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Research article

hCG and hyperglycosylated hCG in the establishment and evolution of hemochorial placentation

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Abstract

The evolution of regular chorionic gonadotropin (CG) and hyperglycosylated CG are linked with the evolution of hemochorial placentation in primates. Recent research with humans shows that regular CG promotes spiral artery angiogenesis and hyperglycosylated CG controls invasion by implanting trophoblast cells. It is inferred that the evolution of regular CG and hyperglycosylated CG in early simian primates, the first species to produce these CG forms, established hemochorial placentation in this species. The circulating half-lives, and thus the circulating concentrations, of regular CG and hyperglycosylated CG increased in advanced simian primates and increased further in humans, seemingly causing greater myometrial invasion and superior angiogenesis in hemochorial placentation in advanced primates and humans. Advanced hemochorial placentation is associated with relatively high proportions of pregnancy failures in humans. This can be explained by considering human implantation inadequate in terms of invasion requirements. The demanding implantation required by the human embryo is seemingly dependent on adequate production of hyperglycosylated CG. Failures in hemochorial placentation invasion lead to anoxia and cause preeclampsia and eclampsia uniquely in humans, which can also be attributed to inadequate hyperglycosylated CG signaling. We propose here that inadequate regular CG and hyperglycosylated CG molecules are the evolutionary causes of these obstetric complications in humans.

Keywords: hCG; Regular CG; Hyperglycosylated CG; Hemochorial placentation; Brain; Evolution pregnancy failure; Preeclampsia

1. Introduction

The human hemochorial placentation process has been recognized for over 30 years (Lockett, 1974). It is widely believed that human hemochorial placentation evolved from the more primitive hemochorial placentation seen in advanced and lower simian primates (Lockett, 1974), and that the ultra-efficient hemochorial placentation system in humans and advanced primates is essential for the nutritional and energy requirements needed for the development of larger brains in these species (Martin, 1981, 1996; Cunnane et al., 1993; Gibbons, 1998). It has also been known for 28 years that chorionic gonadotropin (CG) forms arose in the lower simian primates, around the same time as the appearance of hemochorial placentation (Fiddes and Goodman, 1980; Maston and Ruvolo, 2002; Burton, 2006; Luckett, 1974; Martin, 1996). We examine here the parallel evolution of chorionic gonadotropin forms and hemochorial placentation, and their key roles in the nutritional evolution of the brain.

2. Chorionic gonadotropin and hemochorial placentation

In recent years, research has focused on exposing the chemistry and physiology of regular CG. It is

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increasingly clear that regular CG is not just a hormone, as determined in 1920, for promoting corpus luteal progesterone production (Hirose, 1920). Multiple centres have shown luteinising hormone (LH)/regular CG receptors on spiral arteries in the myometrium and decidua, the arteries of hemochorial placentation, and demonstrated a role for CG in the angiogenesis of these spiral arteries as the hemochorial placentation system is established during pregnancy (Lei et al., 1992; Rao and Alsip, 2001; Herr et al., 2007; Zygmunt et al., 2002, 2003; Toth et al., 2001). Recently, studies of human isolated artery segments following *in vivo* human CG (hCG) injections show that hCG decreases vascular resistance in the artery, dilating the arteries and promoting blood flow (Toth et al., 2001). Functions have also been proposed for regular CG in the fusion or differentiation of trophoblast cells, promoting the conversion of cytotrophoblast to syncytiotrophoblast cells (Shi et al., 1993). Functional LH/regular CG receptors have also been located at other sites, like the decidual and fetal membranes in pregnancy (Lei and Rao, 1992), and in the brain (Lei et al., 1993). Exact roles for these receptors are yet to be established. Regular CG is produced by differentiated syncytiotrophoblast cells, the so-called functional placental cells (Jameson and Hollenberg, 1993; Kovalevskaya et al., 2002; Cole et al., 2006b, 2006c). Hyperglycosylated CG, a variant of regular CG, is made by the invasive cytotrophoblast cells of the placenta in humans (Kovalevskaya et al., 2002; Cole et al., 2006b, 2006c; Handschuh et al., 2007a). Hyperglycosylated CG is notably larger than regular CG (41,000 da *versus* 37,000 da), with four double size O-linked oligosaccharides and four larger N-linked sugar side chains defining a structurally separate molecule to regular CG (Cole, 1987; Elliott et al., 1997; Amano et al., 1988; Cole et al., 2006b, 2006c).

Hyperglycosylated CG has been proposed to be a major cytotrophoblast invasion signal in hemochorial placentation (Cole et al., 2006b, 2006c; Lei et al., 1999; Handschuh et al., 2007a; Hamade et al., 2005; Sasaki et al., 2008). Hyperglycosylated hCG is produced specifically by extravillous cytotrophoblast cells (Handschuh et al., 2007a, 2007b), where it is thought to have a role in promoting invasion during placentation (Handschuh et al., 2007a; Cole et al., 2006b). While it has been shown that hyperglycosylated hCG acts as an autocrine factor blocking cytotrophoblast apoptosis (Hamade et al., 2005), a receptor through which its invasive action is mediated remains unidentified. Invasion distinguishes hemochorial placentation from more primitive placentation models. Considering their specific invasion and angiogenesis functions, we hypothesised that regular CG and hyperglycosylated CG evolved parallel to hemochorial placentation because they played central roles in establishing the key invasive and vascular placentation modes that characterize hemochorial placentation. We propose that hyperglycosylated CG drives extravillous cytotrophoblast cells to invade the uterus and implant as deep as possible in the myometrium, and that regular CG promotes spiral artery growth and multiplicity to meet and provide nutrition to the invading villi.

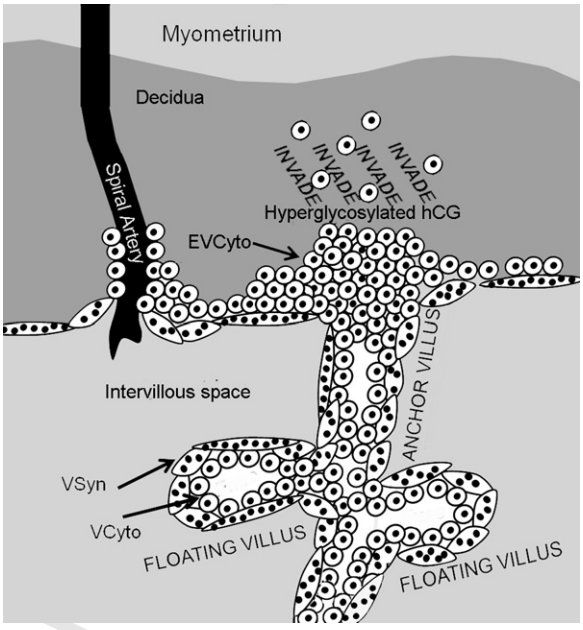

Fig. 1. A schematic diagram illustrating invading villus trophoblast at 4–6 weeks of gestation. VSyn is villous intermediate syncytiotrophoblast cells, VCyto is villous cytotrophoblast cells and EVCyto is extravillous cytotrophoblast cells. The schematic shows anchoring villus with EVCyto and floating villus components. Hyperglycosylated hCG from ECyto is shown in the invading myometrium, while regular hCG from VSyn acts in spiral artery angiogenesis and fusion of VCyto to VSyn. The figure is based on previous publications (Handschuh et al., 2007a; Kennedy et al., 2007; Tarrade et al., 2001).

Fig. 1 illustrates a placental villus with the anchoring and floating components at 4–6 weeks gestation, with the extravillous cytotrophoblast cells on the anchoring villus producing hyperglycosylated CG to drive deeper invasion, and the regular CG produced by syncytiotrophoblast cells driving spiral artery angiogenesis and the fusion of cytotrophoblast cells.

3. Evolution of chorionic gonadotropin

Production of the hormone CG evolved in the lower simian primate at about the same time as hemochorial placentation commenced in primates (Fiddes and Goodman, 1980; Maston and Ruvolo, 2002; Burton,

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Table 1
Parallelisms between placental implantation and invasion characteristics, presence and oligosaccharides structures of CG and CG-H, and relative brain masses in primates. Table summarizes published data (Martin, 1996; Cunnane et al., 1993; Gibbons, 1998; Bambra, 1987; Burton, 2006; Luckett, 1974; Nisula and Wehmann, 1980; Maston and Ruvolo, 2002; Crawford et al., 1986; Elliott et al., 1997). Using a logarithmic equation $1/\log(1/2\text{time}) = 1/pI - 11.6$ a relationship was observed between known p*I* and circulating half time of LH and CG. The circulating half times of lower simian CG and advanced simian CG were estimated by this means.

Species	Implantation characteristics	Depth of invasion	CG/CG-H oligosaccharides, p*I*	Circulating half time	Brain mass (%)
(1) Primates					
Human	Hemochorial	Through decidua to 1/3rd myometrium	4 O- and 4 N-linked, p*I* 3.5	2100 min	2.4
Advanced simian primate (baboon, orangutan)	Hemochorial	Through decidua to 1/10th myometrium	3 O- and 3 N-linked, p*I* 4.9	240 min	0.74
Lower simian primate (marmoset, cebus monkey)	Hemochorial	Through decidua only	2 O- and 3 N-linked, p*I* 6.3	70 min	0.17
Prosimian primate (lemur)	Epitheliochorial	No invasion	No CG forms produced		0.07
(2) Mammals (examples)					
Cetacea (whale)	Epitheliochorial	No invasion	No CG forms produced		0.08
Equus (horse)	Epitheliochorial	No invasion	No CG forms produced		0.11
Bos taurus (cow)	Epitheliochorial	No invasion	No CG-H produced		0.09

2006; Luckett, 1974; Martin, 1996). Placentation in primitive prosimian primates such as the lemur is epitheliochorial, and relatively non-invasive. In this form of placentation, the placenta is loosely attached to the decidua and nutrients diffuse from the maternal circulation through the decidua into the placenta (Table 1). Prosimian primates produced no form of CG (Table 1). Lower simian primates such as the marmoset and cebus monkey evolved with a form of CG. This is thought to have occurred following duplication of the LH β-subunit gene; in the duplicate gene a deletion mutation occurred so that the termination codon coded for an amino acid, and transcription continued through for a further 24 codons until a further termination codon was reached. The result was a CG β-subunit which was 145 amino acids in length, compared with the LH β-subunit, 121 amino acids in length (Fig. 2). The C-terminal extension was mostly a Ser and Pro polymer. Like LH, the first form of CG in lower simian primates had 3 N-linked oligosaccharides and in addition 2 O-linked oligosaccharides on the new C-terminal extension (Maston and Ruvolo, 2002; Fiddes and Goodman, 1980). We propose that hyperglycosylated CG derived from cytotrophoblast cells and regular CG derived from syncytiotrophoblast cells started hemochorial placentation, with hyperglycosylated hCG starting placental invasion and regular CG starting the needed spiral artery angiogenesis.

It appears that additional changes in CG occurred with further species evolution, through advanced simian primates such as the orangutan and baboon, and then with hominids such as humans. The CG molecule underwent multiple point mutations so that advanced simian CG had 3 N-linked oligosaccharides (like lower simian primates) and 3, rather than 2, O-linked oligosaccharides on the C-terminal extension (Fig. 2). After multiple mutations, human CG evolved with 4 N-linked oligosaccharides and 4 O-linked oligosaccharides on the C-terminal extension (Bambra, 1987; Maston and Ruvolo, 2002; Crawford et al., 1986; Elliott et al., 1997).

The mean isoelectric point (p*I*) of the root molecule LH is 8.1 (Suginami et al., 1985). It has just 3 acidic N-linked oligosaccharides. The mean p*I* of lower simian CG or the initial CG with 3 acidic N-linked and 2 acidic O-linked sugar structures is 6.3; advanced simian CG with 3 acidic N-linked and 3 acidic O-linked sugar structures has a mean p*I* of 4.9; human CG with 4 acidic N-linked and 4 acidic O-linked sugar structures has a mean p*I* of 3.5 (Bambra, 1987; Maston and Ruvolo, 2002; Crawford et al., 1986; Cole et al., 2004, 2008). Clearly, the acidity of these gonadotropins increased with evolution as more and more N- and O-linked oligosaccharides were added as a result of mutations, from LH with 3 sugar side chains to human CG with 8 sugar side chains (Fig. 2). The increasing acidity of

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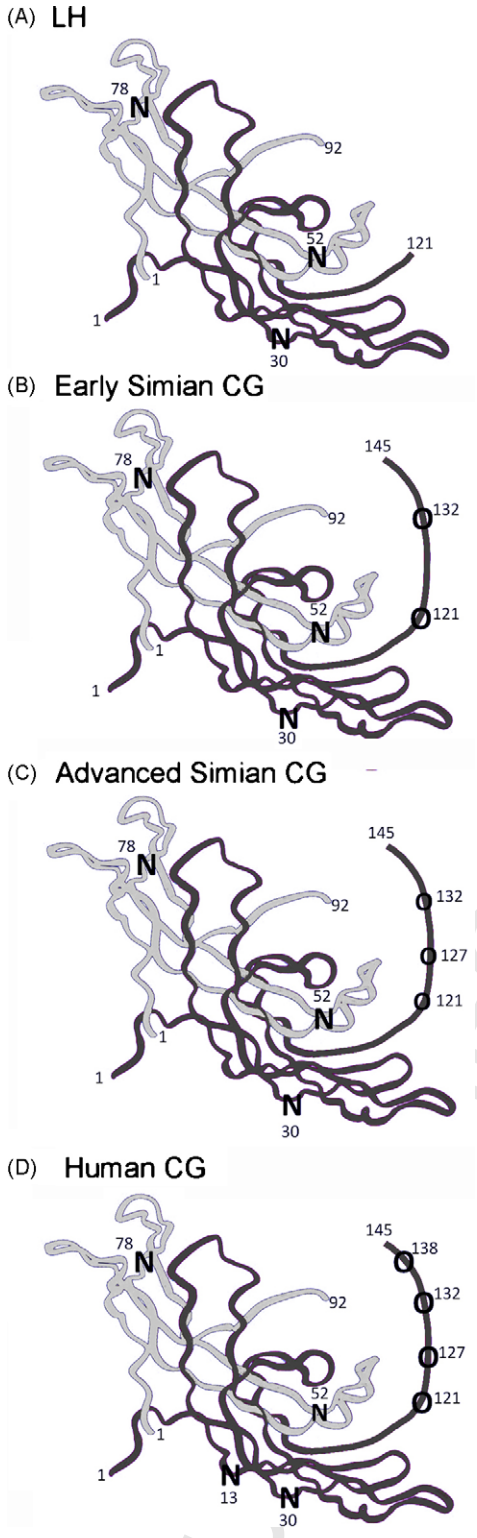

Fig. 2. The structure of LH and CG produced by early and advanced simian primates and humans. The light grey line is a ribbon model of the structure of the α-subunit, and the dark grey line is a ribbon model of the structure of the β-subunit (Wu et al., 1994; Elliott et al., 1997).

sugar has physiological implications, since increasing acidity repels the kidney glomerular basement membrane (which is also acidic), thus preventing excretion. As such, LH has a circulating half-life of 25 min, while hCG has a circulating half time of 2100 min (Nisula and Wehmann, 1980). It is assumed that lower simian CG and advanced simian CG had circulating half times within these extremes, according to their p*I*s. Using a logarithmic equation [1/log(1/2time) = 1/p*I*–11.6], a relationship was observed between p*I* and circulating half-life, and the half-lives of lower simian CG (70 min) and advanced simian CG (240 min) were estimated (Table 1). It is assumed that the circulating concentrations of CG and CG-H are proportional to their respective circulating half-life values, being extremely small in lower simians, in the middle range in advanced simian and extremely high in humans.

As published previously (Sutton and Cole, 2004), hyperglycosylated CG and regular CG both have similar p*I* isotopes in the range of 2.9–4.1. The mean p*I* for both molecules is 3.5. While hyperglycosylated CG and regular CG may have similar clearance half-lives, hyperglycosylated hCG has a more rapid subunit dissociation time (4300 min) compared to regular CG (48,000 min) (Cole et al., 2003). Overall therefore, the hyperglycosylated CG dimer may disappear from the circulation somewhat faster (circulating half-life of 2100 min, dissociation half-life of 4300 min) than regular CG.

We conclude that as CG evolved and was retained at higher and higher circulating concentrations, hyperglycosylated hCG promoted increasingly deeper placental invasion through the decidua and into the myometrium. Higher concentrations of regular CG promoted more and more potent angiogenesis. As reported, CG and trophoblast villi solely invade the myometrium leading to minimally active hemochorial placentation in the lower simian. Villi invade to one-tenth the thickness of the myometrium in advanced simian primates and to one-third the thickness of the myometrium and to greatest efficiency in humans (Pijnenborg, 1996; Gibbons, 1998; Jauniaux et al., 2006). In this respect, the evolution of CG parallels the evolution of hemochorial placentation.

4. Chorionic gonadotropin, hemochorial placentation and evolution of the brain

Humans have evolved with a uniquely large brain to body mass ratio compared with other primates and other mammals (Table 1) (Gibbons, 1998; Martin, 1981, 1996, 2003; Kliman, 2000; Cunnane et al., 1993; Jauniaux et al., 2000). While data from newborn primates is difficult to collect, the human newborn brain repre-

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sents 11% of body mass (Jordaan, 2005). In humans over 60% of the fetal energy intake is used to support the developing brain's nutritional needs compared with 20% in other primates and mammalian species (Gibbons, 1998; Robillard et al., 2003b; Martin, 1981, 1996, 2003; Cunnane et al., 1993; Pijnenborg, 1996). Brain size is related to the combination of body mass and the nutritional support of the developing progeny (Martin, 1981). The increase in brain size seen in advanced primates and humans correlates with the large energy demands of advanced primate and human fetuses (Gibbons, 1998; Robillard et al., 2003b; Martin, 1981, 1996, 2003; Cunnane et al., 1993; Pijnenborg, 1996). Numerous studies support the concept that advanced primates, and to an even greater extent humans, have evolved unique, deeper and more efficient placental invasion mechanisms and hemochorial placentation systems to support the nutritional demands of the larger embryonic brains (Table 1) (Gibbons, 1998; Robillard et al., 2003b; Martin, 1981, 1996, 2003; Kliman, 2000; Cunnane et al., 1993; Jauniaux et al., 2006).

Table 1 shows that advanced primates and humans have a much greater brain to body mass than other primates and mammals (Gibbons, 1998; Martin, 1981, 1996, 2003; Robillard et al., 2003a). In primitive prosimian primates such as lemurs, no placental invasion of the uterus occurs at implantation (epitheliochorial implantation); the placenta simply links to the decidua and nutrition transfer is limited to simple diffusion from maternal arteries into the placenta. With such placentation, lemurs have a 0.07% brain to body mass. In lower simian primates such as the marmoset and cebus monkey, placental invasion does occur, extending through the thickness of the endometrial decidua. This permits an increase to 0.17% brain to body mass. In advanced simian primates such as baboon and the orangutan, invasion extends through the decidua to one-tenth the width of the myometrium, permitting a more efficient hemochorial implantation. This allows these advanced primates to achieve a 0.74% brain to body mass (Gibbons, 1998; Pijnenborg, 1996). Placentation in humans is unique, with the blastocyst becoming completely embedded within the maternal endometrium (Gibbons, 1998; Jauniaux et al., 2006; Pijnenborg, 1996). Invasion extents to one-third the width of the myometrium. This provides the most efficient hemochorial implantation, permitting the 2.4% brain to body mass. A serial relationship between implantation, invasion and brain mass is observed from prosimian primates to lower simian primates, to advanced simian primates to humans (Gibbons, 1998; Robillard et al., 2003b; Martin, 1981, 1996; Cunnane et al., 1993; Pijnenborg, 1996).

Considering these data in combination with the evolution of CG forms and hemochorial placentation discussed in the previous sections of this review, we propose that the appearance and evolution of CG is at the nutritional root of evolutionary advancements in primate and human brains. It appears that brain size started growing relative to body mass with the appearance of CG in lower simian primates and the initiation of hemochorial placentation. With multiple mutations, CG evolved with more and more oligosaccharides making the molecules more and more acidic. With this, circulating levels of CG forms became higher and higher; in parallel, hemochorial placentation become more and more efficient and invaded more deeply (Lockett, 1974; Pijnenborg, 1996; Gibbons, 1998; Jauniaux et al., 2006). In line with these improvements in efficiency of nutrient delivery, species with larger and larger brain sizes developed (Table 1).

While it is possible that the evolutionary pathway that started primate species on the road to becoming human may have started with the evolution of CG, this is just one part of the story. The CG evolution pathway may be the key in explaining how nutrition was delivered to allow the *in utero* development of a very large brain for body size. That LH/regular hCG receptors are found in the hypothalami, hippocampi brainstem and cerebellum of the brain (Lei et al., 1993), may also suggest a role for regular CG in intelligent brain development. Furthermore, CG must be considered in the context of other key evolutionary events and molecules involved in the development of superior consciousness, intelligence, communication skills and emotions that define a human.

5. Evolutionary complications of chorionic gonadotropin and hemochorial placentation

Compared to other primates, multiple obstetric complications are unique to humans. Humans developed the most extreme placentation process to permit development of the resource-demanding human brain (Fig. 1). While it has been estimated that up to 41% of pregnancies in humans do not succeed (16% miscarriage, 25% early pregnancy losses or biochemical pregnancies), only ≤10% pregnancy failures are observed in other primate species and most mammalian species (Jauniaux et al., 2006; Wilmut et al., 1986). Previous studies have identified two-thirds of human pregnancy failures to be due to inappropriate implantation (Jauniaux et al., 2006). Similarly, two-thirds of pregnancy failures can be explained by inadequate human hyperglycosylated CG production on the day of implantation of the blastocyst (Sasaki et al., 2008). It has been recently established that pregnancy induced hypertension (PIH),

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preeclampsia and eclampsia are complications of incomplete hemochorial placentation mechanisms at the end of the first trimester of pregnancy. These lead to anoxia and to deadly hypertension disorders later in pregnancy (Robillard et al., 2003a; Burton, 2004), complications that are unique to humans. This has also now been linked to low human hyperglycosylated hCG production at the end of the first trimester of pregnancy (Bahado-Singh et al., 2002). Measurement of hyperglycosylated hCG at the end of the first trimester of pregnancy can be a sensitive test for predicting PIH, preeclampsia and eclampsia in pregnancy (Bahado-Singh et al., 2002). High circulating concentrations of hyperglycosylated CG, the invasion stimulus, are unique to human hyperglycosylated CG. Humans uniquely develop choriocarcinoma and invasive moles, in which invasion by trophoblast cells is not regulated, presumably a complication of humans having hyperglycosylated CH as such a potent invasion stimulus (Cole et al., 2006a, 2006b, 2006c).

Here we connect together for the first time the evolution of CG forms and hemochorial placentation. Taken together, CG forms may not only be the signal for hemochorial placentation and the driving force for the nutrition system needed to support brain growth, but also the sources of multiple major obstetrical and malignant diseases in humans. These fertility limitations and diseases may be considered evolutionary limitations in humans, derived from the extreme demands of human placentation. Identification of an association between the roles of regular CG and hyperglycosylated CG with hemochorial placentation may be the first step in finding cures and treatments for the negative consequences of such an evolutionary development: pregnancy failure, PIH/preeclampsia/eclampsia and choriocarcinoma/invasive mole. It is feasible that pregnancy failure and PIH/preeclampsia/eclampsia could be treatable with hyperglycosylated CG administration and that choriocarcinoma and invasive mole may be treatable with human antibodies targeted at or vaccines against hyperglycosylated CG.

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