# The Placenta, a Transducer Linking Maternal Nutrition to Adult Disease in the Offspring?

Roger Smith and Kaushik Maiti

Mothers and Babies Research Centre, Hunter Medical Research Institute, John Hunter Hospital, Newcastle 2305, New South Wales, Australia

This month's Journal carries an article from Shanghai on the regulation of glucose transporters (GLUT) in human placenta (1). The studies bring a possible new player into the ongoing drama of nutritional regulation of fetal growth and development. The *in vitro* studies by Gao *et al.* (1) examined the effects of CRH on mRNA and protein concentrations of GLUT1 and GLUT3. Using a variety of techniques, including small interfering RNA for the corticotrophin releasing hormone receptor type 1 (CRH-R1) receptor, antibodies to the receptor, and receptor blockers, the studies convincingly show that CRH stimulates trophoblast production of GLUT1 and inhibits the expression of GLUT3 via the CRH-R1 receptor.

The area is of increasing interest as data accumulate that fetal growth is an important determinant of adult health. The Barker hypothesis posits that restricted intrauterine growth associated with the birth of a small infant leads to early onset diabetes, hypertension, and ischemic heart disease (2). This hypothesis is linked to the concept of phenotypic plasticity, a widespread phenomenon in nature whereby the environment interacts with the genome to determine an organism's phenotype (3). In the setting of intrauterine growth restriction, it is proposed that impaired nutrient transfer to the fetus leads to the development of a metabolic phenotype that is adapted to an environment low in nutrients. The fetus adapted to low nutrients that is then born into a Western society with high-energy diets is maladapted, develops obesity, diabetes, hypertension, and early heart disease. There are strong animal data for this scenario; however, human data are more limited (4).

Given the importance of optimizing fetal growth, the pathway to optimal fetal growth becomes of great interest. Unfortunately, this pathway is very poorly characterized. Worldwide, low birth weight is very common, leading to a recent Gates Foundation call for studies on the underlying mechanisms leading to impaired fetal growth (http://www.grandchallenges.org/GCGHDocs/Healthy_Growth_Rules_and_Guidelines.pdf). Although conditions such as preeclampsia are well-known associates of impaired growth, there is little knowledge on the etiology of most cases. Major deficiencies in knowledge extend to even what might be the ideal diet for a pregnant woman to produce a healthy baby with an optimum metabolic phenotype for the 21st century. National guidelines for maternal intakes exist, but these are not founded on a sound evidence base of longitudinal studies of infant outcomes (5). Recent research on comparative nutritional intakes of protein, fat, and carbohydrate suggest that all animals have a genetically determined target intake of macronutrients (6). This work strongly suggests that an ideal target intake would exist for pregnant women, but this has not yet been defined.

With an ideal maternal intake, the placenta is the port via which this nutrition is transported to the fetus. How exactly this occurs and how it is regulated again remains unclear. Nutrient sensing by the fetus may involve the IGF axis within the fetal liver (7). How is nutrient sensing performed by the placenta on behalf of the fetus? Syncytiotrophoblast expression of GLUT1 is stimulated by placental variant growth hormone, which increases across gestation as does GLUT1; so perhaps again the IGF axis is central (8). How does the placenta determine how much nutrient will be invested in placental growth and how much transferred to the fetus for fetal growth? How does the placenta regulate the nutrient mix it provides to the fetus and is the ideal nutrient mix for the mother the same for the fetus?

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.
Copyright © 2012 by The Endocrine Society
doi: 10.1210/en.2012-1010 Received January 5, 2012. Accepted January 23, 2012.

**For article see page 1464**

Abbreviation: CRH-R1, Corticotrophin releasing hormone receptor type 1; GLUT, glucose transporter.

These are large questions that need to be answered to guide policy in providing food for the world's pregnant women to optimize fetal growth and improve long-term health for the next generation to inhabit the planet.

Returning to the paper by Gao *et al.* (1), it is intriguing to consider how placental CRH may play a role in glucose transport to the fetus. Hypothalamic CRH is stress responsive and anorexic, but what of placental CRH? Placental CRH is expressed from the same gene as that in the hypothalamus, but it is regulated quite differently. During pregnancy, maternal plasma levels of CRH increase exponentially, peaking at the time of delivery (9). Although many parts of the CRH promoter mediate its complex responses to acute and chronic stress in the hypothalamus, in the placenta, regulation appears to be restricted to the cAMP response element. At the cAMP promoter site estrogens, progesterone and glucocorticoids interact through the cAMP response element-binding protein and jun to regulate placental CRH expression (10–14). The placental CRH is expressed in the syncytiotrophoblast cells of the placenta (15), which are derived from cytotrophoblasts by fusion mediated by the endogenous retrovirus coat proteins syncytin 1 and 2 (16). The exponential rise in placental CRH may be due to a positive feedforward loop, by which placental CRH stimulates pituitary ACTH leading to increased adrenal cortisol, which paradoxically stimulates placental CRH production (contrary to its inhibitory effect on hypothalamic CRH expression). Alternatively, the increasing CRH may be due to the exponential increase in syncytiotrophoblast tissue mass that occurs with advancing gestation (17). Either way, the rate of increase in placental CRH is directly associated with the timing of birth, so that rapid rates of increase are seen in women who deliver preterm, whereas slow rates occur in women who deliver late (18). The link with gestational age and delivery is thought to occur via a direct action on the fetal adrenal leading to increased dehydroepiandrosterone production, which is 16 hydroxylated in the fetal liver and then converted in the placenta to estriol. The exponential increase in CRH at the end of pregnancy correlates well with an increase in estriol at this time (19). This relationship between CRH and estriol is restricted to the apes, including humans, and the difficulties of conducting experimental studies in these species means that the only work performed has been correlative and longitudinal. It may be that the changes in CRH represent a pattern of placental maturation that is itself linked to the onset of labor.

The levels of placental CRH as reflected in fetal cord blood are also increased in the setting of fetal growth restriction (20). If Gao *et al.* (1) are correct, increased CRH production may represent a compensation by the placenta in an attempt to improve nutrient transport, in the form of glucose, to the fetus. Placental CRH is also elevated in preeclampsia (21), which is associated with growth restriction. How the placenta senses the fetal nutrient deficiency and how the production of CRH may be increased in this setting remains unclear. Perhaps, in the placenta, the stress-responsive regulation of the CRH gene remains active and the relative hypoglycemia is a stressor in the placenta as it is in the hypothalamus.

As always, new data pose new questions. The studies have been performed in purified cytotrophoblasts cultured for 3 d. There is no data on the apical to basal distribution of the GLUT1 receptors in this model, yet previous studies suggest that it is the basal GLUT1 receptor population that is the rate-limiting determinant of placental glucose transport (8). This cannot be assessed using purified and cultured cytotrophoblasts but could be examined in explants. The expression of GLUT1 in placental cells is within syncytiotrophoblasts rather than their precursors the cytotrophoblasts. Because fusion of cytotrophoblasts is stimulated by cAMP, and CRH activation of CRH-R1 mediates increased cAMP, it is possible that the increased GLUT1 mirrors an increase in formation of syncytium rather than a specific effect of CRH on GLUT1 production (22). It will be interesting to learn if CRH can directly stimulate not only GLUT1 expression but also increased glucose transport. Finally, because placental CRH production is limited to higher primates, *in vivo* studies in a primate would be required to demonstrate a physiological effect of CRH on glucose transport to the fetus (23).

The work of Gao *et al.* (1) is another step in our understanding of the endocrinology of the largest endocrine organ, the placenta.

## Acknowledgments

Address all correspondence and requests for reprints to: Roger Smith, John Hunter Hospital, Newcastle 2305, New South Wales, Australia. E-mail: roger.smith@newcastle.edu.au.

Disclosure Summary: The authors have nothing to disclose.

## References

1. **Gao L, Lv C, Xu C, Li Y, Cui X, Gu H, Ni X** 2012 Differential Regulation of Glucose Transporters Mediated by CRH Receptor Type 1 and Type 2 in Human Placental Trophoblasts. Endocrinology 153:1464–1471
2. **Barker DJ** 2004 Developmental origins of adult health and disease. J Epidemiol Community Health 58:114–115
3. **Werner EE, Hal DJ** 1976 Niche shifts in sunfishes: experimental evidence and significance. Science 191:404–406
4. **McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC,**

**Bennett PH** 1994 Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? BMJ 308:942–945
5. **Blumfield ML, Hure AJ, Macdonald-Wicks LK, Patterson AJ, Smith R, Collins CE** 2011 Disparities exist between National food group recommendations and the dietary intakes of women. BMC Women's Health 11:37
6. **Mayntz D, Raubenheimer D, Salomon M, Toft S, Simpson SJ** 2005 Nutrient-specific foraging in invertebrate predators. Science 307: 111–113
7. **Li C, Schlabritz-Loutsevitch NE, Hubbard GB, Han V, Nygard K, Cox LA, McDonald TJ, Nathanielsz PW** 2009 Effects of maternal global nutrient restriction on fetal baboon hepatic insulin-like growth factor system genes and gene products. Endocrinology 150: 4634–4642
8. **Baumann MU, Deborde S, Illsley NP** 2002 Placental glucose transfer and fetal growth. Endocrine 19:13–22
9. **Goland RS, Wardlaw SL, Blum M, Tropper PJ, Stark RI** 1988 Biologically active corticotropin-releasing hormone in maternal and fetal plasma during pregnancy. Am J Obstet Gynecol 159:884–890
10. **Cheng YH, Nicholson RC, King B, Chan EC, Fitter JT, Smith R** 2000 Corticotropin-releasing hormone gene expression in primary placental cells is modulated by cyclic adenosine 3′,5′-monophosphate. J Clin Endocrinol Metab 85:1239–1244
11. **Cheng YH, Nicholson RC, King B, Chan EC, Fitter JT, Smith R** 2000 Glucocorticoid stimulation of corticotropin-releasing hormone gene expression requires a cyclic adenosine 3′,5′-monophosphate regulatory element in human primary placental cytotrophoblast cells. J Clin Endocrinol Metab 85:1937–1945
12. **King BR, Smith R, Nicholson RC** 2002 Novel glucocorticoid and cAMP interactions on the CRH gene promoter. Mol Cell Endocrinol 194:19–28
13. **Ni X, Hou Y, Yang R, Tang X, Smith R, Nicholson RC** 2004 Progesterone receptors A and B differentially modulate corticotropin-releasing hormone gene expression through a cAMP regulatory element. Cell Mol Life Sci 61:1114–1122
14. **Ni X, Nicholson RC, King BR, Chan EC, Read MA, Smith R** 2002 Estrogen represses whereas the estrogen-antagonist ICI 182780 stimulates placental CRH gene expression. J Clin Endocrinol Metab 87:3774–3778
15. **Riley SC, Walton JC, Herlick JM, Challis JR** 1991 The localization and distribution of corticotropin-releasing hormone in the human placenta and fetal membranes throughout gestation. J Clin Endocrinol Metab 72:1001–1007
16. **Chuang HC, Chang CW, Chang GD, Yao TP, Chen H** 2006 Histone deacetylase 3 binds to and regulates the GCMa transcription factor. Nucleic Acids Res 34:1459–1469
17. **Fogarty NM, Mayhew TM, Ferguson-Smith AC, Burton GJ** 2011 A quantitative analysis of transcriptionally active syncytiotrophoblast nuclei across human gestation. J Anat 219:601–610
18. **McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R** 1995 A placental clock controlling the length of human pregnancy. Nat Med 1:460–463
19. **Smith R, Smith JI, Shen X, Engel PJ, Bowman ME, McGrath SA, Bisits AM, McElduff P, Giles WB, Smith DW** 2009 Patterns of plasma corticotropin-releasing hormone, progesterone, estradiol, and estriol change and the onset of human labor. J Clin Endocrinol Metab 94:2066–2074
20. **Goland RS, Jozak S, Warren WB, Conwell IM, Stark RI, Tropper PJ** 1993 Elevated levels of umbilical cord plasma corticotropin-releasing hormone in growth-retarded fetuses. J Clin Endocrinol Metab 77:1174–1179
21. **Goland RS, Tropper PJ, Warren WB, Stark RI, Jozak SM, Conwell IM** 1995 Concentrations of corticotrophin-releasing hormone in the umbilical-cord blood of pregnancies complicated by pre-eclampsia. Reprod Fertil Dev 7:1227–1230
22. **Ogura K, Sakata M, Okamoto Y, Yasui Y, Tadokoro C, Yoshimoto Y, Yamaguchi M, Kurachi H, Maeda T, Murata Y** 2000 8-Bromo-cyclicAMP stimulates glucose transporter-1 expression in a human choriocarcinoma cell line. J Endocrinol 164:171–178
23. **Robinson BG, Arbiser JL, Emanuel RL, Majzoub JA** 1989 Species-specific placental corticotropin releasing hormone messenger RNA and peptide expression. Mol Cell Endocrinol 62:337–341

THE ENDOCRINE SOCIETY®

**Register Now for ENDO 2012 and Save**
June 23–26, 2012, Houston, Texas
Early Registration Deadline: May 1, 2012
www.endo-society.org/endo2012