Maternal Nutrition, Developmental Programming, and the Small Intestine[1]

Nutrición maternal, programación del desarrollo y el intestino delgado

Caton, J. S.[2] and Meyer, A. M. [3]

[2] Center for Nutrition and Pregnancy, Department of Animal Sciences, North Dakota State University, Fargo 58108. Contact: Department of Animal Sciences, North Dakota State University, Fargo, ND. 58108. Joel.Caton@ndsu.edu
[3]Division of Animal Sciences, University of Missouri, Columbia 65211

Fecha de recepción: 15 Septiembre 2017
Fecha de aceptación: 15 Diciembre 2017

Introduction

Small intestinal growth and function are critical for optimal animal growth and health, playing a major role in nutrient digestion and absorption, energy and nutrient expenditure, and immunological competence. Small intestinal growth and development are often overlooked but essential processes driving metabolism, immunology, survival, and growth. The small intestine not only serves as the main site for digestion and absorption of nutrients, but it is also a major energy and nutrient sink due to its high metabolic activity and rapid turnover. Changes in small intestinal mass, cellularity, and oxygen consumption have been demonstrated during feed restriction and in response to specific nutrients. The effects of in utero environment have become a major area of study in animal and human nutrition, physiology, and epidemiology research, as evidenced by the hundreds of reviews on the subject. In livestock, intrauterine growth restriction (IUGR) results in impaired fetal development, low birth weight offspring, and decreased long-term production. Programming of growth and development in livestock may be driven by many factors, but often occurs in response to compromised nutrient supply to developing offspring. Because the small intestine is critical to animal growth, health, and production and is responsive to its luminal and extraluminal environment, early life effects on small intestinal development likely play a significant role in observed programming of later animal health and performance, including in the acquisition of nutrients during the pre- and postnatal periods. Additionally, impacts of gestational nutrition on the maternal small intestine may change

1 Portions of this article were previously published as a review paper (American Society for Nutrition. Adv, Nutr, 2016;7:169–178; doi:10.3945/an.115.010405) and the Florida Ruminant Nutrition Conference, 2017 and presented here in accordance with granted author rights as outlined in policies of Adv. Nutr and American Society of Nutrition. Portions of the data were also presented at the symposium “Maternal/Fetal Nutrition and Programming: What Have We Learned from Farm Animal Models?” held 28 March 2015 at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2015 in Boston, MA.

ISBN 2462 – 8050 (en línea)

nutrient delivery to offspring, both in utero and during lactation. This review will focus on impacts of nutrition during pregnancy on maternal and offspring small intestines and focus on data from ruminant livestock models.

Fetal Small Intestinal Growth and Development

There are multiple developmental windows for the small intestine during fetal, perinatal, and neonatal periods. Organogenesis generally occurs during early to mid-gestation, followed by rapid fetal growth in the last third of gestation, then preparation for the transition from the uterine to outside environment during the perinatal period. In addition to these windows, the small intestine continues to develop postnatally and even into maturity.

Evidence of Developmental Programming of the Offspring Small Intestine

Intrauterine Growth Restriction:

Effects of IUGR on the small intestine generally include reduced mass and/or length of the small intestine, decreased villus and crypt density, villus height and/or width, crypt depth, and mucosal size suggest that reduced mass may also be accompanied by reduced functional area and development. Additionally decreases in proliferation and cellular differentiation suggest altered crypt proliferative dynamics. Although effects of IUGR on the small intestine have been better characterized prenatally or immediately after birth, these effects persist postnatally.

Gene expression in the small intestine has also been altered by IUGR. Piglets identified as IUGR had altered jejunal protein expression, including 7 down-regulated and 4 up-regulated. Altered ileal gene expression was also observed in IUGR compared with normal piglets, although these were affected by day of sampling (birth vs. d 2 or 5 postnatally). At each time point, genes differentially expressed included those involved in macromolecule metabolism, biosynthesis, and cellular metabolism.

Although many of the reported effects of IUGR on the small intestine appear to be negative, this is not always the case. For example, jejunal lactase and maltase were greater for IUGR rats than control at birth, although this did not extend past the immediate postnatal period (Qui et al., 2005). These authors suggested that increased digestive enzyme production at birth was an adaptive mechanism allowing IUGR neonates to have increased digestive capacity. In another study, ileal adherent bacterial numbers were increased for IUGR pigs at d 2 postnatally (D'Inca et al., 2010), indicating that IUGR can alter bacterial colonization of the small intestine postnatally.

Maternal Nutrient Manipulation during Gestation

Fetal. Nutrient restriction during early and mid-gestation does not appear to impact fetal small intestinal growth. Nutrient restriction during early and mid-

gestation can increase jejunal crypt proliferation at d 125 of gestation in fetal calves. Additionally, when nutrient restricted cows were realimented, total vascularity of the fetal small intestine was increased at d 245 of gestation. These data suggest that nutrient restriction increased the efficiency of the fetal small intestine, perhaps similarly to the “thrifty phenotype” hypothesis (Hales and Barker, 1992), which has been postulated to describe fetal development changes that increase survival in the face of negative environment or poor nutrition (Wells, 2007).

Maternal nutrient restriction of ewes in mid- and late gestation has decreased small intestinal mass and jejunal hypertrophy (protein:DNA), despite a lack of differences in jejunal proliferation. Lambs from nutrient restricted ewes had decreased total jejunal microvascular volume concurrently with reduced jejunal mRNA expression of soluble guanylate cyclase (GUCY1B3), a NO receptor involved in vasodilation and angiogenesis. Conversely, small intestinal mass of fetal lambs from ewes that were nutrient restricted during the last 3 wk of gestation was unaffected, suggesting that longer periods of maternal nutrient restriction are necessary to affect the fetal small intestine. Nutrient restriction during mid- and late gestation has increased oxygen consumption per unit of small intestine in late-term fetal lambs.

Postnatal. Changes in maternal nutrition in late gestation may negatively affect gut maturation. Cortisol and fetal swallowing of amniotic fluid both play an important role in the small intestinal maturation process (Sangild et al., 2000; Trahair and Sangild, 2004). For example, expression of vascular endothelial growth factor (VEGF) in the fetal small intestine, which is important for angiogenesis of the growing tissue, is likely cortisol-dependent in sheep (Holmes et al., 2008). Maternal cortisol levels are often changed by gestational plane of nutrition (Symonds et al., 2007; Lemley et al., 2014), and nutrient content of the amnion has been altered by nutrient restriction in ewes (Kwon et al., 2004), indicating that maternal nutrition may have an even greater impact during final prenatal maturation. Small intestinal function is particularly important in livestock species that rely upon transfer of passive immunity from immunoglobulins in colostrum (e.g. cattle and sheep); and colostrum also contains a cadre of growth factors, hormones, and nutrients which are crucial for small intestinal development (Quigley et al., 1988; Xu, 1996; Sangild et al., 2000, Berni Canani et al., 2008). Colostrum production has been decreased by both nutrient restriction and over nutrition in ewes (Swanson et al., 2008; Meyer et al., 2011), which could also have further implications in perinatal small intestinal maturation.

There are few data from ruminant developmental programming models investigating small intestinal parameters postnatally. Two studies have investigated postnatal lamb small intestinal growth and vascularity after mid- and late gestation nutrient restriction or over-nourishment. These data demonstrate that 20-d old lambs have continued alterations in jejunal hyperplasia, vascularity, and gene expression, even when lambs were fed a common artificial colostrum and milk replacer after birth and managed

ISBN 2462 – 8050 (en línea)

together. Moreover, jejunal proliferation, vascularity, and gene expression were also affected by gestational nutrition in 180-d old lambs in a similar model, demonstrating that changes to the small intestine may persist well into life. In both 20- and 180-d old lambs, glucagon-like peptide 2 (GLP-2) expression was altered, although in opposite ways. This GLP-2 is very important for small intestinal development, including in growth and vascularization, making it a possible mechanism for small intestinal changes observed in these studies.

It has also been demonstrated that maternal intake of specific nutrients such as selenium during gestation can impact fetal small intestinal development. Fetuses from ewes fed supranutritional selenium throughout gestation had increased jejunal hypertrophy and decreased jejunal VEGF mRNA expression. In addition, form and level of maternal selenium supplementation during gestation have impacted fetal jejunal hypertrophy. Even when lambs were fed similar diets postnatally, high selenium during gestation has continued to impact lamb jejunal measures at d 20 and 180 of age, suggesting long-term impacts of this micronutrient fed prenatally or compensation by offspring after normal selenium intakes postnatally.

Maternal Small Intestinal Adaptations

Adaptation to Nutrient Manipulation

Nutritional Plane. Small intestinal growth and function are known to change with nutrient intake, so it should come as no surprise that they change with nutritional plane during pregnancy. Most of the studies cited here include treatments that vary in nutrient intake and bulk density of feed, both of which impact the small intestine.

In general, alteration of nutritional plane during early gestation alone does not seem to affect mass of the ruminant small intestine even though over nutrition during this period increased indices of jejunal hypertrophy. Impacts of nutrient restriction during early and mid- or mid-gestation are more variable; and either has decreased or not affected maternal small intestinal mass when measured immediately after nutrient restriction. Dams rebounded when nutrient restriction was followed by realimentation in late gestation, and small intestinal mass was not different from controls near term.

In most studies, small intestinal mass has responded to nutritional plane during both mid- and late gestation or late gestation only when measured at the end of the restriction period. Changes in cellularity have been observed in these studies, indicating that both hypertrophy and hyperplasia may play a role in growth differences, even when no change in mass was observed. Little is known about the impacts of gestational nutrition on small intestinal energy use, but one study reported that oxygen consumption was increased per unit of tissue in nutrient restricted ewes. Jejunal vascularity has responded to nutritional plane during gestation in several studies in ewes.

Specific Nutrients. There have been few published studies to date investigating the effect of specific nutrient intake during gestation on the maternal small intestine. In a series of studies to determine impacts of supranutritional selenium in ewes during gestation, results have been variable. High selenium diets fed during gestation have had no effect (Neville et al., 2008; Carlson et al., 2009), increased (Reed et al., 2007), and decreased (Meyer et al., 2012) primiparous ewe small intestinal mass. When small intestinal mass was increased, no effects of selenium on cellularity measures, proliferation, or vascularity were observed (Reed et al., 2007). Alternatively, supranutritional selenium decreased DNA concentration in other studies (Neville et al., 2008; Carlson et al., 2009), with proliferative rate of crypt cells unaffected (Carlson et al., 2009) or increased by selenium (Neville et al., 2008). Expression of the VEGF and NO systems has been impacted by high selenium, where supranutritional selenium has reduced mRNA of VEGF and its receptors (Neville et al., 2010; Meyer et al., 2012). When high selenium was removed from the diet during lactation, small intestinal mass of ewes increased within the first 20 d to that of control-fed ewes (Meyer et al., 2012). It is unclear what caused differences in responses to high selenium in these studies, although selenium source and level of supplementation appear to alter small intestinal response, and thus likely influenced results.

Future Directions

Further research is necessary to better understand the role of the maternal small intestine in providing nutrients to the fetus and postnatal offspring and to advance knowledge of the effects of maternal nutrition on programming of offspring small intestinal growth and function. Additionally, research in the role of epigenetics and the microbiome in programming of the small intestine are lacking. A better understanding of the effects of nutrition on the maternal and offspring small intestine will allow for development of management strategies to optimize the livestock efficiency.

References

Berni Canani, R., A. Passariello, V. Buccigrossi, G. Terrin, and A. Guarino. 2008. The nutritional modulation of the evolving intestine. J. Clin. Gastroenterol. 42:S197-S200.

Carlson, D. B., J. J. Reed, P. P. Borowicz, J. B. Taylor, L. P. Reynolds, T. L. Neville, D. A. Redmer, K. A. Vonnahme, and J. S. Caton. 2009. Effects of dietary selenium supply and timing of nutrient restriction during gestation on maternal growth and body composition of pregnant adolescent ewes. J. Anim. Sci. 87: 669-680.

D'Inca, R, M. Kloareg, C. Gras-Le Guen, and I. Le Hueron-Luron. 2010. Intrauterine growth restriction modifies the developmental pattern of intestinal

ISBN 2462 – 8050 (en línea)

structure transcriptomic profile, and bacterial colonization in neonatal pigs. J. Nutr. doi: 10.3945/jn.109.116822.

Hales, C. N., and D. J. P. Barker. 1992. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 35:595-601.

Holmes, K, S. D. Charnock Jones, A. J. Forhead, D. A. Giussani, A. L. Fowden, D. Licence, S. Kempster, and G. C. S. Smith. 2008. Localization and control of expression of VEGF-A and the VEGFR-2 receptor in fetal sheep intestines. Ped. Res. 63:143-148.

Kwon, H, S. P. Ford, F. W. Bazer, T. E. Spencer, P. W. Nathanielsz, M. J. Nijlan, B. W. Hess, and G. Wu. 2004. Maternal nutrient restriction reduces concentrations of amino acids and polyamines in ovine maternal and fetal plasma and fetal fluids. Biol. Reprod. 71:901-908.

Lemley, C. O., A. M. Meyer, T. L. Neville, D. M. Hallford, L. E. Camacho, K. R. Maddock-Carlin, T. A. Wilmoth, M. E. Wilson, G. A. Perry, D. A. Redmer, L. P. Reynolds, J. S. Caton, and K. A. Vonnahme. 2014. Dietary selenium and nutritional plane alters maternal endocrine profiles during pregnancy and lactation. Domestic Animal Endocrinology. Domestic Animal Endocrinology 46:1-11.

Meyer, A. M., T. L. Neville, J. J. Reed, J. B. Taylor, L. P. Reynolds, D. A. Redmer, C. J. Hammer, K. A. Vonnahme, and J. S. Caton. 2013. Maternal nutritional plane and selenium supply during gestation impacts visceral organ mass and intestinal growth and vascularity of neonatal lamb offspring. J. Anim. Sci. 91:2628-2639.

Meyer, A. M., J. J. Reed, T. L. Neville, J. F. Thorson, K. R. Maddock-Carlin, J. B. Taylor, L. P. Reynolds, D. A. Redmer, J. S. Luther, C. J. Hammer, K. A. Vonnahme, and J. S. Caton. 2011. Nutritional plane and selenium supply during gestation impact on yield and nutrient composition of colostrum and milk in primiparous ewes. J. Anim. Sci. 89:1627-1639.

Meyer, A. M., J. J. Reed, T. L. Neville, J. B. Taylor, L. P. Reynolds, D. A. Redmer, K. A. Vonnahme, and J. S. Caton. 2012. Effects of nutritional plane and selenium supply during gestation on visceral organ mass and indices of intestinal growth and vascularity in primiparous ewes at parturition and during early lactation. J. Anim. Sci. 90:2733-2749.

Neville, T. L., D. A. Redmer, , P. P. Borowicz, J. J. Reed, M. A. Ward, M. L. Johnson, J. B. Taylor, S. A. Soto-Navarro, K. A. Vonnahme, L. P. Reynolds, and J. S. Caton. 2010. Maternal dietary restriction and selenium supply alters mRNA expression of angiogenic factors in maternal intestine, mammary gland, and fetal jejunal tissues during late gestation in pregnant ewe lambs. J. Anim. Sci. 88: 2692-2702

Neville, T. L., M. A. Ward, J. J. Reed, S. A. Soto-Navarro, S. L. Julius, P. P. Borowicz, J. B. Taylor, D. A. Redmer, L. P. Reynolds, and J. S. Caton. 2008. Effects of level and source of dietary selenium on maternal and fetal body weight, visceral organ mass, cellularity estimates, and jejunal vascularity in pregnant ewe lambs. J. Anim. Sci. 86:890-901.

Qiu, X. S., T. T. Huang, Z. Y. Shen, H. Y. Deng, and Z Y. Ke. 2005. Effect of early nutrition on intestine development of intrauterine growth retardation in rats and its correlation to leptin. World Journal of Gastroenterology. 11:4419-4422.

Quigley, J. D., III., and J. J. Drewry. 1988. Nutrient and immunity transfer from cow to calf pre- and postcalving. J. Dairy Sci. 81:2779-2790.

Reed, J. J., M. A. Ward, K. A. Vonnahme, T. L. Neville, S. L. Julius, P. P. Borowicz, J. B. Taylor, D. A. Redmer, A. T. Grazul-Bilska, L. P. Reynolds, and J. S. Caton. 2007. Effects of selenium supply and dietary restriction on maternal and fetal body weight, visceral organ mass, cellularity estimates, and jejeunal vascularity in pregnant ewe lambs. J. Anim. Sci. 85:2721-2733

Sangild, P. T., A. L. Fowden, and J. F. Trahair. 2000. How does the foetal gastrointestinal tract develop in preparation for enteral nutrition after birth. Livest. Prod. Sci. 66:141-150.

Swanson, T. J., C. J. Hammer, J. S. Luther, D. B. Carlson, J. B. Taylor, D. A. Redmer, T. L. Neville, J. J. Reed, L. P. Reynolds, J. S. Caton, and K. A. Vonnahme. 2008. Effects of gestational plane of nutrition and selenium supplementation on mammary development and colostrum quality in pregnant ewe lambs. J. Anim. Sci. 86:2415-2423.

Symonds, M. E., T. Stephenson, D. S. Gardner, and H. Budge. 2007. Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. Repro. Fertil. Dev.19:53-62.

Trahair, J. F., and P. T. Sangild. 2002. Studying the development of the small intestine: philosophical and anatomical perspectives. Edtion ed. In: R. Zabielski, P. C. Gregory, and B. Westrom, eds. Biol. of the Intest. Growing Anim. Amsterdam: Elsevier Science:1-54.

Wells, J. C. K. 2007.The thrifty phenotype as an adaptive maternal effect. Biol. Rev. 82:143-172.

Xu, R. J. 1996. Development of the newborn GI tract and its relation to colostrum/milk intake: A review. Repro. Fertil. Dev. 8:35-48.

ISBN 2462 – 8050 (en línea)