Do Not Turn to the Hypothalamus for Feedback on Stress If You Are Growth Restricted

David S. Gardner and Kirsten R. Poore

School of Veterinary Medicine and Science (D.S.G.), University of Nottingham, Sutton Bonington Campus, Leicestershire LE12 5RD, United Kingdom; and Faculty of Medicine (K.R.P.), University of Southampton, Southampton General Hospital, Southampton SO16 6YD, United Kingdom

Up-regulation of the Fetal Baboon Hypothalamo-Pituitary-Adrenal Axis in Intrauterine Growth Restriction: Coincidence with Hypothalamic Glucocorticoid Receptor Insensitivity and Leptin Receptor Down-regulation

Intrauterine growth restriction (IUGR) is clearly defined, allowing nongovernmental agencies to classify the proportion of babies born with IUGR (<10% percentile of the recommended gender-specific birth weight for gestational age reference curves) (1) or, where gestational age is not available, to be born of low birth weight (LBW) defined as below 2500 g. The distinction between these classifications is important, because a definition of LBW per se may seriously underestimate the true proportion of babies to have suffered IUGR relative to their growth potential. Even in affluent countries, the proportion of babies born LBW falls between 4% and 10% (2). The short-term outcome for these babies is a failure to thrive, greater susceptibility to infection, and consequently higher rates of neonatal mortality. Equally, the longer-term forecast is a greater risk of suffering metabolic disease in adulthood and a greater likelihood of multiple morbidities over the life course, a concept that has become known as the Developmental Origins of Health and Disease (3).

Fetal growth is primarily substrate driven, through an adequate supply of glucose, amino acids, and lactate, and in absolute terms, growth is greatest over the last third of gestation (4, 5). Poor fetal growth is largely due to 1) placental insufficiency or 2) maternal malnutrition, ie, under- or overnutrition. Each is characterized in the fetal compartment by either a gross reduction in nutrient availability or an altered pattern of micro/macronutrient flux (ie, fetal malnutrition). Near to term, when the fetus has the greatest demand for nutrients, it has been suggested that "nutritional stress" in the fetal compartment is a key factor responsible for initiating parturition (6). The fetal hypothalamus perceives the signal and responds by activating both adrenocorticotrophic hormone and cortisol production, which rise in parallel, facilitated by desensitization to negative feedback in the hypothalamus (6). The relationship between maternal and fetal nutrition is, however, not linear; the placenta substantially modifies the fetal nutritional milieu (7). Hence, such a complex and dynamic process has likely frustrated the progress of mechanistic research, causally linking maternal diet with fetal malnutrition and later adverse outcomes in the adult offspring. Rather, Developmental Origins of Health and Disease postulates that fetal malnutrition is engendered by maternal malnutrition through alterations in the relative pattern of micronutrient (eg, amino acids, methyl groups, polyamines, cofactors) availability in the fetal compartment, together with concomitant effects on fetal hormones. Inappropriate exposure to such an unbalanced micronutrient environment through key developmental phases such as when brain regions like the hypothalamus are acquiring, and fixing, structural, and functional relationships (8) may leave a permanent mark on the offspring such that later function is reset. For example, in a clinical study, mild birth weight variation within monozygotic twin pairs was accompanied by appreciable differences in postnatal intelligence quotient and brain anatomy that persisted at least into late adolescence (9). In an animal model of maternal diabetes (ie, very low maternal insulin throughout pregnancy in streptozotocin-treated rats), fetal hypothalamic feeding circuits were reorganized such

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.

Received May 3, 2013. Accepted May 15, 2013.

For article see page 2365

Abbreviations: HPAA, hypothalamic-pituitary-adrenal axis; IUGR, intrauterine growth restriction; LBW, low birth weight.

that the ensuing adult offspring had consistently greater food intake and elevated fasted glucose levels. Effects mechanistically linked to an insensitivity to leptin action in the hypothalamus; effectively, the animals had a diminished satiety signal (10).

The vulnerability of brain regional development to malnutrition has largely been described in experimental animal models (11), because prospective, randomized trials in humans are unethical. In animal models, there are important comparative aspects of brain development to take into account. For example, the equivalent timing of growth for some brain regions is postnatal in rodents and prenatal in man (11). Thus, a strength of the study by Li et al (12) is that a mechanistic experiment has been conducted in a nonhuman primate model, a species with very similar brain anatomy and one in which the timing of regional brain development is virtually identical to man. Previous work from this group had characterized how maternal undernutrition of baboons (70% of ad libitum intake of controls) altered the pattern, but not total, availability of amino acids in the fetal compartment when measured at 90 days (0.5 gestation) (13) but still had marked anatomical effects on the immature and developing fetal neocortex (14).

Here, with continued nutrient restriction to 165 days (0.9 gestation), the authors have now characterized further effects of maternal undernutrition on the function of the fetal brain during late gestation, specifically now the paleocortex rather than neocortex. Fetal baboons exposed to maternal undernutrition had premature activation of their hypothalamic-pituitary-adrenal axis (HPAA), characterized by high plasma adrenocorticotrophin and cortisol (12). Such inappropriate exposure of the vulnerable brain to high glucocorticoids has been shown by others to have long lasting, even intergenerational, effects (15, 16). The study goes on to provide a mechanistic insight for premature HPAA activation, desensitization of the paraventricular nucleus to short and long-loop feedback by adrenocorticotropin and cortisol, respectively, plus a diminution of sensitivity to alternative inhibitory inputs, such as leptin. If the effects reported here in the paraventricular nucleus (12), but also in the arcuate nucleus (17), persist into adult life, then potential effects on the long-term regulation of energy balance (with presumed obesity as a consequence) may be speculated. Note, a small positive energy balance, over a long period of time, can have a significant impact on adiposity (18).

The current study does, however, leave some questions unanswered. It is known that the fetal and adult HPAA functions differently between males and females (19–21), but the current study with a mixed sex sample population is likely underpowered to determine any potential sex-specificity. Furthermore, the primary outcome of the study, a central insensitivity to HPAA feedback, is based upon an association, rather than a direct measure, and so caution should be exercised when interpreting the results. In addition, any potential contribution from altered sensitivity to trophic input in the adrenal has not been addressed. Future studies using, for example, freshly harvested tissue explants whereby receptor-ligand interaction and subcellular translocation (or lack of) could be directly observed would provide more conclusive evidence. The study is based on spot-samples during late gestation: as such, the longer-term effects of these changes in HPAA remain unknown given the differences, sometimes opposite, effects observed between fetal and neonatal/adult life (22). Although the authors frame their rationale in the context of IUGR, an observed effect size of 17% (decrease in fetal weight as a result of maternal undernutrition) is a relatively mild retardation of fetal growth, making the current results all the more interesting; would individuals with true IUGR express a more extreme phenotype? Lastly, taking an evolutionary perspective, it is an open question as to whether data on changes in the biology of hypothalamic nutrient signaling in a primate born lean (baboon, ~3% body fat) may be translated successfully to one born fat (human, ~15% body fat) (23).

Taken together with other work from this group, the study of Li et al (12) provides proof-of-principle evidence that mild variation in maternal diet can have marked impacts on the anatomy of the fetal brain with functional consequences later in gestation. The longer-term impact of these effects, and how they may be subsequently modified by the postnatal environment, will no doubt become known in the years to come.

Acknowledgments

Address all correspondence and requests for reprints to: David S. Gardner, School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington Campus, Leicestershire LE12 5RD, United Kingdom. E-mail: david.gardner@nottingham.ac.uk.

Disclosure Summary: The authors have nothing to disclose.

References

1. **World Health Organization.** Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee; 1995.
2. **UNICEF Office of Research.** *Child Well-Being in Rich Countries: A Comparative Overview*. Innocenti Report Card 11, UNICEF Office of Research, Florence, Italy; 2013.
3. **Gluckman PD, Hanson MA, Cooper C, Thornburg KL.** Effect of in

utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359:61–73.
4. **Karlberg J, Jalil F, Lam B, Low L, Yeung CY.** Linear growth retardation in relation to the three phases of growth. *Eur J Clin Nutr*. 1994;48(suppl 1):S25–S43.
5. **Battaglia FC, Meschia G.** Principal substrates of fetal metabolism. *Physiol Rev*. 1978;58:499–527.
6. **McMillen IC, Phillips ID, Ross JT, Robinson JS, Owens JA.** Chronic stress—the key to parturition? *Reprod Fertil Dev*. 1995;7:499–507.
7. **Battaglia FC.** In vivo characteristics of placental amino acid transport and metabolism in ovine pregnancy—a review. *Placenta*. 2002; 23(suppl A):S3–S8.
8. **Dobbing J, Smart JL.** Vulnerability of developing brain and behaviour. *Br Med Bull*. 1974;30:164–168.
9. **Raznahan A, Greenstein D, Lee NR, Clasen LS, Giedd JN.** Prenatal growth in humans and postnatal brain maturation into late adolescence. *Proc Natl Acad Sci USA*. 2012;109:11366–11371.
10. **Steculorum SM, Bouret SG.** Maternal diabetes compromises the organization of hypothalamic feeding circuits and impairs leptin sensitivity in offspring. *Endocrinology*. 2011;152:4171–4179.
11. **Dobbing J, Sands J.** Comparative aspects of the brain growth spurt. *Early Hum Dev*. 1979;3:79–83.
12. **Li C, Ramahi E, Nijland MJ, Choi J, Myers DA, Nathanielsz PW, McDonald TJ.** Up-regulation of the fetal baboon hypothalamo-pituitary-adrenal axis in intrauterine growth restriction: coincidence with hypothalamic glucocorticoid receptor insensitivity and leptin receptor down-regulation. *Endocrinology*. 2013;154:2365–2373.
13. **McDonald TJ, Wu G, Nijland MJ, Jenkins SL, Nathanielsz PW, Jansson T.** Effect of 30 % nutrient restriction in the first half of gestation on maternal and fetal baboon serum amino acid concentrations. *Br J Nutr*. 2013;109:1382–1388.
14. **Antonow-Schlorke I, Schwab M, Cox LA, et al.** Vulnerability of the fetal primate brain to moderate reduction in maternal global nutrient availability. *Proc Natl Acad Sci USA*. 2011;108(7):3011–3016.
15. **Seckl JR, Holmes MC.** Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nat Clin Pract Endocrinol Metab*. 2007;3:479–488.
16. **Meaney MJ, Diorio J, Francis D, et al.** Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Dev Neurosci*. 1996; 18:61–72.
17. **Li C, McDonald TJ, Wu G, Nijland MJ, Nathanielsz PW.** Intrauterine growth restriction alters term fetal baboon hypothalamic appetitive peptide balance. *J Endocrinol*. 2013;217:275–282.
18. **Levine JA, Lanningham-Foster LM, McCrady SK, et al.** Interindividual variation in posture allocation: possible role in human obesity. *Science*. 2005;307:584–586.
19. **Giussani DA, Fletcher AJ, Gardner DS.** Sex differences in the ovine fetal cortisol response to stress. *Pediatr Res*. 2011;69:118–122.
20. **Kirschbaum C, Wüst S, Hellhammer D.** Consistent sex differences in cortisol responses to psychological stress. *Psychosom Med*. 1992; 54:648–657.
21. **Poore KR, Boullin JP, Cleal JK, et al.** Sex- and age-specific effects of nutrition in early gestation and early postnatal life on hypothalamo-pituitary-adrenal axis and sympathoadrenal function in adult sheep. *J Physiol*. 2010;588:2219–2237.
22. **Hoet JJ, Hanson MA.** Intrauterine nutrition: its importance during critical periods for cardiovascular and endocrine development. *J Physiol*. 1999;514(pt 3):617–627.
23. **Kuzawa CW.** Beyond feast-famine: brain evolution, human life history, and the metabolic syndrome. In: Muehlenbein MP, ed. *Human Evolutionary Biology*. Cambridge, United Kingdom: Cambridge University Press; 2010:518–527.