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Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid

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Human chorionic gonadotropin (hCG) is a glycoprotein hormone that has structural similarity to TSH. At the time of the peak hCG levels in normal pregnancy, serum TSH levels fall and bear a mirror image to the hCG peak. This reduction in TSH suggests that hCG causes an increased secretion of T4 and T3.

Women with hyperemisis gravidarum often have high hCG levels that cause transient hyperthyroidsm. In the vast majority of such patients, there will be spontaneous remission of the increased thyroid function when the vomiting stops in several weeks. When there are clinical features of hyperthyroidism, it is be reasonable to treat with antithyroid drugs or a beta-adrenergic blocker, but treatment is rarely required beyond 22 weeks of gestation.

Hyperthyroidism or increased thyroid function has been reported in many patients with trophoblastic tumors, either hydatiditform mole or choriocarcinoma. The diagnosis of hydatidiform mole is made by ultrasonography that shows a 'snowstorm' appearance without a fetus. Hydatidiform moles secrete large amounts of hCG proportional to the mass of the tumor. The development of hyperthyroidism requires hCG levels of >200 U/ml that are sustained for several weeks. Removal of the mole cures the hyperthyroidism. There have been many case reports of hyperthyroidism in women with choriocarcinoma and high hCG levels. The principal therapy is chemotherapy, usually given at a specialized center. With effective chemotherapy, long-term survival exceeds 95%.

A unique family with recurrent gestational hyperthyroidism associated with hyperemesis gravidarum was found to have a mutation in the extracellular domain of the TSH receptor that made it responsive to normal levels of hCG.

Key words: human chorionic gonadotropin; thyrotropin; pregnancy; hyperemesis gravidarum; hydatidiform mole; choriocarcinoma; mutant thyroid-stimulating hormone receptor.

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HCG BIOCHEMISTRY AND PHYSIOLOGY

Biochemistry

Human chorionic gonadotropin (HCG) is a member of the glycoprotein hormone family that is composed of a common α-subunit and a hormone-specific β-subunit, non-covalently associated.[1] The α-subunit of HCG, that is common to the pituitary hormones, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteininzing hormone (LH), consists of a polypeptide chain of 92 amino acid residues containing two N-linked oligosaccharide side-chains. The hCG β-subunit consists of 145 residues with two N-linked and four O-linked oligosaccharides. Figure 1 shows the structure of the HCG subunits. The TSH β-subunit is composed of 112 residues and one N-linked oligosaccaride. The β-subunits of both possess 12 half-cysteine residues at highly conserved positions. Three disulphide bonds form a cystine knot structure, identical in both hormones and essential for binding to the receptor.[2] HCG and LH bind to the same receptor.

A single gene on chromosome 6 encodes the α-subunit.[3] The genes that encode the β-subunits are in a cluster on chromosome 19. There are eight genes for the β-subunit of HCG/LH. One gene codes for LH, and seven genes code for HCG, but only three are actively transcribed. Only primates and horses have genes for β-HCG. A single base deletion in the β-LH gene caused a read-through mutation of a stop signal in the β-LH gene, resulting in the extended carboxyteminal 33 amino acid sequence of β-HCG.

HCG, molecular weight 36 700, contains 30% carbohydrate, the highest carbohydrate content of any human hormone. In contrast with the approximate 1 hour plasma half-life of LH, that of HCG is about 24 hour because of its high sialic acid content that prevents uptake and degradation by the liver. The complete hCG molecule is synthesized primarily in the syncytiotrophoblast. Small amounts of the α and β subunits are also secreted.

Pattern of secretion

Secretion of HCG begins very early in pregnancy and peaks at 9–11 weeks of pregnancy (Figure 2). Peak levels are in the range 30–100 U/l and last for only a few days, then gradually decline to a nadir of 5–10 U/l at about 20 weeks, where they remain throughout the latter half of pregnancy. The peak levels bear a relation to the mass of the placenta. Peak levels are higher and more prolonged when there are multiple fetuses.

Glycoprotein hormone receptors

The glycoprotein hormone receptors are members of the large superfamily of G-protein-coupled seven-transmembrane receptors. They share a high degree of homology (~70%) in their transmembrane domains.[4] The main differences are found in the large amino-terminal extracellular domain involved in binding of the hormone. In the extracellular domain, the LH/CG receptor has 45% homology with the TSH receptor.[4–6]

Function of HCG

The best known biological function of hCG is the maintenance of the function of the corpus luteum, resulting in continued progesterone production. However, progesterone

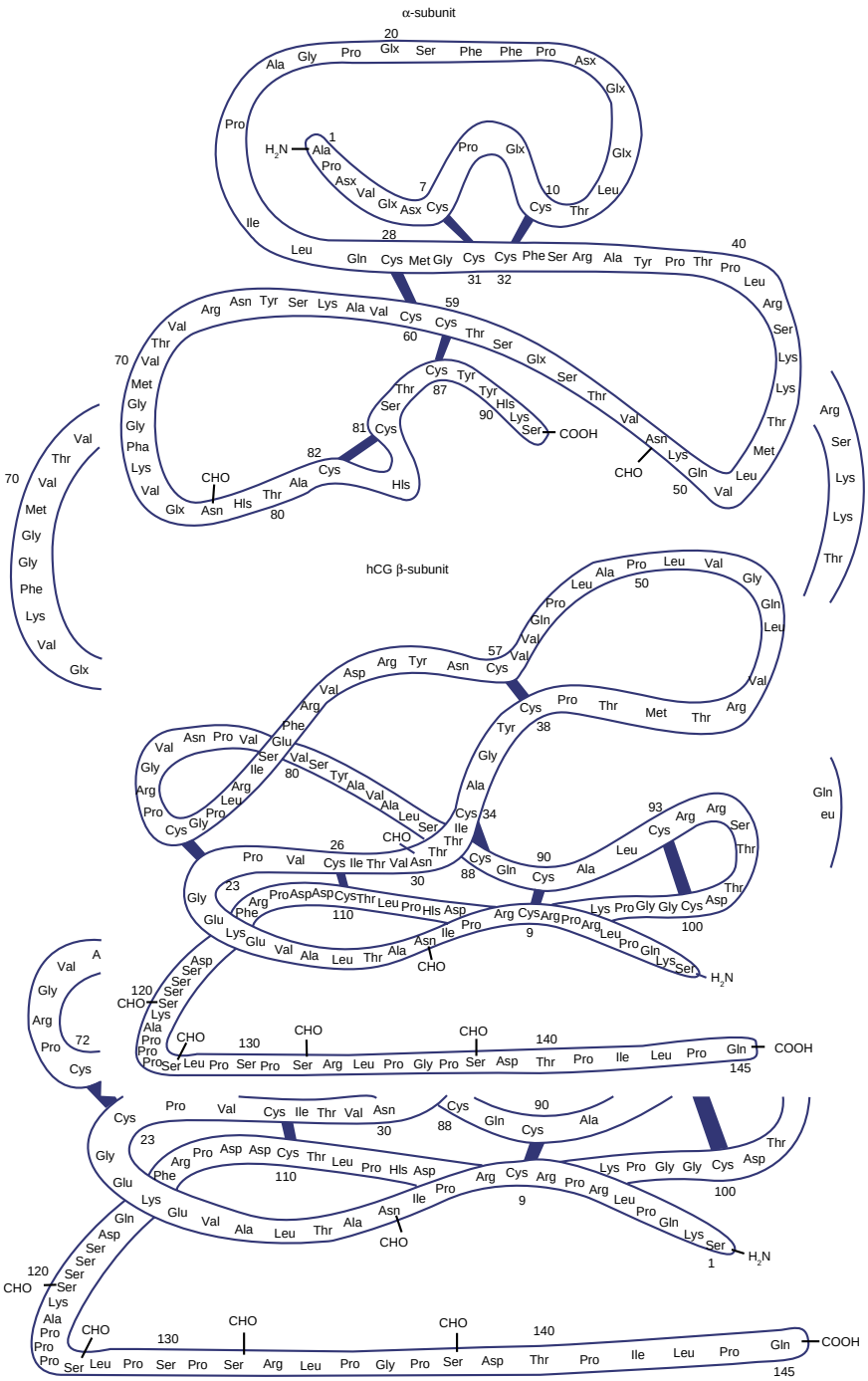

Figure 1. Schematic representations of the alpha and beta subunits of hCG (from Ren SC, Braunstein GD, *Sem. Reprod. Biol.* 1992; 10:95–105, reprinted by permission).

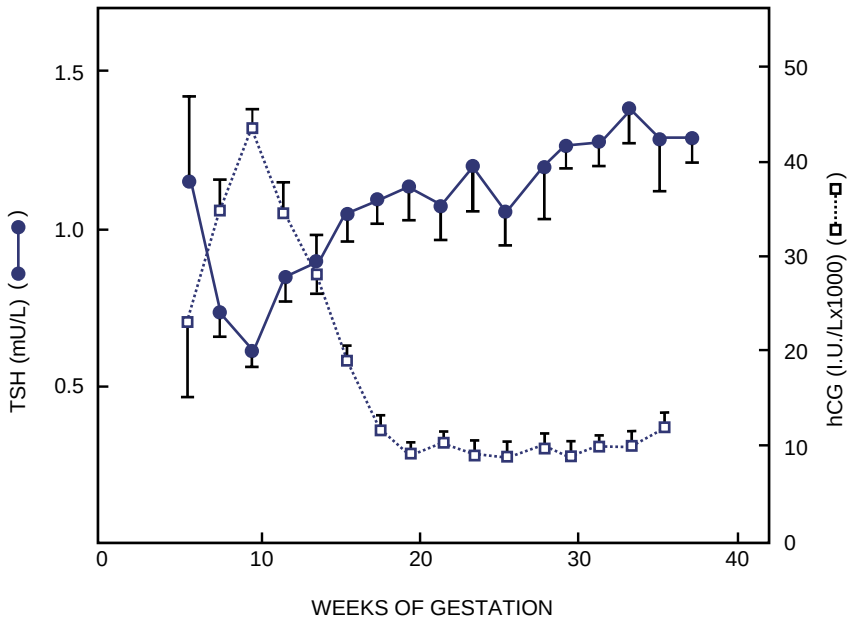

Figure 2. Serum hCG and TSH as a function of gestational age. (with permission[9]). © 1990 The Endocrine Society.

synthesis by the corpus luteum begins to decline at about 6 weeks, several weeks before peak hCG secretion. Until the seventh week of pregnancy, the survival of the pregnancy depends on the steroids from the corpus luteum.

A second function of HCG is stimulation of fetal testicular secretion of tesotosterone that attains a maximum at approximately the same time in gestation when the maximal levels of hCG are attained. Thus, at a critical time in sexual differentiation of the male fetus, hCG, entering fetal plasma from the syncytiotrophoblast, stimulates the replication of fetal testicular Leydig cells and testosterone synthesis to promote male sexual differentiation.

Thyrotropic action in normal pregnancy

At the time of the peak hCG levels in normal pregnancy, serum TSH levels fall and bear a mirror image to the hCG peak[7–9] (Figure 2). This reduction in TSH can now be measured with precision with current sensitive TSH assays. The increase of HCG most likely causes an increased secretion of T4 and T3[8,9], but this is difficult to establish with certainty because the increased thyroxine-binding globulin (TBG) level of pregnancy may confound the measurement of small changes in free thyroid hormone levels, and data in the literature are contradictory. Several reports show that free T3 or T4 levels are significantly elevated at the time when hCG levels are maximal.[8–11] It is likely that the HCG-induced thyroid secretion increases free T4 and free T3 levels, albeit within the normal range. Thyroid-stimulating activity in sera of normal pregnant women shows a significant correlation with serum hCG levels.[12,13] In bioassays, hCG is only about $1/10^4$ as potent as hTSH during normal pregnancy.[14] It is likely that the thyrotropic activity of hCG during its peak secretion overrides the normal operation of the hypothalamic-pituitary-thyroid feedback system.[8,15]

In a systematic survey of pregnant women in Brussels during the first trimester, 20% had a suppressed serum TSH level and increased serum thyroxine concentration, and in 1% this was associated with clinical features of hyperthyroidism.[16] In Asian women in Singapore at 8–14 weeks of pregnancy, 33% had suppressed TSH and 11% had suppressed TSH and elevated free T4 levels.[17]

Assays of thyrotropic action of HCG

HCG has thyroid-stimulating activity in bioassays in mice, rats, chicks and men.[18–20] Administration of single doses of large amounts of commercial HCG to men cause the release of thyroidal radiodidine, even though the peak HCG levels attained were only 25–42 U/ml.[21] HCG stimulates iodide uptake, adenylate cyclase, and DNA synthesis in cultured rat thyroid cells.[22] HCG stimulates iodide uptake by increasing the mRNA and protein level of the sodium/iodide symporter.[23] In Chinese hamster ovary (CHO) cells transfected with the human TSH receptor, hCG increased adenylate cyclase and DNA synthesis.[24,25] These studies demonstrated unequivally that HCG activates the TSH receptor and is a weak thyrotropin. LH and hCG lacking the C-terminal peptide of the beta subunit were almost ten-fold more active in this system.[25] In clinical situations such as primary hypogonadism, the elevated levels of LH are several orders of magnitude below those required to activate the TSH receptor.

Metabolism of HCG

The hCG immunoreactivity in serum is a mixture of hCG-related molecules, including intact hCG, nicked hCG (missing the peptide linkage at β44–45 or β47–48), carbohydrate variants of hCG, hCG missing β-C-terminal tail, hCG free α-subunit and free β-subunit.[26] Nicks of the hCG molecule frequently occur in a hydrophobic loop in the hCG β-subunit, which is held in place by a disulfide link between Cys38 and Cys57 (Figure 1). Nicking of the hCG molecule may result from the deactivation and degradation pathway of hCG in serum and urine.[27] The nicking of the peptide bonds reduces the binding of hCG to its receptor and causes a loss of 80% of its steriodogenic activity.[28] Nicked hCG preparations, obtained from patients with trophoblastic disease and by enzymatic digestion of intact hCG, had approximately 1.5–2-fold the potency of intact hCG for stimulation of recombinant human TSH receptor.[29] Therefore, the thyrotropic activity of hCG is also influenced by the metabolism of the hCG molecule.

Role of carbohydrate in thyrotropic action of hCG

The biologic activity of glycoprotein hormones is influenced by the number and structure of the oligosaccharide side chains. Extensive variations are possible in the branched oligosaccharide structures, contributing to considerable heterogeneity of glycoprotein hormones.[30] Deglycosylation and/or desialylation of hCG enhances its thyrotropic potency in rat (FRTL-5) thyroid cells.[31,32] Basic hCG isoforms with lower sialic acid content extracted from hydatidiform moles were more potent in activation of adenylate cyclase, and showed a high ratio of bioactivity/immunoactivity (B/I) in CHO cells tranfected with human TSH receptors.[33] This is consistent with the finding that the β-C-terminal tail-truncated hCG with higher thyrotropic potency is substantially deglycosylated and desialylated in the β-subunit in comparison with intact hCG because all four O-linked glycosylation sites occur within the missing C-terminal extension.[25]

Although removal of sialic acid from hCG enhances its TSH receptor binding, it also reduces its plasma half-life because sialic acid blocks the high affinity for and rapid

uptake of hCG by hepatic receptors for asialoglycoproteins.[34] Therefore, it is likely that the thyrotropic activity of hCG is regulated by two factors: the amount of desialylated hCG produced from trophoblast cells and its plasma half-life.[25] The precise nature of the thyrotropic molecular variant of hCG is controversial. HCG that is less sialylated activates the TSH receptor to a greater extent[14], as has been reported in gestational thyrotoxicosis.[14] However, lack of sialic acid reduces its half-life. More acidic variants of hCG have a longer half-life and, therefore, a more prolonged action.[35,36]

HYPEREMESIS GRAVIDARUM

Definition and prevalence

Hyperemesis gravidarum occurs in about 1.5% of pregnancies and is probably more prevalent in Asian women than in Caucasians.[37] The incidence is 4.5% in Kuwait.[38] It is characterized by prolonged and severe nausea and vomiting in early pregnancy that leads to a loss of 5% body weight, dehydration and ketosis.[39] It frequently results in hyponatremia, hypokalemia, hypochloremic alkalosis, and abnormalities of liver function. Other causes of vomiting must be excluded. There is a correlation between the degree of vomiting and the serum hCG level (Figure 3).[39] Management includes hospitalization, intravenous fluid and electrolyte replacement, thiamine supplementation, conventional antiemetics, and psychological support.

Increased thyroid function

There are many reports of series of hyperemesis patients whose thyroid function has been studied. A study in Belgium reported that free thyroxine index was increased in 25 of 33 consecutive hyperemesis patients, of whom six were treated with methimazole until euthyroid.[40] However, free thyroxine index normalized in all patients, regardless of therapy. A study of 25 patients with hyperemesis in England found that ten had increased free thyroxine levels.[41] Those with increased free thyroxine had suppressed TSH responses to thyrotropin-releasing hormone. The free thyroxine levels normalized when the vomiting stopped and remained normal postpartum. In contrast, a 39 year-old woman presented with severe hyperemesis at 8 weeks pregnancy and very high serum hCG level.[42] Although she was treated with methimazole suppositories until euthyroid at 18 weeks, her vomiting persisted until delivery, suggesting that the vomiting was not caused by the increased thyroid function. A study of 71 patients with hyperemesis in Hong Kong revealed that one-third had high free T4 and one-fifth had high free T3 levels.[43] In those with elevated free thyroid hormone levels, serum hCG was higher. A study in Israel of 41 consecutive admissions with hyperemesis showed that free thyroxine was increased in 11 patients.[44] Four were treated with propylthiouracil because of tachycardia, two of whom had goiter. Thyroxine levels returned to normal in the untreated patients when the hyperemesis abated. A study in Turkey of 24 patients with hyperemesis reported that their free T3, free T4 and hCG levels were significantly higher than those of controls.[45] Twin pregnancies are more often associated with sustained elevation of hCG and hyperemesis gravidarum.[37,46]

A prospective study of 57 consecutive patients with hyperemesis in Los Angeles compared them with 57 women of similar gestational age.[39] In the hyperemesis patients, TSH was suppressed in 60%, free T4 was increased in 46%, while free T3 index

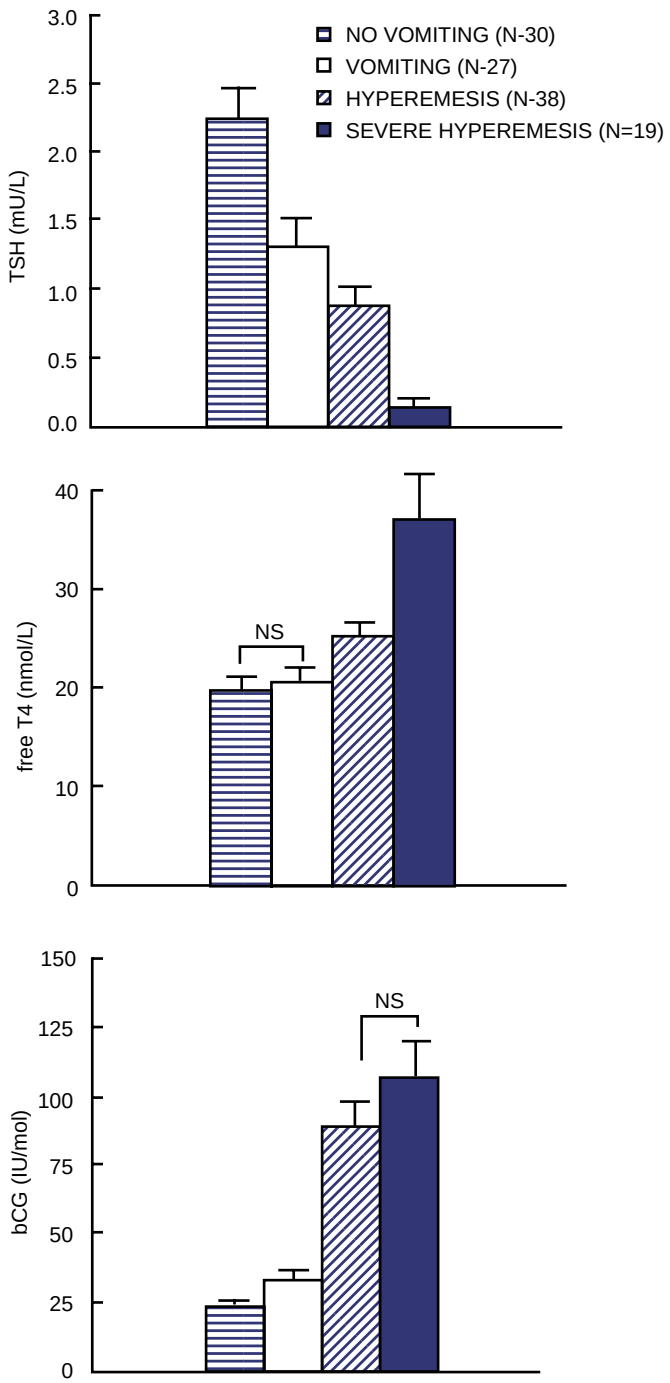

Figure 3. Relation between the severity of vomiting and serum concentratons of TSH, free T4, and hCG (mean ± SE). Hormone concentrations differed significantly between each group of patients except as indicated by NS. (with permission[39]). © 1992 The Endocrine Society.

was increased in only 12%. The explanation for the relatively lower T3 compared with T4 may be that caloric deprivation impaired conversion of T4 to T3. Serum HCG levels were three-fold higher in the hyperemesis patients than in the controls (Figure 3). No patient in this study had goiter or clinical features of hyperthyroidism. For the entire group, the degree of biochemical hyperthyoidism and the hCG concentration correlated with the severity of vomiting (Figure 3). There was an inverse correlation between the serum HCG and the serum TSH levels and a direct correlation of HCG with free T4 levels (Figure 4). Thyrotropic activity in the serum, estimated by bioassay,

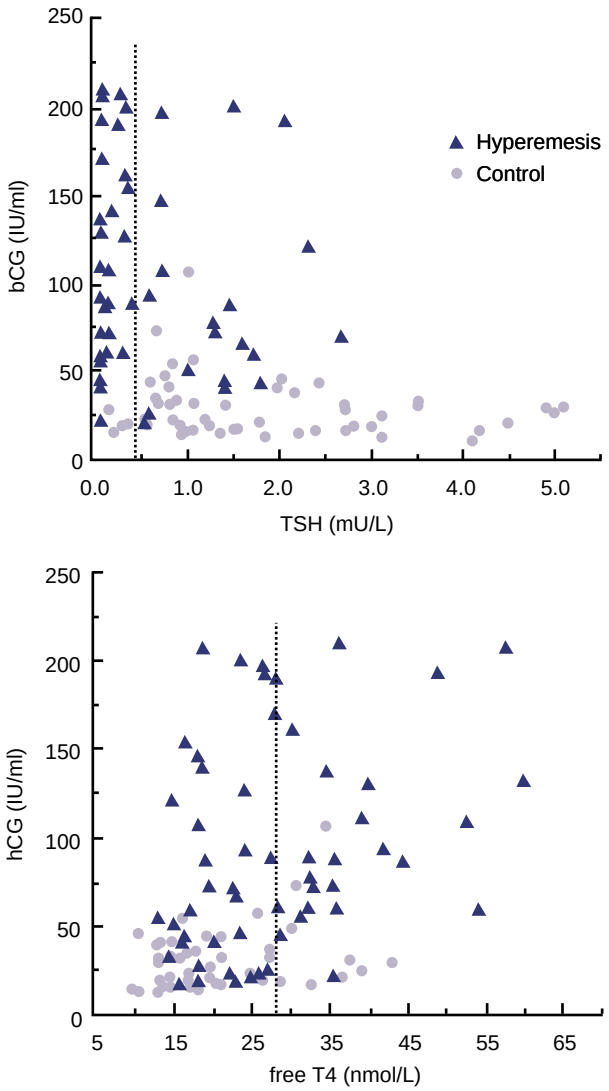

Figure 4. Correlation of serum hCG vs serum free T4 ($r = 0.45, P < 0.001$) and serum TSH ($r = -0.48, P < 0.001$) in hyperemessis and control subjects. (with permission[39]). © 1992 The Endocrine Society.

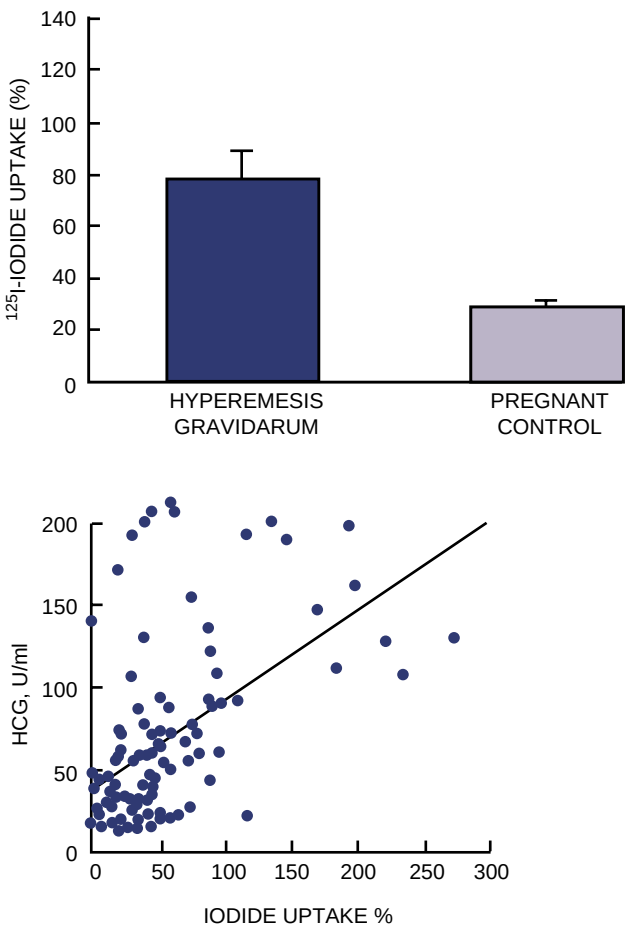

Figure 5. Upper panel, serum thyrotropic activity (measured as iodide uptake in cultured rat cells) in hyperemeis patients and pregnant controls, mean ± SE, $P < 0.001$). Lower panel, correlation of serum hCG vs serum thyrotropic activity in hyperemesis and pregnant controls, $r = 0.50, P < 0.001$ (with permission[39]). © 1992 The Endocrine Society.

correlated with the hCG concentration (Figure 5). The authors concluded that hCG was responsible for the increased hyroid function.

Etiology of hyperemesis gravidarum gravidarum

The etiology of hyperemesis gravidarum gravidarum is unknown. It may be related to the high hCG level and possibly some action of hCG that is still unclear. The increased thyroid function, or clinical hyperthyroidism, is attributed to the effect of hCG on the TSH receptor. The vomiting may be related to increased levels of estradiol, or another steroid induced by hCG. Although estradiol levels in hyperemesis patients were higher than those of a control group, there was considerable overlap.[39] Increased estradiol levels were found in women with hyperemesis in the US during the first trimester compared

with control subjects.[47] A recent study in Greece found that higher levels of estradiol were associated with nausea with or without vomiting up to the 27th week of pregnancy.[48]

Syndrome of transient hyperthyroidsm of hyperemesis gravidarum

The syndrome of transient hyperthyroidsm of hyperemesis gravidarum should be considered in any woman presenting with biochemical evidence of hyperthyroidism in early pregnancy. In the vast majority of these patients, there will be spontaneous remission of the increased thyroid function when the vomiting stops in several weeks. Antithyroid drug therapy is unnecessary. However, some patients with hyperemesis have frank clinical hyperthyroidism. Because the clinical hyperthyroidism in these patients differs from that of classical Graves' disease, it has been called 'gestational thyrotoxicosis'. It has the following characteristics: thyrotoxic symptoms in early pregnancy, marked increase in serum FT3 and FT4, association with hyperemesis gravidarum, spontaneous disappearance in the latter half of pregnancy, negative thyroid peroxidase antibody, negative TSH receptor antibody, usually an absence of goiter, and circulating hCG with high biological activity.[49]

It is be reasonable to treat these patients with antithyroid drugs or a beta-adrenergic blocker, depending on the clinical features, but treatment is rarely required beyond 22 weeks of gestation. However, there are no controlled clinical trials that can be used for a guide to management.

Hyperplacentosis, a rare condition in which the placenta is enlarged and hCG concentration is very high, may cause clinical hyperthyroidism that remits promptly after delivery of the placenta.[50]

HCG isoforms with thyrotropic activity

Five patients with gestational thyrotoxicosis and hyperemesis were shown to have circulating asialo-hCG with high thyrotropic bioactivity.[51] Another group confirmed the potent thyrotropic activity of asialo-hCG in a human thyroid follicle bioassay.[52] In contrast, one study reported a preponderance of acidic variants of hCG in the serum of patients with hyperemesis gravidarum.[35] Another study found a similar distribution of HCG isoforms in sera of hyperemesis patients and controls[36], however, the thyroid hormone concentrations correlated to the absolute HCG concentration and the proportion of acidic isoforms. The acidic variants with higher sialic acid content would be expected to have a longer serum half-life. These reports support the concept that the absolute amount of HCG plays a role in stimulating thyroid function.

PLACENTAL TUMORS

Hydatidiform mole

Hyperthyroidism or increased thyroid function has been reported in many patients with trophoblastic tumors, either hydatiditform mole or choriocarcinoma.[33,52–54] In the US, hydatidiform mole occurs between 0.5 and 2.5 per 1000 pregnancies.[55] It is more common in Asian and Latin American countries. The prevalence is greatest in women

over 50 or less than age 15. Women who have had a previous mole have a greater risk of further molar pregnancies.

The mole consists of vesicles of swollen hydropic villi of various sizes, and there is an absence of fetal tissue. The karyotype is paternal. The usual clinical presentation is that of a threatened abortion with vaginal bleeding. In one-half of the patients, the uterus is large for the date of the pregnancy, About one-fifth of the women have hyperemesis, and 5–10% have toxemia, which is unusual in early pregnancy. The diagnosis is made by ultrasonography that shows a 'snowstorm' appearance without a fetus. The current widespread use of ultrasound for monitoring pregnancy has resulted in earlier diagnosis when the tumor mass is smaller.[56] In one study, moles were evaluated at a mean gestational age of 8.5 weeks during the period 1994–97 vs 17.0 weeks during 1969–75.[57] Hydatidiform moles secrete large amounts of HCG, and the HCG level is proportional to the mass of the tumor.

The prevalence of increased thyroid function in patients with hydatidiform mole has been reported as 25–64%.[54,55] About 5% have clinical hyperthyroidism.[58] In a study of 14 women with hydatidiform mole in 1975, nine were hyperthyroid.[53] Serum HCG levels varied from 150–3000 U/ml. Thyroid-stimulating activity, measured by bioassay in mice, was found in all sera, and there was a close correlation between this activity, the serum HCG, and the T3 level. Removal of the mole caused a dramatic fall in serum levels of T3, T4, HCG and thytropic activity (Figure 6). The data suggested that HCG, itself, when present in large amounts that are several-fold the peak levels of pregnancy, stimulates thyroid function and may cause hyperthyroidism.

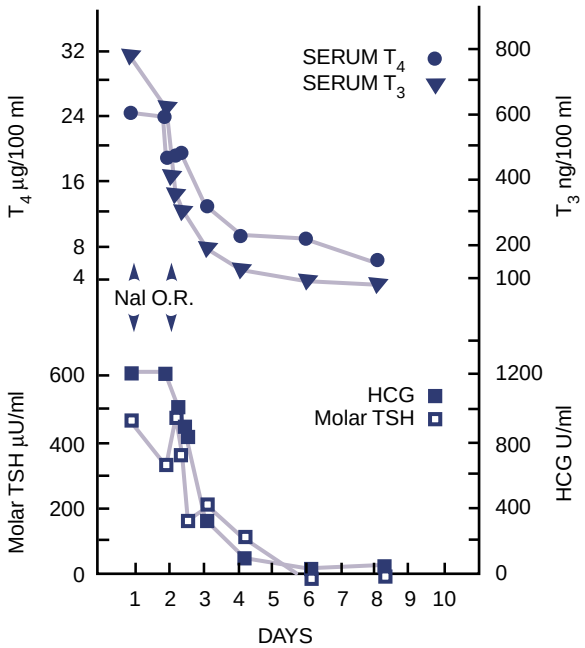

Figure 6. Serum T4, T3, hCG, and molar TSH (measured by bioassay in mice) in a patient with hydatidiform mole and hyperthyroidism. She was treated with sodium iodide intravenously and then had evacuation of the mole by hysterectomy (OR). There was a parallel fall in the hCG and molar TSH concentrations. (with permission[53]).

The diagnosis of hyperthyroidism, or increased thyroid function, is established by finding elevated serum free T_4 and T_3 concentrations and suppressed serum TSH level. Thyroid radioiodine uptake is greatly increased.[59] In general, the development of hysterotomy requires hCG levels of $>$200 U/ml that are sustained for several weeks.

HCG extracted from molar tissue showed molecular heterogeneity with a significant amount of basic molecules containing less sialic acid than normal, highly purified HCG.[33] The more basic, partially desialylated isoforms of hCG had a much higher ratio of biologic to immunologic activity than the more acidic forms. The partially desialylated HCG, because of its greater thyrotropic activity, may be responsible for hyperthyroidism in some patients with trophoblastic disease. Therefore, the thyrotropic potency of hCG in patients with trophoblastic disease should be considered not only based on its immunoreactivity but also on its biological activity.

Therapy consists of evacuation of the mole by suction curettage or removal by hysterotomy. This results in prompt reduction in thyroid hormone levels, hCG and thyroid-stimulating activity. Monitoring serum HCG is essential in follow-up to detect persistence of molar tissue or the development of choriocarcinoma.

Choriocarcinoma

Choriocarcinoma occurs in one in 20 000 to one in 40 000 pregnancies in the US and Europe.[60] About half of the cases occur in women with previously diagnosed hydatidiform moles, but only 3–5% of women with moles develop choriocarcinoma. Patients usually present within 1 year of the previous conception. Pathologically, the tumors consist of large sheets of syncytiotrophoblastic and cytotrophoblastic cells, hemorrhage, necrosis and absence of hydropic villi. The tumors invade blood vessels and progress to hemorrhagic metastases. The natural history is rapid progression, spread to distant organs, especially lungs and vagina, and less commonly the brain and liver. Without treatment, death occurs within a few months. Patients present with vaginal bleeding, hemoptysis if there are lung metastases, focal neurologic signs indicative of brain metastases, and often profound weight loss.

There have been many case reports of hyperthyroidism in women with choriocarcinoma.[61–63] In addition, there are 17 cases of choriocarcinoma in men usually in testicular tumors, less often in extragonadal sites.[64–66] The precise prevalence of hyperthyroidism in patients with trophoblastic tumors is unknown. It was found in five of 20 patients with trophoblastic disease evaluated at a referral center in 1 year[67], three of these five thyrotoxic patients had choriocarcinoma, and two had hydatidiform moles. In another study, 30 of 52 patients with gestational trophoblastic tumors were found to be thyrotoxic.[68]

Less than 3% of the oligosaccharide side chains of hCG derived from a choriocarcinoma contained sialic acid, whereas that of normal hCG was mostly sialylated.[69] This is consistent with other reports of the preponderance of basic isoforms of HCG in trophoblastic tumors.

The principal therapy of choriocarcinoma is chemotherapy. Patients should be referred to a specialized center. With effective chemotherapy, long-term survival is very high. In the UK, overall long-term survival exceeds 95%.[70] In low-risk disesase the cure rate is virtually 100%, whereas for high-risk patients it is 86%. Cure of the choriocarcinoma results in a cure of the hyperthyroidism.[61–63,67]

TSH RECEPTOR MUTATION

A woman with recurrent gestational hyperthyroidism associated with hyperemesis gravidarum and a TSH receptor mutation was recently reported.[71] After two miscarriages, she had hyperemesis early in pregnancy, along with overt biochemical hyperthyroidism. She had a small diffuse goiter and no evidence of Graves' eye disease. Hyperthyroidism was diagnosed and treated with propylthiouracil throughout the pregnancy. The drug was discontinued postpartum and normal thyroid function ensued. During her next pregnancy, she had a recurrence of hyperthyroidism associated with hyperemeis gravidarum, and was again treated with propylthiouracil.

The patient's mother had a diagnosis of Graves' disease during her second and third gestations. The mother's first pregnancy was complicated by hyperemesis, and terminated in miscarriage. During her next pregnancy, she had tremor, tachycardia, anxiety and hyperemesis. Thyroid function tests revealed hyperthyroidism. She was treated with antithyroid drugs throughout pregnancy, the hyperemesis resolved, and she delivered a healthy female baby, the proband. The hyperthyroidism improved in the postpartum period allowing for discontinuation of antithyroid drugs. The following

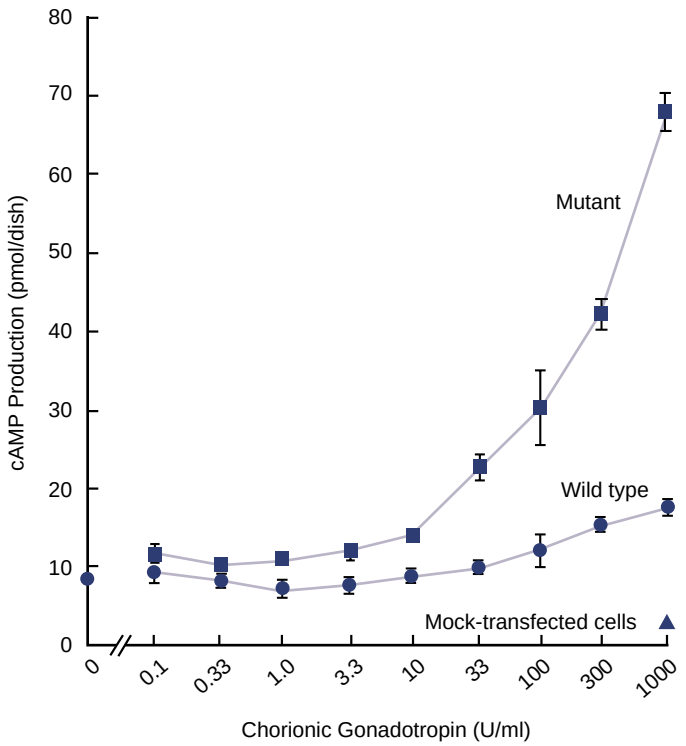

Figure 7. Functional characteristics of the mutant thyrotropin receptor in COS-7 cells, showing the effect of stimulation of cAMP production by graded concentrations of hCG in cells transfected with wild-type or mutant thyrotropin receptor. (with permission[71]).

pregnancy was also complicated by hyperemesis and hyperthyroidism, requiring treatment with antithyroid drugs, and followed by recovery of normal thyroid function postpartum.

Study of the TSH receptor of the patient disclosed the substitution of guanine for adenine at codon 183 in exon 7 in one allele, resulting in substitution of arginine for lysine in the middle portion of the extracellular domain of the TSH receptor, a region of the receptor in contact with the ligand. The patient's mother was heterozygous for the same mutation. The mutant TSH receptor was transfected into COS cells and was shown to be much more sensitive to hCG than the wild-type receptor (Figure 7). It is likely that the hereditary gestational hyperthyroidism in this family was due to hypersensitivity of the mutant TSH receptor to hCG. This unique mutation has not yet been reported in other families.

Recent work has shown that substitution of methionine, asparagjne or glutamine for the lysine 183 in the TSH receptor increased its affinity toward hCG, the gain of function was attributed to the release of a nearby glutmate resudue at 157 from a salt bridge with lysine 183.[2]

SUMMARY

HCG has thyroid stimulating activity and may cause hyperthyroidism in women with hyperemesis gravidarum or trophoblastic tumors in women who have high levels of hCG.

In the vast majority of women with hyperemesis gravidarum, there will be spontaneous remission of the increased thyroid function when the vomiting stops in several weeks.

Routine ultrasonography has led to an earlier diagnosis of hydatidiform mole, with a smaller mass of tumor and lower hCG levels. The development of hyperthyroidism requires hCG levels of $>$200 U/ml that are sustained for several weeks. Removal of the mole cures the hyperthyroidism. In patients with choriocarcinoma and high hCG levels causing hyperthyroidsim, the principal therapy is chemotherapy, usually given at a specialized center.

A unique family with recurrent gestational hyperthyroidism associated with hyperemesis gravidarum was found to have a mutation in the extracellular domain of the TSH receptor that made it responsive to normal levels of hCG.

Research agenda

- additional studies should be carried out to characterize the HCG that has thyroid-stimulating activity in patients with hyperthyroidsm of hyperemesis gravidarum

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