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EDITORIAL

Perinatal nutritional programming of health and metabolic adult disease

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Abstract

Data indicate that perinatal nutritional insults not only have short-term consequences on the growth velocity of the fetus/neonate but also sensitize to the development of metabolic adult diseases. The pathophysiological mechanisms involved in the so-called "Developmental Origin of Health and Adult Diseases" are still largely unknown and depend on the type of alteration (nutritional, psychological, endocrine disruptors, *etc.*), its intensity and duration, species, sex and the time during which it is applied. Perinatal stress, *via* disturbances of both hypothalamo-pituitary-adrenal (HPA) axis and sympatho-adrenal-system (SAS), as well as brain-adipose axis and pancreas alterations could play a crucial role. Interestingly, it has been demonstrated that perinatal insults may be transmitted transgenerationally, suggesting that these long-term consequences may be inherited *via* epigenetic mechanisms. Finally, since the placenta has been demonstrated to be sensitive to perinatal nutritional manipulations, the identification of placental markers may thus represent an important new avenue to identify the more susceptible babies prone to developing metabolic diseases.

Key words: Nutritional programming; Epigenetic; Metabolic diseases; Perinatal stress; Placenta; Transgenerational effect; Mitochondria; Brain-adipose axis

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INTRODUCTION

There is growing evidence from both epidemiological studies in humans and experimental ones in animals that perinatal maternal nutrition (undernutrition or overnutrition) has long-lasting consequences and sensitizes the offspring to the development of several chronic diseases such as metabolic syndrome (obesity, hypertension and type 2 diabetes). During the prenatal period, maternal undernutrition is responsible for intra uterine growth retardation (IUGR), resulting in low birth weight. In contrast, maternal diabetes during or before pregnancy is frequently associated with the birth of macrosomic babies. Interestingly, IUGR and macrosomia increase the propensity to develop similar chronic adult diseases although the pathophysiological mechanisms involved may be different. It is thus suggested that nutritional imbalances *in utero* and in early postnatal life play a crucial role in the development of chronic adult metabolic diseases. The main focus of this special issue will be to summarize the more recent findings in this field of research, known as developmental origin of health and adult diseases (DOHAD) hypothesis[1].

PLACENTA IS A SENSITIVE TARGET OF THE PRENATAL NUTRITIONAL ENVIRONMENT

There are several causes that may disturb the prenatal

growth of the fetus, including maternal nutrition, pre-eclampsia, placenta dysfunction or gestational diabetes. In the latter situation, depending on maternal, placental and fetal parameters, newborns may present a low birth weight for a normal gestational age (thus reflecting an IUGR) or in contrast be macrosomic. This important cause of intrauterine malprogramming is reviewed by Vambergue *et al*[2]. In their manuscript entitled "Consequences of gestational and pregestational diabetes on placental function and birth weight", they also discuss the way by which the placenta is presumably a compromised target that largely suffers the impact of maternal diabetes or IUGR. The identification of placental markers may thus represent an important new avenue to identify the more susceptible babies prone to develop metabolic diseases.

CRITICAL DEVELOPMENTAL TIME-WINDOWS DICTATE METABOLIC OUTCOMES

The long-term consequences of perinatal insults are extremely variable and depend on several parameters such as the type of "stressor" (nutritional, psychological, toxins, endocrine disruptors, viruses, *etc.*), its intensity and duration, species, sex and the time during which it is applied. This introduces the important notion of critical windows of developmental plasticity which stipulates that depending on the moment the stressor is applied, it may or may not induce an irreversible change in developmental trajectory and exert long-term deleterious effects. Once again, the critical time-windows may vary according to species, organs and presumably sex. Interestingly, several reports suggest, at least in animal models, that developmental programming of metabolic diseases is potentially reversible by nutritional or targeted interventions during the period of developmental plasticity. The identification of critical time-windows is thus a promising way to explore in order to offer new therapeutic strategies. This important field of research is reviewed by Mark Vickers in this special issue in a manuscript entitled "Developmental programming of the metabolic syndrome-critical windows for intervention"[3].

PERINATAL STRESS MAY CONTRIBUTE TO THE PROGRAMMING OF ADULT METABOLIC DISEASES

The physiological mechanisms involved in perinatal programming of metabolic diseases remain to be elucidated but several experimental data indicate that dysfunction of stress neuroendocrine systems such as the hypothalamo-pituitary-adrenal (HPA) axis and sympatho-adrenal system (SAS) might play a key role[4]. Since glucocorticoids and catecholamines, the respective final products of HPA axis and SAS, are involved both in the adaptation to stress as well as in the regulation of several metabolic parameters such as glycemia and blood pressure, the modification of their production may participate in the programming of metabolic diseases. In a manuscript entitled "Is perinatal neuroendocrine programming involved in the development of chronic metabolic adult disease", David Phillips reviews how alterations of neuroendocrine stress systems during the course of development may modify the structure and physiology of the adults towards a phenotype adapted for adversity, which is advantageous if the adverse environment persists in adulthood[5]. By contrast, these hormonal and phenotypical perinatal adaptations may lead to diseases if there is a subsequent modification of nutritional environment such as overnutrition and obesity.

MATERNAL PERINATAL NUTRITION MAY PROGRAM OBESITY *VIA* ALTERATIONS OF THE BRAIN-ADIPOSE AXIS

Maternal under- or overnutrition during the perinatal period are both responsible for the increased propensity to develop metabolic diseases, particularly obesity, suggesting that nutritional imbalances are crucial determinants. In their review ("The mechanisms behind early life nutrition and adult disease outcome"), Elena Velkoska and Margaret Morris summarize the way by which these nutritional insults may have long-term programming effects[6]. In particular, they summarize the central and peripheral mechanisms that could be modified by perinatal nutritional insults, with a particular focus on the brain-adipose axis which is a very sensitive target. Recent results from their team indicate that paternal obesity might also play a key role in the programming of metabolic diseases in the offspring, highlighting the possibility that unhealthy paternal diets can reprogram gene expression in offspring. This opens new avenues and reminds us that we also have to take into account the role of the father whose importance has been always neglected so far, at least in the case of DOHAD hypothesis.

PERINATAL NUTRITIONAL PROGRAMMING OF AUTONOMOUS NERVOUS SYSTEM MAY SENSITIZE TO THE DEVELOPMENT OF TYPE 2 DIABETES

Although all animal models of maternal nutrition during gestation and/or lactation do not all result in modification of birth weight, they are invariably responsible for impaired glucose metabolism in the adult offspring, demonstrating that the pancreas is a particularly sensitive target of perinatal insults. The precise mechanisms involved in the dysfunction of the pancreas are still be elucidated but stress neuroendocrine systems may also be important factors. Interestingly, Paulo Mathias and his collabora-

tors provide strong evidence that the autonomic nervous system, *via* the release of acetylcholine and the presence of several muscarinic receptors in pancreatic islets, may play an unsuspected role[7]. In their manuscript ("Perinatal protein restriction during lactation programs changes to autonomous nervous system and insulin secretion regulation in adult life"), they suggest that pancreatic dysfunctions may be attributed, at least in part, to an imbalance of autonomic nervous system activity.

PERINATAL NUTRITIONAL PROGRAMMING OF PANCREATIC ISLET ANGIOGENESIS MAY CONDITION BETA CELL FUNCTION

Usually, alteration of insulin secretion is associated with a deficit in the β-cell mass in the offspring resulting from changes in the development and functional capacity of the endocrine pancreas and modifications in insulin sensitivity in tissues such as muscle, liver and adipose tissue. In a manuscript entitled "Nutritional programming of pancreatic β-cell plasticity", David Hill indicates that these alterations are associated with developmental changes in the islet microvasculature[8]. Although these modifications are irreversible if the nutritional insult persists postnatally, reversal strategies could be used soon after birth. David Hill reports that β-cells indeed exhibit an inducible plasticity and that a treatment using statins or bone-marrow-derived stem cells is indeed able to induce angiogenesis in the islet microvasculature as well as enhanced proliferation of remaining β-cells. The author also summarizes the beneficial effects of metformin and exercise on the pancreatic function, suggesting that a beta cell phenotype programmed towards risk of adult diabetes through early nutritional insults can be reversed by both pharmaceutical and lifestyle interventions, pointing out the necessity to identify early markers of adult metabolic diseases.

PERINATAL MITOCHONDRIA PROGRAMMING MAY CONTRIBUTE TO THE DEVELOPMENT OF TYPE 2 DIABETES

Another recent and interesting area concerns the putative involvement of mitochondrial dysfunctions that may be involved in the development of type 2 diabetes. Brigitte Reusens and colleagues, in a manuscript entitled "Alteration of mitochondrial function in adult rat offspring of malnourished dams", give an overview of the effects of mitochondrial alterations when the intrauterine nutritional environment has been insulted[9]. Several nutritional perturbations such as maternal protein restriction modify ATP production and decrease insulin release in response to glucose stimulation. In addition, that kind of regimen also aggravates the disturbed balance between antioxidant enzymes, leading thus to β-cell dysfunction. They also explain the way by which mitochondria programming targets specific pathways depending on the type of the prenatal diet as well as the sex of the progeny. Although most of the studies have been performed in male animals, it is becoming increasingly clear that ongoing studies will also have to be performed in females.

PERINATAL NUTRITIONAL PROGRAMMING MAY BE TRANSMITTED TRANSGENERATIONALLY

One of the most fascinating finding of perinatal programming is that adverse consequences of altered developmental environment can be passed transgenerationally from first generation to the next generations *via* mechanisms that do not involve genetic modification. This new concept, reviewed by E Zambrano ("The transgenerational effects in developmental programming of metabolic diseases"), has been observed both from epidemiological studies in humans as well as in animal experimental models of perinatal insults such as nutrient restriction or overfeeding during gestation and/or lactation, uterine blood flow restriction, experimental maternal diabetes and fetal overexposure to synthetic glucocorticoids[10]. In light of these observations, it becomes necessary to identify people at risk of developing metabolic diseases to minimize the risk of transmission of these pathologies to future generations.

EPIGENETIC MECHANISMS ARE INVOLVED IN THE LONG-TERM CONSEQUENCES OF PERINATAL NUTRITIONAL PROGRAMMING

The way by which perinatal insults have long-term consequences is reviewed by Claudine Junien and colleagues in a manuscript entitled "Epigenetic mechanisms involved in developmental nutritional programming"[11]. As briefly evoked above, the resulting sustained modification of gene expression is not due to genetic mutations but rather involves epigenetic mechanisms that act particularly on DNA methylation as well as histones post-translational modifications. These epigenetic changes are tissue-specific and the question remains as to whether surrogate tissues obtained by minimally invasive procedures, such as the placenta or cord blood, truly reflect early programming *in utero* or whether adult tissues and cells, such as lymphocytes, monocytes or buccal smears, mirror the lifelong metabolic memory. Most epigenetic studies have addressed the long-term effects on a small number of epigenetic marks of environmental stressors in human and animal models. Recent studies have demonstrated a sexual dimorphism both for programming trajectories and in response to the same environmental insult, suggesting the existence of different epigenetic mechanisms in males and

females. The increasing numbers of studies based on high throughput technologies have revealed additional complexity in epigenetic processes but are necessary steps to identify epigenetic marks. A better knowledge of the epigenomes in response to developmental insults might help to envisage new therapeutic strategies aiming at modifying the methylation state of target genes using specific regimen. After all, we are what we eat.

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