Perinatal programming of the endocrine pancreas by maternal diabetes: impact on the development of the β-cell mass and glucose homeostasis in the offspring

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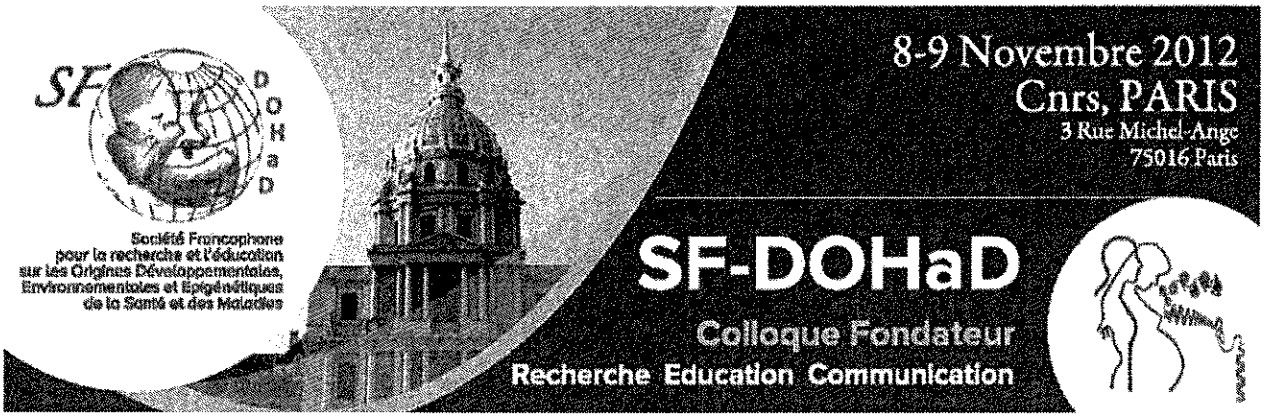

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maternal diabetes has both short- and long-term consequences on pancreatic β-cell function. White adipose tissue depots and skeletal muscle are sensitive programming targets in intrauterine growth restriction (IUGR). In premature infants, epigenetic modifications of the AMOT gene, involved in angiogenesis, may participate in the development of adult hypertension. Maternal diabetes programs vascular functions of conductance and resistance arteries, which may contribute to hypertension. High-protein feeding in IUGR rat neonates programs long-term metabolic alterations. High-fat regimen has more deleterious consequences in weaned than in adult rats. Children sleep pattern may influence adiposity and overweight.

ORAL N°65

Childhood adversity as a risk for cancer: findings from the 1958 British Birth Cohort Study

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Adverse psychosocial exposures during childhood may result in biological changes and health behaviours potentially involved in the development of cancer in adulthood. The objective of our study was thus to analyse whether Adverse Childhood Experiences (ACE) are associated with an increased risk of cancer. The National Child Development Study (NCDS) is a prospective birth cohort study with data collected over 50 years. The NCDS included all live births during 1 week in March 1958 ($n = 18,558$) in Great Britain. Self-reported cancer incidence was based on 533 participants reporting having had cancer at some point and 6080 reporting never having cancer. ACE was measured using reports of: (1) child in care, (2) physical neglect, (3) child's or family's contact with the prison service, (4) parental separation because of divorce, death or other, (5) family experience of mental illness and (6) family experience of substance abuse (0–6), to test for a relationship with cancer. Information on socio-economic characteristics, pregnancy and birth were extracted as potential confounders, and information on behaviours as potential mediators (smoking, alcohol, BMI). Multivariate models were run using multiple-imputed data to account for missing data in the cohort. The prevalence of reporting a cancer before 50 years of age was 14.5% for those with two or more adversities and 6.4% for those with none ($P < 0.0001$). The odds of reporting a cancer increases twofold when an individual has experienced two or more adversities in childhood *v.* individuals who experienced no such adversities (OR: 2.04, 95% CI: 1.42–2.87, $P < 0.0001$), after adjusting for early life confounding factors and adult mediating factors. It was particularly true for women (OR: 2.3, 95% CI: 1.51–3.44, $P < 0.0001$, respectively, for female respondents who had experienced two or more adversities in childhood). An accumulation of ACEs had a positive association with cancer incidence, which could be in part a direct effect involving biological processes. Exposure to adversity in childhood should be considered as a potential risk factor for cancer.

Key words: cancer, early development and adult disease, epidemiology/public health, lifecourse

Statement of interest: Authors report no conflict of interest.

ORAL N°46

Perinatal programming of the endocrine pancreas by maternal diabetes: impact on the development of the β-cell mass and glucose homeostasis in the offspring

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In recent years, epidemiological findings had strongly suggested that *in utero* exposure to maternal diabetes is associated with abnormal insulin secretion and glucose homeostasis in the offspring and may participate in the excess of maternal transmission in type 2 diabetes (T2D). From human studies, isolation of the respective contribution of genetic *v.* perinatal environmental factors is hardly attainable. The Goto-Kakizaki (GK) rat is a spontaneous model of T2D with decreased β-cell mass observed as early as in fetal life, followed by altered β-cell function during postnatal life. This model is a useful tool to investigate whether the deficit of pancreatic β-cell number is determined genetically, environmentally or both. The aim of our work was to determine the contribution of the maternal hyperglycemia on the development of β-cell mass and function in a normal Wistar conceptus (in the absence of diabetes predisposing genes). Using an embryo transfer technology, we implated fertilized Wistar oocytes into pseudo-pregnant diabetic GK females. β-cell mass, cell proliferation and cell neogenesis were measured in the pancreas of E18.5 fetuses. The pups were either suckled by their GK mothers or cross-fostered to non-diabetic Wistar dams to evaluate the proper influence of perinatal nutritional environment. β-cell mass, basal glycemia and glucose tolerance were measured in 8–10 weeks old offspring. We showed that maternal diabetes impairs early development of the β-cell mass in Wistar offspring. This defect is maintained in the pancreas of adult

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

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ORAL N°34

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

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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.[1] Under chow diet, hyperleptinemic and hypercorticosteronemic 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.[2] These observations raised questions regarding the role of the glucocorticoid WAT environment on the development of adiposity.[3] 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.[2] 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.[4]

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

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ORAL N°4

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

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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.