Archivos de Zootecnia
Journal website: https://www.uco.es/ucopress/az/index.php/az/
ORAL COMMUNICATION

Implications of prenatal programming in Iberian pig production

Gonzalez-Bulnes, A.[1@]; Astiz, S.[1]; Ovilo, C.[2]; Isabel, B.[3]; Lopez-Bote, C.[3]; Torres-Rovira, L.[1]; Ayuso, M.[3]; Vazquez-Gomez, M.[3] and Garcia-Contreras, C.[2]

[1]Departamento de Reproducción Animal. INIA, Madrid, Spain.
[2]Departamento de Mejora Genética Animal. INIA, Madrid, Spain.
[3]Departamento de Producción Animal. Facultad de Veterinaria, Universidad Complutense de Madrid, Madrid, Spain.

Additional keywords

Embryo.
Epigenetics.
Fetus.
Pregnancy.

SUMMARY

This article reviews several aspects of prenatal programming in the Iberian pig. Research on factors affecting adult phenotype and homeorhesis in different species has addressed both genetic predisposition and the determinant role of nutrition during the prenatal period. Both over- and undernutrition (this latter by maternal malnutrition or by placental insufficiency) may alter the genome expression and the components and functions of different body systems in the offspring, resulting in modifications of body development and composition, metabolic disorders and increased health risk. This article reviews how in swine, and specifically in the Iberian breed, the exposure of fetuses to malnutrition, commonly by maternal undernutrition or placental insufficiency, is very frequent at advanced pregnancy. Offspring exposed to maternal undernutrition during the two last thirds of gestation are smaller at birth since they are affected by intrauterine growth retardation (IUGR). In lean breeds, both males and females have compromised postnatal growth and increased fat accumulation and metabolic disorders during fattening periods. In the Iberian breed, postnatal growth in case of prenatal exposure to low-energy diets depends on sex, with the postnatal growth in males being affected similarly to lean breeds, whilst their sisters evidence a compensatory growth as early as during the suckling period. After that, in response to high-energy diets during the fattening period, both males and females show increased adiposity at subcutaneous, visceral and intramuscular locations, high incidence of metabolic disorders and significant changes in intramuscular fatty-acid composition, when compared to piglets that did not suffer undernutrition during the intrauterine life.

Implicaciones de la programación prenatal en la producción de cerdo ibérico

Palabras clave adicionales

Embrión.
Epigenética.
Feto.
Gestación.

RESUMEN

El presente artículo revisa diversos aspectos de la programación prenatal en el cerdo ibérico. La investigación sobre los factores que condicionan el fenotipo adulto y la homeorresis en diferentes especies ha abordado tanto la predisposición genética como el papel determinante de la nutrición durante el período prenatal. Tanto la sobrenutrición como la subnutrición en la etapa fetal (la segunda por subnutrición materna o por insuficiencia placentaria) pueden alterar la expresión del genoma y los componentes y funciones de los diferentes sistemas en la descendencia, lo que da lugar a alteraciones en el desarrollo y composición corporal, aparición de trastornos metabólicos y un mayor riesgo para la salud. En los cerdos, y específicamente en la raza ibérica, la exposición de los fetos a la sub/desnutrición, comúnmente por desnutrición materna o insuficiencia placentaria, tiene una alta incidencia en fases avanzadas de gestación. Los lechones expuestos a desnutrición materna durante los dos últimos tercios de la gestación son más pequeños al nacer, ya que se ven afectados por un proceso denominado 'retraso del crecimiento intrauterino' o IUGR por sus siglas en inglés. En razas magras, tanto los machos como las hembras ven comprometido su crecimiento postnatal y se produce un aumento de la acumulación de grasa y aparición de trastornos metabólicos durante los períodos de engorde. En la raza ibérica, el crecimiento postnatal en el caso de la exposición prenatal a dietas de baja energía depende del sexo. Así, el crecimiento postnatal en los machos se ve afectado de forma similar a las razas magras, mientras que sus hermanas muestran un crecimiento compensatorio muy temprano, durante el período de lactación, antes del destete. Posteriormente, en respuesta a las dietas con alto contenido energético que se utilizan durante el período de engorde, tanto los machos como las hembras presentan aumento de adiposidad a nivel subcutáneo, visceral e intramuscular, presentan una mayor incidencia de trastornos metabólicos y presentan cambios significativos en la composición intramuscular de ácidos grasos, con respecto a los lechones que no habían sufrido subnutrición durante su vida intrauterina.

Information

Cronología del artículo.
Recibido/Received: 15.01.2017
Aceptado/Accepted: 08.07.2017
On-line: 15.01.2018
Correspondencia a los autores/Contact e-mail:
bulnes@inia.es

INTRODUCTION

Mediterranean pigs have been reared in semi-feral, free-ranging conditions for centuries and have developed a *thrifty genotype* for the accommodation to seasonal cycles of feasting and famine to which they are exposed in their environment. However, currently, the traditional management of the Iberian pigs is chang-

ing to production systems that are more intensive, including strategies for increasing prolificacy. Iberian pig production is characterized by a lower prolificacy than modern commercial breeds (Lopez-Bote 1998) and diminishing production costs by reducing food intake during pregnancy.

Prolificacy in swine, as in other multiparous species, depends on the number of ovulations and on the incidence of embryo losses during pregnancy. The selection of highly-prolific dam lines has been mainly focused in the selection of genotypes with high ovulatory rate. However, when ovulatory rate is high, the increases in the number of ovulations fail to correspond with proportional increases in the number of newborns (Freking et al. 2007, Rosendo et al. 2007). In this case, the rate of embryo losses is the determinant factor for prolificacy.

The rate of embryo losses is determined by embryo viability and uterine capacity. The number of ovulations corresponds to the number of preimplantational embryos (leaving aside a small percentage of fertilization failures, around 5%; Whittemore & Kyriazakis 2006). Later on, prolificacy in females with high ovulatory rate is modulated by embryo losses at implantational and early post-implantational stages (Foxcroft et al. 2006; Freking et al. 2007), partly due to embryo viability and partly due to competition for the uterine space available for implantation (*uterine capacity*). Afterwards, *in uteri,* with a high number of developing embryos, placental growth is jeopardized due to the limited space (Town et al. 2004; Van der Waaij et al. 2010). Deficiencies in placental growth affect conceptus development by deficiencies in the supply of nutrients and oxygen, causing foetal losses and compromising the growth of some of the surviving foetuses in a process referred to as 'intrauterine growth retardation' (IUGR). In fact, occurrence of IUGR is commonly found in many littermates of high-prolific lines (Ashworth et al. 2001; Foxcroft et al. 2006; Wu et al. 2006). Incidence of IUGR may be also increased by maternal nutritional deficiencies (Metges et al. 2012), hampering the nutrient supply of the foetuses. In Iberian pigs, there are emerging evidence of a high IUGR incidence in larger litters or in case of nutritional limitations (Gonzalez-Añover et al. 2011; Gonzalez-Bulnes et al. 2012). Thus, the present article reviews several aspects of prenatal programming in the Iberian pig.

Intrauterine growth retardation and prenatal programming

IUGR piglets are predisposed to high neonatal morbidity and mortality rates, with early death or life-long alterations in their development, health and welfare (Wu et al. 2006).

In extreme IUGR individuals, deficiencies of brain development are unavoidable and viability of the neonate is strongly compromised, leading to death. In less-critical IUGRs, health and welfare are compromised by gastrointestinal, metabolic, respiratory and immune dysfunctions. First, health of any neonate is largely dependent on adequate gastrointestinal development and, thus, adequate food absorption and utilization. IUGR individuals are affected by alterations in development, morphology and function of the intestine, which predispose to feeding intolerance and digestive diseases. At the same time, an adequate liver development is essential for the metabolism of glucose, amino acids, proteins, lipids, vitamins and minerals. Furthermore, piglets are born without antibodies or cell-mediated immunity; antibodies are only obtained from the mother through the colostrum during the first hours of life (Rooke & Bland 2002). Hence, any problem concerning suckling or passive immunity transfer from colostrum will increase susceptibility to infection. Finally, IUGR foetuses are affected by abnormalities in the airways and lungs causing impaired adaptation to the extrauterine respiratory function. For these reasons, most IUGR piglets die before weaning, whilst the growth, health and welfare of the surviving IUGR animals will remain hampered by these conditionings, which exacerbate with age.

In fact, viable IUGR individuals are affected by the process named 'prenatal programming', with profound consequences on fetal and post-natal development. The conceptus, during prenatal development, develops through different dynamic stages, from fertilization to implantation and later organogenesis and enlargement. In these stages, the developing offspring is highly susceptible to changes in the intrauterine environment and is able to modify its genome expression by epigenetic changes ('prenatal programming') for adjusting to *in utero* conditions, as mediated through the placenta, in a sex dependent manner. The main factor negatively affecting intrauterine environment is malnutrition, due to global, macronutrient or micronutrient excess or deficiency of either maternal or placental origin.

Postnatal effects of prenatal programming in Iberian pigs

The exposure of Iberian sows to malnutrition during pregnancy modifies offspring growth patterns depending on the timing of exposure to malnutrition.

The exposure to undernutrition during the period of fetal development (two last thirds of pregnancy), as previously described, is related to appearance of IUGR processes and a higher prevalence of low birth-weight newborns (Barbero et al. 2013; Gonzalez-Bulnes et al. 2012; Ovilo et al. 2014). Subsequently, during postnatal development, there is a noteworthy sex-related effect in growth patterns caused by prenatal programming. Male offspring have a compromised postnatal growth and remain smaller than male piglets not exposed to maternal undernutrition, like in lean breeds. However, their sisters evidence a compensatory growth and reach weights and sizes similar to those of normal females, as early as during the suckling period (Gonzalez-Bulnes et al. 2012). Such catch-up growth of females is favored by differences in fetal development that prioritize the growth of vital organs (brain, liver, and intestine; Torres-Rovira et al. 2013), and also by changes in the hypothalamic expression of genes, mainly in genes coding for anorexigenic peptides (*LEPR* and *POMC*; Ovilo et al. 2014).

In contrast, the exposure to an inadequate nutrition during the entire pregnancy (either under- or overnutrition) is associated to offspring similar in birth-size

to offspring developed under adequate nutritional conditions (Barbero et al. 2013). Nevertheless, in case of exposure to obesogenic diets during the juvenile development, like in the fattening period, these individuals that suffered intrauterine malnutrition have a significantly increased body corpulence and fat content, when compared to the offspring born from pregnancies with an adequate diet. Moreover, programmed individuals are prone to the so-called metabolic syndrome. There is also a sex-related effect, since male piglets from pregnancies with adequate nutritional conditions or exposed to malnutrition during the entire pregnancy remain larger and heavier than the females during lactation before weaning. Afterwards, during the juvenile development and adulthood, the males from pregnancies with adequate nutrition remain heavier and larger than the females. Conversely, in litters born from both over- and underfed pregnancies, female piglets show enhanced growth patterns and therefore reach similar body weight, corpulence and adiposity to those of their male littermates (Gonzalez-Bulnes et al. 2013). The exposure to either over- or undernutrition during pregnancy has also a significant effect on female reproductive features, with an earlier age of puberty onset than females born from pregnancies with adequate diets (Gonzalez-Bulnes et al. 2013). At adulthood, females exposed to prenatal undernutrition show a lower prolificacy, whilst no effects are found in females exposed to prenatal overnutrition.

ACKNOWLEDGMENTS

We would like to thank the support from the Spanish and European administrations (specifically from the Spanish Ministries of Science and Innovation and of Economy and Competitiveness, through the projects AGL2010-21991-C03-00 and AGL2013-48121-C3-0-R). Our deepest thanks to the continuous efforts from the staff of our groups and departments, and from other research centres, companies, breeders associations and farmers for the achievement of the results used in this review.

BIBLIOGRAPHY

Ashworth, CJ, Finch, AM, Page, KR, Nwagwu, MO, & McArdle, HJ 2001, 'Causes and consequences of fetal growth retardation in pigs', *Reproduction Supplements*, vol. 58, pp. 233-46.

Barbero, A, Astiz, S, Lopez-Bote, CJ, Perez-Solana, ML, Ayuso, M, Garcia-Real, I, & Gonzalez-Bulnes, A. 2013 'Maternal malnutrition and offspring sex determine juvenile obesity and metabolic disorders in a swine model of leptin resistance', *PLoS One*, vol. 8, pp. e78424.

Foxcroft, GR, Dixon, WT, Novak, S, Putman, CT, Town, SC, & Vinsky, MD 2006, 'The biological basis for prenatal programming of postnatal performance in pigs', *Journal of Animal Science*, vol. 84, pp. E105-112.

Freking, BA, Leymaster, KA, Vallet, JL, & Christenson, RK 2007, 'Number of fetuses and conceptus growth throughout gestation in lines of pigs selected for ovulation rate or uterine capacity', *Journal of Animal Science*, vol. 85, pp. 2093–2103.

Gonzalez-Añover, P, Encinas, T, Torres-Rovira, L, Pallares, P, Muñoz-Frutos, J, Gomez-Izquierdo, E, Sanchez-Sanchez, R, & Gonzalez-Bulnes, A 2011, 'Ovulation rate, embryo mortality and intrauterine growth retardation in obese swine with gene polymorphisms for leptin and melanocortin receptors', *Theriogenology*, vol. 75, pp. 34-41.

Gonzalez-Bulnes, A, Astiz, S, Sanchez-Sanchez, R, Perez-Solana, ML, & Gomez-Fidalgo, E 2013, 'Maternal diet-induced obesity in swine with leptin resistance modifies puberty and pregnancy outputs of the adult offspring', *Journal of Developmental Origins of Health and Disease*, vol. 4, pp. 290–5.

Gonzalez-Bulnes, A, Ovilo, C, Lopez-Bote, CJ, Astiz, S, Ayuso, M, Perez-Solana, ML, Sanchez-Sanchez, R, & Torres-Rovira, L 2012, 'Gender-specific early postnatal catch-up growth after intrauterine growth retardation by food restriction in swine with obesity/leptin resistance', *Reproduction*, vol. 144, pp. 269-78.

Lopez-Bote, C 1998. 'Sustained utilization of the Iberian pig breed', *Meat Science*, vol. 49, pp. S17–27.

Metges, CC, Lang, IS, Hennig, U, Brüssow, KP, Kanitz, E, Tuchscherer, M, Schneider, F, Weitzel, JM, Steinhoff-Ooste,r A, Sauerwein, H, Bellmann, O, Nürnberg, G, Rehfeldt, C, & Otten, W 2012, 'Intrauterine growth retarded progeny of pregnant sows fed high protein:low carbohydrate diet is related to metabolic energy deficit', *PLoS One*, vol. 7, pp. e31390.

Ovilo, C, Gonzalez-Bulnes, A, Benitez, R, Ayuso, M, Barbero, A, Perez-Solana, ML, Barragan, C, Astiz, S, Fernandez, A, Lopez-Bote, C 2014, 'Prenatal programming in an obese swine model: sex-related effects of maternal energy restriction on morphology, metabolism and hypothalamic gene expression', *British Journal of Nutrition*, vol. 111, pp. 735–46.

Rooke, JA, & Bland, IM 2002, 'The acquisition of passive immunity in the newborn piglet', *Livestock Production Science*, vol. 78, pp. 13-23.

Rosendo, A, Druet, T, Gogué, J, Canario, L, & Bidanel, JP 2007, 'Correlated responses for litter traits to 6 generations of selection for ovulation rate or prenatal survival in French Large White pigs', J *Journal of Animal Science*, vol. 85, pp. 1615–24.

Torres-Rovira, L, Tarrade, A, Astiz, S, Mourier, E, Perez-Solana, M, de la Cruz, P, Gomez-Fidalgo, E, Sanchez-Sanchez, R, Chavatte-Palmer, P, & Gonzalez-Bulnes, A 2013 'Sex and breed-dependent organ development and metabolic responses in fetuses from lean and obese/leptin resistant swine', *PLoS One*, vol. 8, pp. e66728.

Town, SC, Putman, CT, Turchinsky, NJ, Dixon, WT, & Foxcroft, GR 2004, 'Number of conceptuses in utero affects porcine fetal muscle development', *Reproduction*, vol. 128, pp. 443-54.

Van der Waaij, EH, Hazeleger, W, Soede, NM, Laurenssen, BFA, & Kemp, B 2010, 'Effect of excessive, hormonally induced intrauterine crowding in the gilt on fetal development on day 40 of pregnancy', *Journal of Animal Science*, vol. 88, pp. 2611–19.

Whittemore, CT, & Kyriazakis, I. 'Whittemore's Science and Practice of Pig Production', 3rd Edition Wiley-Blackwell. 2006.

Wu, G, Bazer, FW, Wallace, JM, & Spencer, TE 2006, 'Board-invited review: intrauterine growth retardation: implications for the animal sciences', *Journal of Animal Science*, vol. 84, pp. 2316-37.