Short and long-term influences of intra-uterine growth restriction on muscle and adipose tissue properties and metabolic flexibility

Florence Gondret, Isabelle Louveau, Marie-Christine Pere, Marie-Hélène Perruchot, Isabelle Le Huërou-Luron, Louis L. Lefaucheux

To cite this version:

Florence Gondret, Isabelle Louveau, Marie-Christine Pere, Marie-Hélène Perruchot, Isabelle Le Huërou-Luron, et al.. Short and long-term influences of intra-uterine growth restriction on muscle and adipose tissue properties and metabolic flexibility. Colloque fondateur de La Société Francophone Origines Développementales de la Santé (SF-DOHaD), Nov 2012, Paris, France. hal-02746660

HAL Id: hal-02746660
https://hal.inrae.fr/hal-02746660
Submitted on 3 Jun 2020
offspring reared either by Wistar or by diabetic GK dams. In this group, the glucose tolerance was also altered in the adult offspring. Taken together, our data provide evidence for a deleterious impact of maternal hyperglycemia on β-cell development and growth in Wistar offspring at no spontaneous risk of diabetes. These data contribute to the better understanding of the effects of exposure to maternal diabetic environment and could bear important public health implications in the present context of growing diabetes epidemic.

Key words: β-cell mass, developmental programming, gestational diabetes, glucose tolerance

Statement of interest: The authors declare no conflict of interest.

ORAL N°34

Maternal prenatal undernutrition programs adipose tissue gene expression in adult male rat offspring


EA4489, Unité Environnement Périnatal et Croissance, Université Lille Nord de France, Lille, France

Epidemiological studies have shown that maternal undernutrition during pregnancy leads to intrauterine growth retardation and low birth weight, and may predispose individuals to the development of metabolic syndrome in adulthood. In order to unravel the underlying mechanisms, we have developed a model of prenatal maternal 70% food-restricted diet throughout gestation in pregnant female rats called FR30. Adult male FR30 offspring showed mild hypertension, impaired glucose intolerance and hyperphagia associated with dysregulated light/dark-phase food intake rhythm. Under chow diet, hyperleptinemic and hypercortisolemic FR30 rats did not show overt obesity but were predisposed to fat accumulation. Indeed, FR30 rats exhibited a greater adipocyte area with a global increase of white adipose tissue (WAT) lipogenic gene expression profile. Despite no further adipocyte hypertrophy, high-fat (HF)-fed adult FR30 offspring displayed a more important weight gain with a global increase in WAT adipogenesis mRNA transcript profile. In WAT FR30HF, higher leptin sensitivity and enhanced 11b-HSD2 mRNA (that catalyses the interconversion of adipogenic active corticosterone to inactive 11-dehydrocorticosterone) expression levels might be seen as mechanisms designed to limit fat deposition by counteracting adipogenesis. These observations raised questions regarding the role of the glucocorticoid WAT environment on the development of adiposity. In addition, gene expression levels of many peptide precursors and receptors showed marked modifications. It can be seen as either an adipogenesis predisposition or protective mechanisms against further adiposity. Overall, programming occurred in a WAT depot-specific manner in FR30 offspring. In accordance with dysregulated light/dark-phase food intake rhythm, we also found that the daily transcriptional profile of several clock genes was modified within WAT FR30 offspring. Our data indicated that circadian clock underwent long-term nutritional programming that might contribute to the development of adiposity in adulthood.

Key words: animal, fetal programming, metabolic syndrome, obesity

References

Email: christophe breton@univ-lille1.fr

ORAL N°4

Short- and long-term influences of intrauterine growth restriction on muscle and adipose tissue properties and metabolic flexibility

F. Gondret1,2, I. Louveau1,2, M. C. Père1,2, M. H. Perruchot1,2, I. Le Huërou-Luron4 and L. Lefaucheur1,2

1INRA, UMR1348 Pegase, Saint-Gilles, France; 2AgroCampus-Ouest, UMR1348 Pegase, Rennes, France; 3UR1341 ADNC, Saint-Gilles, France

Intrauterine growth restriction (IUGR) is associated with several health problems throughout life. Our program aimed at investigating the mechanisms underlying adipose tissue and skeletal muscle development in IUGR pigs, a species of importance for meat industry worldwide and a broadly used biomedical model for adiposity. Pairs of piglets were chosen within litters to have either a medium or a small weight at different stages of gestation or at birth. Because of the hypothesis of a relationship between high-protein (HP) intake in IUGR children and their later adiposity, a subset of IUGR piglets was fed HP formula during suckling, whereas others received a control formula (AP) that mimicked the sow milk composition. In skeletal muscle, the ratio between adult fast and embryonic myosin heavy-chain isoforms was twofold lower in small fetuses than in their medium littermates at 2 days before birth, denoting a lower muscular maturity in IUGR animals. In subcutaneous fat, IUGR counteracted the normal fall of DLK1/Pref-1 expression during gestation, and blunted the temporal increase in expression levels of many differentiating and lipogenic genes; the differences between weight groups were exacerbated around birth. These differences were not associated with modifications in circulating concentrations of energy-producing metabolites between weight groups.
The distribution of HP formula to IUGR piglets resulted in accelerated growth rate and in a temporary reduction in adiposity (until weaning) compared with piglets fed AP formula. This was associated with a decrease in the expression levels of genes related to glucose utilization and lipid anabolism in adipose tissues. In 160-day-old pigs having being fed HP formula, adipocytes were enlarged and their lipogenic rates were reduced. Thus, IUGR affects the temporal development of muscle and adipose tissue. Altogether, dietary strategies at different periods should be further tested to modulate stem cell lineage, tissue development and reinitating optimal growth trajectories.

**Key words:** body composition, developmental programming, fetal growth, newborn, plasticity

**Statement of interest:** Authors report no conflict of interest.

Email: florence.gondret@rennes.inra.fr

---

**POSTER N°13**

**Angiogenesis and the programming of hypertension: developmental changes in the methylation profile of the AMOT gene in cord blood endothelial progenitor cells**

G. Vinci, C. Buffat, S. Simoncini, I. Ligi, D. Vaiman, F. Dignat-George and U. Simeoni

**INSEM U1016, INSEM U1076 & Service de Médecine Néonatale, AP-HM, Marseille, France**

Premature birth has been associated with increased risk of hypertension at adulthood. Perturbations of angiogenesis may play a key role in the ‘early programming’ of adult arterial hypertension. Circulating endothelial progenitor cells are involved in angiogenesis and may participate to later hypertension; previous work in our group demonstrated that preterm newborns (with a low birth weight) have a reduced number, decreased self-renewal capacity and decreased angiogenic function of endothelial colony-forming cells (ECFC). Epigenetic changes in the fetus that occur relatively late in human pregnancy can contribute to disease susceptibility and may be molecular mediators of ‘early programming’. Furthermore, supplemental evidence reveals an association between gestational age and a differential methylation of genes. The characterization of early epigenetic modifications of genes involved in angiogenesis would increase the chances to identify epigenetic biomarkers of the ‘early programming’ of adult hypertension in premature infants. The AMOT gene is a key regulator of angiogenesis; its expression is reduced in the cord blood ECFC of preterm newborns. However, the epigenetic analysis of the AMOT gene in the context of prematurity is unexplored. We therefore performed a comparative analysis of the DNA methylation profile of the AMOT promoter CpG island in the cord blood ECFC of 15 preterm (gestational age between 28 and 36 weeks) and 13 term newborns (>37 weeks).

Results of cloning–sequencing experiments showed that some CpG dinucleotides are differentially methylated in the two newborn populations: in fact, a methylation at 4.5% of CpG dinucleotides was found in preterm newborns against 2.5% in term newborns ($\chi^2 = 3.842037097; P$-value $P = 1.7e^{-02}$). By pyrosequencing experiments, we identified five CpG dinucleotides differentially methylated in term and preterm newborns. Furthermore, this CpG-targeted methylation showed a statistically significant decrease with increasing gestational age ($P$-value between $P = 3.5e^{-02}$ and $P = 1.3e^{-05}$). These results suggest that, given its crucial role in the regulation of angiogenesis, the methylation of the AMOT gene could be an epigenetic biomarker of adverse programming of angiogenesis because of preterm birth. Future studies in hypertensive adults born preterm or at term may elucidate the role of epigenetics and of the AMOT gene methylation in the programming of hypertension.

**Key words:** developmental origins of adult disease, epigenetics, fetal programming, hypertension/blood pressure, prematurity/preterm birth

**Statement of interest:** Authors report no conflict of interest.

**References**


Email: giovanna.vinci@inserm.fr

---

**POSTER N°49**

**Vascular endothelium and early markers of adult cardiovascular disease**

M. Saint-Faust1, F. Sabatier2, F. Dignat-George2 and U. Simeoni2,3

1. **Unité de Médecine Néonatale, Hôpitaux Pédiatriques CHU-Lenval, Nice, France**; 2. **Physiopathologie de l’endothélium vasculaire, UMR 608, Marseille, France**; 3. **Unité de Médecine Néonatale, Hôpital de La Conception, Marseille, France**

Cardiovascular disease is a major concern of global health worldwide. Perinatal programming, identification of risk factors and early management of adult disease is a widely used search path and should be a priority. Our interest is focused on the vascular endothelium, whose key role has been demonstrated in many chronic diseases. The aim of our study is to examine the effects of fetal and neonatal biometries and growth in endothelial integrity. We assume the existence of early markers of endothelial dysfunction. We included 149 volunteers in the main study, healthy and aged from 18 to 30 years, including 39 in an advanced study. Circulating endothelial progenitors, counted by flow cytometry, such as CD34+/CD45−/KDR+, were positively correlated with...