Monitoring blood plasma leptin and lactogenic hormones in pregnant sows

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The mechanism of action of leptin in pregnant breeding sows, in which hyperphagia is managed through dietary strategies, is yet to be clarified. The aim of this study was to monitor leptin concentrations and their interactions with lactogenic hormones in Large White × Landrace breeding multiparous sows (n = 15). All sows showed a normal body condition (mean body condition score: 2.96). Blood samples were collected the day after weaning the litters, at insemination, every 15 days up to day 45 of pregnancy and every 7 days from day 46 to farrowing. At delivery, the placenta was collected for the analysis of leptin and leptin receptor expressions. Plasma leptin levels increased from the end of mid gestation (day 72) and remained high until farrowing (P < 0.05). As expected, plasma prolactin (PRL), low during most of pregnancy, increased during the 2 weeks before farrowing (P < 0.05), whereas progesterone levels reached plateau at 30 days of gestation and decreased at farrowing (P < 0.05). Cortisol levels peaked close to farrowing (P < 0.05). Leptin was expressed in the placenta, where the receptor expression analysis showed the presence of the short form but not of the long form. A positive correlation was found between leptin and PRL concentrations during mid (r = 0.430; P < 0.001) and late pregnancy (r = 0.687; P < 0.001), and with progesterone in early pregnancy (r = 0.462; P < 0.05). During late gestation, a positive correlation was observed between leptin and cortisol (r = 0.585; P < 0.001). Our results suggested that, in restrictively fed pregnant sows, the leptin levels increased from the end of mid pregnancy to delivery, confirming the presence of leptin resistance. We showed a correlation between leptin and lactogenic hormones during different stages of pregnancy in sows. Lactogenic hormones show pregnancy-specific changes in their secretion and all may become involved in modulating leptin signal.

Keywords: swine, leptin, lactogenic hormones, pregnancy

Implications

The energy demands during pregnancy require an adaptation in the endocrine system regulating energy intake. This is especially important for restrictively fed sows in commercial environments. Leptin is recognized as a principal regulator of energy balance during gestation as well. Improving our knowledge of leptin mechanisms during pregnancy may help in maintaining productive efficiency in the modern pig herd. The nutritional environment in which the fetus grows and develops has the potential to have long-term effects on body composition as well as metabolic health of the offspring.

Introduction

Pregnancy is a period of dramatic body changes with weight gain, increased fat stores, new tissue synthesis and significant hormonal and metabolic changes (Machteld et al., 2000). Hyperphagia during pregnancy is a very early event, which takes place in advance of an increased energy requirement (Trujillo et al., 2011). The energy demands during pregnancy require an adaptation in the homeostatic pathways regulating food intake so as to create a positive energy balance (Grattan et al., 2007). As a consequence of a pregnancy, relevant neuroendocrine changes occur. Leptin, the product of the ob gene, is an adipocyte signal for satiety (Zhang et al., 1994), and it is recognized as a principal regulator of fat mass (Grattan et al., 2007). Leptin-sensitive neurons influence the feeding behavior, co-ordinating the activity of orexigenic and anorexigenic peptides (Trayhurn et al., 2006). In rats and humans, leptin levels in blood increase during gestation because of placenta formation (Forhead and Fowden, 2009). However, hyperleptinemia during pregnancy does not decrease food intake because of the downregulation of leptin receptors in the ventro medial nuclei of the hypothalamus. This produces a state of central resistance to the usual actions of leptin (Bruton and Russell, 2008). It seems likely

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that these adaptive mechanisms are driven by the hormonal changes during pregnancy (Sauvè and Woodside, 2000; Grattan et al., 2007; Augustine and Grattan, 2008).

During pregnancy, leptin functions in animals such as swine, where the hyperphagia is managed through dietary strategies, are yet to be clarified. It has been shown that, during the early gestation, voluntary feed intake in sows fed ad libitum is two to three times as high as the requirements (Nissen et al., 2003). In pig farming, to maximize the health of sows, it is necessary to adjust the energy level to maintain an optimal body condition during the reproductive cycle. A surplus in energy supply during gestation may lead to high adiposity at delivery, with detrimental effects not only on piglet vitality but also on the feeding behavior of sows during lactation (Amédi et al., 2014). For these reasons, breeding pregnant sows are commonly provided with a limited amount of feed, which is equal to 50% to 60% of their ad libitum intake (Guillemet et al., 2006).

The study of the ways in which the endocrine system manages the nutrients in pregnancy is fundamental to optimize the great potential of the in utero environment and its impact on future physiological and biochemical systems, including long-term function and health of the offspring. We assessed concentrations of plasma leptin and their associations with changes in concentrations of plasma lactogenic hormones during pregnancy in restrictively fed sows.

Material and methods

Animals and experimental procedures

At weaning, 15 Large White × Landrace sows having a mean (±s.d.) body condition score of 2.96 ± 0.5 were used. Mean (±s.d.) parity order was 3.2 ± 0.9. The sows were mated within 7.3 ± 1.1 days from weaning. Cervical artificial insemination (AI) was performed with disposable spiral-tip catheters (Agrizoo San Marino s.r.l, San Marino, Italy). Sows were inseminated 12 and 24 h after estrus detection, using 3 × 10^7 spermatzoa/80 ml (Modena Vita; Seneitaly s.r.l., Saliceto San Giuliano, MO, Italy). Twenty-five days after insemination, the sows were subjected to ultrasound examinations (Aloka SSD 500®. Wallingford, CT, USA; linear probe 5.0 MHz) and all of them were found to be pregnant. During pregnancy, all sows received a mixed diet (12.8 MJ/kg DE, 13.8% CP, 0.68% lys, 6.6% crude fiber, as-fed basis) offered ad libitum. Blood samples were also collected at day 10 and 20 of lactation, the sows were subjected to ultrasound examination (Agrizoo San Marino s.r.l, San Marino, Italy). Sows were inseminated 12 and 24 h after estrus detection, using 3 × 10^7 spermatzoa/80 ml (Modena Vita; Seneitaly s.r.l., Saliceto San Giuliano, MO, Italy). Twenty-five days after insemination, the sows were inseminated using disposable spiral-tip catheters (Agrizoo San Marino s.r.l, San Marino, Italy). Sows were inseminated 12 and 24 h after estrus detection, using 3 × 10^7 spermatzoa/80 ml (Modena Vita; Seneitaly s.r.l., Saliceto San Giuliano, MO, Italy). Twenty-five days after insemination, the sows were subjected to ultrasound examinations (Aloka SSD 500®. Wallingford, CT, USA; linear probe 5.0 MHz) and all of them were found to be pregnant. During pregnancy, all sows received a mixed diet (12.8 MJ/kg DE, 13.8% CP, 0.68% lys, 6.6% crude fiber, as-fed basis) offered ad libitum. Blood samples were also collected at day 10 and 20 of lactation, the sows were subjected to ultrasound examination (Agrizoo San Marino s.r.l, San Marino, Italy). Sows were inseminated 12 and 24 h after estrus detection, using 3 × 10^7 spermatzoa/80 ml (Modena Vita; Seneitaly s.r.l., Saliceto San Giuliano, MO, Italy). Twenty-five days after insemination, the sows were inseminated using disposable spiral-tip catheters (Agrizoo San Marino s.r.l, San Marino, Italy). Sows were inseminated 12 and 24 h after estrus detection, using 3 × 10^7 spermatzoa/80 ml (Modena Vita; Seneitaly s.r.l., Saliceto San Giuliano, MO, Italy). Twenty-five days after insemination, the sows were subjected to ultrasound examinations (Aloka SSD 500®. Wallingford, CT, USA; linear probe 5.0 MHz) and all of them were found to be pregnant. During pregnancy, all sows received a mixed diet (12.8 MJ/kg DE, 13.8% CP, 0.68% lys, 6.6% crude fiber, as-fed basis) offered ad libitum.

Blood samples were collected using jugular venopuncture in 10-ml vacutainer tubes with lithium heparin the day after the weaning of previous litters, at AI, every 15 days up to day 45 of pregnancy and every 7 days from day 46 to farrowing. Blood samples were also collected at day 10 and 20 of lactation. Samples were immediately centrifuged (1800 × g for 10 min) and plasma was collected and stored at −20°C until analysis. At farrowing, individual piglet placenta (n = 160) were separated, carefully washed and opened over the whole length at the anti-mesometrial side. A 5 cm × 5 cm quadrant, equidistant between the edge and the center, was removed and stored at −80°C until analysis.

Hormone assays

Leptin levels in plasma were determined by a commercial kit (Multispecies Leptin RIA; Linco Research, St. Louis, MO, USA; Summer et al., 2009). The sensitivity of the method was 100 pg/ml and the variability coefficients within and among samples were 4.2% and 7.1%, respectively. Plasma prolactin (PRL) levels were determined by a previously validated ELISA test (Borghetti et al., 2006). Effective dose (ED)90, ED50 and ED10 were 0.011, 0.123 and 3.00 ng/ml, respectively. The intra- and inter-assay coefficients were 4.5% and 7.0%, respectively. Progesterone levels were determined by a validated radioimmunoassay (RIA) (Pondera et al., 2000). The intra- and inter-assay coefficients were 5.8% and 10.3%, respectively. Plasma samples were assayed for cortisol by a validated RIA (Borghetti et al., 2006). The intra- and inter-assay coefficients were 5.3% and 6.7%, respectively.

Placental expression of leptin and its receptors

All molecular biology reagents were purchased from Ambion Inc. (Foster City, CA, USA), unless otherwise specified. Total RNA was extracted by TRI Reagent® solution (Applied Biosystems, Monza, Italy), according to the manufacturer’s instructions. The RNA quantification was carried out by a spectrophotometer (GENEQUANT pro®, Amersham Pharmacia, UK). Reverse-transcription (RT) PCR was carried out using a Ready-to-go™ You-Prime First-Strand Beads kit (Amersham Pharmacia Biotech UK Limited, Little Chalfont, Buckinghamshire, UK), as described by the manufacturer. Two micrograms of total RNA was used in the RT reaction. Aliquots (5 µl) from the generated cDNA were used for subsequent PCR amplification in the reaction buffer containing 1.5 µl MgCl2 (50 mM), 1 µl dNTPs (12.5 mM) and 1 µl Taq DNA polymerase (1 µg/µl) to a final volume of 50 µl. Primers for leptin and its receptors (short and long form) were used at the concentration of 2.5 µM (MWG BIOTECH, Ebersberg, Germany). Amplification was carried out for 27 cycles, when the reaction was in the middle of the linear range (before reaching the amplification plateau). Each cycle consisted of denaturation at 94°C for 1 min, annealing at specific temperature for each primer set for 1 min and extension at 72°C for 1 min. At the end of the 27th cycle, an additional extension was carried out for 5 min. Specific primer sets used, their annealing temperature and amplified product size (expressed in base pairs, bp) are summarized in Table 1. An 18S RNA (no. 1717, Quantum RNA; Ambion Inc.) was used as an internal positive control for a relative quantitative PCR. To amplify the 18S fragment (324 bp) without reaching the plateau phase, 18S PCR alternate primer pairs (5 µM; ratio, 2 : 8), according to the instructions of the manufacturers. PCR products were visualized after electrophoresis on 2% agarose gel with SYBR® Safe DNA gel stain (Invitrogen s.r.l., San
Blood plasma leptin in pregnant sows

Table 1  Sequences of PCR primers, annealing temperature (°C) and PCR product size (bp)

<table>
<thead>
<tr>
<th>Primer set</th>
<th>Annealing Temperature (°C)</th>
<th>Product size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (GenBank NM_213840). F: 5′-CCC TGC TTG CAC TTG GTA GC-3′ R: 5′-CTG CCA CAC GAG TCT TTG-3′</td>
<td>54</td>
<td>658</td>
</tr>
<tr>
<td>Leptin receptor (short form) (GenBank NM092422).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F: 5′-GAAGGAGTGGGAAAACCAAG-3′ R: 5′-CCACCATATGTTAACTCTCAG-3′</td>
<td>55</td>
<td>365</td>
</tr>
<tr>
<td>Leptin receptor (long form) (GenBank AF167719.1).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F: 5′-GAAGGAGTGGGAAAACCAAG-3′ R: 5′-CATAGGTACCCTCAGTACCCTC-3′</td>
<td>55</td>
<td>433</td>
</tr>
</tbody>
</table>

Figure 1  Plasma leptin (a), prolactin (PRL) (b), progesterone (c) and cortisol (d) concentrations in sows (n = 15). Blood sampling period started at day −7 before AI (0) and ended at day 20 after farrowing (f). Error bars indicate standard deviation. Significant differences (P < 0.05) among samplings are labeled with different letters.

Giuliano, Milanese, Italy. The gel was analyzed on a computerized densitometry program (Scion Capture Driver 1.2 for Image-Pro Plus; Scion Corporation, Frederick, MD, USA). The values are presented as the ratio, expressed in relative arbitrary units (RAU), of the band intensities of the PCR products over those of the corresponding ribosomal 18S PCR product. The Pearson correlation analysis was performed among leptin and lactogenic hormones during pregnancy. For this aim, the pregnancy period was divided into the following three sub-periods: early pregnancy, from day 15 to 45; mid pregnancy, from day 52 to 79; and late pregnancy, from day 86 to farrowing. The significance level was set at P < 0.05.

Results

Leptin

The mean plasma leptin concentrations over the period of study are shown in Figure 1a. At 7 days before AI, mean (±s.d.)
plasma values were 1.54 ± 0.36 ng/ml, whereas at insemination (day 0) leptin concentration significantly increased (3.73 ± 0.98 ng/ml; *P < 0.05) to return approximately to starter levels up to 30 days of pregnancy (*P > 0.05). From day 30 to day 65, the plasma levels of leptin ranged from 2.5 to 3 ng/ml. At the end of mid gestation (day 72), leptin concentration significantly increased (*P < 0.05): the highest concentrations of leptin were reached at day 107 (5.91 ± 0.69 ng/ml) of pregnancy and at farrowing (5.84 ± 1.72 ng/ml). At 10 and 20 days after farrowing, plasma leptin levels drastically decreased (*P < 0.05) to 2.20 ± 0.34 and 1.72 ± 0.57 ng/ml, respectively.

**PRL**
As shown in Figure 1b, plasma PRL levels were 4.16 ± 0.87 ng/ml at day −7 and 2.40 ± 1.09 at AI (*P > 0.05). Until late gestation (day 93), its concentration did not change (*P > 0.05). The PRL concentration increased 2 weeks before farrowing to reach the peak at farrowing (67.83 ± 4.91 ng/ml; *P < 0.05). A positive correlation (*P < 0.01) was observed between changes in plasma PRL and leptin levels during mid and late pregnancy (Table 2). After farrowing, PRL concentrations were 55.39 ± 3.12 ng/ml (day 10) and 39.53 ± 1.62 ng/ml (day 20) (*P < 0.05).

**Progesterone**
Plasma progesterone level (Figure 1c) at day −7 was 6.07 ± 0.34 ng/ml, and then it decreased at AI (0.28 ± 0.05 ng/ml; *P < 0.05). From the beginning of early gestation (day 15), the levels increased 10-fold to reach the peak at farrowing (5.91 ± 0.69 ng/ml; *P < 0.05). A positive correlation (*P < 0.01) was observed between progesterone and leptin. At 10 and 20 days after farrowing, plasma progesterone levels were 0.98 ± 0.03 and 0.87 ± 0.05 ng/ml, respectively (*P < 0.05).

**Cortisol**
Plasma cortisol concentration (Figure 1d) dropped from 17.62 ± 2.7 ng/ml at day −7 to 11.94 ± 1.88 ng/ml at AI (*P < 0.05). During early and mid pregnancy, mean cortisol levels remained around 10 ng/ml (*P > 0.05). A significant increase (*P < 0.05) was observed close to farrowing (107 days: 32.92 ± 2.54 ng/ml) and at farrowing (37.67 ± 4.10 ng/ml). A significant correlation (*P < 0.01) between changes in plasma cortisol and leptin levels was observed in late pregnancy.

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<tr>
<th>Period</th>
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</tr>
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<td>0.005</td>
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**Table 2**

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seem to affect the presence of leptin resistance. These results underline the functional importance of the central leptin resistance to allow increased nutrient availability for the fetus, as hypothesized by Tessier et al. (2013) and Ladyman (2008). Leptin receptors are expressed in a variety of isoforms, the major form involved in BW regulation being the long form (Vaisse et al., 1996). In rats, hyperleptinemia, during healthy pregnancy, leads to central leptin resistance by downregulation of the full-length leptin receptor in the hypothalamus and increased circulation of soluble receptor isoforms (Brunton and Russell, 2008). The widespread expression of short leptin receptor isoforms in tissues throughout the mammalian body points out that leptin also acts at periphery as a factor able to modify tissue metabolism (Harris, 2000). We observed the expression of the short leptin receptor form in the placental tissue at delivery, confirming a direct involvement of leptin on fetal metabolism. The presence of leptin receptors in placenta suggests autocrine or paracrine effects of leptin on processes essential to ensure an adequate nutrient supply for fetal growth and development, that is, angiogenesis (Grattan et al., 2007; Anagnostoulis et al., 2008; Ladyman, 2008; Tessier et al., 2013). We did not find the presence of the long form of leptin receptor, but this result was not unexpected for two reasons. First, the long-form receptor is expressed in high levels in the hypothalamus and is well characterized in central leptin action, that is, regulating appetite and metabolic rate. Second, our data concerned only the end of pregnancy; leptin receptors have been found to be regulated and to change under certain circumstances such as pregnancy. In several species, the expression of multiple forms of the leptin receptor switch in placenta during the course of pregnancy (Edwards et al., 2004; Smolinska et al., 2009).

Pregnancy-induced changes in BW regulation are normal physiological parts of maternal adaptation, and they are likely to be induced by the hormonal changes that accompany pregnancy. Lactogenic hormones such as progesterone, PRL and cortisol are involved (Grattan et al., 2007; Augustine and Grattan, 2008; Ladyman et al., 2010). Progesterone, a powerful orexigenic hormone, induces weight gain and greater fat depots to promote a positive energy balance. In pregnant females, progesterone hampered lipostatic control, inhibiting the concurrent enhancement in plasma and cerebrospinal fluid leptin levels expected from the increased fat mass (Grueso et al., 2001). During early pregnancy, when increase in fat stores is limited in restrictively fed pregnant sows, a positive correlation between leptin and progesterone was observed.

A similar distribution of leptin and PRL receptors in the rodent hypothalamus and brainstem was observed, and this has allowed us to hypothesize a cross talk between leptin and PRL signaling (Nagashii et al., 2014). Recent findings suggest a potential role for PRL signaling in the induction of leptin resistance in pseudopregnant rats (Augustine and Grattan, 2008). Our data have shown a positive correlation between PRL and leptin in mid and late pregnancy. The exact neuroendocrine changes are currently unknown; however, they may involve a loss in functional leptin receptors in key hypothalamic nuclei or a loss in leptin signaling via intracellular signaling cascades. The leptin and PRL crosstalk is more evident during lactation. In sows, hypophagia commonly occurs during the 1st week of lactation, (Cools et al., 2013) and in this period leptin levels were low (Summer et al., 2009). Low leptin and high PRL concentrations could trigger at brain level the mechanism increasing food intake. In this regard, Roy et al. (2007) reported a direct effect of PRL on orexigenic neuropeptide Y expression to satisfy the high energy demand for milk production. Glucocorticoids, whose main representative is cortisol, are potent regulators of leptin expression (Houseknecht and Portocarrero, 1998). In mice, hyperleptinemia during pregnancy results from corticosterone-dependent upregulation of leptin secretion. In late pregnancy, we observed a positive correlation between leptin and cortisol. During pregnancy, glucocorticoids belong to factors that reduce insulin sensitivity in the dam, activate adipogenesis by differentiation of pre-adipocytes (Breton, 2013) and promote, in sheep, the synthesis and secretion of leptin in the fetus (Forhead and Fowden, 2009). It has been suggested that the glucocorticoid surge that is characteristic of late gestation may also downregulate placental leptin production (Sugden et al., 2001). Changes in either fetal or maternal leptin levels may be important for parturition or late fetal development.

In summary, these findings suggest that lactogenic hormones are involved in altering leptin signal during different stages of pregnancy in sows. In the restrictively fed pregnant sow model, leptin resistance contributes mainly to allow increased nutrient availability for the fetus. The expression of the short leptin receptor in the placenta strengthens this hypothesis.

Acknowledgments

All the authors equally contributed to the paper.

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