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ADVERSE EFFECTS OF NUTRITIONAL PROGRAMMING DURING PRENATAL AND EARLY POSTNATAL LIFE, SOME ASPECTS OF REGULATION AND POTENTIAL PREVENTION AND TREATMENTS

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Nutritional programming, regulation and some ways for prevention/treatment to ameliorate or normalize adverse outcomes of programming are discussed. Epidemiological studies in human and animal experiments showed that nutrition during fetal and neonatal life may lead to related disorders in adulthood. But several argues may question its validity arising the question of the adequate models used to reproduce human situations. Protein level in milk formula intake by infant during neonatal life is discussed. Body weight at birth reflects the product growth trajectory during fetal life. Low birth weight is considered as the result of an adverse growth trajectory and is often associated with later metabolic diseases in adult age. But, the sum of prenatal growth trajectory, rapid growth in early infancy (catch up growth), early adiposity rebound in childhood must be considered to determine the origins of later diseases in adulthood. The review focuses the regulation of nutritional imprinting on hormonal and epigenetic mechanisms which are complementary. The HPA axis and GH-IGF axis may have a crucial role in the regulation induced by nutritional programming. The persistent alterations seem to be a consequence, at least in part, of elevated insulin levels during 'critical periods" of pre- and early postnatal development. Also, leptin seems to play an important role in this complex system. New knowledge about these mechanisms involved suggest the development of new, rational, and effective preventive and/or therapeutic options before and/or after birth. Thus, early infancy may provide an opportunity for intervention aimed at reducing later disease risk.

Key words: *nutritional programming, metabolic diseases, intrauterine growth retardation, catch-up and breast-feeding, mother and offspring nutrition*

Abbreviations: ACTH- adrenocoticothropin hormone; AgR- agouti-related peptide; BMI- body mass index; BW- birth weight; CART- cocaine- and amphetamine-related transcript; CNS- central nervous system; GAL- galanin; GH- growth hormone; GI- gastrointestinal; GIT- gastrointestinal tract; HPA axis- hypothalamic-pituitary-adrenal axis; Ig- immunoglobulin; IGF- insulin growth factor; IGFBP- binding protein; IUGR- intrauterine growth retardation; LGA- large for gestational age; MSH- alpha-melanocyte-stimulating hormone; NO- nitric oxide; NPY- neuropeptide Y; POMC- proopiomelanocortin, SGA- small for gestational age; SNS- sympathetic nervous system; T_3- triodothyronine

INTRODUCTION

Morphological and functional characteristics in mammals develop according to the individual genome. However, there is a growing body of evidence from epidemiological studies in humans and from controlled investigations in animal models that genome regulation is largely modified by the nutritional environment such as an amount and composition of nutrients available to the offspring during prenatal and neonatal periods (1-5). These observations even led some to suggest that the genetic impact is perhaps overestimated since, as an example, it has been estimated that 62% of the variation in human birth weight (BW) results from the intrauterine environment (including nutrition), compared with 20% and 18% resulting from maternal and paternal genes, respectively (6). It has been recognized that ontogenetic development involves developmental plasticity which implies that one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development (7). There are numerous studies showing that a suboptimal *in utero* environment (resulting in *e.g.* quantitative or qualitative fetal growth retardation or modification), as well as suboptimal nutrition during early neonatal life alters development. This situation can predispose the individual to lifelong health problems like metabolic syndrome or related diseases (such as glucose intolerance, insulin resistance, cardiovascular disease, hypertension, and obesity) (1, 2, 5, 8-17). These observations are in keeping with the 'predictive adaptive response' hypothesis

(18), an extension of Hales and Barker's 'thrifty phenotype' hypothesis (19) or the 'fetal origins' hypothesis. This phenomenon has been termed nutritional, developmental or metabolic programming which frequently involves intrauterine growth retardation (IUGR) or nutritional inadequacies during early postnatal life. Thus, programming is defined as the induction, silencing or restriction of development of a permanent somatic structure or physiological system with long term effects for function. This may be caused by stimuli or disturbing factors (*e.g*. nutritional insults) acting during a sensitive time period (i.e. time of maximal growth of a tissue) or being a line of consecutive events affecting fetal growth quality (20, 21). Programming is based on the observation that environmental changes can reset the developmental path during a critical period of life, when the tissues still have some plasticity and are in a higher proliferating and differentiating phase (22). The effects of such stimuli can be reflected in lower than average BW.

The objective of this review is to summarize data on nutritional factors affecting fetal and postnatal development, with particular attention to energy intake and macronutrient composition. The importance of low birth weight, and growth rate for the occurrence of programming effects are examined as well as recent knowledge concerning some regulations. Finally, we suggest some ways for prevention and/or treatments to ameliorate or normalize adverse outcomes of programming.

NUTRITIONAL PROGRAMMING: RELATION WITH ENERGY INTAKE AND MACRONUTRIENT COMPOSITION

Experiments focusing on maternal overnutrition during pregnancy and in the offspring postnatally provide data relevant to the dietary habits in the Western world and emerging economies. In contrast, maternal restriction followed by adult overnutrition can serve as a model for conditions in developing nations, immigrant populations and as consequences of *in utero* growth restriction from placental disorders (23-25).

Nutrition of the pregnant mother

The "fetal origin" hypothesis proposes that alteration in fetal nutrition and endocrine status results in developmental adaptations that permanently change structure, physiology, and metabolism, thereby predisposing individual to disease in adult life (26). Thus, concerning nutrition during fetal period, Armitage *et al*. (24) have summarized evidence for the programming of key criteria of the metabolic syndrome, such as insulin resistance, adiposity, hypertension and dyslipidemia caused by different types of maternal nutritional insufficiencies affecting also placental function. Most often, these results were obtained from epidemiological studies in humans or experiments using rodent and ovine models where animals were fed high-fat diets or diets with caloric and/or protein restrictions. It is, however, difficult to draw general conclusions because there is a great variety of imbalanced maternal nutrient supply (*e.g*. differences in protein/carbohydrate ratio, fatty acid composition, *etc*.). Another factor which seems to be important is the period of maternal ingestion of these diets during pregnancy, *e.g*. inadequate nutrition during preconception, mid or late pregnancy, whole pregnancy or pregnancy and lactation (27).

Maternal undernutrition in the ewe (28, 29) or maternal protein restriction in the rat (30) during periconceptional or preimplantation periods resulted in modifications of embryo development leading to abnormalities of the offspring in late gestation and postnatal periods. When sows enter pregnancy in poor nutritional condition with decreased body reserves, this can negatively affect the growth and development of early embryos (31), although at this stage, embryos have little size and their absolute protein requirements are very low (32). In ewes, undernutrition during the maximal growth of the placenta (in sheep 28-80 gestational days) resulted in an increase of adiposity of the offspring at term whereas undernutrition during late gestation reduces body fat (27). Poor nutrition of the mother during maximal placenta growth has been reported to influence fetal growth and BW in human babies (33). Taken together, it seems that exposure to dietary energy and protein restriction may impact upon specific physiological control systems in adult life (34, 35). In humans, global food restriction during early gestation influenced the cardiovascular system, reflected as an increased risk of coronary heart disease (36). Whereas nutrient restriction during late gestation, coincident with the period of maximal fetal growth, affected intermediary metabolism, in particular, glucose insulin homeostasis, leading to an increased risk of diabetes type 2 (37).

In rat study, undernutrition applied to several successive generations had a cumulative effect on reproductive performances, during several generations. Thus, ingestion of protein deficient diet during 12 generations resulted progressively in more important fetal growth retardation. When the mothers received the standard diet, it was necessary to wait for three generations to observe normal development (38). In the same way, rat fetuses exposed to an "abnormal" nutrition of their mother had a vascular response abnormal during two generations (39).

Maternal overnutrition (high fat, high energy, high protein feeding) consequences are less elaborated than the effects of undernutrition as recently reported in rodent and sheep species (40). Maternal overnutrition during the premating period or early pregnancy often results in increased porcine embryo or fetal mortality (41, 42). Interestingly, like underfeeding, once pregnancy is established, overfeeding retards fetal growth in piglet (43) and in offspring of adolescent ewes (44). Feeding pregnant rats with a high protein diet resulted in a "reprogramming" of body weight, body fat content, energy expenditure, and blood pressure (45, 46). Likewise in the pig, protein overnutrition during pregnancy was shown to lead to lower BW (47). Maternal high fat feeding in rats can result in a cardiovascular dysfunction or in a metabolic syndrome like phenotype of the adult offspring (25, 48). High carbohydrate diets in early pregnancy are associated with babies with low BW (49) and with higher blood pressure in middle age (50). Also, in pregnant women, supplementation with products supplying energy in form of protein resulted in decreased offspring BW (51-53). An association between meat intake of pregnant women and hypercholesteremia of the offspring at the age 28-30 years has been reported which might be the consequence of a higher protein, fat or iron intake or a combination of these (54). Epidemiological data indicated that high maternal dietary protein intake in late pregnancy affects BW and blood pressure (55).

Data reported so far concerned mostly the quantitative aspect, i.e. the amount of energy, fat and/or protein in the maternal diet the fetus of which was exposed to as factors predisposing the development of chronic diseases during adult age. Moreover, these data concerns extreme nutritional conditions *in utero* such as diabetes or famine which may have some effects on subsequent obesity. There is currently little to suggest that markers of a normal range of intrauterine conditions, such as pregnancy weight gain or BW associated with subsequent adiposity (56). Thus, it has to be considered at least two points. 1) Changing the concentration of one nutrient can alter the ratios and/or nutrient density of several other nutrients in the mother diet. According to Harding (20), there may be, however, many other factors involved such as the ratios of macro- and micro-nutrient delivered to the fetus, amino acid

composition and fluctuations of nutrient supply during pregnancy as well as interactions between nutrients. 2) No data are available concerning the true contributions of nutritional substances brought to the fetus. It would be necessary to do proxy measures of intrauterine conditions at different stages of gestations, *e.g*., dietary intakes or weight gain in each trimester of pregnancy (56).

Nutrition of the young from birth to weaning

It has been long known in the rat, that under- or overnutrition during the suckling period resulted in modification of growth throughout postnatal life (57). Compared to control, larger milk volume and greater energy intake especially from the higher milk fat content, from the early days of lactation resulted in a faster growth in pup (58). In rat, postnatal overnutrition resulted in increase of body weight as well as modifications in fatty acid composition of membrane lipids from erythrocytes, thrombocytes and liver mitochondria in 3, 6 and 11 months old animals. The observed changes of membrane fatty acid composition emphasize that not only functional but also structural properties are affected by the amount of energy and nutrients intake during the postnatal period and could reflect in a certain extent a long-term influences as augmentation of lipogenesis (59). In rat, the effects of under- and overnutrition were studied in suckling offspring coming from large and small litters respectively compared with normal litters. The early postnatally overnourished animals showed a higher body weight gain during the sucking period through juvenile life until adulthood associated with enhanced mean food intake and developed hyperinsulinism that may represent a predisposing factor for the development of metabolic disease risk in later life. Although the effects of early postnatal overnourishment are important, results demonstrate that it is possible for long-term overnutrition postweaning to override these effects in adulthood (60). In the contrary, no differences were found in undernourished animals from 30 days of life (61). In the experiments on the effects of food restriction in rats, Remmers *et al*. (62) have shown that neonatal food restriction reduced growth in all body dimensions and energy intake throughout life and programmed rats to remain small and lean in adult life, with a lower food intake.

By manipulating the diet of the mother, it was shown that nutritional programming is related to milk composition. Thus, lower total milk energy intake by pups during lactation resulted in a lower body weight during this period but also after weaning even if the animals were fed a normal diet (63). A change from fat-rich (rat milk) to carbohydrate-rich (high caloric milk formula) without alterations in the total energy content for newborn rat pups, resulted in the immediate onset of chronic hyperinsulminemia and adult-onset obesity (64). Similarly, exposure to a high-carbohydrate milk formula during the suckling period resulted in the immediate onset of hyperinsulinemia and its persistence throughout adulthood, despite the removal of the high-carbohydrate nutritional stimulus at weaning (65-67). In neonatal rats, higher protein intake *via* the enteral route led to enhanced short term weight gain, insulin resistance, and modified expression of glucose transporters. However, these differences were not sustained in the adult life (68).

In human neonates, high protein milk formula (2 vs. 1.5 g/100 ml) were suggested in small for gestational age (SGA) and/or IUGR baby to increase psychomotoric development at the age of 8 years (69) but this practice was more recently counter versed, underlining there was no effect on psychomotor development, with a risk to induce later diseases in adult age (70). Particularly, the importance of precocious adiposity rebound usually observed between 2 and 6 years of age could be linked to the quantity of proteins consumed during the first year of life (71-72). Nowadays in France, an epidemiological study using a large number of babies is underway. Its aims are to test the effect of the protein level (2.15 vs 1.45 g/100 mL) in milk formula for IUGR babies on the psychomotor development as well as body composition, metabolic parameters and hormonal status.

Nutritional programming revisited

The notion has been put forward that early mal-nutrition could be involved in the increase of diabetes and obesity incidence worldwide over the last two decades. However, it is unclear to which extent the world's obesity epidemic and its related disorders can be explained by the developmental origin (73, 74). As an example, following an epidemiological study in children at the age of 5, 6, 7 and 8 years, there was no evidence that predictive adaptative responses made by the fetus or infant affected the child's weight or insulin resistance later in childhood (75). Thus, Lucas *et al.* (76) who have initiated the malprogramming notion have themselves suggested a "revisited hypothesis" concerning "fetal origins of adult disease". Conclusions drawn from epidemiological studies linking low BW and incidence of adult metabolic disease have been criticized for several reasons (77-79). Firstly, body weight at birth is a measure easily available but not very meaningful in regard to the nutrient supply or nutritional status of the mother during pregnancy, and developmental stage at the time of birth. In particular, results of epidemiological studies are sometimes expressed without to take into account of confounding factors such as social class, education, alcohol intake and smoking that are known to affect BW in humans, as well as to contribuate of adult body size and weight (77, 80-83). Secondly, studies showing an association between BW and adult disease, two events spaced apart by two to six decades, are retrospective and are hampered by recall biases and lack of information on events (*e.g*. catch-up growth, quality and quantity of feeding between birth and weaning). Thirdly, there is also the possibility of genetic influences on BW also implicated in the risk of adult metabolic disease since the first type 2 diabetes-susceptibility allele were identified to be reproducibly associated with birth weight (84). Although skepticism in regard to epidemiological evidence for fetal programming is justified, nevertheless, there is a large body of work in animal models showing a causative relation between fetal nutrient exposure and adult health disorders. However, one should keep in mind that most animal models and in particular rodent models can be far from the developmental trajectories in humans. More generally, important differences in physiology, metabolism, placental structure and function necessitate caution in the interpretation of animal experiments in their application to humans (20).

A vast literature published over the past decade report nutritional programming and its adverse effects. But, often the initial cause is difficult to evidence as it is illustrated by several examples. Maternal nutrition is only the first link in a chain of nutritional mechanisms that supply the demands of the growing fetus and nutrients supply to the fetus. Placental vascular architecture and function, and fetal cardiovascular function are important links in the chain. An association between BW and susceptibility to vascular diseases in the adulthood does not prove causality and it is argued that the associations are confounded by other factors. Furthermore, there are differences between studies involving children and adolescents compared with adults; the associations are more apparent in adult populations (85). The effects of rapid weight gain in infancy are hard to isolate because infancy weight gain is related both to intrauterine growth and to post (infancy) growth (86).

In summary, epidemiological studies in human and animal experiments show that alterations in maternal nutrition can have long-term effects on the offspring that are relevant to human disease in adult age. Exposure to excess or a poor level of nutrition *in utero* can result in an increase of offspring adiposity in later life. Effects of maternal nutritional manipulation at defined stages of gestation coincide with embryogenesis, maximal placental and fetal growth and long-term outcomes from these three developmental "windows" appear to be very different: brain and cardiovascular function being most sensitive to influences in the embryonic period and, kidney during placental development and adipose tissue in the fetal phase (5). After birth, over- and undernutrition also could affect the growth trajectory and predispose individual to later diseases in adult life. This arise the question of protein levels in milk formula intake by infant during neonatal life. Finally, the hypothesis suggesting that early nutritional environmental conditions during fetal and neonatal life could lead to related disorders in adulthood is revisited since several argues may question its validity, the major point probably being the validation of epidemiological studies *a posteriori* and the lack of an adequate model to reproduce human physiology.

IMPORTANCE OF LOW BIRTH WEIGHT AND CATCH UP GROWTH

Low BW and accelerated postnatal catch up growth during early life are independent risk factors for adult diseases. As they are intimately linked, it is difficult to determine their independent contributions *per se*. Evidence could be derived from animal model of diseases, in which it is possible to dissect more clearly the independent role of IUGR, low BW and catch up growth in mediating disease risk. Thus, recent data obtained from rats and mice show that accelerated postnatal growth is a trigger for the development of adult diseases and, ultimately, can affect longevity (87).

Low birth weight

Neonatal body weight and size are the result of intrauterine growth. Low BW is commonly occurring phenomenon in humans and other mammalian species. It increases fetal and neonatal mortality and inhibits normal growth for a long time thereafter. In 1975, it was already reported that mean gain/kg BW/d was increased in "small-for-dates" infants compared with control and that mean milk intake per day at the age of 2 months and mean weight gain/day were greater (88). Since this time, in human studies, various neonatal conditions, i.e. babies small for gestational age (SGA, $<10^{th}$ percentile), low BW due to prematurity and IUGR (birth weight <2.500 g) are often used synonymously although these conditions have different origins. Intra uterine growth retardation implies an underlying unphysiological and/or pathological process that prevents the fetus from meeting its optimal growth potential (89, 90). At short term, the rate of total energy expenditure is greater in low BW compared with normal healthy term infant (91). Moreover, surviving infants with IUGR are often at increased risk of neurological, respiratory, intestinal, and circulatory disorders during the neonatal period (92). At long term, IUGR in animal models, caused by maternal undernutrition or placental insufficiencies, is usually associated with several modifications: decrease of growth performance, organ dysfunction and abnormal development, not so good neonatal health, cardiovascular disorders, hormonal imbalance, metabolic disorders, changes in body composition (increased fat mass) and meat quality. Growth of other tissues, most notably brain, is relatively unimpaired. Thinness of impaired babies could be due to poor muscle and small abdominal viscera (4, 89, 93-95). Generally, babies born with low BW have an adverse profile of glucose and insulin metabolism. These associations with low BW extend across the normal range of BW and reflect slow fetal growth rather than premature birth. Several observations suggest that low BW, thinness at 2 y of age and an increase of body mass index (BMI) after the age of 2 years are each associated with the development of insulin resistance in later life (26, 96). Thus, BW is considered as an indicator and/or has been ascribed as a predictive value for the occurrence of adverse programming effects in the offspring.

Causes of the low BW can be altered nutrient, metabolite and/or hormone concentrations in the maternal and fetal circulation (4, 14, 97), and IUGR phenomenon and its consequences could be in relation with nutritional programming. However, there are also other known factors affecting fetal growth such as pregnancy at adolescent age, decreased placenta mass or activity (98). Physical factors such as temperature indirectly affect uterine blood flow and thus nutrient and oxygen supply to the fetus (94, 98, 99), or social factors (83) may also play a role. In addition to deprivation or excess of nutrients, fetal growth retardation can be caused by chemical insults during pregnancy (14).

However, programming effects are not necessary associated with the occurrence of a low BW (100). In newborns, some measures (ponderal index, abdominal circumference, *etc*.) are more closely related to disease risk than BW itself (20). Although in a number of investigations in the sheep, nutrient restriction in the pregnant ewe that caused postnatal changes in growth, body composition and metabolic health of the offspring, had no effect on BW in these individuals (101-104). Results in sheep point to the possibility that physiological effects of metabolic programming can (102, 104) but do not need to be associated with IUGR, i.e. low BW (101-104). These observations suggest that BW does not always reflect the qualitative growth and the maturity of the newborn. Moreover, programming effects are thought to be maximized during critical windows of rapid organ growth, resulting in the asymmetrical growth. Reduced size of those organs, however, do not explain the complex effects observed, suggesting that there is a continuum or consecutive events affecting body growth rate (20). Thus, the high level of interrelations between maternal nutrition in pregnancy, prenatal growth, and postnatal growth emphasizes the need to consider the full growth trajectory in studies of developmental origins of adult diseases (106).

Catch up growth and breast feeding

Catch up grow. Catch up growth is a key physiologic process for SGA-born individuals to achieve a normal final height (107). It is generally defined as a growth velocity (of body weight gain in particular) greater than the median for chronological age and gender (89) and most often, is characterized by a disproportionately higher rate of fat gain relative to lean tissue gain, and that such catch up fat is in part driven by energy conservation mechanisms operating *via* suppressed thermogenesis (108). Catch-up growth appears also to be driven by decreased satiety (88). Neonatal rat undergrowth due to maternal protein restriction during pregnancy showed rapid catch up growth when provided appropriate newborn nutrition (109). Results of rat studies imply that not BW in itself but the catch-up growth as a consequence of low BW is at least partly responsible for the programming effects observed in later age. Even more extreme is the proposition that accelerated postnatal growth alone can explain early origins of the cardiovascular disease (110). Birth weight is weakly associated with later BMI,

whereas rapid weight gain in infancy is associated with incidences of obesity in later life (56, 111, 112). In Western population, greater relative weight gain during early infancy was positively associated with later fat mass and central fat distribution and with fat-free mass. Rapid weight gain in infancy has also been discussed as a risk factor of later obesity (113). More generally catch-up growth early in life (after fetal, neonatal or infantile retardation) is a major risk factor for later obesity, type-2 diabetes and cardiovascular diseases (108).

Growth-retarded neonatal rats accumulated more body fat when they were postnatally overnourished (114, 115). In humans, low BW was associated with an increased rate of coronary heart disease, type 2 diabetes mellitus (26), particularly if the growth rate was high during early postnatal period (110, 116). The glucose intolerance observed in young adult pigs is probably linked with the insulin resistance and early catch-up growth in low BW piglets (117). Generally, energy and nutrient dense diets cause accelerated growth (body weight gain in particular) in early infancy and may be a risk factor for the development of the metabolic syndrome and diabetes type 2 (78, 118). Low BW followed by early postnatal catch-up could be a risk factor for later obesity and disease risk, and the development of insulin resistance and increased central adiposity may be a very feature of this growth pattern (119-121). The amount of visceral fat in post-catch-up SGA children was excessive by the age of 6 years (122). Low body weight at birth and during infancy in humans associated with catch up growth between three and 11 years of age could result in increased incidence of cardiovascular diseases, diabetes type 2, and hypertension (123-125). It seems that the time during which catch up growth occurs can influence long-term body weight and composition. Restricting energy intake in neonatal rats during early postnatal life (suckling) causes some catch up growth post-weaning but the animals stay permanently smaller and lighter than the control group (62). Thus it seems that early life patterns predict subsequent disease risk. Existing evidence suggests two primary pathways whereby the body composition development contributes to disease risk. First, poor growth during fetal life and infancy appears to constrain permanently a lean mass, thereby constraining metabolic capacity to tolerate an energy-rich diet. Second, rapid catch-up growth and childhood weight gain diverts energy disproportionately to adipose tissue, particularly in the abdomen, thereby increasing metabolic load. These complementary processes may account for disease risk being greatest in those born small who subsequently become large (126). Following offspring from a community from birth to age 21, it was concluded that the growth pattern of the at-risk group most often associated with increased risk of chronic disease (small at birth, relatively heavy as an adult), was characterized by more rapid growth in the first postnatal months (106). Finally, using obesity as an example, the importance of understanding growth trajectories is highlighted by the wide range of studies showing the development of obesity risk at young ages, the ability of rapid growth or early overweight to predict later overweight, and the persistence of obesity through adolescence into adulthood. However, a recent study using bilateral ligation of the uterine artery in rats on d 17 of pregnancy shows that it leads neither to IUGR nor to neonatal catch-up growth, i.e., to none of the etiological factors of human “small baby syndrome”, suggesting that publication bias (concerning this model) is evident as it was proposed by meta-analyses (127). Moreover, recent data suggest that the consequences of fetal growth restriction on body composition are evolving beyond the period of early postnatal catch-up since over 8 y follow-up, adult born SGA gained more BMI than appropriate for gestational age, resulting in greater fat mass with more abdominal fat (128).

Catch-up growth in early infancy could be associated with a high intake of energy and macronutrients *via* formula feeding during the first weeks of life (116, 129). When neonates born SGA are fed protein-enriched formula, more than 80% of the infants reach a normal height for age by 3 years-old (130). Infant 4-6 months of age had a significant higher body weight gain when receiving a formula containing 18 g protein/L compared with an isocaloric formula containing 15 g protein/L (131). Classical studies suggest that protein enriched formula (nearly >80%) enhance neurodevelopment (69). The benefit of high-protein diets on neurological development remains debated since differences have been found by Morley *et al*. (70) after the first 9 months of life. On the other hand a neurodevelopment observed at the age of 7 years was similar or better in breastfeed infants than in the infants fed protein-enriched formula (132). Mature human milk contains between 8 and 12 g/L true protein. Infants receiving the formula consumed up to 66-70% more protein than their breastfed counterparts (133). In addition, energy density in commercial formula is routinely increased to compensate for the higher total energy expenditure found in low BW babies (91). This practice could play a key role in the development of adiposity in the infants (134).

Breastfeeding. In human, breast milk alone can meet nutrient needs during the first 6 months, with the possible exception of vitamin D in certain populations and iron in infants of relatively low BW (135). Thus, considering the quality of milk intake by the young mammal, breast milk is defined as gold standard. With lingual and gastric lipase, human breast milk provides the third source of lipase for infants who are breast fed; a similar situation exists in the digestion of complex carbohydrates since alternative enzymes for their hydrolysis include also mammary amylase (136). This is important since it has been shown that total disaccharidase activities were depressed in IURG fetuses (139) mainly due to mucosal atrophy (138). Newborn infants offered formula *ad libitum* every four hours consumed much larger amounts than breastfed infants fed according to the same schedule and, weight loss was more marked in breast-fed infants on day 2 of life (139). In the second half of infancy (6-18 mo) breastfed infants tend to gain less weight and usually are leaner than are formula-fed infants during the first 12 mo. This difference does not seem to be result of nutritional deficits but rather infant self-regulation of energy intake (134, 140, 141).

Exclusive long breastfeeding in particular and supplementation with vitamin D in infancy are reported to confer partial protection against β-cell autoimmunity. Also, the literature indicated that exclusive breastfeeding for at least 2 months and prolonged overall breast feeding protects against diabetes type 2, at least among some populations (78). Breastfeeding duration considered independently showed a significant protective association with childhood overweight at age 4 y (142) and with protection against later obesity (143). Similarly, the prevalence of obesity of babies coming from overweight mother measured at 4, 5 and 6 d of age, was 3 times less important than that early bottle fed (144). There was evidence that breastfeeding for ≥6 months was associated with a reduction in risk of overweight measured at 9-10 y of age and defined on the basis of high measure of fat mass (145). In school children aged 6 to 14 y, prevalence of overweight/obesity was lower in breast-fed children compared with never breast-fed and this prevalence is not confounded by socioeconomic status (146). Finally, longer breastfeeding correlated inversely with percentage of body fat at 8 y of age, for boys but not for girls (75).

In summary, size at birth reflects the product of the fetus’s growth trajectory and maternoplacental capacity to supply sufficient nutrients to maintain that trajectory. Low BW is considered as the result of an adverse growth trajectory and is often associated with later metabolic diseases in adult age. But, synthetically, analysis of the bibliography suggests that the sum of prenatal growth trajectory, rapid growth in early infancy

(catch-up growth), early adiposity rebound in childhood must be considered to determine the origins of later diseases in adulthood. Finally, breast milk is defined as gold standard, and the breast-feeding practice is discussed.

POTENTIAL MECHANISMS INVOLVED IN PROGRAMMING

In a recent review, Saenger *et al.* (89) has described the factors which could be implicated during fetal life (maternal nutrition, placenta size and function, sex, genetic and endocrine factors, *etc*.) and during postnatal growth (perinatal nutrition of the mother, insults and mainly hormonal factors). The intrauterine environment is not only important for fetal development and survival but it also impacts - as a consequence - on further postnatal development and health. The regulation of fetal development involves a number of multidirectional interactions between the mother, placenta and fetus. As a priority, the mother supplies nutrients and oxygen to the fetus *via* placental circulation. The placenta is the site of exchange between mother and fetus and regulates fetal development *via* production and metabolism of growth-regulating hormones such as insulin growth factors (IGFs), growth hormone(GH)/prolactin family, glucocorticoids, and many others (147, 148).

Genetic or environmental regulation? Intervention of nutrition.

The mechanisms controlling nutritional programming are very complex. As an example, the regulation of energy balance and the etiology of obesity can be modified by numerous genetic, hormonal, neural, metabolic, behavioral, social and obesogenic influences. Many studies showed a strong genetic link with obesity. In humans, epidemiological studies have shown that the mother body weight has an influence on the weight and BMI of their offspring (149-151), but, in contrast, the father's body weight does not seem to be implicated. However, as reported by Procter (17), the environment has to be, at least partially, responsible for a rapid rise in obesity, as evidenced by several observations: 1) the fact that the rise in childhood obesity has been so rapid (that is not in agreement with a slow evolution of gene defects to pass between generations), 2) migrants studies suggest a strong influence of environmental factors on obesity rate and 3) as developing countries (where there are over- and underweight children in the same family) switch to more Western diet and reduced physical activity level, the prevalence of obesity in children is rising. Also, Procter (17) analyzed the causes of the disease and concluded that we need multilevel approaches to understand the origins (genetic as well environmental, including nutritional programming) in order to have prevention strategies that can be successfully implanted.

The "Barker hypothesis" postulates that a number of organ structures and associated functions undergo programming during embryonic and fetal life, which determines the set point of physiological and metabolic responses that carry into adulthood (14). Several studies, however, showed that the critical period is extended until the neonatal period (25, 72, 81, 152, 153). The proposal that nutrition in fetal life is a central stimulus for programming for susceptibility to adult disease is now supported by three main sets of evidence: 1) manipulation of nutrition during pregnancy in animals can produce a number of phenomena observed in the epidemiological studies, 2) there are "pseudo experiments" of maternal nutritional manipulation in human pregnancy, most notably that of the Dutch Hunger Winter, 3) the third line evidence supporting nutrition as a likely programming stimulus is essentially that of biological plausibility based on current knowledge of the regulation of mammalian fetal growth (20). Similar arguments can be described during neonatal life. Indeed, two major mechanisms have been suggested to be involved in intrauterine programming: neuro-hormonal and molecular phenomena (14).

Concerning intergenerational regulation, according to Gluckman *et al*. (2) three mechanisms could be implicated: 1) epigenetic modification of DNA, 2) genital tract of the mother during the first part of the fetal life and, 3) changes in metabolic homeostasis, induced in the fetus or the newborn which could affect vascular and metabolic functions when female offspring are pregnant. At the molecular level, adaptative responses could be based on the regulatory mechanisms of physiology with appropriated changes in gene expressions. A model gathering the most part of these regulations was suggested by Drake and Walker (154).

Endocrinology and biochemical mechanisms

Many studies demonstrated a number of modifications in metabolism controlling hormones. Thus a lot of hormones or (neuro)peptides could be implicated, but it is difficult to establish the true role played by each of them. Moreover, before birth, maternal hormones and/or peptides (insulin, IGFs, GH, thyroid hormone, *etc.*) do not cross the placenta in physiologically important quantities but may indirectly regulate nutrient partitioning between the maternal, placental and fetal compartments; thus the fetus and placenta function are a largely autonomous unit in term of endocrinology.

1. Programming during fetal stage

Glucocorticoids. Programming of the corticotropic function is one of the mechanisms suggested to explain partly the phenomena and alterations of the glucocorticoid hormones and the hyppocampal-hypothalamic-pituitary-adrenal (HPA) axis, in particular, have drawn considerable attention. An increased passage of active glucocorticoids from the mother to the fetus can act, at the central nervous system level, to program an enhanced response to stress and, at the peripheral level, in adipose tissue to induce an increased local glucocorticoid exposure and sensitivity (155). Concentrations of these hormones *in utero* can be elevated by nutritional perturbation. Variations in the hormone levels are paralleled by altered expression of glucocorticoid receptors (that confer hormonal actions) and the associated genes of receptors, enzymes, ions channels, and transporters that are regulated by the glucocorticoids, as well as ontogenic deviation of HPA axis. Hence, these endocrine changes can be both the cause and the consequence of intrauterine programming (40, 156, 157). Cortisol response to ACTH and insulin-induced hypoglycemia has been shown to be elevated in low BW pigs, consistent with programming of the HPA axis function during impaired early growth (158). In pregnant rat, blockage (by administration of 11-hydroxysteroid dehydrogenase inhibitors) of placental inactivation of endogenous glucocorticoids throughout pregnancy reduces BW and results in hypertension and glucose tolerance in offspring during adult life (159, 160). In contrary, the exposure to the excess of glucocorticoids *in utero* results in offspring with a variety of adverse physiological outcomes, including cognitive impairment (161) insulin resistance (162), hyperleptinemia (163), and hypertension (164). Glucocorticoids could modify gene expression in placenta and/or fetus resulting in long term effects on growth and predisposition to cardiovascular diseases (165).

Leptin. Leptin is an adipocyte-derived hormone that decreases food intake and body weight, *via* its receptor in the hypothalamus. In human, the development of adipose tissue and

the accumulation of fat mass are the major determinants of fetal and neonatal serum leptin levels (166). It seems important to underline that leptin receptor is expressed in various tissues. In addition to adipose tissue-derived leptin, placenta-derived leptin may act on the hypothalamus, and regulate maternal energy expenditure and neuroendocrine functions. On the other hand, placental leptin may also act on maternal peripheral tissues, such as muscle, liver, or pancreas, and regulate glucose metabolism and insulin sensitivity. In addition, placental leptin is transferred to the fetus and may regulate fetal development and growth (167). Thus, it was demonstrated that maternal plasma leptin levels correlate with the degree of fetal growth restriction originating from deterioration of placental function, suggesting a pathophysiological significance of increased leptin in pregnant women (168). Fetus exposition to over- or undernutrition resulted in an increase of adiposity and the level of circulating leptin in the later life (adolescent and/or adult). In 60 days-old pup of pregnant rat fed a protein free diet, leptin plasma level is reduced (169). The presence of leptin and associated energy regulation are indispensable in the acceleration of obesity on a high-fat diet caused by undernutrition *in utero* and the premature leptin surge plays an essential role as a programming signal in the developmental origins of the obesity during the early neonatal period (170). Before birth, there is a nutrient regulation of the synthesis and secretion of leptin and this hormone acts at central or peripheral target sites. Some mechanisms whereby an alteration in nutrient supply during fetal life may act to programme the synthesis, secretion or actions of leptin to result in an increased risk of postnatal obesity are described (23). Leptin seems to be a hormone that possesses all the characteristics of a signaling factor of nutritional and, more generally, environmental conditioning to different levels of nutrient supply during life. The prenatal or neonatal level of leptin can modify neuronal and adipocyte plasticity, thus enabling the animal to adapt in order to resist to a lower nutrient supply. However, if those conditions change to a higher nutrient supply, the organism can develop the metabolic syndrome if imprinted by poor nutritional conditions (22).

Interactions of the leptin with other hormones. In bovine and porcine species, leptin receptor mRNA has been found in numerous central and peripheral tissues including tissues producing regulatory substances (171, 172). This means that leptin could have an influence on these tissues, as well as on the production of other regulators. As an example, functional leptin receptors are expressed in pancreatic islet cells, as early as the fetal stage of development of these micro-organs. Leptin stimulates proliferation of fetal islet cells and might play a role in determining islet cell mass at birth (173). In ovine, the expression of leptin in fetal adipose tissue may be positively regulated by factors that also regulate fetal body growth, such as insulin or IGFs (174). Moreover, leptin is a potent stimulator of spontaneous GH secretion pulses (175).

Somatotrophic axis. The secretion of IGF-I is largely dependent upon GH, but in contrast to GH, its circulating concentrations show only small individual variations (176). Compared to *ad libitum* fed, restricted fed pregnant rat (30% of the *ad libitum* intake) throughout pregnancy showed plasma IGF-I level reduced during the whole gestation as well as lower placental weights. The offspring had a lower body weight from birth to d 90, lower IFG-I levels from d 22 of gestation until d 9 after birth, a lower plasma insulin level and a lower I^{125}-bovine GH specific binding to liver membranes resulting in a postnatal modification of the somatotrophic axis (177). Growth-retarded new born infants have been shown to have reduced number of pancreatic β-cells and a reduction of insulin secretion (178). Thus, there is evidence to suggest that there are factors limiting growth of neonates since IUGR is associated with less mature pancreas which could be a factor limiting postnatal catch up growth (136). In adult human, IGF-I was shown to be correlated positively with height and inversely with age, BMI, systolic blood pressure and total cholesterol (179). However, following an epidemiological study, urinary GH and serum IGF-I are not related to BW, other measurements at birth, or weight at 1 year. These data, in contrast to previous studies in children or young adults, do not support the hypothesis that IGF-I concentrations are programmed by intra-uterine events, as assessed by BW, in late middle age (180). Similarly, there is no evidence that reduced fetal growth programs IGF-I concentrations in old age (181). Given the anabolic effects of the GH/IGF-I axis, people tall during childhood with low lean body mass as adults may be in risk of the late-life GH/IGF-I axis dysfunction (181). A bibliographical study realized by Dunger *et al*. (182) suggested that following prenatal growth restraint, catch up growth driven by reduced satiety can led to the insulin resistance and visceral fat accumulation. On the other hand, height gain and IGF-I levels may be more important markers of β-cell mass and the supplement risk for the development of diabetes type 2 (183). In singleton offspring coming from nutrient restricted ewes, the BW and weight at 3 years-old were similar to that of control, but smaller livers were observed and the abundance of mRNA levels for GH and IGF-II receptors was lower in the livers of nutrient restricted offspring (103).

Interactions with nervous system. In humans, leptin stimulates Sympathetic Nervous System (SNS) activities (183) and increases arterial blood pressure (184) that can result in chronic disease. In rat, *in vivo* and *in vitro* studies have shown a role for altered autonomic activity, including increase in the parasympathetic and decrease in sympathetic activity in 100 d-old animals in the maintenance of hyperinsulinemia in the response to the high-carbohydrate dietary intervention during suckling period (185, 186). The idea of programming is based on the observation that environmental changes (including nutrition) can reset the developmental path during intrauterine development leading to metabolic diseases. The pathogenesis of the syndrome is not based on genetic defects but on altered genetic expression as a consequence of an adaptation to environmental changes during fetal development. Data obtained *in vivo* in animal models evidence for a disturbed endocrine communication between central nervous system (CNS), adipose tissue and the endocrine pancreas in the pathogenesis of programming-induced obesity (187). Indeed, an alteration in the regulation of appetite regulatory neuropeptides within the fetal hypothalamus (see next part) is clearly one potential mechanism whereby a transplacental increase in substrate supply, which occurs in pregnancies complicated by maternal glucose intolerance, may lead to a subsequent increase in childhood and adult obesity (188). In the case of obesity, a regulatory mechanism, including insulin action, was suggested by Landsberg (189). More generally, Godfrey and Barker (1) have proposed a scheme including different factors which might be implicated in the fetal development and nutritional programming acquisition, where they underline the importance of the cortico-hypothalamo-hypophysal axis.

IUGR and endocrine and biochemical mechanisms. In two reviews concerning the mechanisms involved in the IUGR apparition, Wu *et al*. (4, 92) underlined crucial role of nitric oxide (NO) and polyamines in placental and fetal growth in relation with the unusual abundance of the arginine-family amino acids. Tacking account of the available bibliography, mainly from animal studies, authors suggested that both maternal under- and overnutrition reduce placental blood flows and stunt fetal growth. Impaired placental synthesis of NO (a major vasodilator and angiogenesis factor) and polyamines (key regulators of DNA and protein synthesis) may provide a unified

explanation for IUGR in response to the 2 extremes of nutritional problems with the same pregnancy outcome. Nevertheless, it was shown in human that cord insulin concentration was lower and cord cortisol higher in SGA newborn than in appropriate weight for gestational age (190).

2. Programming after birth

Insulin. In young weaned rats, alterations in plasma insulin level, modifications of the expression of insulin encoding genes and its secretion, , were evidenced in relation to prenatal and early postnatal nutrition. It was also the case for modifications in hypothalamus activity (191-193). This phenomenon occurs according to the fact that development of endocrine pancreas is vulnerable to nutritional insults during the late fetal period and the immediate postnatal period. Indeed, during these periods, permanent structural and functional alterations can occur (194). Deregulation and overstimulation of the pancreatic insulin secretion during a critical period of rat neonates was reported to lead to the temporary hyperinsulinism. It was suggested to be the cause of the overweight and increased diabetes susceptibility in the adult age (195). In rats nursed by dams fed a restricted protein diet during lactation, insufficient insulin secretion was detected at 2 months of age (169) or during the two first weeks of postnatal life (196). This phenomenon could be related to (and was perhaps the cause of) a change of metabolism in pancreatic islets. Using adequate experimental procedure, Thompson *et al*. (197) were able to show a clear distinction between the effects of IUGR and postnatal hypercaloric nutrition in rats. IUGR (induced *via* maternal undernutrition) led to insulin hypersecretion accompanied by maintained insulin sensitivity. Postnatal hypercaloric nutrition, on the other hand, led to the insulin resistance. Circulating IGFBP-2 in adulthood, a marker for insulin sensitivity, was inversely associated with current adiposity, but overweight children who became relatively lean adults were more insulin sensitive than thinner children. These findings may indicate predictive programming of later IGFBP-2 levels in response to the metabolic effects of childhood adiposity. This suggests that childhood adiposity may not impact on adult levels of insulin resistance to the extent predicted from cross-sectional associations with obesity in adulthood. (198).

Growth hormone and growth factors. In adult rats, feed a diet with low protein level during the first three weeks following weaning a decreased the range of the GH pulses and reduced insulin level were observed following glucose ingestion. These observations suggest that protein quantity ingested after weaning plays an important role in the control of GH secretion by central nervous system, as well as for the sensitization of the pancreatic β cells to glucose (199). In humans, on the other hand it seems that there was only weak evidence that the chronic disease risk in adulthood of children with BMI may be mediated by IGF-I levels (198).

Leptin and its interactions with other hormones. Both nutrition and adiposity regulate plasma leptin synthesis in early postnatal life, but in contrast to adulthood, the effects of nutrition appear to be predominant (200). During the postnatal period, leptin and insulin may be associated with energy intake and expenditure, as well as growth and feeding reprogramming due to the malnutrition (169). Early hyperinsulinism occurs as a result of early postnatal overfeeding. In rats, endogenous hyperinsulinism, as well as peripheral or intrahypothalamic insulin treatment during perinatal development, may lead to "malprogramming" of the neuroendocrine system that regulates body weight, food intake and metabolism. This results in an increased predisposition to obesity and increased risk of diabetes throughout life. Similar malprogramming may occur due to perinatal hypercortisolism and hyperleptinism (201). In rats, several hormonal changes are associated with malnutrition during lactation (higher triodothyronine (T_3), lower prolactin or higher leptin levels, but not the change in corticosteron). Thus the hormones could be considered possible programming factors (22). Moreover, a scheme has been suggested concerning programming of the thyroid function. It provides a new insight regarding the physiological importance of nutritional and hormonal status and consequent changes in the leptin levels during neonatal period. The bibliographical data suggest that leptin may play an important regulatory role in the thyroid-pituitary axis in adults, with potential consequences for the metabolic rate and body weight.

Interactions with nervous system. In recent decade, it has been shown that the CNS plays a key role in the regulation of food intake, body weight and energy balance *via* several orexigenic neuropeptides, such as neuropeptide Y (NPY), galanin (GAL), agouti-related peptide (AgRP), orexin and anorexigenic neuropeptides: proopiomelanocortin (POMC), α-melanocyte-stimulating hormone (MSH) and cocaine- and amphetamine-related transcript (CART). Moreover, experiments in animals have implicated the fetal hypothalamus as a key site that can be programmed by transient changes in prenatal endocrine status (202).

In mice, it has been shown that only during the neonatal period leptin has a potential to modulate development of neuronal circuitries in the hypothalamus (203). Neonatal exposure to maternal diabetes through the intake of dam's milk in rats led to a complex malprogramming of hypothalamic orexigenic and anorectic circuits that are critically involved in the life-long regulation of the appetite, body weight and metabolism (204). Juvenile food-restricted rats reduced CART gene expression and increased MSH expression. In middle-aged rats, POMC and CART mRNA levels were reduced. The ratio between expression of orexigenic and anorexigenic peptides was increased in juvenile, but not in middle-aged food-restricted rats. Thus, in rats, early postnatal food-restriction can alter the programming of hypothalamic regulation of the energy balance. If energy balance regulation is similarly affected in perinatally malnourished humans, temporarily increased orexigenic stimulation may offer a partial explanation for the increased obesity risk (205). In rats overfed during early postnatal period, an acquired resistance of the hypothalamic NPY system to the increased levels of insulin and/or leptin was suggested (206, 207). In response to high-fat diet after weaning, leptin treated rats (equivalent to five times the amount of leptin ingested normally acquired from maternal milk during the sucking period) showed lower hypothalamic NPY/POMC mRNA ratio and a lower cytokine signaling 3 (SOSC-3) mRNA levels when compared to control animals (208). SOSC-3, which is increased by both insulin and leptin *via* a crosstalk between the signaling pathways, plays an important role in the intracellular feedback of those two hormones (22). Also, the data give morphological support to the programming hypothesis, since different levels of leptin during hypothalamic morphogenesis could permanently change the distribution of excitatory or inhibitory synapses to NPY or POMC neurons, permanently modifying the response to orexigenic or anorexigenic stimuli (22). A high-carbohydrate milk formula fed to 12 days-old rats altered the activity of autonomic nervous system and contributed to the development of hyperinsulinemia. It was caused by enhanced insulin secretory response to glucose stimulation through the increased parasympathetic and decreased sympathetic signaling (185, 186). The hypothalamic-pituitary-adrenal activity, as well as sympathoadrenal system, can be altered permanently by a variation in glucocorticoid exposure due to maternal protein deficiency during pregnancy and lactation. All of these factors have been shown to lead to the obesity and metabolic syndrome in animal models (209-211).

Hyperinsulinemia during catch up growth in early life, induced by permanent changes in hypothalamic morphology and in the functional state of sympathoadrenal system, has also been implicated in the programming of later obesity (209).

There are a number of appetite controlling hormones, such as ghrelin (212), obestatin (213), orexins (214, 215) and apelin (216). These peptides are also involved in the control of energy metabolism, thermoregulation, digestion and reproduction thereby providing and integrated control over major animal activities in accordance with food availability. However, their possible involvement in the development of metabolic syndromes needs to be further investigated.

3. Epigenetic mechanisms

Genetic determinants of fetal growth restraint, through programming or epigenetic effects on the fetus may be the important links between size at birth and diseases in adulthood (217). Thus, in addition to the hormonal regulation, an epigenetic hypothesis of the regulation of the intrauterine supply and demand for the nutrients by imprinted genes has been advanced to account for fetal programming (29, 152, 218-222). As an example, glucocorticoid receptor genes are hypomethylated and their expression increased in the liver of young offspring of low protein fed dams (223). These mechanistic pathways were more recently approached than those concerning hormones and peptides.

Epigenetic control of gene expression involves modification of the genome but not the alterations of the DNA sequence. It is typically mediated by changes in the DNA methylation pattern and/or modifications of chromatin packaging *via* alterations in histone acetylation. These mechanisms may influence gene expression by transcriptional silencing of the modified allele (218) and, therefore, may affect phenotype without changing the DNA sequence *per se*. Thus, these molecular events might contribute to a mechanism, which stably fixes the transient exposure conditions in early life (prenatal and neonatal) to changes in the gene expression programming prevailing long after the exposure is done (222, 224, 225).

In this way, Heijmans *et al*. (226) have shown that individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944-45, exhibited less DNA methylation of the imprinted IGF2 gene six decades later, compared with their unexposed, same-sex siblings. As another example, Park *et al*. (227) tried to determine whether epigenetic modifications may play a role in the development of adult diabetes following IUGR. They used a rodent model of IUGR based on lower expression levels of *Pdx1*, a pancreatic and duodenal homeobox 1 transcription factor critical for β cell function and development. This model inspires animals to develop diabetes in adulthood. Authors found that the expression of *Pdx1* was permanently reduced in IUGR β cells and underwent epigenetic modifications throughout animal development, providing insight into the origins of type 2 diabetes following IUGR. These data seem to be the first to describe the ontogeny of chromatin remodeling *in vivo*, from the fetus to the onset of disease. It contributes an empirical support for the hypothesis that early-life environmental conditions can cause epigenetic changes in mammals that persist throughout the life.

Finally, genomic techniques started to appear in the scientific field of nutrition programming. As an example, study of gene expression in aorta tissue in young rats, the mothers of which were fed lipid enriched diet revealed increase (often two-fold) in the expression of more than two hundred mRNA sequences of the genome and the sequences of mitochondrial specific mRNA when compared with controls (228). Among these genes, present were those encoding collagen, elastin and NO synthetase (25). A decrease of the copy number in the mitochondria has also been observed (228).

In summary, there is evidence that the HPA axis, as well as GH-IGF axis may have a crucial role in the regulation induced by nutritional programming, as it was reviewed by Holt and Byrne (85) and Plagemann (201). Central and peripheral nervous systems play also an important role *via* various peptides. Thus, the observations in different models of fetal and neonatal hyperinsulinemia and hyperleptinaemia showing that a perinatally acquired disorganization, malprogramming and resistance of orexigenic as well as anorexigenic neurons in the hypothalamus might contribute to the occurrence of hyperphagia, overweight and hyperinsulinaemia throughout later life. These persistent alterations seem to be a consequence, at least in part, of elevated insulin levels during 'critical periods" of pre- and early postnatal development (201). In this complex system and among the regulatory factors that imprint the program in developing immature organism, leptin seems to be a hormone that plays a crucial role. Also, there is evidence for both environmental and genetic mechanisms. Thus, hormonal regulation and epigenetic mechanisms are complementary. Acting as critical endogenous effectors that transmit environmental information to the genome, hormones, neurotransmitters and cytokines (as immune cell hormones) may play a decisive role in the processes of nutritional malprogramming (201). Bergmann *et al*. (90) thought that no overarching model is available to explain how the epigenetic and hormonal tuning, which accompany intrauterine malnutrition from preconception through pregnancy, can program the regulatory systems of fundamental life processes. They concluded that the theoretical concepts of a thrifty phenotype (19) and of a predictive adaptative response (48) offer a comprehensive approach to understand the empirical and experimental findings.

POTENTIAL PREVENTION AND/OR TREATMENT

Understanding the mechanisms implicated is difficult but essential to establish appropriate intervention to prevent or delay adult diseases. As an example, early diagnostic of metabolic and hormonal disturbances is important in children with IUGR, in order to prevent a compensatory catch-up growth and its subsequent obesity. Thus, it is an important scientific and public-health objective to define protective and predisposing effects on early nutrition on the development of metabolic diseases, since early feeding can potentially be modified to minimize the risk of later chronic diseases (78). In addition to an improvement of the health of the pregnant woman, early diagnosis of metabolic and hormonal disturbances is important in children with IUGR, in order to prevent a compensatory catch-up growth and its subsequent obesity, and to set up a therapeutic intervention against the deleterious consequences of hypercorticism (155). Finally, onset of metabolic diseases in the adult age is linked to the events that occur during critical windows (prenatal and neonatal periods). They determine the opportunity windows when prevention and/or treatment could succeed. After fetal growth restraint in populations at risk from type 2 diabetes or metabolic syndrome, the time window for early intervention may have to be advanced to the prepubertal childhood (122). Similarly, results obtained by Botton *et al*. (229) support the hypothesis of 2 critical windows in early childhood associated with the later risk of obesity: up to 6 months and from 2 years onward. The study of the determinants of growth during these periods is a major importance for the prevention of diseases in adolescence and adulthood.

Prevention

In the case of low BW infant, a highly significant risk factor for stunting, especially in the first 6 months, early interventions are vital. Lack of breast-feeding and early introduction of weaning

foods are thought to increase the risks in the early postnatal period. Prevention of stunting requires prenatal intervention to optimize BW and promotion of full breast-feeding in the early postnatal months, followed by continued breast-feeding supplemented with high quality weaning food (230). In the case of obesity, it is now known that the prevalence of obesity is rising at young age and that there are difficulties and lack of success to achieve weight loss. Child obesity has serious health consequences and it seems important to focus efforts on very early prevention. Prevention of the diseases may depend on prevention of imbalances in fetal growth or imbalances between prenatal and postnatal growth, or imbalances in nutrients supply to the fetus.

1. Prevention before birth

Clinical treatment of the mother. From a clinical point of view, numerous observations reported in the bibliography, point out the possibility of primary prevention of lifelong increased disposition to obesity, diabetes and subsequent risks by screening for and treatment of maternal diabetes during pregnancy, the main cause of growth retardation (201).

Nutritional recommendations for the mother. In most nutritional programming experiments in animal models or epidemiological studies in human, the degree of maternal under- or overfeeding during pregnancy is rather severe (see part 1). It remains to be determined whether a more subtly altered nutrient composition close to the recommended intake levels is relevant for fetal programming and has a long-term consequences for health and performance. Nevertheless, the food intake of the pregnant mother must be in balance with the levels recommended for the different species. Thus, supplements in the undernutrition cases or more equilibrated feeding in the cases of overnutrition, could be provided, since improving maternal nutrition status can be a mean to enhance fetal growth in immature pregnant mammals (231). As an example, it is possible to achieve the same prenatal growth trajectory and final birth weight in adolescent sheep as in mature sheep if the adolescent dam is optimally nourished throughout gestation (98).

Glucose. One key nutrient that may modulate the long-term metabolic effects is the supply of glucose from the mother to the fetus, because it is sensitive to both global changes in food intake, maternal glucocorticoid status and an increase in the carbohydrate content of the diet (5). Thus, maintenance of a balanced and appropriate supply of glucose from the mother to the fetus may be pivotal in ensuring optimal embryonic, placental and fetal growth and consequently may prevent risk of adult diseases.

Taurine and arginine. The level of taurine in milk was considered as important as the quantity of proteins (131). Pregnant female rat fed a protein deficient diet produced offspring which had reduced insulin secretion, and supplementation of the diet with taurine allowed reestablishing a normal secretion of the hormone (232). In view of the crucial role of the arginine-dependent metabolic pathways, intravenous or oral administration of arginine may provide a potentially novel solution to enhance placental-fetal blood flow (and subsequent transfer of nutrients and oxygen), thereby improving fetal growth and decreasing the probability of IUGR newborn (92).

Antioxidants (minerals and vitamins). A deficiency in antioxidant minerals or vitamins reduces the survival rate and growth of embryos and fetuses (233). As an example, folic acid supplementation is recommended for pregnant women to avoid newborn anomalies at birth. It seems that the beneficial effects of folic acid are obtained *via* modification of homocysteine level (234, 235) which could play an important role in nutritional imprinting phenomenon (236). Folic acid supplementation could also prevent epigenetic modification of hepatic gene expression in the offspring (223).

Hormonal treatments for prevention. To our knowledge, no hormonal treatments have been used up to now to prevent long-term effects of nutritional programming of the embryo and fetus. But some results could suggest ways to counterpart the risk of later diseases in offspring. The elevation of blood pressure in the low protein rat model is prevented by maternal blockage of glucocorticoid synthesis (237). Maternal GH treatment during gestation alters maternal nutrient partitioning in favor of uteroplacental growth in the overnourished adolescent sheep (44).

More generally, only in the case of IUGR, Wu *et al*. (4, 92) have reviewed causes and consequences of IUGR in livestock with a tentative description of the regulation. In tacking account of the mechanisms involved, they have suggested potential solutions to prevent this abnormal phenomenon by different treatments of the dam: hormonal therapy, dietary supplementation with energy, protein concentrates, or both, adequate nutritional support for immature pregnant dams, provision of antioxidant nutrients, and manipulations of the arginine-NO/polyamine pathway.

2. Prevention after birth

Breast feeding. At short term, infants who were breastfed exclusively for 6 months or more appear to have a significantly reduced risk of one or more episodes of GIT infection and present less morbidity from GIT infection than infants who were mixed breastfed at 3 or 4 months of age. No deficits have been demonstrated in growth among infants from either developing or developed countries who were exclusively breastfed for 6 months or longer (238). Moreover, breastfeeding helps to maintain hydration status during diarrhea attacks (239). In offspring with diabetic mothers, breastfeeding duration of at least four weeks has been associated with a reduced risk of overweight at two years of age (240). At middle term, in SGA babies, breast-feeding brought a substantial advantage in the Bayley motor scale as well an advantage in the metal scale (70).

At long term, the relationship between breastfeeding and protection against later obesity and metabolic diseases showed a beneficial effect (129, 241, 242) all the more that leptin concentrations of human milk are not different in the mothers of obese and non-obese infants suggesting that milk-borne leptin has no significant effect on adiposity during infancy (243). The long term benefit obtained with breastfeeding may be attributed to a better energy regulation in breast fed infants, compared with bottle-fed ones. The introduction of solid foods increases the energy density of the diet (244); therefore, breastfeeding for longer periods also may improve energy regulation (75). Moreover, the higher circulating leptin levels observed in breast feeding might be important for body weight regulation in later life (245).

The reduction in the risk for overweight and obesity is more likely to be related to the properties of human milk than for factors associated with beast feeding (246). At least in developing-country settings, when iron stores of newborn infants may be suboptimal, exclusive breastfeeding without iron supplementation through 6 months of age may compromise hematological status (238). In developing-country, given the importance of diarrhea as a determinant of stunting, effective interventions should include improvement of water quality and sanitation, coupled with promotion of breast feeding (230). Thus, the case for breastfeeding is already strong and well established, based on a combination of other short- and long-term benefits, including as examples, improved neural and psychosocial development, less allergic disease, and potentially lower blood cholesterol levels in later life (129).

Nutritional recommendations. Nutritional recommendations for humans taking account of the age are now available in the most of the countries. In the highly developed countries in

particular they even reflect the environmental conditions and are frequently updated to incorporate new knowledge from the scientific field. Following the data reported in this review, the first recommendation is to avoid early postnatal overfeeding.

Leptin given orally. Leptin-treated rats (intake of the equivalent of five times the amount of leptin ingested normally from maternal milk) had, in the adulthood, lower body weight, lower fat content and consumed fewer calories than their untreated controls at 6 months of age. The observations were consistent even if high-fat diet was provided since weaning. This means that the animals that received leptin during lactation become more protected against fat accumulation in adult life and seem to be more sensitive to the short- and long-term regulation of food intake by leptin (208).

Treatment

1. Nutritional treatment

Milk formula or breast feeding? Diabetes decreases lactation through a suppressive effect on milk synthesis/supply rather than on milk release (247), resulting in an undernutrition of offspring. Moreover, neonatal exposure to maternal diabetes through the intake of dam's milk in rats led to a complex malprogramming of hypothalamic orexigenic and anorexigenic circuits that are critically involved in the lifelong regulation of food intake, body weight and metabolism (248). This may indicate a pathogenic effect of breast milk from diabetic mothers and suggest the utilization of formula as soon as the end of colostral period.

In very low BW human babies, breast milk feeding increased at a short term the Bayley Mental Developmental Index in comparison with formula intake. The potential long-term benefit may be the optimization of the cognitive potential and reduced need for early intervention in the education service (249). Interestingly, in appropriate for gestational age infants, although no differences in anthropometric measurements, BMI and skin-fold thickness were found between breast-fed and formula-fed infant in the first 4 months of life, leptin serum values were higher in the first one (250). This observation, probably in relation with the lack of leptin level in milk formula, give arguments to recommend breast-feeding to protected against fat accumulation in adult life.

Relative undernutrition in early life in the SGA infants has been shown to be associated with diminished insulin resistance in adolescents (251) giving a supplemental argument to follow the nutritional recommendations. Feeding SGA infants with nutrient-enriched milk formula after a hospital discharge is thought to result in a better psychological development. That could change as it is counter-parted by the negative long term effect of catch up. In fact, there are no data from randomized controlled trials to determine weather feeding SGA infants with nutrient-enriched formula milk complement to their psychological development more than breast-feeding (252). Similarly, a meta-analysis suggests that high protein intake (≥3 but <4 g/kg/d) by SGA babies (<2.5 kg) from formula accelerates weight gain in comparison with normal protein intake (<3 g/kg/d). Although accelerated weight gain is considered to be a positive effect, increase in other outcome measures examined (blood urea nitrogen levels, increased metabolic acidosis, *etc*.) may represent a negative or ambivalent effect and limited information was available regarding the impact of higher formula protein intakes on long term outcomes (253).

Nutrients in milk formula. Since taurine is the most abundant amino acid in breast milk, taurine supplementation in formula was tested in low BW infants. At short-term, intestinal fat absorption was increased but no significant effects were observed on growth parameters during neonatal period and until three to four months of age. Very limited data are reported concerning neonatal mortality and morbidities and no data on long-term growth or neurological outcomes (254). In prenatally programmed adult hyperleptinemia (associated with elevated leptin mRNA expression in adipose tissue) and hypertension in the 6 months-old rats (obtained by administration of glucocorticoid in diet of their mothers), an ingestion of a high ω-3 diet instead of a standard diet completely eliminated the adverse programming outcomes (255).

Diet composition after weaning. Rats overfed from an early age (small litter size) develop subsequent increase in body weight, along with profound changes of central and peripheral mediators involved in the regulation of feeding and body weight (see the previous chapter). Although the effects of early postnatal overnourishment are important, by 16 weeks, the effect of litter size was masked by that of diet, postweaning. Thus, small and normal litter animals fed a high-fat diet had similar increases in body weight, plasma insulin, leptin and adinopectine concentrations, leptin mRNA and fat mass relative to the chow-fed animals (control). Moreover, NPY concentration in the paraventricular nucleus of the hypothalamus was reduced in high-fat-fed animals (61). In rat, adult hypertension was induced by maternal low-protein diet during the second half of gestation. After being weaned at 3 week, the offspring exposure to low-Na diet (0.03 vs. 0.2%) during 3 wk totally prevented the development of hypertension and the effect lasted throughout the 6-16 wk period. Conversely, 3-wk exposure to high-Na diet (3.0 vs. 0.2%) increased the severity of the later hypertension and did not prevent the hyperreninemia (256).

2. Hormonal treatment

Leptin treatment. During neonatal period, administration of leptin to rats that were undernourished *in utero* reverses the metabolic phenotype of insulin resistance and obesity that would otherwise develop in these animals when fed high-fat diet (257). Moreover, leptin treatment of neonatal *ob/ob* mice on days 4-12 of life reverse the reduction in POMC neurons and the increase in NPY neuron projection (203). Interestingly, in humans, newborns with IUGR had lower serum leptin level than those with normal growth and leptin levels were positively correlated with BMI (166). Similarly, in piglets IUGR may be characterized by altered leptin receptor distribution within the hypothalamic structures involved in metabolic regulation (258). Leptin administration in IUGR induced, after just a few days, a rapid increase in the weight and size of animals with apparent improvement of organs involved in metabolic regulation (pancreas, liver and, to a minor extend, kidneys) and suspected structural histological modifications (259). During milking period, peripheral leptin administration modifies hormone (insulin, GH) and metabolite (glucose) levels in the young pig (260). Indeed, leptin treatment seems to be efficient in the atrial species but could be also in the precocial species like swine and human. Similarly, it was shown that leptin replacement is able to reverse metabolic complications in the majority of children with Berardinelli-Seip congenital lipoatrophy (261). It remains to be determined whether such a beneficial effect can be maintained on a long-term basis and whether it can prevent or at least delay the development of more severe complications in the adulthood. However, in neonatal rat fed high-fat-diet in combination with prenatal undernutrition, leptin administration has produced either increased, normal or decreased adiposity in adulthood (62, 205).

GH or IGF treatment. The objective of GH treatment in short children born SGA, is to accelerate linear growth in early childhood as much as possible to achieve rapid catch-up growth and to maintain normal growth in later childhood. But it seems that there are differences in sexual response to GH treatment

(262). The conditions of GH therapy and its consequences are well described by Saenger *et al*. (89) and Ong *et al.* (263). The benefits of GH therapy are not just in terms of height, but also in body composition and possibly blood pressure and lipid levels. However, there is the risk of side effects and long-term complications, particularly related to the expected metabolic effects of GH in inducing insulin resistance and hyperinsulinaemia (263). As an example in rat, GH treatment reduced hypertension and improved cardiovascular function in animals exposed to adverse environmental conditions during fetal or postnatal life (264). The ultimate objective is to normalize adult height without the nocive effects observed in children fed protein-enriched formula milk. In pregnant rat, there were no significant effects of either IGF-I or GH treatment on fetal weight, placental weight, fetal organ weights or circulating IGF-I levels in both *ad libitum* fed and 30% *ad libitum* fed fetuses. Offspring of 30% *ad libitum* fed dams remained significantly growth retarded postnatally and showed elevated blood pressure in later life (265). Additional data must be obtained even if, as an example, further progress is anticipated to include methods to attenuate the risk of side effects after GH administration.

In summary, the new knowledge about the mechanisms involved in the nutritional malprogramming suggests the development of new, rational, and effective preventive and/or therapeutic options before and/or after birth. It seems imperative to focus efforts on very early prevention. The data gathered in this paper show some ways which probably will be developed in the near future and can generate some promising results. Breast-feeding could be suggested to protect the adverse effects of malprogramming during fetal life and/or that resulting from early infancy, even though that between 2000 and 2005, sixteen studies have been published with conflicting data regarding the potential protective effect of this practice on childhood obesity (266). Now, breast-feeding is recommended for all infants, and it seems that it may beneficial in those born SGA and/or IUGR. The preventing effect of breast feeding on overweight and obesity is an important additional argument for the promotion of breast-feeding in industrialized countries. In another way, the results obtained in the epigenetic regulation field could suggest therapeutic agents that will be novel for the prevention of common diseases with late-onset phenotypes. Finally, early infancy may provide an opportunity for intervention aimed at reducing later disease risk.

CONCLUSION

This review underlines the effects of nutritional programming along the life. Generally, it seems to be established that quantity and/or quality of nutrition during the very early stages of life (from conception until neonatal stage) could have an impact on adolescence and adulthood. This impact can pass by as a short term effect as in the case of the birth weight. As the first point underlined in this conclusion, it seems difficult to determine the origin of the disorders observed at mid- and long-term, and thus, to determine independent contributions of nutrition (of mother, fetus and young) or of birth weight (and catch-up growth which often follows) *per se*.

Nutritional programming concept was suggested by epidemiological studies in human and confirmed by animal experiments. It is extremely difficult to perform studies in human because of the multitude of ethical issues and risks associated with unproven therapies in a vulnerable population, in addition to limitations of time and sampling procedures. Thus, the epidemiological approach has several important limitations. *In vivo* and *in vitro* experiments conducted in animal models are particularly relevant and essential since they are complementary with human epidemiological studies (267). Unfortunately, studies in rodent largely dominate the scant literature to date. Thus, appropriate and reproducible models, among the animal species and the stages of development which are the nearest to that of human species remain to be established in order to uncover the nutritional and physiopathological bases of the disease which could appear in adulthood. To justify its utilization, the physiological conditions of the model study must be well described.

Another interesting idea seems to rise and will be the third point underlined in the conclusion. In nutrition field, data concerning nutritional programming were obtained in the context of placental adaptation, intra-uterine environment including fetal nutrition and/or that of the pregnant mother as well as postnatal nutrition of offspring. Moreover, in mammal, the short-, mid- and long-term effects of nutritional programming were examined at several biological levels: system functions (respiration and circulation), organs (spleen, liver and kidney), tissues (muscular and adipose tissues), as well as at cellular and molecular levels. But, so far a few studies were undertaken to elucidate the effects on the gastrointestinal tract (except for the endocrine pancreas) which must play a key role in the nutrition of the organism. The whole wellbeing of the newborn animal and baby depends on the gastrointestinal tract being functionally capable of digesting the diet components and absorbing the nutrients. Taken together these points, data concerning nutritional imprinting are missing the effects on gastrointestinal tract. Due to the important consequences of nutritional programming observed at short, middle and long term, scientific research must be developed in this field, mainly in an adequate animal model.

Finally, in humans, as it was underlined by numerous papers, scientific field of nutritional programming is emerging and represents a matter of major public health and clinical importance. In this context, it is necessary to define protective and predisposing effects of early nutrition on the development of later chronic diseases, since early feeding can be potentially modified to minimize the risk of later chronic diseases. Thus, understanding of the potential biological mechanisms involved, as well as the biology and time concerns (critical windows) are crucially important for public health program in adequate prevention and/or treatment. It is also relevant to give directions for research effort at understanding the antecedents of the adult disease. From both perspectives of the increased health risk to the individual and the high economic cost of treatment of metabolic disease, it is important that we preferentially prevent them from occurring, To make the point, this emerging scientific domain could help the future research and the future public health.

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