounts of hormones, including human chorionic gonadotropin (hCG) [5]. Thus, anomalies in ST formation or function may interfere with main functions of the placenta and directly alter foetal growth.

The deep invasion of the EVT within the uterine wall, remodelling of usa and the important ST hormonal functions (in particular hCG), are specific to humans. Poor placentation is directly involved in many pregnancy diseases, including FGR, preeclampsia and prematurity.

2. Human chorionic gonadotropin

Specific to humans, hCG is a complex and highly glycosylated glycoprotein of about 37 kDa composed of two glycosylated subunits which are non-covalently associated. The α-subunit is identical to the pituitary gonadotropin hormones (luteinizing hormone: LH, follicle-stimulating hormone: FSH, thyroid-stimulating hormone: TSH), contains 92 amino acids with two N-glycosylation sites, and is encoded by a single gene (CGA) located on chromosome 6q21.1-23 [6]. The β-subunits are distinct and confers the biological specificity to the hormone. The hCG β-subunit contains 145 amino acids with two sites of N-glycosylation and four sites of O-glycosylation, and is encoded by a cluster of genes that have evolved by duplication from LHB. The CGB subunit is encoded by any one of the six nonallelic genes *CGB8*, *CGB7*, *CGB5*, *CGB3*, *CGB2*, and *CGB1* present on chromosome 19q13.32 [7–9]. *CGB1* and *CGB2* are two pseudogenes, whereas the other *CGB* genes are regrouped in two subtypes: type 1 (*CGB7*) and type 2 (*CGB3*, *CGB5*, and *CGB8*), which correspond to two different proteins that differ from three amino acids [10]. CGβ5 is expressed predominantly in the placenta [11]. Whereas hCGα is produced in large excess, hCGβ represents a step limiting for hCG synthesis.

After implantation, hCG is the first trophoblast signal detected in the maternal blood and is used to diagnose pregnancy. hCG and free hCGβ are detected in the maternal blood from the first week of gestation (WG), and their levels increase until reaching a peak at 10–12 WG and then decrease gradually,