The Evolution of the Primate, Hominid and Human Brain

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Abstract

Human evolution involved four brain enhancement steps. The first step of brain size enhancement occurred in lower simian primates (brain size 0.17%-0.19% of body weight). The second step occurred in advanced simian primates (brain size 0.66%-0.78% of body weight). The third step occurred among early hominids (brain size 1.0%-1.2% of body weight), and the fourth of final step occurred among humanoids (brain size 2.1%-2.7% of body weight).

This brain enhancement occurred in response to brain growth genes or brain growth factor proteins. Brain growth was very much limited by the efficiency of fetal nutrition or placentation. In many respects it was the efficiency of placentation and implantation that controlled brain growth expanding brain growth to the limit that placentation could allow.

Brain growth was initially blocked by inefficiency of epitheliochorial placentation. It was the initial evolution of chorionic gonadotropin (CG) and hyperglycosylated CG that promoted the creation of hemochorial placentation, and the implantation of the placenta. This occurred in lower simian primates and so was followed by initial implantation and hemochorial placentation. This permitted the first step in brain growth. The CG gene underwent mutation with advanced simian primates and a higher biological activity CG and hyperglycosylated hCG resulted. This drove more efficient implantation and placentation and so primates developed a bigger brain, the second step in brain growth. The CG gene underwent further mutation with early hominids and a higher biological activity CG and hyperglycosylated hCG resulted. This drove even more efficient implantation and placentation and so early hominids developed a bigger brain, the third step in brain growth. The CG gene underwent mutation with humanoids and a higher biological activity CG and hyperglycosylated hCG resulted. This drove the most efficient implantation and placentation and so humanoids developed the biggest brain, the fourth step in brain growth.

Keywords: hCG Hyperglycosylate; hCG Prosimian primate; Lower simian primate; Advanced simian primate; Early hominid human

Introduction

A major question is how did primates, hominids and humans develop a large brain [1-4]? Most mammals and early primates had a small brain, approximately 0.1% of total weight. Brain growth was limited by epitheliochorial placentation and inefficient mechanisms for transporting nutrition from mother to fetus, nutrients had to pass through five tissue layers [1-4]. How was this surmounted to permit the expanding brain among primates, hominids and humans? This question is addressed in this review.

This introduction has the function of introducing all the ingredients involved in the chorionic gonadotropin (CG)/hyperglycosylated CG human evolution model, and for describing the sources of all data provided. The ingredients involved in this model are CG and hyperglycosylated hCG [5-8], and the brain growth genes and growth factors MCPH1, ASPM, CD5RAP2, CENPJ, WDR62, CEP152 and STIL genes [9-19].

Two independent molecules are a major part of the brain size explanation, chorionic gonadotropin (CG) and hyperglycosylated CG. The placenta in pregnancy comprises mononucleated cytotrophoblast cells. These fuse together to form multinucleated syncytiotrophoblast cells. Anywhere from 3 to 50 cytotrophoblast cells fuse to form syncytiotrophoblast cells with 3-50 nuclei. Cytotrophoblast cells are growing placental cells. Syncytiotrophoblast cell do not grow, they strictly arise from fusion of cytotrophoblast cells. Cytotrophoblast cells produce the hyperglycosylated autocrine hyperglycosylated CG and not any hCG. Fused syncytiotrophoblast cells while having the same genes as cytotrophoblast cells do not express the molecule N-acetylgucosaminyl transferase-V1 the enzyme that branches or hyperglycosylates the O-linked sugars on CG. It produces the un-hyperglycosylated hormone hCG [20].

The hormone CG and the autocrine hyperglycosylated CG function together in generating and managing hemochorial placentation [6,21-24]. Hemochorial placentation is a much more efficient mechanism of placentation than epitheliochorial placentation involving invasion potentially deep into the uterus. Hemochorial placentation involves generation of a tank of maternal blood, and passage of nutrients across a single layer of syncytiotrophoblast cells to enter the umbilical or fetal circulation [6,21].

Published studies show that hyperglycosylated CG is an autocrine acting as an antagonist on transforming growth factor-ß (TGFß) receptor [25,26]. hCG, in contrast, is a hormone acting on a joint luteinizing hormone (LH)/CG receptor. Hyperglycosylated CG functions to drive implantation of pregnancy. This is achieved by hyperglycosylated CG promoting growth of the blastocysts, and its invasion deep into the uterus [5,27]. Hyperglycosylated CG also drives placental tissue growth during pregnancy by promoting cytotrophoblast cell growth.

Brain growth promoting genes and the ced5 growth factors are very much involved in primate, hominid and human brain development [9,10]. Studies show that deficiencies and mutations in these brain size
promoting genes in the human fetus leads to microcephaly disorders in infants, with brains as small as 1.0% of body weight, vs. normal mean brain of 2.4% of body weight. Microcephaly leads to gross mental retardation and premature chromosomal condensation (PCC). A total of seven distinct brain growth genes have now been identified coding for brain growth factors. These are the MCPH1 gene also known as microcephalin gene [11-13], WDR62 gene [14], CDKSRAP2 gene [15], CEP152 gene [16], ASPM gene [17], CENPJ gene [15] and STIL gene [18]. Small mutational differences have been noted in MCPH1, ASPM, CDKSRAP2, CENPJ genes in early and advanced primates and humans, indicating gene and brain growth factor advancement with evolution [11,12,15,17].

MCPH1 was the first gene in which mutations were directly shown to cause microcephaly [11-13,19]. MCPH1 first evolved with lower simian primates that evolved 37 million years ago, some of the earliest minimally intelligent primates. Major differences have been observed in MCPH1 in lower simian primates like the gibbon and cebus monkey, with advanced simian primates like orangutan and chimpanzee and with humans. It is proposed that during primate and human evolution the divergence in MCPH1 due to mutations led to functional modifications. That these modifications are the molecular mechanisms of how MCPH1 contributed to brain enlargement in primates and greater enlargement in human evolution [11,17]. Seemingly MCPH1 and other brain growth genes played a major role in the evolutionary enlargement of the brain.

Multiple sources of data are provided here. Multiple brain size information is presented and discussed, this is data published by [2,4,28-30]. Information on primate and hominid CG isoelectric point (pI) was provided by [2,4,28]. Data on human CG circulating blood half-life was provided by [31]. The circulating blood half-life (C/L) of lower simian primate CG, and advanced simian primate CG was estimated using the following equation C/L = (1/pI × 12)4 established for CG and luteinizing hormone (LH).

The Evolution of CG and Hyperglycosylated CG

The molecules CG and hyperglycosylated CG first appeared in lower simian primates. These molecules directly evolved from deletion mutation in LH ß-subunit gene (Figure 1). LH ß-subunit evolved from Gonadotropin Ancestral Hormone-II (GAH-II), found today in some fish. GAH-II evolved from the ancestral a-subunit, a ß-subunit- a-subunit dimer. This directly evolved from TGFß (Figure 1) [32-35]. Hyperglycosylated CG is the first of this group of TGFß evolutionary descendent to express common TGFß sequences and to be an antagonist of the TGFß receptor [25,26].

It is interesting that LH was a single gonadotropin molecule. That the new molecules CG and hyperglycosylated CG evolved from LH by deletion mutation. That the CG/hyperglycosylated hCG single gene is expressed by cytotrophoblast cells and fused syncytiotrophoblast cells to make two independent molecules hyperglycosylated CG and CG vary just in carbohydrate structure, CG binding a joint LH/CG hormone receptor and hyperglycosylated CG antagonizing an ancestral TGFß receptor [25,26].

The lower simian primate CG and hyperglycosylated hCG had three N-linked oligosaccharides and two O-linked oligosaccharides. With mutations in the C-terminal peptide of the ß-subunit of CG and hyperglycosylated CG additional Ser amino acids appeared. In advanced simian primates the molecules had three O-linked oligosaccharides. With further mutations leading to further Ser amino acids the hominid molecules had four O-linked oligosaccharides. Finally, with further mutation in the core of hCG ß-subunit leading to addition Asn amino acid residues an additional N-linked oligosaccharide was added to the human molecules. The human molecule has 4 N-linked and 4 O-linked oligosaccharides [7-8,36].

Each oligosaccharides terminated with sialic acid sugar residues, making the molecules more acidic [20,36]. The acidity of lower simian CG was isoelectric point (pI)=6.3 (Table 1). The acidity of the advanced simian molecules was pI=4.9. The acidity of the hominid molecule is unknown since blood is not available. Finally, the human molecule is pI=3.5. With increasing acidity the blood circulating half-life of molecules increased dramatically. It is estimated that the circulating half-life of lower simian primate molecules was 2.4 hours, the half-life of advanced simian primate molecules was estimated as 6.0 hours, the half-life of the hominid molecule is unknown while the half-life of the human molecule was 37 hours [4,7,8,28,31] (Table 1).

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![Figure 1: The evolution of CG and hyperglycosylated CG.](image-url)

| Species                  | Placenta   | Implantation depth | Brain size % of body weight | CG pI (half-life) | CG # oligosaccharides |
|--------------------------|------------|--------------------|------------------------------|------------------|------------------------|
| Prosimian                | Epitheliochorial | 0%                 | 0.07%                        | None             |                        |
| Lower simian primate     | Hemochorial | 0.3%               | 0.17%                        | 6.3 (2.4 hr)     | 5                      |
| Advanced simian primate  | Hemochorial | 10%                | 0.74%                        | 4.9 (6.0 hr)     | 6                      |
| Early hominid            |             |                    |                              | 1.2%             |                        |
| Human                    | Hemochorial | 30%                | 2.4%                         | 3.5 (37 hr)      | 8                      |

Table 1: CG and hyperglycosylated CG and the evolution of the brain. Table summarizes published data [4,7,8,28]. Circulating half-life is factual in humans and estimated from pI values and an equation in primates. No blood samples available from early hominids, brain size from skull determinations.
The Brain Growth Factor Entanglement

MCPH1, ASPM, CD5RAP2, CENPJ, WDR62, CEP152 and STIL genes and their brain growth factor promoted brain growth among primates, hominids and humans. Did they, however, manage brain growth and cause the enlargement in brain size among lower and advanced simian primates, hominids and humans?

In mammals brain enlargement was completely blocked by the nutritional inefficiency of non-invasive epitheliochorial placentation. In epitheliochorial placentation essential nutrients such as glucose, oxygen and amino acids had to cross five layers of maternal and placental tissue to reach the fetal circulation from the maternal circulation. This was the principal placentation mechanism in mammals which was too inefficient of a placentation mechanism to permit brain and nervous tissue to reach the fetal circulation from the maternal circulation. This permits much deeper implantation (to 10% of uterine thickness) and more efficient construction of hemochorial placentation. Brain growth genes limit brain size to 0.74% of body weight (Table 1). Following many more mutations to CG and hyperglycosylated CG and the addition of multiple more oligosaccharides (Table 1), CG and hyperglycosylated CG become much more acidic still with humans, pl 3.5. This permits much deeper implantation (to 30% of uterine thickness) and much more efficient in construction of hemochorial placentation. Brain growth genes limit brain size to 2.4% of body weight (Table 1). An in between situation between advanced simian primate and humans in the early hominid presentation with a brain size of 1.2% of body weight. This is the CG/hyperglycosylated CG human evolution model with CG and hyperglycosylated CG controlling brain size [7,8,32].

CG and Hyperglycosylated CG in Lower Simian primates

CG and hyperglycosylated CG first evolved in lower simian primates [4,28]. A deletion mutation occurred in the LH ß-subunit gene leading to the first CG and hyperglycosylated CG. As shown in (Figure 2), a deletion mutation occurred at CAA, codon responding to amino acid 114, on the LH ß-subunit gene. LH ß-subunit was 121 amino acids long. The consequences of the deletion mutation was formation of gene coding for CG ß-subunit 145 amino acids long (Figure 2) [4,28]. LH is normally expressed by pituitary gonadotrope

![Figure 2: A deletion mutation in the LH ß-subunit gene.](image-url)
mutations occurred in the core of the CG β-subunit molecule, and had significantly larger brains, 1.2% of body weight, from skull sizes. To determine the precise pI and precise half-life, we do know that they cannot get blood from early hominids because they are all extinct and this led to much more efficient hemochorial placentation. While we evolved. These were significantly more acidic than the advanced simian primate molecule with a much longer circulating half-life. This led to much more efficient hemochorial placentation, 2.4% of body weight (Table 1). Hyperglycosylated CG did not invade the uterus deeply and only developed minimal villous cells. The resulting hemochorial placentation was very inefficient; barely much better that epitheliochorial placentation the system used by prosimian primates, lower simian primates ancestors. While the brain size in prosimian primates was 0.07% of body weight, a slightly enlarged brain, 0.17% of body weight was found in lower simian primates with the evolution of CG, hyperglycosylated CG, and hemochorial placentation.

Figure 3 illustrates the inefficient hemochorial placentation in lower simian primates. That it is not significantly implanted in the uterus (implanted to depth of decidua), and has minimal trophoblast villous cells (Figure 3). Figure 3 also illustrates the more efficient hemochorial placentation in advanced simian primates and humans.

Mutations in CG and Hyperglycosylated CG in Advanced Simian Primates, Hominids and Humans

With progressing evolution advanced simian primates evolved from lower simian primates. Further mutation occurred at the C-terminal peptide of hCG β-subunit, leading to additional Ser residues. The 3 N-linked oligosaccharide 2 O-linked oligosaccharide structure of lower simian primates, pI=6.3, became 3 N-lined oligosaccharides and 3 O-linked oligosaccharide structure, more acidic, pI=4.9, in advanced simian primates. The increased acidity increased the circulating half-life from 2.4 hours to 6.0 hours. With this improvement hyperglycosylated hCG started invading the uterus deeper, from decidua width of 0.3% to 10% width of uterus (Table 1). Hyperglycosylated CG and hCG promoted villous tissue growth greater. Hemochorial placentation in advanced simian primates is illustrated in (Figure 3). With these major advances in hemochorial placentation fetuses were produced with a significantly larger brain size, 0.74% of body weight (Table 1).

Evolution progressed to early hominids. Further mutations occurred in hCG β-subunit C-terminal peptide, and now molecules with 3 N-linked oligosaccharides and 4 O-linked oligosaccharides evolved. These were significantly more acidic that the advanced simian primate molecule with a much longer circulating half-life. This led to much more efficient hemochorial placentation. While we cannot get blood from early hominids because they are all extinct and determine the precise pI and precise half-life, we do know that they had significantly larger brains, 1.2% of body weight, from skull sizes (Table 1).

Finally, evolution progressed even further to humans. Further mutations occurred in the core of the CG β-subunit molecule, and now molecules with 4 N-linked oligosaccharides and 4 O-linked oligosaccharides evolves. These were significantly more acidic, pI=3.5, than the hominid molecules with very much longer circulating half-life, 37 hours half-life. This led to very much more efficient hemochorial placentation (Figure 3). Humans like homo erectus and homo neanderthalensis developed a much larger brain to match the more efficient hemochorial placentation, 2.4% of body weight (Table 1).

This is how advanced primates, early hominids and humans evolved, through the growing acidity of CG, longer circulating half-lives and advancing hemochorial placentation.

The CG/hyperglycosylated CG Evolution Model

The complete CG/hyperglycosylated hCG evolution model is shown in (Figure 4). As shown, advancing glycosylation, acidity and circulating half-life of CG and hyperglycosylated hCG controls advancing implantation and advancing hemochorial placentation which leads to brain growth gene expression and action leading to increasing brain growth. As a confirmation, shown in (Figure 5) is brain size among multiple primates hominids and humanoids. As shown, brain size total fits with the concept of 5 very clear brain growth groups, prosimian primates. Group 1 (Figure 5) is prosimian primates and the earliest primates, stem primate. These used inefficient
The CG/Hyperglycosylated CG Human Evolution Model

Figure 4: The complete CG/hyperglycosylated CG evolution model.

Figure 5: Evolution of the primate, hominid and human brain. Percentage values are brain size, % of body weight.
epitheliochorial placentation. The brains size was 0.07%-0.08% of total body weight. Group 2 (Figure 5) is lower simian primates where hemochorial placentation and implantation was introduced with brains 0.17%-0.19% of total body weight. Group 3 (Figure 5) is advanced simian primates or intelligent great apes with hemochorial placentation, with brains of 0.66%-0.78% of total body weight. Group 4 (Figure 5) is early hominids, and a brain size of 1.0-1.2% of total body weight, Group 5 (Figure 5) is humanoids or advanced hominids with hemochorial placentation, and a brain size of 2.1-2.7% of body weight. These 5 groups very much coincide with the five groups shown in Figure 4 or the evolution model.

Also shown in Figure 5 are the five CG sugar structure classifications, no CG, CG 5 sugar side chains, CG 6 sugar structures, CG 7 sugar structures, CG 8 sugar structures. It is the sugar structure that make CG and hyperglycosylated hCG more and more acidic, and having longer and longer circulation half-life. How the proposed models fits in exactly with the five brain size groups and the five sugar side chain groups very much confirms the correctness and validity of the model.

There is one section of the model that is very much unconfirmed. This is the early hominid group, group 4. All that is available in this group is extinct skeletons. Without blood or urine or a source of CG and hyperglycosylated CG from early hominids we are unable to confirm the structures of CG and hyperglycosylated CG. It is assumed in Figures 4 and 5 that early hominid CG has seven oligosaccharides. This is very much assumed since it fits everything together but cannot be confirmed.

Looking at human evolution as a single entity, it appears that the human brain developed in four steps (Figures 4 and 5). From prosimian to lower simian primates, from lower simian primates to advanced simian primates, from advanced simian primates to early hominids and from early hominids to humanoids. Lower simian primates evolved 37 million years ago, so that the staged development of the large human brain took 37 million years. The development of the human brain took 37 million years driven by advancing mutation in the CG/hyperglycosylated CG molecule.

It is the evolution of CG and hyperglycosylated CG alone that led to the four clear steps in the development of the human brain and presented in the "CG/hyperglycosylated CG human evolution model" (Figure 4). Yes it is important that these primates' brains were continuously promoted by seven brain growth genes and their coded proteins. But brain growth, however, was only permitted by the evolution of forever improving promoters of hemochorial placentation and implantation, CG and hyperglycosylated CG.

Considering Darwin’s evolution model, the human evolution model described here is somewhat strange. Normally, positive mutations, such as those which occurred with CG and hyperglycosylated CG might take on 100 or more functions. Positive mutation may cause a hardening of a beak or mouth leading to better eating, a strengthening of any one of 50 muscles leading to increased strength, and improvement in liver enzyme functions, an improvement in vocal functions, better wiggling of toes, and so on. Furthermore, most mutation do not lead to positive outcomes. Mutation may not happen at all. As such the odds of a mutation in the CG gene leading to increased CG biological activity may be very small, perhaps 1 in 1000 or 1 in 10,000 offspring. In the "CG/hyperglycosylated CG human evolution model", it appears like four mutation in the CG gene leading to major improvement in brain size occurred in a row, prosimian primate - (1)- lower simian primate - (2)- advanced simian primate - (3)- early hominids - (4)- humanoids. Four 1 in 1000 or in 10,000 events occurring in a row appears like planned evolution rather than Darwinian evolution with remote odds of anywhere between 1 in a trillion and 1 in 10 quadrillion. This indicates that human brain development may have been planned rather than randomly evolved through Darwinian evolution. In this respect "the CG/hyperglycosylated CG human evolution model” could be suggestive of God’s involvement in planning human creation as indicated in the Bible.

Planning the evolution of humans required the many mutations needed to develop seven brain growth genes. It required the evolution of CG and hyperglycosylated CG to start implantation and hemochorial placentation. Finally it required the sequential evolution of an basic, advanced, more advanced and super advanced variant of CG and hyperglycosylated CG. Hundreds of species mutations were needed for a potential coordinated possible evolution plan.

Complications of CG Evolution

Unfortunately the story does not end with the evolution of humans. Multiple complications have been found in humans as complexities of having a super-ultra-potent growth factors in their genome, CG and hyperglycosylated CG.

Research has shown that miscarriages and biochemical pregnancies are the source of 15% and 25% of pregnancy failures among pregnant women. Ongoing research shows that these are largely due to inefficient or improper implantation of pregnancy. As shown in (Figure 6), pregnancy failure is primarily due to deficient supply of hyperglycosylated CG during implantation of human pregnancies [42,43]. As shown, in normal term pregnancy 70 of 70 cases produce >40% hyperglycosylated CG (Figure 6). In contrast, 49 of 63 failing pregnancies produced <40% hyperglycosylated CG (Figure 6).

Research shows that cancers produce hyperglycosylated hCG and hyperglycosylated CG free ß-subunit [46,47]. That both act on a TGFß receptor to promote cancer cell invasion (production of metalloproteinases and collagenases), cancer cell growth and block cancer cell apoptosis. These variants of hyperglycosylated hCG drive most cancers. It appears that cancer cells steal this super-ultra-potent
growth factor from the human genome as part of carcinogenesis, and use it to drive malignancies. An antibody to hyperglycosylated hCGβ is looking promising as a possible cancer cure [46–49].

All the research that has been completed has been limited to humans. It is possible that hyperglycosylated CG causes similar miscarriage and cancer limitations in lower simian primates and advanced simian primates. While hyperglycosylated CG is not so much of a super-ultra-potent growth factor in these primate species it may still cause problems.

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