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Programming of intermediate metabolism in young lambs affected by late gestational maternal undernourishment

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1Department of Basic Animal and Veterinary Sciences, Faculty of Life Sciences, University of Copenhagen, Frederiksberg; 2Department of Animal Health, Welfare and Nutrition, Faculty of Agricultural Sciences, University of Aarhus, Tjele, Denmark; and 3Department of Animal Science, Faculty of Agriculture, The University of Western Australia, Nedland, Western Australia, Australia

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Husted SM, Nielsen MO, Tygesen MP, Kiani A, Blache D, Ingvartsen KL. Programming of intermediate metabolism in young lambs affected by late gestational maternal undernourishment. Am J Physiol Endocrinol Metab 293: E548–E557, 2007. First published May 15, 2007; doi:10.1152/ajpendo.00441.2006.—Effects of moderate maternal undernourishment during late gestation on the intermediary metabolism and maturational changes in young lambs were investigated. 20 twin-bearing sheep, bred to two different rams, were randomly allocated the last 6 wk of gestation to either a NORM diet [barley, protein supplement, and silage ad libitum $\sim 15$ MJ metabolizable energy (ME)/day] or a LOW diet (50% of ME intake in NORM, offered exclusively as silage $\sim 7$ MJ ME/day). Post partum, ewes were fed to requirement. After weaning, lambs were fed concentrate and hay ad libitum. At 10 and 19 wk of age, lambs were subjected to an intravenous glucose tolerance test (IGTT) followed by 24 h of fasting. Heat energy (HE) was determined in a respiration chamber at 9 or 20 wk of age. LOW lambs had a lower birth weight and continued to be lighter throughout the experiment. Glucose tolerance did not differ between groups. However, 19-wk-old LOW lambs secreted less insulin during IGTT, released more NEFA, and tended to have lower leptin during fasting than NORM. Surprisingly, several metabolite and hormone responses during IGTT and fasting were greatly influenced by the paternal heritage. In conclusion, when lambs entered adolescence (19 wk) programming effects of late prenatal malnutrition on the glucose-insulin homeostasis and metabolism were manifested: LOW lambs had less insulin-secretory capacity, but this was apparently compensated for by increased target tissue sensitivity for insulin, and adipose lipolytic capacity increased during fasting. Thereby, glucose may be spared through increased lipid oxidation, but overall energetic efficiency is apparently deteriorated rather than improved.

OVER THE LAST DECADE, retrospective epidemiological studies and extensive animal studies have revealed an inverse relationship between fetal and/or early postnatal development and the risk of developing insulin resistance, hypertension, metabolic syndrome, coronary heart disease, and type 2 diabetes later in life (1, 2, 26, 37).

Epidemiological studies conducted in humans from Hertfordshire and Preston, UK, have established a link between lower birth weight or weight at 1 yr of age and impaired glucose tolerance and subsequent development of type 2 diabetes (24, 44), syndrome X (type 2 diabetes, hypertension, and hyperlipidemia) (2) and higher incidence of death from ische-

mic heart disease (3). Hales and Barker hypothesized in the “thrifty phenotype hypothesis” that this adverse outcome of low birth weight reflects poor maternal nutrition or placental dysfunction leading to fetal malnutrition, which in turn alters the development of structure and function of a variety of organs i.e., pancreas (23) and liver (14). Studies of both young ($\sim 32$ yr) and older ($\sim 66$ yr) twins dissimilar for type 2 diabetes and/or glucose tolerance support the hypothesis of a strong environmental rather than a genetic influence, since birth weights were lower in both the diabetic or glucose-intolerant monozygotic and dizygotic twins compared with their glucose-tolerant or nondiabetic cotwins (6, 45). It is important to keep in mind that a wide range of different insults during and even before pregnancy, like maternal malnutrition, reduced uterine blood flow, impaired function of placenta, or reduced fetal blood flow all are very likely to result in fetal undernourishment and subsequent impaired fetal growth and reduced birth weight.

The outcome of fetal undernourishment later in life appears to depend largely on the timing of the insult. Some of the most convincing data regarding development of different adverse effects and the prenatal timing have come from the retrospective studies of hunger examining the Dutch Winter Famine. Subjects exposed to famine in early gestation had a higher prevalence of coronary heart disease at 50 yr of age compared with nonexposed subjects or subjects exposed to famine during mid and late gestation (49). However, the glucose tolerance at 50 yr of age was decreased most among subjects who were exposed to famine during mid or late gestation compared with non exposed subjects or subjects exposed during early gestation (47). Furthermore the obesity rate among young men (19 yr of age) showed completely opposite trends. Compared with nonexposed subjects, exposure to undernutrition in late gestation and early postnatal life resulted in a low obesity rate, which was in sharp contrast to a high obesity rate in young men exposed during early gestation (48). Since the different organ systems develop and differentiate in a predetermined manner, it is not surprising that the timing of a nutritional insult may result in more or less distinct phenotypic consequences later in life. For instance, the functional development of the fetal pancreas during mid to late gestation (17) is of great importance for the glucose-insulin homeostasis both in the fetus and in later life.
A few animal studies have been set up to model these epidemiologic findings and confirmed effects of undernourishment in early gestation on cardiovascular function (18, 27, 33), whereas exposure to prenatal undernourishment during late gestation affected intermediary metabolism, especially glucose-insulin homeostasis (4, 19) and pancreatic β-cell development, as a predisposing factor of impaired glucose tolerance in adult offspring (4). Another study with sheep severely undernourished for either 10 or 20 days during late gestation suggested that birth weight rather than maternal nutrition during late gestation, had an impact on glucose tolerance tested at 5 and 30 mo of age, (36). However, in most other animal studies able to replicate the epidemiological findings and produce risk factors of type 2 diabetes, such as hypertension and insulin resistance in adult offspring, the maternal undernourishment was prolonged throughout gestation and lactation (16, 32, 41, 44). To clarify the impact of prenatal undernourishment confined to only late gestation, on glucose-insulin metabolism and homeostasis in the offspring, further investigation is needed.

With normal maturation and aging, glucose tolerance changes, perhaps in a species-specific manner (21). In both rat and sheep, glucose tolerance has been found to decrease between the early postnatal life and early adulthood due to normal maturational loss of insulin sensitivity (7, 12, 21). The age-dependent change in glucose tolerance, however, appears to be accelerated in offspring that have experienced prenatal undernourishment. In young adult life, prenatally undernourished offspring are demonstrated to have a better glucose tolerance (25).

It was therefore hypothesized that moderate global maternal undernourishment in late gestation programs the glucose-insulin homeostasis and, hence, intermediary and quantitative metabolism in the offspring and that these programming effects change and become manifested in an age-dependent way during early postnatal life.

To elucidate the above hypotheses, twin-pregnant ewes were subjected to moderate global undernourishment during the last 6 (of 21) wk of gestation, and the impacts on glucose-insulin homeostasis and heat energy production were evaluated in adolescent offspring at two different ages and in the fed and fasted states.

**MATERIALS AND METHODS**

**Experimental Animals and Design**

Forty Shropshire lambs of both sexes, born in April 2003 from 20 twin-bearing ewes in their second or third parity, were used in the experiment at 10 and 19 wk of age. Their mothers were evenly selected from two herds, bred during natural breeding season to two different rams, which differed in the standard breeding index for slaughter quality (34) (index value 93 vs. 117) referred to hereafter as SQ- and SQ+ respectively. On the basis of twin pregnancy and even distribution of body condition score (BCS) 70 days pre partum, the ewes were randomly allocated to feeding treatment (NORM and LOW), for the last 6 wk pre partum, as described below. The characteristics of the experimental animals are presented in Table 1. The experiment was conducted from December 2002 to July 2003 at the large laboratory animal facility, Rørendegården, The Royal Veterinary and Agricultural University, Tåstrup, Denmark. All experimental procedures were approved by The National Committee on Animal Experimentation, Denmark.

**Experimental Housing and Feeding**

Prior to the experimental period, the ewes were kept on pasture but allowed a 2-wk period for adaptation to indoor experimental conditions. During the experimental period, ewes and lambs were housed in family pens (1 × 2 m), and later, at weaning, 8 wk post partum, the ewes were returned to pasture and the lambs were left indoors in individual pens (1 × 1 m) with shaving bedding. The last 6 wk pre partum, the ewes were fed the experimental diets. The two diets were composed as an ad libitum diet designed to approximately fulfill daily requirements, according to Danish requirements for protein and energy (46): silage ad libitum [2.64 kg per feed unit (FU) and 7.9% crude protein intake during lactation, g/day 378 329 0.014 Feed intake (ME) during lactation, MJ/day 21–25 15–24 0.030

<table>
<thead>
<tr>
<th>Pre Partum Feeding Level (Ewe)</th>
<th>NORM</th>
<th>LOW</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of twin pregnant ewes*</td>
<td>11</td>
<td>9</td>
<td>0.767</td>
</tr>
<tr>
<td>Weight of ewes 6 wk pre partum, kg</td>
<td>69.9±4.2</td>
<td>70.5±2.3</td>
<td>0.283</td>
</tr>
<tr>
<td>BCS of ewes 6 wk pre partum</td>
<td>4.3±0.1</td>
<td>4.1±0.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight of ewes just prior to partum, kg</td>
<td>78.5±3.0</td>
<td>70.5±2.8</td>
<td>0.050</td>
</tr>
<tr>
<td>BCS of ewes just prior to partum</td>
<td>4.2±0.2</td>
<td>3.3±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Feed intake (ME) the last 6 wk pre partum, MJ/day</td>
<td>3.4±1.7</td>
<td>1.7±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crude protein intake the last 6 wk pre partum, g/day</td>
<td>229</td>
<td>112</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Feed intake (ME) during lactation, MJ/day</td>
<td>21–25</td>
<td>15–24</td>
<td>0.030</td>
</tr>
<tr>
<td>Crude protein intake during lactation, g/day</td>
<td>378</td>
<td>329</td>
<td>0.014</td>
</tr>
<tr>
<td>No. of lambs†</td>
<td>21</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as least square means ± SE except feed intake and birth weight, which are presented as a range. *Uneven nos. of ewes in the 2 groups were due to exclusion of 2 ewes from the LOW group (fed the restricted diet) because of stillbirth of 1 of the twin lambs. †One male lamb died of urolithiasis just after weaning. BCS, body condition score, scale from 1 to 5 (very lean to very fat); ME, metabolizable energy; DGR, daily growth rate.