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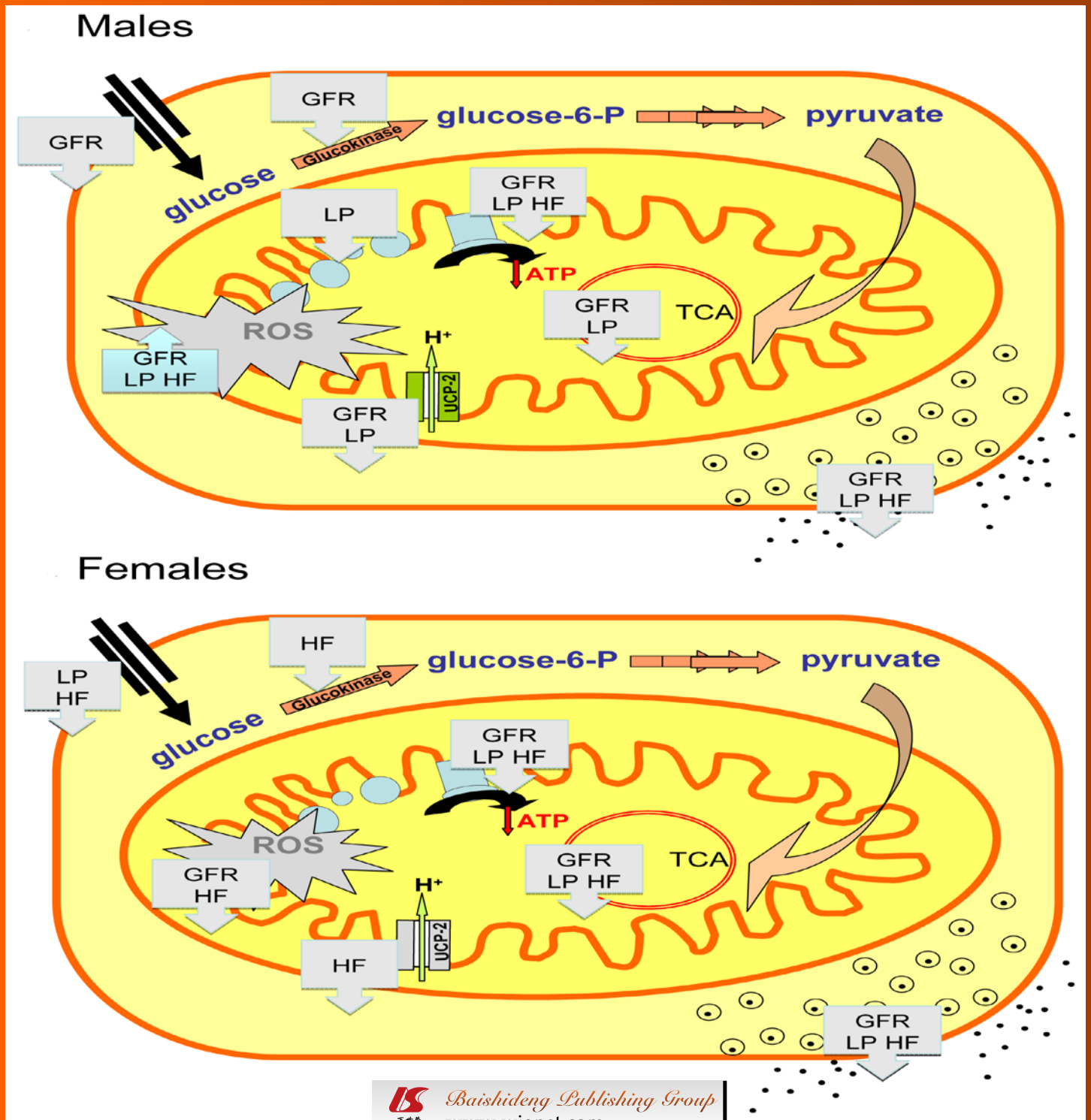

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EDITORIAL

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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TOPIC HIGHLIGHT

Didier Vieau, Professor, *Series Editor*

Developmental programming of the metabolic syndrome - critical windows for intervention

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Abstract

Metabolic disease results from a complex interaction of many factors, including genetic, physiological, behavioral and environmental influences. The recent rate at which these diseases have increased suggests that environmental and behavioral influences, rather than genetic causes, are fuelling the present epidemic. In this context, the developmental origins of health and disease hypothesis has highlighted the link between the periconceptual, fetal and early infant phases of life and the subsequent development of adult obesity and the metabolic syndrome. Although the mechanisms are yet to be fully elucidated, this programming was generally considered an irreversible change in developmental trajectory. Recent work in animal models suggests that developmental programming of metabolic disorders is potentially reversible by nutritional or targeted therapeutic interventions during the period of developmental plasticity. This review will discuss critical windows of developmental plasticity and possible avenues to ameliorate the development of postnatal metabolic disorders following an adverse early life environment.

Key words: Developmental programming; Metabolic syndrome; Obesity; Type 2 diabetes; Leptin; Animal models; Predictive adaptive responses

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INTRODUCTION

The rates of obesity and the metabolic syndrome are currently at epidemic proportions. Once considered a problem of developed countries, overweight and obesity are now dramatically on the rise in developing economies, particularly in urban settings. Globally, over one billion adults are overweight and with 400 million obese, it has been ranked as a critical public health issue[1-4]. Furthermore, over 20 million children under 5-year old are overweight. This marked increase in childhood obesity and related metabolic disorders will translate to a further increase in adult obesity, predicted to reach 2.3 billion by 2015[4-6]. It is a widely held view that the development of an obesogenic environment, due to ease of access to highly calorific food and reduced energy expenditure in work and leisure activities, is the primary cause of obesity and related metabolic disorders, particularly type 2 diabetes (T2DM)[7]. Metabolic syndrome is a com-

mon complex trait comprising of a set of risk factors for cardiovascular disease and T2DM and is likely the result of complex interactions between genes, dietary intake, physical activity and the environment. Although a number of genes have been identified that are associated with obesity and metabolic syndrome in humans[7,8], the genetic component of this condition cannot account for the dramatic increase in the prevalence of obesity and the metabolic syndrome in recent years. Relevant epidemiological and experimental studies have highlighted a relationship between the periconceptual, fetal and early infant phases of life and the subsequent development of adult metabolic disorders[9-11]. The terms "developmental programming" and the "Developmental Origins of Adult Health and Disease" are preferentially used to describe these associations. The mechanisms underlying developmental programming and the role of genetic *vs* environmental factors remain speculative. One general thesis is that, in response to an adverse intrauterine environment, the fetus adapts its physiological development to maximize its immediate chances for survival. These adaptations may include resetting of set points of metabolic homeostasis and endocrine systems and the down-regulation of growth, commonly reflected in an altered birth phenotype. More recently, the "predictive adaptive response (PARs)" hypothesis proposes that the degree of mismatch between the pre- and postnatal environments is a major determinant of subsequent disease[12,13]. Thus, it is thought that whilst these changes in fetal physiology may be beneficial for short term survival *in utero,* they may be maladaptive in postnatal life, contributing to poor health outcomes when offspring are exposed to catch-up growth, diet-induced obesity and other factors[13,14].

DEVELOPMENTAL PROGRAMMING OF THE METABOLIC SYNDROME - EVIDENCE FROM EPIDEMIOLOGICAL AND CLINICAL STUDIES

Following the initial work of Barker and colleagues that demonstrated a relationship between low birth weight and an increased risk of hypertension, obesity, insulin resistance and dislipidemia[15-17], the importance of maternal nutrition and, in particular, the effect of poor nutrition on birth weight and development of adult disease was addressed in studies of famine exposure. The most widely reported of these being the Dutch Hunger Winter of 1944-1945[11,18-20] where the timing of the exposure was a major determinant in phenotypic outcomes. Whereas famine exposure during early gestation was associated with adult hypertension[18], reduced maternal caloric intake in late gestation was associated with an increased adult adiposity and glucose intolerance[11,21]. Famine exposure in late gestation led to a greater impairment of glucose tolerance than during early or mid-gestation. The rate of obesity was higher in men exposed in the first half of gestation and lower in men exposed in the last trimester of gestation as compared to non-exposed men[11]. However, the data derived from those exposed to famine during the siege of Leningrad did not show any relationship between birth weight and adult metabolic sequelae[22]. Thus, while fetal exposure to a substrate limited environment at most stages of development appears to lead to adult dysregulation of metabolism, the precise mechanisms responsible may vary with the timing of exposure. The disparity between the Dutch and the Leningrad studies may be explained by the PARs hypothesis - in the Dutch offspring, nutrition was plentiful following the famine and thus was mismatched to the predicted environment. In the Leningrad cohort, nutritional status was poor both before and after the period of famine and thus the PAR may have been appropriate for the postnatal environment experienced[23].

In historically undernourished, recently urbanised populations such as India, where individuals of low birth weight are exposed to a high-fat western diet, the incidence of obesity and T2DM is reaching epidemic proportions[24]. Work by Yajnik and colleagues have shown that although Indian babies are born with low birth weight, they exhibit relatively increased visceral adiposity[24]. This is consistent with other studies of small babies, showing a disproportionate abdominal fat mass during adult life, despite a lower body mass index[25]. Although there is considerable debate whether catch-up growth in early postnatal life is beneficial or not, most studies suggested that postnatal "catch-up" growth is associated with adverse outcomes in later life[22,26]. Interestingly, work by Parsons *et al*[27] found that men with a lower birth weight who exhibited catch-up growth and achieved a greater proportion of their adult height by age 7, had a risk of obesity comparable to that of men with higher birth weights.

Being born small for gestational age (SGA) is known to be associated with an increased risk of developing the components of the metabolic syndrome, although the biological mechanisms underlying this association are still unclear. Children born SGA followed by catch-up growth have been shown to have elevated serum leptin concentrations which are significantly correlated with insulin sensitivity parameters[28]. Work by Eriksson *et al*[29] demonstrated that the ponderal index at birth was a reliable predictor of later obesity and they also found that an early adiposity rebound in babies born of low birth weight was associated with obesity in adult life.

Although prenatal growth restriction has clearly demonstrated influences on long term adiposity, it is important to recognise that the relationship between birth weight and later life pathophysiology is not linear. Large for gestational age babies are also at risk of obesity and diabetes, associations that have been supported by a number of studies investigating the long term effects of maternal hypoglycaemia [diabetes or gestational diabetes (GDM)][30-34]. In developed societies and societies transitioning to first world diets and lifestyle habits, caloric and/or fat consumption are generally excessive and therefore, unremarkably, maternal obesity is now a common pregnancy com-

plication[35,36]. Children exposed to maternal obesity are at an increased risk of developing the metabolic syndrome; even though some obese mothers do not fulfil the clinical criteria for GDM, they may still have metabolic factors that affect fetal growth and postnatal outcomes[37]. Maternal obesity is associated with obstetric complications, including fetal and neonatal death and poor lactation outcomes, and is the most significant predictor of childhood obesity[38,39] and metabolic syndrome in offspring[37]. Importantly, these effects may be self-perpetuating, as offspring of obese mothers are themselves prone to obesity, giving rise to transgenerational effects[40,41].

DEVELOPMENTAL PROGRAMMING OF THE METABOLIC SYNDROME - EVIDENCE FROM ANIMAL MODELS

Animal models have been extensively used to study the basic physiological principles of the developmental origins of health and disease (DOHaD) hypothesis and are essential to the search for the mechanistic links between prenatal and postnatal influences and risk for developing the metabolic syndrome in later life. Although epidemiological data suggest that developmental programming occurs within the normal range of birth size[42,43], most experimental work has focused on significant restriction of fetal growth in the assumption that insults impairing fetal growth are likely to be those triggering developmental programming. Several approaches have been adopted to induce early growth restriction in animals. These aim to elucidate the relationship between early growth restriction and adult onset disease and provide a framework for investigating the underlying mechanisms. In the rodent, obesity and metabolic disorders have been induced in offspring by maternal global undernutrition[44-48], a low protein diet[49], maternal uterine artery ligation[50,51], maternal dexamethasone (DEX) treatment[52], maternal anemia[53] or prenatal cytokine exposure[54]. In this context however, intrauterine growth restriction (IUGR) is not essential to developmental programming but is merely a surrogate for evidence that fetal development may be adversely affected.

Epidemiological studies demonstrate that fetal growth restriction correlates with adult disease, implying that fetal nutritional deprivation is a strong stimulus for programming[55]. So, experimental animal models were developed using controlled maternal caloric intake or protein or macronutrient deficiency. However, in many developed societies, maternal and postnatal caloric intake can be excessive. A number of researchers have shown that programmed obesity may represent a U-shaped curve with a higher prevalence of adult obesity occurring in individuals who were on either deprived or excessive planes of maternal nutrition[25,55-58].

MATERNAL UNDERNUTRITION

The early work of Barker and colleagues highlighted the role of fetal nutrition as the primary factor involved in the developmental origins of adult disease. Within the laboratory, early life undernutrition can be achieved through maternal dietary restriction during pregnancy and/or lactation and in some cases during the periconceptional period[59,60]. At present, those investigating the mechanistic links between maternal undernutrition and adult disease generally utilize one of two dietary protocols in the rodent; global undernutrition or isocaloric low protein diets, with the maternal low protein (MLP) diet being the more extensively used[61-65]. The MLP model involves ad-libitum feeding to pregnant rats a low protein diet containing 5%-9% (w/w) protein (casein), generally a little under half the protein content but equivalent in energy of a control diet containing 18%-20% (w/w) protein[61,66]. Offspring from protein restricted mothers are 15%-20% lighter at birth[63] than offspring of control fed mothers. Extending the MLP diet throughout the period of lactation increases the weight difference and permanently limits later growth. If MLP offspring are cross-fostered to mothers fed a control diet, they exhibit rapid catch-up growth[63]. This appears to have a detrimental effect on life span, which results in premature death associated with accelerated loss of kidney telomeric DNA[67]. Altered insulin sensitivity of adipocytes in MLP offspring has also been well documented; the findings of these studies show that enhanced activation of insulin receptor substrate-1 associated phosphatidylinositol 3-kinase (PI3K) activity may be the key to improvements in insulin sensitivity[68]. However, alterations in PI3K subunit expression indicate that the adipocytes of MLP offspring may be resistant to insulin's antilipolytic effects[68].

Experimental observations in the MLP diet model of developmental programming highlight many potential mechanisms that may be involved in the pathogenesis of obesity and T2DM. These mechanisms include both physical and functional changes to various organ and endocrine systems. Gene ontogeny analysis of visceral adipose tissue (VAT) from MLP rat offspring revealed a global up-regulation of genes involved in carbohydrate, lipid and protein metabolism[69]. Thus VAT in the MLP model is marked by dynamic changes in the transcriptional profile of key metabolic genes.

Global undernutrition during pregnancy is a widely used approach to induce nutritional programming of obesity. Various models have been developed with different levels of undernutrition during different periods of pregnancy. In the rat, a moderate nutritional restriction (70% of normal intake) in the first 18 d of pregnancy results in offspring with significant IUGR that catch up in body weight to that of controls by postnatal day 20. These abnormalities increase with age and are most pronounced in male offspring[70].

We have developed rodent models of developmental programming using global maternal undernutrition throughout pregnancy[47,71]. When dams are fed at 30% of ad-libitum intake throughout pregnancy (i.e. a severe level of undernutrition), offspring birth weights and placental

weights are 25%-30% lower than offspring of control fed mothers. These offspring display increased adiposity, hypertension, hyperinsulinemia, hyperleptinemia, reduced locomotor activity, leptin resistance and hyperphagia in adult life[47,72,73]. Severe global undernutrition has also been shown to result in altered neuroendocrine gene expression, including pro-opiomelanocortin (POMC), agouti-related peptide and neuropeptide Y[74,75]. When the degree of undernutrition is reduced to a more moderate level, i.e. 50% of *ad-libitum*, offspring still display a significant level of obesity in postnatal life. Of note, if pre-weaning catch-up growth in offspring is prevented by maintaining the mothers on the restricted diet throughout lactation, offspring do not develop an obese phenotype (authors unpublished observations and[76]). This is similar to reports in the MLP model where continuation of the low protein diet into lactation prevents the development of the metabolic phenotype, once again highlighting the possible adverse consequences of catch-up growth[76].

Although maternal macronutrient malnutrition has been well studied, the role of maternal micronutrient restriction has not been widely investigated. From the limited data available, maternal micronutrient restriction has been directly associated with the developmental programming of several features of the metabolic syndrome. Maternal iron deficiency has been a focus of recent studies with several features of the metabolic syndrome observed in offspring following maternal iron deprivation[36]. Work by Gambling *et al*[77] highlighted that the timing of iron supplementation is critical in reversing the effects of maternal anemia on the developing fetus and postnatal sequelae in offspring. These data correlate well with human studies showing that iron supplementation during pregnancy leads to a higher mean birth weight and reduced incidence of low birth weight infants[78].

Maternal chromium restriction significantly increased body weight and fat percentage, especially central adiposity, in both male and female rat offspring[79,80]. Restricted vitamin intake during pregnancy has been shown to increase the phenotypic expression of obesity and components of the metabolic syndrome in both female and male rats fed a post-weaning obesogenic diet[81]. Maternal and perinatal magnesium restriction has also been shown to predispose rat pups to insulin resistance and glucose intolerance[82,83].

MATERNAL OBESITY

Over recent years there has been an increasing focus on developing models of maternal obesity. Several obesogenic models, primarily in the rodent, show a relatively common phenotype of metabolic disorders in offspring, although the magnitude of effects differs with the timing of the nutritional challenge and diet composition[84].

A maternal cafeteria or high fat diet has been shown to induce obesity, insulin and leptin resistance[58,85,86], hypertension[87-89], hepatic steatosis and non-alcoholic fatty liver disease in offspring[90-92]. Even mild maternal overnutrition has been shown to induce increased adiposity, glucose intolerance and altered brain appetite regulators in offspring[93]. We have recently shown that a moderate maternal high fat diet (HF) results in significant obesity and hyperinsulinemia in male and female offspring, independent of the level of post-weaning diet[56]. Furthermore, in pregnancies which have been complicated by maternal diabetes, GDM or impaired glucose tolerance, offspring have been shown to be at an enhanced risk of developing features of the metabolic syndrome[94-97]. In the sheep, maternal obesity has been shown to accelerate fetal pancreatic β-cell but not α-cell development[98]. Fetuses from obese ewes show increased systemic insulin levels due to increased glucose exposure and/or cortisol-induced acceleration of fetal β-cell maturation, which may contribute to premature β-cell function loss, and lead to a predisposition for obesity and metabolic disease.

The PARs hypothesis suggests that disease only manifests when the actual nutritional environment diverges from that which was predicted. So, it is notable that evidence for the programming of obesity and features of the metabolic syndrome come from both nutrient restriction (caloric, protein, iron) and fat-feeding studies, which suggests a commonality of mechanism[99].

ROLE OF EPIGENETICS

The ability of developmental plasticity to generate biological variation from one genotype is well understood and interest has emerged in the clinical significance of epigenetic processes, particularly those influenced by the external environment[100]. There is increasing evidence that "marked" regions of DNA can become "unmarked" under the influence of dietary nutrients. This gives hope for reversing propensities for metabolic disorders and other diseases that were acquired in the womb[101].

Experimental data in rodents and recent observations in humans suggest that epigenetic changes in regulatory and growth-related genes play a significant role in mediating the patho-physiological phenotypes derived from developmental programming[102,103]. Epigenetic processes lead to heritable changes in gene function by altering DNA chemistry independent of sequence and may be responsible for tissue-specific gene expression during differentiation. These mechanisms may underlie the processes of developmental plasticity[104]. Examples of epigenetic regulation include coordinated changes in the methylation of cytosine in cytosine-guanine (CpG) dinucleotides in the promoter regions of specific genes, changes in chromatin structure through histone modification (acetylation, methylation, *etc.*) and post-transcriptional control by microRNA[104]. Histone modifications in conjunction with DNA methylation regulate chromatin structure and gene expression. However, it is still debated where early life and/or environmental factors can influence the "histone" code in a manner similar to their influence on DNA methylation[105].

Adversity during pregnancy or early neonatal life in ex-

perimental programming models result in changes in promoter methylation, therefore, directly or indirectly, affect gene expression in pathways associated with a range of physiological processes[106]. For example, in the rat, altered promoter methylation and downstream changes in gene expression have been shown for the hepatic glucocorticoid receptor (GR) and the peroxisome proliferator-activated receptor-α (PPAR-α)[107,108], influencing carbohydrate and lipid metabolism[109,110]. Similar epigenetic changes have been observed in *p53* in the kidney[111] and the angiotensin Ⅱ type 1b receptor in the adrenal gland[112], influencing renal apoptosis and pressor responses, respectively, and in the hypothalamic GR[113,114], influencing stress responses. The phenotypic effects of epigenetic modifications during development may not manifest until later in life, especially if they affect genes modulating responses to later environmental challenges, such as dietary challenges with a high-fat diet. The timing of the developmental windows and the induction of epigenetic changes in key physiological systems are not well characterized, but it appears to extend from the periconceptional period[115] into postnatal life[113,114]. There is also evidence from studies in twins for changes in the human epigenome related to age and the environment[116,117]. Many of the genes regulated by epigenetic change do not appear to be classically imprinted (expressed according to the parental origin of the allele), although some imprinted genes may show altered expression after perturbations during early development, such as if blastocyst culture *in vitro* is prolonged[118].

It is hypothesized that alterations in early life nutrition can influence DNA methylation since one-carbon metabolism is dependent upon dietary methyl donors and cofactors, including folic acid, choline and vitamin B_{12}[102,119]. Maternal dietary manipulations such as low protein exposure result in aberrant changes in DNA methylation in key genes which can be prevented by maternal dietary supplementation with cofactors[107]. Protein restriction in pregnant rats has been shown to induce a significant loss of DNA methylation concomitant with increased expression of key hepatic genes, including the GR and PPAR-α[107]. These epigenetic changes, a result of altered DNA methyltransferase 1 activity[108], were prevented with maternal folate supplementation[107]. Intriguingly, other models of early life adversity, apart from nutrition, have also been shown to influence epigenetic regulation of gene expression. Using a model of maternal uterine artery ligation, a comparison of IUGR *vs* normal rats revealed changes in DNA methylation at a number of novel loci, not limited to canonical CpG islands or promoters. The specific loci affected were in proximity to genes with important roles in β-cell function and development[120]. Also, shown in this model is that after the onset of T2DM in adulthood, the CpG island in the proximal promoter for pancreatic duodenal homeobox (Pdx1) was methylated, resulting in permanent silencing of the Pdx1 locus[121]. Meaney and colleagues have extensively investigated the role of maternal care during neonatal life on epigenetic regulation of gene expression patterns in the brains of offspring born to "low-caring" mothers. In their studies they demonstrate that an increased level of maternal care in the first week of life alters DNA methylation at specific CpGs in the GR gene promoter in the hippocampus of the offspring and in turn leads to a phenotype similar to that of maternal undernutrition models. Reversal of the epigenetic change leads to reversal of the phenotypes. Furthermore, Meaney's team has shown that alterations in offspring behavior may be modified by postnatal environmental enrichment and that these phenotypes can be passed from one generation to the next[122-124]. These results provide evidence for the role of social conditions beyond the postnatal period in altering patterns of maternal care and thus offspring phenotype and illustrate the interaction between the effects of postnatal and post-weaning environments.

Prenatal undernutrition has been shown to induce changes in histone H3 and H4 acetylation, consistent with facilitated transcription, in the GR gene in the liver[125]. From a mechanistic standpoint, studies in humans linking epigenetic change to metabolic disease risk remain very limited although there is some evidence for the inheritance of tissue specific DNA methylation patterns[126]. Differences in environmental exposure lead to different patterns of epigenetic marking in the somatic tissues of individuals. Twin studies show that DNA methylation and histone acetylation patterns diverged more strongly in older twin pairs with more marked life history differences[117].

It has been shown that the promoter in the leptin gene is subject to epigenetic programming and leptin gene expression can be modulated by DNA methylation[127-129]. Recent studies report that impaired glucose tolerance during pregnancy is associated with adaptations in leptin gene DNA methylation although the functional significance of these changes is not yet clear[130]. Yokomori *et al*[131] demonstrated that methylation of specific CpG sites and a methylation-sensitive protein could contribute to changes in leptin gene expression during adipocyte differentiation in 3T3-L1 cells. The same group has also shown that both methylation of specific CpG sites and a methylation-sensitive transcription factor contribute to GLUT4 gene regulation during preadipocyte to adipocyte differentiation[132]. In addition, differential DNA methylation was observed in promoters of genes involved in glucose metabolism including GLUT4[132] and uncoupling protein 2[133], both major contributors to the development of T2DM.

Epigenetic regulators work on the basis that exposure to environmental factors during critical periods of development permanently alters the structure or function of specific metabolic systems. Therefore, developmental epigenetics is believed to establish 'adaptive phenotypes' to meet the demands of the later-life environment[105,134]. Implicit in this concept is an important process of causality on the cellular level, regulating growth and tissue differentiation and involving chemical changes to the DNA or of associated proteins. Once the mechanistic basis of the disease is understood, epigenetic processes are po-

tentially reversible and intervention and strategies aimed at reversal could be devised and implemented. However, there are still many key questions to be answered[105]: How plastic is the system for intervention and reversal and what are the critical windows of development at which strategies should be targeted; how many generations does it take to reverse an epigenetic imprint and can surrogate markers be used for disease prediction?

CRITICAL WINDOWS OF DEVELOPMENT AND AVENUES FOR INTERVENTION

Maternal health and nutrition are key determinants in influencing infant growth but the precise molecular mechanisms underlying this relationship are largely unclear, although it is evident that there are critical windows of plasticity when these effects are important. Evidence from animal studies has shown that nutritional and pharmacological interventions may be able to ameliorate or reverse the consequences associated with developmental programming.

One of the earliest examples of intervention was that of maternal taurine supplementation to MLP dams. Studies have shown that taurine concentrations are low in diabetic and pre-diabetic states and that physiological plasma taurine levels are important for adequate β-cell function and insulin action[135]. In MLP rat offspring, β-cell mass is decreased at birth and metabolic perturbations last through adulthood even though a normal diet is given after birth or after weaning[136]. However, supplementing taurine to MLP dams restored normal release of insulin from MLP fetal islets, demonstrating how important taurine is to the development of normal fetal β-cell function[137].

However, MLP diets of differing composition used in different laboratories have yielded inconsistent data on the relationship between maternal protein intake and offspring blood pressure[66]. A critical role of methionine content in the MLP model was highlighted in work by Langley-Evans *et al*[66] and Rees *et al*[138,139] whereby different levels of methionine resulted in the MLP diets leading to different phenotypic outcomes. Several maternal dietary co-factors have also been shown to prevent the development of hypertension in offspring of MLP dams although the mechanisms are not well established. Maternal supplementation with glycine[140,141], folic acid[142,143] and choline (authors unpublished observations) has been shown to prevent programming-induced elevations in systolic blood pressure in offspring in postnatal life. There is some evidence for an epigenetic basis to these observations utilizing dietary methyl donor and co-factor supplementation; clinically relevant reductions in specific dietary inputs to the methionine/folate cycles during the periconceptional period can lead to widespread epigenetic alterations to DNA methylation in offspring and modify adult health-related phenotypes[107,115]. Moreover, altered methylation of gene promoters induced in the F1 generation by a MLP diet during pregnancy has been shown to be transmitted to the F2 generation, thus representing a mechanism for the transmission of induced phenotypes between generations[110].

There has been a lot of recent focus on the adipokine leptin. It has been proposed that deficiencies in leptin during critical windows of development could lead to a hardwiring of obesity[144]. In adult mammals, leptin acts on the brain to reduce food intake by regulating the activity of neurons in the ARH. Bouret *et al*[145,146] have shown that neural projection pathways from the ARH are permanently disrupted in leptin-deficient (Lep^{ob}/Lep^{ob}) mice. Treatment of Lep^{ob}/Lep^{ob} neonates with exogenous leptin rescues the development of ARH projections and leptin promotes neurite outgrowth from ARH neurons *in vitro*. It is well established that SGA children are hypoleptinemic and cord blood leptin concentrations are significantly diminished[147]. These children go on to develop obesity and leptin resistance in adult life and this can be mimicked experimentally in the rat[47]. Thus, perturbations in perinatal nutrition that alter leptin levels may have enduring consequences for the formation and function of circuits that regulate food intake and body weight[145,146,148,149]. Recent work investigating neonatal systemic leptin treatment in female Wistar rats born following maternal undernutrition has found that leptin prevented the development of diet-induced obesity and associated metabolic sequelae in adult life[150]. Leptin treatment normalised caloric intake, locomotor activity, body weight, fat mass and fasting plasma glucose, insulin, c-peptide and leptin concentrations, suggesting that any effect is not restricted solely to a central mechanism. Moreover, the effects were specific to animals born of low birth weight, with leptin having no effect in animals born to control mothers. The observations of leptin efficacy in the programmed rat have been replicated in the piglet. Work in piglets by Attig *et al*[151] showed that IUGR may be characterized by altered leptin receptor distribution within the hypothalamic structures involved in metabolic regulation and that leptin supplementation partially reversed the IUGR phenotype. The translation of findings across animal models itself bodes well for defining the role of leptin during this critical window of development.

Whether this effect of leptin is central or peripheral is unclear - one possibility is that the period of developmental plasticity is still open and the high leptin levels reverse the cuing effects of prenatal undernutrition[152]. The next piece to the puzzle is the question of the neonatal leptin surge; while the surge is well characterised in normal rodents[153] and may inform a window of intervention, the presence or absence of a leptin surge in humans is uncertain. Although altered maternal nutrition has been shown to alter the timing and duration of the leptin surge, the results are inconsistent across experimental models. Yura *et al*[154] reported a premature onset of the neonatal leptin surge following mild (70% of ad-lib) maternal undernutrition whereas MLP offspring display a delayed leptin surge[155]. Work by Delahaye *et al*[156] showed

that maternal perinatal undernutrition drastically reduced the postnatal leptin surge and altered the development of the POMC neurons in the arucate nucleus of neonatal male offspring. To date, little work has been done in maternal obesogenic models but Kirk *et al*[157] showed a prolonged and amplified leptin surge in neonates following maternal HF feeding.

Recent work in the rodent has shown that both growth hormone (GH) and insulin-like growth factor (IGF)-I can resolve several aspects of the metabolic phenotype in developmentally programmed offspring. Utilizing a model of maternal undernutrition to induce fetal growth restriction, offspring were fed either a chow or high fat diet postnatally. These offspring were hypertensive, obese, hyperphagic, hyperinsulinemic and hyperleptinemic; the effects of which were markedly amplified in the presence of a postnatal high fat diet[47]. Treatment of the adult phenotype with GH normalised systolic blood pressure and reduced fat mass. However, the hyperinsulinemia was exacerbated as a result of the diabetogenic actions of GH[45]. A further study in adult females with IGF-I infusion led to a complete normalisation of adiposity, appetite, fasting plasma insulin and leptin concentrations in developmentally programmed offspring[46]. These studies highlight the role of the somatotropic axis in programmed metabolic disturbances although the longer-term efficacy of such treatments is not known. Trials with GH in small for gestation age children have shown a normalisation in systolic blood pressure which was maintained for the 6 yr duration of treatment[158].

Epidemiological and experimental studies have shown that developmental programming leads to glucose intolerance and an enhanced risk for type 2 diabetes. Work by Park *et al*[121], Raab *et al*[159] and Stoffers *et al*[160] has shown that treatment of neonatal rats with the glucagon-like peptide (GLP)-1 analog Exendin 4 (Ex-4) reverses the adverse consequences of developmental programming and prevents the development of diabetes in adulthood. This occurs because neonatal Ex-4 prevents the progressive reduction in insulin-producing β-cell mass that is observed in IUGR rats over time and expression of Pdx1, a critical regulator of pancreas development and islet differentiation, is restored to normal levels. Although adiposity was not examined in this study, GLPs are known to modify food intake, increase satiety, delay gastric emptying and suppress glucagon release; and therefore further studies are warranted.

The role of possible direct nutritional interventions was highlighted in the work by Wyrwoll *et al*[161]. Pregnant rats were treated with DEX from d13 to term, and offspring were cross-fostered to mothers on either a standard diet or a diet high in omega-3 fatty acids and remained on these diets post-weaning. Maternal DEX reduced birthweight and delayed the onset of puberty in offspring. Hyperleptinemia and increased fat mass developed in offspring by 6-month of age in DEX-exposed animals fed a standard diet but these effects were completely ameliorated by a high omega-3 diet. These results demonstrated for the first time that direct manipulation of postnatal diet can limit adverse outcomes of developmental programming. Furthermore, work by Zambrano *et al*[162] has shown that dietary intervention (changing from an obesogenic HF diet to a normal chow diet) prior to pregnancy and lactation can reverse metabolic programming of male offspring of obese rats.

Although several animal studies have now shown that a range of interventions can reverse or ameliorate programming-induced metabolic disorders, translation to the human setting as regards optimizing maternal health is difficult. Furthermore, some interventions such as leptin have gender-specific effects and may potentiate an adverse metabolic response in normal offspring[150,163]. Some human trials support the initial animal observations. For example, supplementation with iron and folic acid in pregnancy has been shown to increase birthweight but this response was modified by maternal nutritional status, with infants born to women with better short-term nutrition having greater birthweight response[164]. Whether there is an epigenetic basis to these observations similar to those reported for the rat models is not well established although it has been suggested that alterations at the H19 differentially methylated region is a likely mechanism by which folic acid risks and/or benefits are conferred *in utero*[165].

CONCLUSION

Epidemiological, prospective clinical studies and experimental research have clearly shown that the propensity to develop the metabolic syndrome in later life is increased when early life development has been adversely affected. The pathogenesis is not based on genetic defects but on altered genetic expression as a consequence of an adaptation to environmental changes during early life development. However, little is known about the interaction between the pre- and postnatal nutritional environment on either amplification or resolution of the programming phenotype depending on the degree of nutritional match/mismatch. Thus, experiments to examine the PARs hypothesis are required in conjunction with transgenerational work to further the DOHaD paradigm.

The molecular mechanisms underlying developmental programming are only recently beginning to be investigated. Epigenetics has now become a model that is fundamental to research into DOHaD[2]. The two most studied epigenetic mechanisms identified as having a role in the adaptive developmental programming of metabolic disorders are DNA methylation and histone modifications. Availability of dietary methyl donors and cofactors during a critical window of fetal development may influence DNA methylation patterns. Thus, it has been proposed that early methyl donor malnutrition (i.e. excess nutrition or undernutrition) could effectively lead to premature epigenetic aging, thereby conferring an enhanced susceptibility to adult disease in later life[166].

Developmental programming research offers a novel

approach to investigate the mechanistic basis of obesity and related metabolic disorders which in human populations predominantly arise from environmental factors and lifestyle choices. It is notable that the variety of different insults in early life (caloric, protein, iron, fat-fed) produce the same detrimental consequences that occur in adult life, which suggests a common mechanism underlies the developmental early-life programming of adult disease. A recent emerging focus has been on studies aimed at reversing the programmed phenotype; such studies offer an exciting potential for new advances in our understanding of critical windows of developmental plasticity and mechanisms underlying human obesity and related metabolic disorders.

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TOPIC HIGHLIGHT

Didier Vieau, Professor, *Series Editor*

Alteration of mitochondrial function in adult rat offspring of malnourished dams

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Abstract

Under-nutrition as well as over-nutrition during pregnancy has been associated with the development of adult diseases such as diabetes and obesity. Both epigenetic modifications and programming of the mitochondrial function have been recently proposed to explain how altered intrauterine metabolic environment may produce such a phenotype. This review aims to report data reported in several animal models of fetal malnutrition due to maternal low protein or low calorie diet, high fat diet as well as reduction in placental blood flow. We focus our overview on the β cell. We highlight that, notwithstanding early nutritional events, mitochondrial dysfunctions resulting from different alteration by diet or gender are programmed. This may explain the higher propensity to develop obesity and diabetes in later life.

Key words: Fetal programming; β cells; Mitochondria; Maternal malnutrition; Rats

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INTRODUCTION

Before describing and discussing the involvement of the mitochondria in the fetal programming of adult diseases, a brief introduction on the biogenesis and function of mitochondria will be presented.

Mitochondria, their biogenesis and function

It is only recently that the mitochondrial proteome has been considered as a dynamic system generated by the nuclear DNA (nDNA) and the mitochondrial DNA (mtDNA). In most human cells, mitochondria contain 10^3-10^4 copies of a circular genome of 16 569 base-pairs without introns. It contains 37 genes encoding 2 ribosomal RNAs, 22 tRNAs required for mitochondrial protein synthesis and 13 polypeptides[1]. These include 7 of the 46 polypeptides of the complex I (NADH dehydrogenase; ND 1, 2, 3, 4L, 4, 5, 6), one of the 11 proteins of complex Ⅲ (cytochrome b), 3 of the 13 polypeptides of complex Ⅳ (cytochrome c oxidase; COX-1, -2, -3) and 2 of the 16 proteins of complex V (ATP synthase; ATPase-6, -8)[2].

Mitochondrial biogenesis requires a tight coordination between the nDNA and mtDNA to transcribe the genes in the nucleus, as well as in mitochondria. The nDNA-

encoded mitochondrial proteins are translated by using cytosolic ribosomes and selectively imported into the mitochondrion through various import systems[3,4]. These proteins include the four units of the complex Ⅱ, the mtDNA polymerase γ, mitochondrial RNA polymerase, the mitochondrial transcription factor (Tfam), the mitochondrial ribosomal proteins and elongation factors, and the mitochondrial metabolic enzymes[5].

Three factors, i.e. peroxisome proliferator activated receptor γ (PPARγ) coactivator-1α (PGC-1α), nuclear respiratory factor 1 (NRF-1) and Tfam provide a molecular basis for the connection between environmental stimuli and mitochondrial biogenesis. PGC-1α is part of the PGC-1 coactivator family which, in addition to its role in the mitochondrial biogenesis and through its interaction with the PPARγ[6], regulates several functions, including adaptive thermogenesis, glucidic metabolism, fatty acid oxidation and mitochondrial anabolic and catabolic function. NRF-1 and -2 bind to the promoter region of a broad range of mitochondrial genes encoded in the nucleus, including Tfam. NRF-1 turns on Tfam, a key transcriptional factor that translocates into the mitochondria and activates mitochondrial biogenesis and function through mtDNA replication and transcription (Figure 1)[7]. NRF-1 may also affect expression of mitochondrial and metabolic genes[8].

In addition, PGC-1α may promote the mitochondrial biogenesis in a cell type-specific manner with the co-activation of PPARγ. It seems that PPARγ affects mitochondrial biogenesis indirectly by enhancing the expression of PGC-1α since the agonist of PPARγ rosiglitazone, induced endogenous expression of PGC-1α in adipose tissue[9,10]. Through this way, PGC-1α may drive PPARγ[6] and ameliorate symptoms of metabolic disease. In a cell-selective manner, the efficiency of the oxidative phosphorylation process may also be regulated by PGC-1α through the transcriptional control of uncoupling proteins (UCP)[11].

There is a great variation in the mtDNA across different cell types. Whereas somatic cells contain up to 4 000 copies, maternal oocytes may contain as many as 200 000 copies and sperm as few as 100[12]. This is the reason why it is usually accepted that mtDNA is exclusively maternally inherited.

Mitochondria are responsible for the production of energy by oxidizing pyruvate through the tricarboxylic acid (TCA) cycle and lipids through -oxydation. These processes produce reducing equivalents that then drive the electron transport chain (ETC) enclosed within the inner membrane to produce ATP. Inevitably, by the products of oxidative phosphorylation, mitochondria are also the major source of reactive oxygen/nitrogen species (ROS/RNS). Electrons leaking into the mitochondrial matrix can react with molecular oxygen. ROS can occur when electrons are in excess in case of inhibition of oxidative phosphorylation and they can damage macromolecules[13]. ROS can also inhibit the activity of the ETC, specifically the iron-sulfur center-containing enzymes of the complex I and Ⅲ, and mitochondrial aconitase of the TCA cycle[5]. Mitochondria also possesses a major role in the regulation of apoptosis. Indeed, several pro-apoptotic proteins reside in the intermembrane space, including cytochrome c and apoptosis inducing factor[14]. Due to the absence of protective histone proteins, to the close vicinity and the limited DNA repair mechanism, mtDNA is a sensitive target for oxidative DNA damage by ROS[15]. The mutation rate of mtDNA is at least 10 times higher than that of nuclear DNA[5,16].

Equally important, the TCA cycle is critical for several metabolic functions, where its intermediates are used as substrates for *de novo* synthesis of biomolecules[17]. Beside this anabolic process, the TCA cycle also plays a critical role in the catabolism where non-essential as well as essential amino acids are broken down to TCA cycle intermediates and fatty acids are oxidized to acetyl-CoA. So, the different anabolic and catabolic functions of the mitochondria are tightly regulated in response to nutrients such as glucose, amino acids and fatty acids. As shown in case of caloric restriction, adipose tissue features a strong down-regulation of genes involved in energy-generating process such as the TCA cycle and oxidative phosphorylation[18,19]. In the liver, which participates to maintain an adequate level of sugar in the blood, an up-regulation of genes involved in glucogenesis and β-oxidation was noted, whereas genes involved in the TCA cycle and oxidative phosphorylation were down regulated[19]. In the muscle, caloric restriction increased mitochondrial activity, at least in human[20].

Impaired mitochondrial function in metabolic diseases

Given the crucial role of mitochondria for multiple metabolic pathways, tight control of mitochondrial abundance and function is imperative for cellular homeostasis. Therefore, it is not surprising that a link exists between mitochondrial alteration and various diseases including diabetes, cancer and precocious aging[5]. Polymorphic variation in mtDNA has been associated with metabolic diseases. It should be noted that several studies indicate that genomic variation in the 37 mitochondrial genes plays a critical role in apoptotic and metabolic pathways in many tissues including the brain. It is only recently that the mitochondrial proteome has been seen as a dynamic cross talking system generated to adapt the mitochondrial functional capacity to meet the specific needs of the tissue or the disease state[21]. According to the tissue and depending of the functional requirements, the nuclear transcriptional programming of the mitochondrial proteome may vary. This is also true for disease state. For instance, in type 1 diabetes, an adaptation of the liver mitochondrial proteome to support ATP production and fatty acid oxidation was observed[21]. The posttranscriptional modifications are also tissue and disease specific and may modify the localization and function of the mitochondrial proteins and enzymes.

During the process of reduction of oxygen to water by the ETC, ROS/RNS, such as superoxide, hydrogen peroxide, the hydroxyl radical and nitric oxide are generated and cause oxidative damage to target structures. An

imbalance between the production of ROS/RNS and antioxidant defenses plays a major role in inducing alterations in insulin signaling pathways[22].

ROS and RNS are formed during both pro-inflammatory cytokines-mediated β-cell aggression in type 1 diabetes and glucolipotoxicity-mediated β-cell dysfunction in type 2 diabetes[23-26].

At least 1.5% of diabetic patients exhibit mutations in mtDNA[27]. Many studies suggest that mitochondrial dysfunction is critical in insulin-linked pathologies. Fewer mitochondria, lower expression of mitochondrial genes, abnormal mitochondrial morphology and disturbed oxidative phosphorylation are commonly described in insulin target tissues such as the liver, muscle and adipose tissue in the case of type 2 diabetes[28] or obesity[29]. Decrease in the number of mitochondria causes mitochondrial dysfunction[30] and mtDNA density is closely associated with oxidative function which itself is linked to insulin sensitivity. Indeed, it has been shown that a decrease in mtDNA density in peripheral blood cells preceded the development of type 2 diabetes[31]. Moreover, mtDNA density was also associated with abnormal obesity before the onset of type 2 diabetes[32,33]. Mitochondrial dysfunction results in an accumulation of fatty acid metabolites, diacylglycerol and long chain fatty acid CoA which will induce insulin resistance *via* the activation of the phosphokinase C. These changes are accompanied by a decrease in both mitochondrial oxidative activity and ATP biosynthesis.

As already mentioned, several studies with type 2 diabetic patients and non-diabetic subjects with a family history of diabetes featured down regulation of nDNA-encoded mitochondrial genes. For some authors, this may lead to alteration at the level of the mitochondrial biogenesis like the control by PGC-1α and NRF-1[34-36]. However, Morino *et al*[30] did not observe any difference in such factors and suspected a confounding influence such as being overweight. Disruption of the nuclear gene Tfam in cells reproduced pathophysiological features of diabetes[37]. Moreover, maternally inherited alterations in mtDNA that disrupt mitochondrial function are known to cause an insulin-deficient form of diabetes resembling type 1 diabetes[38].

FETAL MITOCHONDRIAL PROGRAMMING

Intrauterine environment is a major contributor to the future of individuals and disturbance at a critical period of development may compromise their health. After the observation made by Hales *et al*[39] in 1991 that men with low birth weight had increased susceptibility to develop type 2 diabetes and cardio-vascular disease, the same association was found throughout the world. Therefore, the concept of "the thrifty phenotype hypothesis" suggested 19 years ago by Hales *et al*[40] is now accepted by the scientific community as being involved in several pathologies such as obesity, insulin resistance, diabetes,

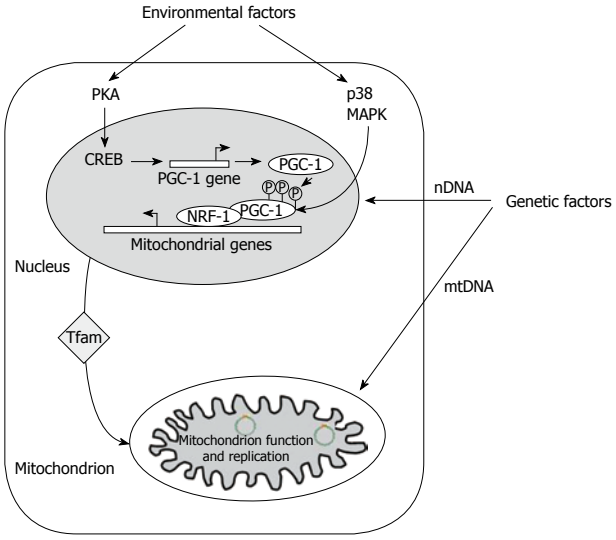

Figure 1 Mitochondrial gene expression and biogenesis. Environmental factors induce PKA and *p38* MAPK pathways. PKA phosphorylates CREB transcription factor, which is involved in the induction of peroxisome proliferator-activated receptor γ coactivator (PGC)-1α gene expression. Activation of *p38* MAPK phosphorylates PGC-1α protein, resulting in its stabilization and activation. PGC-1α activates the expression of the subunits of mitochondrial electron transport chain and Tfam, one of the major regulatory factors for mitochondrial transcription and replication, through the co-activation of nuclear respiratory factor 1-mediated transcription. Tfam subsequently translocates in the mitochondrion and directly increases the transcription and replication of mitochondrial DNA (Adapted from Remacle *et al*[45], 2007).

hypertension, cardiovascular disease and even cancer and precocious aging. The term "thrifty phenotype" suggests that in case of poor fetal nutrition, resulting from either poor maternal nutrition or poor delivery of nutrients to the fetus due to other causes such as placental dysfunction, an adaptive response is set up by the fetus to optimize the growth of key organs like the brain at the expense of other tissues such as muscles, kidneys and endocrine pancreas. It is also accompanied by programmed changes in metabolism, enabling the organisms to efficiently use and store nutrients. Such adaptations are beneficial for the survival of the fetus but may be detrimental later in life, namely when a mismatch occurs between the environment predicted and that one encountered after birth. Then, the concept evolved, introducing the notion of "developmental plasticity" and "predictive adaptive response"[41]. If the insufficient metabolic and nutritional environment is the same during fetal life and early after birth, the adaptation set up by the fetus will be efficient to cope with it but if not, the adaptations are not appropriate and further enhance the risk of developing metabolic diseases later in life.

It is only recently that attention was paid to the involvement of the mitochondria as putative targets for the fetal programming of adult disease. Indeed, it has been proposed that a key adaptation enabling a fetus to survive in a limited energy environment may be a programming of mitochondrial function[42].

The Simmons' group was the first to show in rat that utero-placental insufficiency provoked by uterine artery

ligation targeted the mitochondria because it induced a lower pyruvate oxidation in the muscle[43] and liver[44] of young adult offspring. In muscle, this defect leads to a chronic reduction of ATP available from oxidative phosphorylation, which compromises glucose transporter 4 (GLUT4) recruitment, glucose transport and glycogen synthesis, contributing to insulin resistance and hyperglycaemia of type 2 diabetes[43]. The concept of mitochondrial programming could be especially true for cells that have a high energy requirement, such as the β-cells. Indeed, uteroplacental insufficiency also induces mitochondrial dysfunction in fetal β-cells leading to increased production of ROS, reduced ATP production and decline in mitochondrial ETC complex I and Ⅲ. In turn, this drives damage to mtDNA that may progressively deteriorate the mitochondrial and β-cell function and diabetes may ensue[42].

Although the model of placental insufficiency induced severe fetal growth restriction due to reduction of transfer of nutrients as well as of oxygen to the fetus, more subtle nutritional disturbances in the intrauterine environment have also been shown to program key organ during development. In a general population, nutritional imbalance in the presence of an adequate quantity of calories and oxygen is obviously less drastic but is probably more frequent and may have substantial consequence for the progeny.

For many years we have investigated several models of early malnutrition in rats to understand by which mechanism developmental programming could occur. Most of our research focused on the β-cell development in the fetus and newborn and we have evaluated long-term consequences in offspring of mother fed a low protein diet (LP). We pointed to an alteration at the level of the mitochondria but because insulin resistance, diabetes and obesity are burning throughout the world, we also investigated if a mitochondrial programming could be a common mechanism for several types of nutrient imbalance, including calorie restriction or HF.

If the quantity of calories is adequate during development but the proteins are low, the development of many organs is altered and the islet cell is specifically targeted as reported in several reviews[45] and in some articles of this book. Briefly, although the fetal growth of the offspring from dams fed a LP diet was only reduced by 5%-10%, the fetal β-cell mass was smaller. Such a reduction was demonstrated to be due to a low β-cell proliferation, a reduced islet vascularisation[46-49] and an increased susceptibility of the insulin secreting cell to be destroyed by apoptosis in response to aggressive molecules[50,51]. In addition, these fetal islets secreted less insulin in response to glucose and amino acids[52]. The lower insulin secretion was maintained in young adulthood[51,53]. Later in life, the LP offspring featured also an increased vulnerability to cytokines, ROS[51] and poor capacity to regenerate after streptozotocin destruction (unpublished data). On the basis of such pathological characteristics, we investigated by proteome and microarray analysis if a common pathway could be found and we demonstrated that the mitochondrion through its TCA cycle was the main target. Indeed, 11% of the altered genes founded in the LP fetal islets coded for mitochondrial protein and the expression of almost every gene involved in the TCA cycle was changed by the maternal LP diet[54,55].

Antioxidants defenses

We knew from the literature that the normal adult β-cells possess particularly weak antioxidant defenses activity compared to other organs such as the liver[56,57], but no data were available for fetal and neonatal pancreatic islets. With their first breath, newborns are directly exposed to an increase in oxygen concentration. A few hours later when lactation starts, they are also exposed to another type of nutrition, switching from a diet rich in glucose and amino acids *in utero* to a fatty diet during lactation. A microarray analysis performed on mtRNA from cord whole blood collected after human cesarean section revealed a higher expression of genes involved oxidative stress pathways such as superoxide dismutase (SOD), catalase, peroxiredoxins and UCP[58]. Thus, we investigated the islet antioxidant activity at birth and after weaning in normal rats. While SOD and catalase activity were much lower in islets than in the liver, we found an as efficient glutathione peroxidase activity (GPX) but that, however, decreased thereafter when compared to the liver, weakening the general antioxidant capacity in normal rats postnatally[59]. GPX removes H_2O_2 produced through the dismutation by SOD of the superoxide anion to O_2. When the mother was fed the LP diet we found that the GPX activity was decreased in fetal islets[59]. Then, a temporary efficient GPX activity counterbalancing SOD activity that occurs in normal islets was not possible in LP fetal islets. This alteration may be one explanation for the increased susceptibility of these fetal islets to cytotoxic aggression. If a switch to a normal diet is given to the mother after birth, a reduction of islet antioxidant capacity was observed in the newborn. If the LP diet was maintained until weaning such lowering was not reported. This observation supports the concept of the detrimental effect of a mismatch between a suboptimal environment and a richer environment after birth[60].

We were the first to measure the oxidative stress (OS) and the antioxidant capacity in the islets of 3-month old adult offspring from LP mother. Nitrotyrosine levels were significantly higher in the plasma of offspring when the LP diet was present during fetal life or during fetal life and lactation[59]. Adult islets expressed higher iNOS levels and consequently secreted large amounts of NO[61]. The best way to verify the antioxidant potential of a cell is to measure the activity of the antioxidant enzymes. Maternal LP diet provoked an increased SOD activity in adult islets which should increase the level of H_2O_2, but no concomitant activation of catalase and GPX was observed. This imbalance could lead to higher hydrogen peroxide production that may concur to increased oxidative stress contributing to the alteration of the insulin se-

cretion and the increased vulnerability of the β-cell later in life[51,59].When total SOD activity was measured, the analysis did not allow making a difference between the manganese superoxide dismutase (MnSOD) and the Cu/ZnSOD. An increased expression of Cu/ZnSOD gene but not of MnSOD was observed in the offspring that received a LP diet during gestation or during gestation and lactation. When the LP offspring was analyzed at 15 mo, the expression of both Cu/Zn and MnSOD genes was decreased in the islets[62].

Mitochondrial biogenesis and function

As mentioned above, the participation of mitochondria in the programming of β-cell dysfunction observed in offspring submitted to environmental disorders during early life was proposed recently[27]. Simmons *et al*[42] found that uteroplacental insufficiency during late gestation, which implies nutrient as well as oxygen depletion, induced OS and marked mitochondrial dysfunction in pancreatic islets of the intrauterine growth retardation (IUGR) progeny. Showing that mitochondrial dysfunction was not limited to pancreatic islets[43,44], they proposed that a key factor enabling a fetus to survive in a limited energy environment is a reprogramming of mitochondrial function, which can lead to deleterious effects.

In order to assess whether maternal malnutrition, without restriction of the oxygen supply, should lead to mitochondrial programming in islets, we analyzed parameters of mitochondrial biogenesis and function in adult offspring of dams fed either a protein restriction (LP), a high fat diet (HF) or exposed to a global food restriction (GFR) during gestation.

We found that, independently of the type of prenatal malnutrition, mitochondrial function was affected in pancreatic islets of the adult offspring[53,63]. Thus, maternal malnutrition itself caused mitochondrial dysfunction in pancreatic islets from 3-month old progeny that may predispose to glucose intolerance later in life, namely by affecting insulin secretion[64,65]. *In vitro*, male and female islets from control offspring increased their insulin secretion in response to glucose. This enhancement was less marked in LP offspring and absent in GFR and HF 3-month old animals. This could be associated with dysfunctions in energy metabolism, located for a large part in mitochondria because ATP production was blunted after glucose challenge in islets of male and female progeny from malnourished dams.

It is becoming obvious that the programming is a sex-specific phenomenon[53,63]. Although the common alteration cited above exists, some changes were specific to the maternal diet as well as to the sex of the progeny (Figure 2). For instance, in male progeny, the restriction of nutrients seemed to have more consequences since β-cell mass, as well as the expression of genes coding for proteins involved in energy metabolism and TCA cycle, were found altered to a greater extent in LP and GFR rats than in HF male animals (Figure 2A). Conversely, a maternal diet enriched with animal fat was more pernicious for females because HF females presented much more damage than LP and GFR females (Figure 2B). Also, independently of the type of early malnutrition, the pathway leading to blunted ATP production in malnourished offspring appeared differently in males and females. Indeed, increased basal production of ROS was found only in males of the 3 groups (Figure 2A). This latter long-term consequence of prenatal malnutrition could be a determinant for inducing sex-specific cellular and molecular effects since ROS are known to be able to inactivate the iron-sulfur centers of the ETC complexes and TCA cycle enzymes, resulting in shutdown of mitochondrial energy production[66]. It should be noted that higher ROS production in male islets from LP offspring was congruent with our previous observation showing the influence of early malnutrition on adult antioxidant potential[59]. Manifestation of progression of OS was also reported by others for IUGR male offspring of rats exposed to uteroplacental insufficiency[42]. In these rats, OS was linked to accumulation of mtDNA mutations in islets and blunted ATP production. Indeed, IUGR males presented a reduction by 50% of the activities of both complexes I and Ⅲ at 7-week of age that dropped at 15-week to less than 25% of those of controls[42]. In female offspring that were exposed to low protein, low calorie or HF during prenatal life, we reported that the poor capacity of ATP biosynthesis directly involved a down regulation of crucial factors. Indeed, independently of the type of early malnutrition, each female group showed a reduction in the expression of both malate dehydrogenase and ATP6 which could decrease the mitochondrial energy production through the TCA cycle and the ETC (Figure 2B).

The effect of altered nutrient availability to the fetus on β-cell mitochondrial DNA is puzzling. While reduction of placental blood flow first provoked an increase in the number of mtDNA copies at fetal stage, this number decreased with age under the normal value[42]. We did not find any modification in LP progeny mtDNA but an increase in offspring of mothers 50% underfed or fed a HF during gestation.

Another consequence of early malnutrition which is sex specific was the over expression of PPARγ in islets from LP, GFR and HF males. This strong PPARγ expression might increase ROS production, *via* an enhanced lipid uptake in cells that are not metabolically adjusted to handle this challenge[67]. Moderate amounts of PPARγ are known to be expressed in normal pancreatic β-cell but its fundamental role in these cells is not fully understood[68]. PPARγ appears to be important for glucose homeostasis since PPARγ ligands reduced insulin levels by targeting the insulin gene transcription[69]. Improvement of mitochondrial biogenesis was also associated with enhanced PPARγ function in adipose tissue[9]. Emerging evidence suggests that PPARγ ligands, named thiazolidinediones, offer benefits for preventing or delaying the decline in β-cell function[70,71] through effects on lipid

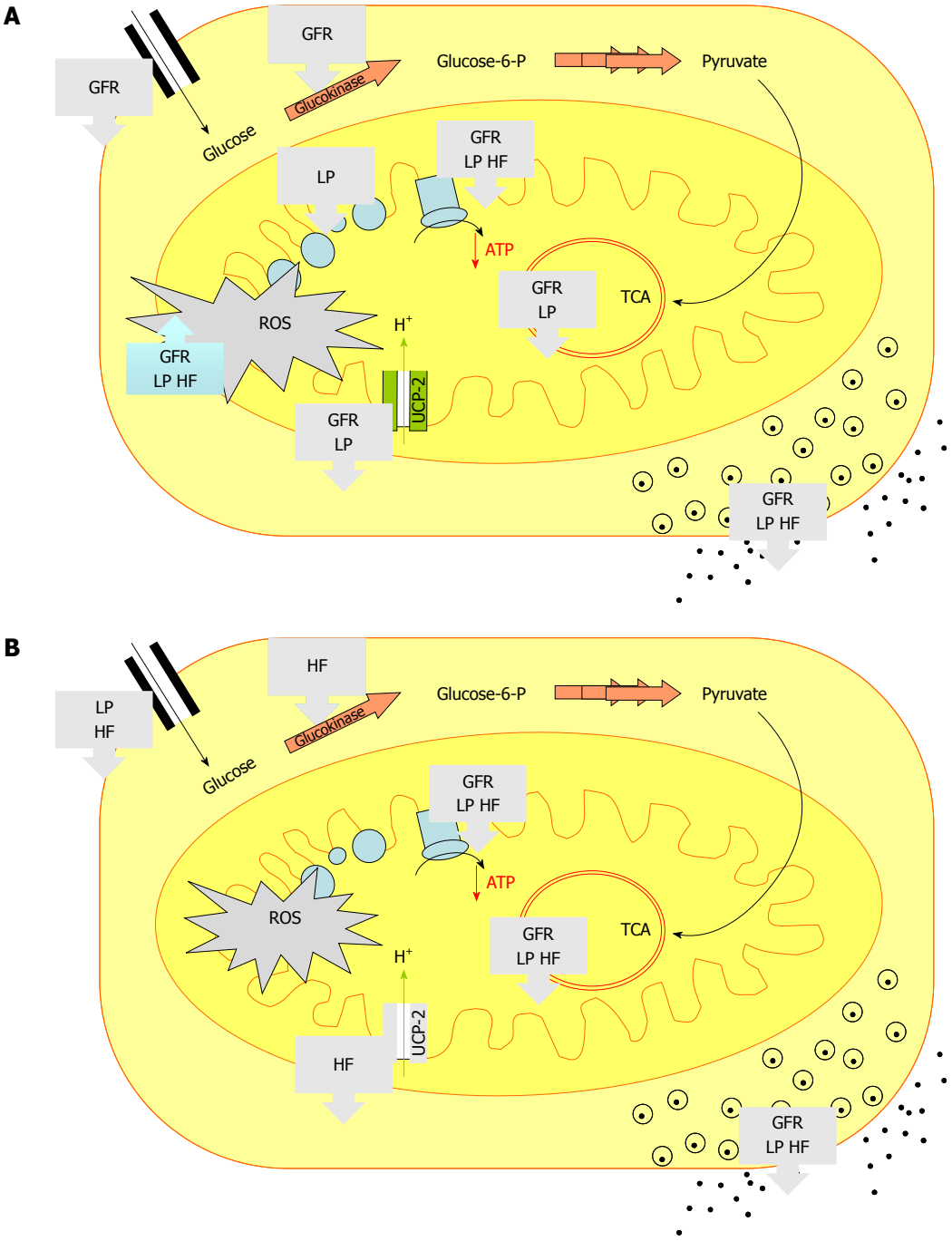

Figure 2 Summary of the main consequences of prenatal malnutrition on metabolic pathways in islets from low protein diet, global food restriction and high fat diet. As shown in the text and extensively described in the related publications[53,63], the entrance of glucose was analyzed through GLUT-2 expression, the glycolysis through glucokinase expression, the TCA through citrate synthase and malate dehydrogenase expression. Reactive oxygen species production, ATP content and insulin secretion in response to glucose were also determined. The arrows indicated an increased or decreased level compared to control offspring. A: Males; B: Females; GLUT: Glucose transporter; TCA: Tricarboxylic acid cycle; GFR: Global food restriction; LP: Low protein diet; HF: High fat diet; ROS: Reactive oxygen; UCP: Uncoupling proteins species.

transport and metabolism, by modulating the expression of genes involved in glucose sensing[68,72] and by reducing ER stress[69]. Although activation of PPARγ results from ligand-dependent heterodimerization of PPARγ with RXR, over expression of PPARγ may induce by itself an increase in GSIS in the absence of exogenous PPARγ ligand[68]. These data could also help to explain that LP males maintained insulin release despite a blunted ATP biosynthesis after glucose challenge. However, we did not show the same correlation for GFR and HF, suggesting that the excessive level of over expression of PPARγ in LP rats could be determinant to GSIS. PPARγ has been reported to induce expression of UCP-2 in β-cells[73], as observed in LP male islets. Thus, as postulated above, the particularly high level of PPARγ expression could be a key factor inducing UCP-2 transcription in LP male islets.

Mitochondrial programming in other organs

Mitochondrial dysfunction is not limited to the pancreatic islets. In the liver, a marked resistance to insulin was observed in the young IUGR progeny prior to the occurrence of diabetes. Oxidation rates of pyruvate, glutamate and succinate were blunted in isolated hepatic mitochondria of very young IUGR offspring. Increased MnSOD protein expression as well as high levels of 4-hydroxynonenal was found already at fetal stage and maintained later in life[44]. We also reported a programming that was sex-specific, at the level of mitochondria in the liver of offspring of malnourished mother[53,63]. After a maternal LP diet, although mtDNA content was reduced in male liver, no expression of genes involved in mitochondrial biogenesis, function and metabolism was found altered while the female offspring presented a lower expression of citrate synthesis and malate dehydrogenase, suggesting that the ATP production could be affected[53]. The liver of GFR and HF males featured a higher expression of ND4L and COX-1, respectively subunits of complexes I and Ⅳ of the ETC encoded by the mtDNA and a reduced level of citrate synthase and malate dehydrogenase mRNA[63]. In the LP offspring, key enzymes that regulate glucose homeostasis were found altered in the young and adult progeny[74]. An increase in hepatic carbonyl concentration and an up-regulation of GPX were also observed in the LP adult progeny which may be indicative of higher oxidative stress[75].

In muscle, the reduced pyruvate oxidation provoked by uteroplacental insufficiency results in a chronic reduction in the supply of ATP available from oxidative phosphorylations, which compromises GLUT4 recruitment, glucose transport and glycogen synthesis, contributing to insulin resistance and hyperglycemia of type 2 diabetes[43].

Park *et al*[76] found that the offspring of dams fed a LP diet during pregnancy and weaning have a lower mtDNA content as well as mtDNA-encoded gene expression in the liver and skeletal muscle. They also reported lower mtDNA levels in the total pancreas[76] which was, however, not corroborated by us when only endocrine pancreas was analyzed[53].

Several reports documented that vascular structure and function can be programmed in early life. It was shown that maternal low protein diet impaired vascularization in the islets[46-49] as well as in the brain[77] and muscle[78]. The vascular change may be associated or not with hypertension later in life. A clear mitochondrial programming at the level of endothelial cell is not yet demonstrated. What is known is that growth restricted neonates exhibited endothelial dysfunction very early in life, predisposing them to atherosclerosis. Higher mitochondrial ROS generation and function are associated with cardio-vascular disease. In neonates with IUGR, increased lipid peroxidation was observed in association with low levels of antioxidants and antioxidant enzyme activity[79]. It is possible that excessive ROS production by placental mitochondria may be released in the fetal circulation and may alter vascular mtDNA[80]. Taylor *et al*[81] searched for mitochondrial abnormalities in the aorta of adult offspring from a mother fed a HF during gestation and lactation and revealed a lower expression of the mitochondrial genome. Four genes of the mitochondrial encoded mRNA were down regulated among which was ATPase-6 and six genes of the nuclear mRNA encoding mitochondrial proteins were under expressed, among which was MnSOD.

CONCLUSION

In conclusion, an alteration in the metabolism and the nutrition of the mother affects the mitochondria in several organs of the progeny. Alterations are observed at birth but aggravate with age. More specifically, imbalance or less availability of nutrients to the β cell, small repeated increases in ROS production, lower ATP synthesis and inadequate antioxidant balance may predispose to β cell dysfunction. Some of these mitochondrial alterations seem more dramatic in male animals than in females in cases of nutritional restriction contributing to the early development of a prediabetic state in male progeny.

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Events Calendar 2011

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AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011 Miami
FL, United States

January 28, 2011
Diabetes UK and External Conferences
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London, United Kingdom

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 16-19, 2011
The 4th International Conference on Advance Technologies & Treatments for Diabetes
London, United Kingdom

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week,
Westin Bayshore, Vancouver
British Columbia, Canada

February 28-March 1, 2011
Childhood & Adolescent Obesity: A Whole-system Strategic Approach
Abu Dhabi, United Arab Emirates

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham
England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology
Jacksonville, FL , United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey
March 28–30, 2011
The Second World Congress on Interventional Therapies for Type 2 Diabetes
New York, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
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May 7-10, 2011
Digestive Disease Week
Chicago, IL, United States

June 2-5, 2011
The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 11-12, 2011
The International Digestive Disease Forum 2011
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June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
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AADE 38th Annual Meeting
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October 19-22, 2011
ISPAD 36th Annual Meeting
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19th United European Gastroenterology Week
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INSTRUCTIONS TO AUTHORS

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The major task of *WJD* is to report rapidly the most recent results in basic and clinical research on diabetes including: metabolic syndrome, functions of α, β, δ and PP cells of the pancreatic islets, effect of insulin and insulin resistance, pancreatic islet transplantation, adipose cells and obesity, clinical trials, clinical diagnosis and treatment, rehabilitation, nursing and prevention. This covers epidemiology, etiology, immunology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, diagnosis and therapeutics. Reports on new techniques for treating diabetes are also welcome.

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The columns in the issues of *WJD* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in diabetes; (9) Brief Article: To briefly report the novel and innovative findings in diabetes research; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJD*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of diabetes mellitus; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in diabetes mellitus.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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