

Developmental programming of energy balance and the metabolic syndrome

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The increasing prevalence of the metabolic syndrome in numerous populations throughout the world is currently of major concern, and presents a huge global health problem. The link between low birth weight and the subsequent development of obesity, disrupted glucose homeostasis and hypertension is now well established, and there is extensive evidence supporting these associations in both epidemiological and experimental studies. Alterations in the secretion of, and responses to, the circulating hormones insulin and leptin are likely candidates in terms of disease development. The aim of current research is to define how the central and peripheral pathways in which these signals exert their effects may be disrupted following poor early growth, and how this disruption contributes to the development of metabolic disease. The present review aims to outline the existing evidence whereby alterations in early growth may programme an individual to be at increased risk of the metabolic syndrome. The development of central appetite and expenditure circuits and of peripheral metabolic tissues, are likely to play a key role in the long-term regulation of energy balance.

Metabolic syndrome: Obesity: 'Thrifty phenotype': Leptin: Energy balance

The metabolic syndrome, a cluster of conditions including impaired glucose tolerance, dyslipidaemia and hypertension (Reaven, 1988), is becoming increasingly prevalent and contributes a major health burden in both developing and developed countries. Associations between fetal and early postnatal nutrition, patterns of growth and the subsequent development of obesity and other metabolic disorders have been shown in numerous epidemiological and clinical studies worldwide, and are supported by investigation in animal models (Hales *et al.* 1996). Developmental programming, whereby alterations in nutrition and growth imposed at critical periods during development result in long-term or permanent effects (Lucas, 1991), has gained much attention over recent years. In an ideal situation, strategies to provide optimal nutrition at crucial points during development would be the most beneficial in terms of minimising disease risk and reducing the substantial public health costs associated with these common metabolic diseases. To achieve these ends, clearly, there needs to be an understanding of the developmental processes involved, the roles played by nutrition and endocrine factors during this time and the 'normal' changes in responsiveness of different tissues throughout life.

Candidate targets for the programming of metabolic disease include central neuroendocrine circuits involved in the regulation of energy balance, as well as changes in peripheral tissue metabolism.

Low birth weight and metabolic disease

It has long been recognised that there is a relationship between impaired early growth and the subsequent development of adult disease. Early epidemiological studies established the association between poor fetal growth and increased risk of developing CVD (Barker & Osmond, 1986), impaired glucose tolerance (Hales *et al.* 1991), and the metabolic syndrome (Barker *et al.* 1993). The 'thrifty phenotype hypothesis' put forward by Hales and Barker in 1992 (see Hales & Barker, 2001), sought to explain why offspring exposed to poor prenatal nutrition are more susceptible to disease in later life. They proposed that in response to impaired nutrient supply (either as a result of maternal malnutrition or reduced placental function), the growing fetus will make adaptations *in utero* in order to maximise metabolic efficiency in relation to the storage

Abbreviations: ARC, arcuate nucleus; MC1-5R, melanocortin 1–5 receptors.

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and usage of fuels, to increase chances of survival postnatally. The programming of such a phenotype will continue to be beneficial if conditions of poor nutrition are extended into postnatal life; however, in the presence of adequate or plentiful nutrition these adaptations become detrimental and predispose to the development of obesity and associated features of the metabolic syndrome. Over the past two decades further epidemiological evidence and results from animal models have provided clear support for this hypothesis (Hales & Barker, 2001).

A reduction in fetal nutrition usually results in a retardation of growth and organ-specific alterations in development, including the preservation of brain growth at the expense of other peripheral organs, such as the kidneys and pancreas (Desai *et al.* 1996). Results from experimental studies in animals have shown that in response to poor maternal nutrition there is a reduction in pancreatic cell mass (Snoeck *et al.* 1990) and in insulin secretory responses (Dahri *et al.* 1991). Alterations in kidney development, including a reduced number of nephrons and associated glomerular hypertrophy, are seen in low-birth-weight subjects, and subsequently confer an increased risk of later renal failure (Zandi-Nejad *et al.* 2006). Changes in body composition, including an increase in adipose mass relative to lean mass, are also associated with low birth weight in man (Yajnik, 2000; Loos *et al.* 2001). As will be addressed, the combination of these factors contributes a much greater risk of developing the serious chronic diseases type 2 diabetes and CVD.

Early growth, body composition and obesity development

Impaired fetal growth, leading to a low birth weight, is associated with increased risk of obesity in childhood and later adult life (Ravelli *et al.* 1976; Gale *et al.* 2001; Kensara *et al.* 2005). In addition to increasing obesity risks, a low birth weight is associated with a tendency to store this excess adipose tissue centrally, which is an additional predictor of later metabolic disturbance (Yajnik, 2003; Bosity-Westphal *et al.* 2005). At the other end of the spectrum, overnutrition during fetal and early life is also associated with a detrimental disease profile in later life (Armitage *et al.* 2005). Both excessive maternal food intake and the consumption of a high-fat diet are associated with increased risks of CVD (Newman *et al.* 1986) and impaired glucose tolerance and diabetes development (McCance *et al.* 1994). Thus, the relationship between birth weight and metabolic disease is such that both those born small or large show increased risk of obesity in later life, leading to a 'J'- or 'U'-shaped relationship (Parsons *et al.* 2001).

Growth during pregnancy, and also during the early postnatal period, plays an important role in long-term health. Individuals who are born small but subsequently undergo catch-up growth during the early postnatal period have a higher extent of adiposity in later childhood and adult life, and increased insulin resistance (Leon *et al.* 1996; Forsen *et al.* 2000; Yajnik, 2000; Jaquet *et al.* 2005). In terms of glucose tolerance, reduced insulin sensitivity is

predicted by increased weight gain during childhood (Yajnik, 2000; Ong & Dunger, 2004). In a study of low-birth-weight individuals the greatest extent of glucose intolerance was found to be present in those who were born small and were currently obese (Barker *et al.* 1993). The findings of these epidemiological studies have been confirmed using animal models, with low birth weight and subsequent development of obesity contributing independently and in an additive manner (Petry *et al.* 1997).

As well as alterations in fat mass, low-birth-weight individuals attain a lower lean muscle mass and strength and reduced bone density (Gale *et al.* 2001; Sayer & Cooper, 2005). Given that muscle is the primary tissue involved in the uptake of glucose, a reduction in the amount of muscle mass would also predict a reduced glucose tolerance, leading to a more rapid or severe decline in metabolic control. In addition, it could also be predicted that a reduction in muscle mass itself would impact on an individual's ability to initiate exercise.

The maternal nutritional and endocrine environment, clearly, play a key role in the development of a growing fetus. Offspring of mothers with diabetes or impaired glucose tolerance, and who are therefore exposed to elevated levels of insulin, glucose and leptin, have increased risks of becoming obese (Plagemann *et al.* 2002; Catalano *et al.* 2003). In addition, infants of diabetic mothers who are fed breast milk from normoglycaemic women have a reduced risk of obesity in later childhood compared with those fed maternal milk (Plagemann *et al.* 2002). Breast-feeding itself has been found to lower obesity risk compared with formula feeding (Dewey, 2003). Postulated reasons for this association are the typically reduced energy intakes and growth rates associated with breast-fed infants (Heinig *et al.* 1993), and altered satiety responses or programmed differences in appetite regulation may also play a role.

Despite the abundant epidemiological evidence for the role of poor early growth predisposing to increased adipose accretion in later life, and its support in animal models, there is a relative paucity of information regarding the underlying mechanisms. There is clearly a need for further research in this area in order to determine the mechanisms involved in this response. In terms of programming effects contributing towards enhanced catch-up fat, it would be expected that in response to undernutrition *in utero*, adipocytes may have an enhanced ability to store fat. However, a recent study (Bieswal *et al.* 2004) has failed to find differences in either the proliferation or lipid-accumulating properties *in vitro* of adipocytes isolated from growth-retarded rats compared with controls. There is some evidence that offspring of protein-restricted dams show an increased hepatic expression of lipogenic enzymes (Maloney *et al.* 2003); however, whether permanent alterations in fuel partitioning may result following early developmental insult remains to be fully investigated.

Regulation of catch-up growth

Increasingly, the role of catch-up growth is receiving attention as being key in the development of metabolic disease. In addition, the fact that tissue-specific alterations

occur is now providing some clues as to how the body responds to a period of deprivation to maximise fuel storage in case of repeated future nutritional restriction. Dulloo and colleagues (see Cettour-Rose *et al.* 2005, Dulloo, 2006) in a number of studies have shown that suppressed thermogenesis is a central process in catch-up growth. More specifically, it has been shown (Cettour-Rose *et al.* 2005) that during periods of re-feeding following semi-starvation, a state that induces suppression of thermogenesis in proportion to fat-store depletion, there is a redistribution of glucose such that skeletal muscle uptake is reduced while adipose tissue uptake is enhanced. Furthermore, adipose tissue fatty acid synthase activity is increased in these re-fed animals. Thus, it appears that coordinated alterations in tissue glucose handling confer a thrifty phenotype and that tissue-specific alterations in insulin sensitivity are involved. The way in which the body senses the reduction in adipose stores, and the signals and effector systems that mediate these responses, remain largely obscure (Dulloo, 2006).

Hypothalamic regulation of energy balance

In normal individuals the regulation of energy balance involves a matching of energy intake with expenditure in order to maintain a relatively stable body weight over an extended period of time. This process should be simple enough, yet in a modern Westernised society, with an overabundance of readily-available foods and an increasingly sedentary lifestyle, excess energy deposition, in the form of adipose tissue, challenges this regulation. When peripheral energy stores are sufficient circulating factors are released in proportion to these stores and they target key centres in the brain to coordinate a reduction in feeding, an increase in expenditure and a suppression of endogenous glucose production (Schwartz *et al.* 2000). Insulin was the first of such satiety signals to be identified. Following feeding, circulating insulin levels increase and insulin enters the brain via a regulated transport mechanism (Baura *et al.* 1993) where it acts to reduce energy intake and body weight (Woods *et al.* 1979). The second key hormone that has been shown to act as such a signal of plentiful fat stores is leptin, a peptide hormone that is secreted predominantly by adipocytes. In the adult circulating leptin levels are related to body mass (Maffei *et al.* 1995), but they are more closely correlated with the extent of adiposity (Liuzzi *et al.* 1999). Leptin, like insulin, is also transported across the blood-brain barrier by a saturable system (Banks *et al.* 1996).

Numerous early ablation studies (Schwartz *et al.* 2000) have indicated a key role for the hypothalamus in the regulation of energy balance. Within the hypothalamus the arcuate nucleus (ARC) is considered to be the initial site to receive input from circulating factors such as insulin and leptin. Two key populations of neurons in the ARC are involved in the 'first-order' sensing of energy stores. The first population express the orexigenic appetite-enhancing signals neuropeptide Y and agouti-related protein. The second population of neurons are those that express the anorexigenic pro-opiomelanocortin and cocaine- and

amphetamine-regulated transcript neuropeptides. Centrally, an increase in insulin or leptin signalling acts to inhibit neuropeptide Y/agouti-related protein neurons of the ARC, while at the same time activating pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript cells, leading ultimately to a reduction in feeding and increase in energy expenditure (Schwartz *et al.* 2000). Conversely, in states of negative energy balance (such as starvation or fasting) leptin and insulin levels drop, feeding responses are increased and expenditure is reduced (Ahima, 2000). Thus, in addition to conveying information regarding whole-body adipose stores, a key role for leptin is in the signalling of more short-term changes in energy flux (Ahima & Flier, 2000). Rapid changes in plasma leptin levels during fasting, in the absence of any change in total adipose tissue mass, are key in mediating the neuroendocrine adaptation to a fasting state (Ahima *et al.* 1996).

Appropriate peripheral secretion and central sensing of leptin and insulin have recently been recognised as key in the maintenance of body weight and glucose homeostasis (Schwartz & Porte, 2005). As in peripheral tissues, hypothalamic insulin signalling involves the insulin receptor substrate-1-phosphatidylinositol 3-kinase pathway (Niswender *et al.* 2003). It is also now clear that leptin and insulin share a common signalling pathway at the level of the hypothalamus (Schwartz & Niswender, 2004). Leptin receptor activation, which leads to the induction of suppressor of cytokine signalling-3 and prevents further signalling at the level of the receptor, also negatively influences insulin signalling (Ueki *et al.* 2004). In obese subjects both insulin and leptin levels are elevated (Liuzzi *et al.* 1999), but these individuals fail to respond appropriately. Central resistance to the anorectic and metabolic effects of these hormones is therefore thought to underlie many of the metabolic complications that arise during obesity. Interestingly, however, it appears that chronic hyperleptinaemia results in the development of selective leptin resistance. Although there is a loss of the appetite-suppressing and metabolism-enhancing effects of leptin, studies in rodents (Correia *et al.* 2002; Rahmouni *et al.* 2005) have shown that there is a preservation of the effects of this hormone on the cardiovascular system. The reasons for this disparity in leptin resistance are as yet unclear, but it provides a mechanism whereby obesity, with its associated hyperleptinaemic state, contributes to elevated blood pressure and associated cardiovascular complications.

In addition to central effects on appetite, leptin also plays a key role in the regulation of peripheral tissue metabolism. Leptin receptors are present in many non-neural tissues, and both direct and indirect (central nervous system-mediated) effects of leptin act to increase sympathetic nervous system activity (Haynes *et al.* 1997). As well as up regulating energy expenditure via central nervous system-mediated pathways, leptin acts to suppress lipogenesis and promote lipid oxidation (Minokoshi *et al.* 2002). This potent anti-steatotic role of leptin, opposing the fat-storing actions of insulin, is thought to be key in preventing ectopic deposition of lipid in non-adipose tissues (particularly muscle and pancreatic islets), and

reducing lipotoxicity, a central process in the development of insulin resistance (Unger, 2003).

Hypothalamic signalling: downstream of the arcuate nucleus

Relatively less understood is the circuitry downstream of the ARC signalling, and the way in which a coordinated alteration in feeding and energy expenditure is achieved. The pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript and neuropeptide Y/agouti-related protein populations of the ARC, mentioned earlier, project to secondary sites within the hypothalamus, including the paraventricular nucleus, the lateral hypothalamic area, dorsal medial nucleus and the ventromedial nucleus. The melanocortin pathway is one efferent outflow that has received a large amount of attention in recent years, given its crucial role in the regulation of energy balance, both in human subjects and animal models. Indeed, in man genetic defects within the melanocortin pathway are the most common forms of monogenic obesity (O'Rahilly *et al.* 2003). The melanocortin peptides are derived from the cleavage of the pro-opiomelanocortin-precursor peptide, and they act through a family of receptors (MC1–5R) to inhibit food intake and increase energy expenditure (Cone, 2005). In terms of energy balance the MC4R subtype is considered to be most crucial, which is supported by the following findings: mutations in this receptor result in severe early-onset obesity in human subjects (Yeo *et al.* 1998); disruption of this gene results in hyperphagia and development of obesity in mice (Huszar *et al.* 1997); over-expression of the endogenous antagonist of the MC4R, agouti, also causes obesity (Klebig *et al.* 1995).

In terms of the downstream integration and possible divergence of appetite and expenditure regulation, a recent study (Balthasar *et al.* 2005) has shown that there is a divergence in the control of these systems downstream of the ARC. Using the obese MC4R-knock-out mouse model MC4R expression was reactivated specifically in hypothalamic sites thought to be critical in mediating the melanocortin actions. When MC4R was restored in paraventricular nucleus and amygdala neurons, a 60% reduction in the obesity associated with the MC4R-knock-out phenotype was observed. Remarkably, this restoration was found to be associated with a correction of the hyperphagia in these animals, but had no effect on energy expenditure. Furthermore, there is now emerging evidence (Zhang & Scarpace, 2006) that targetting of the melanocortin pathway, downstream of leptin actions, may provide a means of circumventing leptin resistance and therefore be of potential clinical relevance in the treatment of obesity.

Leptin: a role in development of energy balance systems

A critical role for leptin in the regulation of body weight is illustrated by the obese phenotype of the *ob/ob* mouse model, which possesses a mutation in the leptin gene and is thus unable to secrete this hormone (Zhang *et al.* 1994).

Administration of leptin to these animals restores body weight to normal as a result of both a suppression of feeding and an increase in thermogenesis (Campfield *et al.* 1995; Halaas *et al.* 1995; Pellemounter *et al.* 1995). Leptin administration to both mutant and wild-type animals promotes the mobilisation of fuels, produces an increase in O₂ consumption and favours the expenditure of lipid as opposed to carbohydrate stores, as shown by a reduced RQ (Hwa *et al.* 1996).

In addition to these metabolic effects in the adult, investigation of an alternative role for leptin during the early postnatal period has been prompted by observations that *ob/ob* mice show impaired central nervous system development, including reduced myelination and structural abnormalities within the hypothalamus (Bereiter & Jeanrenaud, 1979, 1980; Sena *et al.* 1985). In addition, these mice fail to undergo normal reproductive maturation (Chehab *et al.* 1996), suggesting widespread impairments in the development of neuroendocrine systems. With this in mind, Ahima *et al.* (1998) sought to establish the ontogeny of leptin secretion during the early postnatal period in mice, and were able to show that there is a peak in circulating leptin levels during the early postnatal period, and that this rise does not correlate with body weight or body fat content.

In contrast to its effects in the adult rodent, during the early postnatal period leptin is unable to reduce food intake or increase energy expenditure (Mistry *et al.* 1999; Ahima & Flier, 2000). Leptin receptor expression is present in the rodent ARC even during the embryonic period (Matsuda *et al.* 1999; Udagawa *et al.* 2000) and functional indications of leptin receptor signalling pathways are evident following exogenous leptin administration during the early postnatal period (Proulx *et al.* 2002; Bouret *et al.* 2004a). It has been proposed, therefore, that although the components of leptin signalling pathways are present and functional, they are not coupled to downstream regulatory pathways until later in development. Presumably, this state of leptin resistance is beneficial in order that neonatal animals maximise their nutritional intakes.

More recently, the work of Bouret and Simerly (Bouret *et al.* 2004a,b) has shown that the effects of leptin during the early postnatal period are indeed different from those in adulthood. Using the lipophilic tracer, DiI, an elegant series of studies (Bouret *et al.* 2004a) has demonstrated that in mice ARC axonal projections to downstream nuclei are immature at birth and subsequently develop during the first two postnatal weeks, and that distinct target nuclei are innervated at different stages. Furthermore, it was demonstrated (Bouret *et al.* 2004b) that *ob/ob* mice have a reduced innervation of these target nuclei, that neonatal but not adult leptin treatment can reverse these neuroanatomical defects and that leptin has a direct effect on stimulation of neurite outgrowth in hypothalamic explants from postnatal animals. Thus, these studies show distinct roles for leptin at different developmental stages (either neurotrophic during development or anorectic in adulthood; Fig. 1), and in addition show that there is a critical window of timing for the leptin-mediated development of hypothalamic energy balance circuits.

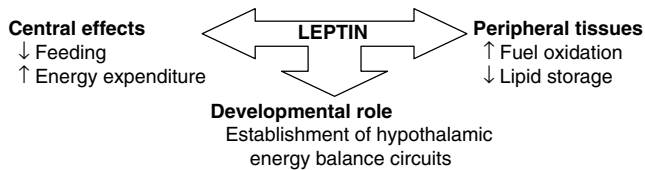


Fig. 1. Diverse roles of leptin in the regulation of energy balance. ↑, Increased; ↓, decreased.

Early-life programming of appetite

Evidence from animal models has shown that permanent changes in appetite pathways can result from alterations in nutrition during early life. Plagemann and coworkers (Plagemann *et al.* 1992, 1999; Davidowa & Plagemann, 2001; Davidowa *et al.* 2003) have made extensive use of a rodent model in which litter size is reduced to three animals per dam for the duration of lactation in order to enhance food availability and therefore increase food intake and body-weight gain. These small-litter offspring have been shown reproducibly (Plagemann *et al.* 1992) to become hyperinsulinaemic in early postnatal life, to exhibit increased weight gain, adiposity and hyperphagia and to be more prone to diabetes in later life. Subsequent work using this model (Plagemann *et al.* 1999) has identified alterations in appetite regulatory pathways, at the level of the hypothalamus, as a result of this postnatal overfeeding. As well as these morphological changes, it has been shown (Davidowa & Plagemann, 2001; Davidowa *et al.* 2003) that these animals are less responsive to the inhibitory effects of leptin and insulin, and thus the overall outcome is an enhanced orexigenic drive.

Subsequent to these findings, and of particular importance in terms of nutritional programming of appetite, it has been shown (Yura *et al.* 2005) that alterations in maternal and neonatal nutrition can alter the profile of the postnatal leptin surge and hypothalamic development. In mice, offspring of dams subjected to undernutrition during pregnancy exhibit a premature leptin surge, and subsequently go on to show an increased susceptibility to weight gain when weaned on to a high-fat diet. The importance of this premature spike as a causal factor in the later development of obesity has been demonstrated by artificially administering a premature leptin surge in normally-fed offspring, which results in the development of a phenotype indistinguishable from that of the undernourished offspring. Thus, it appears that the development of metabolic systems critically involves this postnatal leptin surge, and that this process can be greatly affected by early nutrition. In a rat model of maternal undernutrition it has again been shown (Vickers *et al.* 2005) that offspring go on to develop increased food intake and reduced energy expenditure, but remarkably that administration of leptin for 10 d during the neonatal period can correct this defect. The mechanisms in this case remain unclear. In another recent animal model it has been shown in rats (Desai *et al.* 2005) that maternal nutrient restriction and subsequent re-feeding during the lactational period results in a rapid catch-up growth during the early postnatal period, which is followed by a sustained elevated weight gain into adulthood. These animals have a

lower birth weight and reduced levels of leptin at birth, but in later life attain a higher percentage body fat and became hyperleptinaemic. Together, the results of these animal studies suggest that early leptin levels provide cues that will affect the development of hypothalamic circuitry. It has yet to be determined if alterations in the postnatal leptin profile such as these have lasting effects on hypothalamic neuropeptide levels or programming of this central energy balance circuitry, but no doubt this issue will be the focus of research to come.

In human subjects there has been relatively little research into the ontogeny of early-life leptin levels. Maternal leptin levels are related to adiposity, and breast milk levels also reflect maternal fat mass (Houseknecht *et al.* 1997). Cord blood levels of leptin tend to reflect neonatal fat mass, and low cord leptin has been associated with rapid postnatal weight gain in small-for-gestational-age infants (Ong *et al.* 1999). As addressed previously, this catch-up growth is associated with an increased risk of later obesity and metabolic disease.

Animal models

Numerous animal models have now been established to study the mechanisms through which altered early nutrition and growth can affect the subsequent development of adult disease. Impaired early growth can be induced experimentally by means of maternal protein restriction (Hales *et al.* 1996; Langley-Evans, 1996; Lucas *et al.* 1996), energy restriction (Vickers *et al.* 2000), exposure to excess glucocorticoids (Seckl, 2004), maternal hypoxia (Williams *et al.* 2005), Fe restriction (Lewis *et al.* 2001; Gambling *et al.* 2003) and intrauterine artery ligation (Frampton *et al.* 1990; Simmons *et al.* 2001). In each of these models offspring are growth-retarded, have a lower birth weight and are more prone to disease in adulthood. In cases in which offspring are then subjected to enhanced or excessive nutrition postnatally (by the introduction of a high-fat or highly-palatable diet) the detrimental effects of this early growth restriction are augmented (Vickers *et al.* 2000; Ozanne *et al.* 2004a). Despite different means of inducing impaired growth, the similar phenotypic attributes (altered glucose homeostasis, increased fat deposition and development of hypertension) suggest that common pathways may be involved in the programming of metabolic disease in response to poor early growth. Although extrapolation of findings in animal models cannot be directly applied to the human situation, these models allow the investigation of mechanisms that might be of importance in the development of metabolic diseases.

Of these different models, the maternal low-protein condition is possibly the best characterised, and produces offspring with a phenotype very similar to that of the human metabolic syndrome (Desai *et al.* 1996; Ozanne *et al.* 1997; Ozanne *et al.* 2005). This model therefore represents a useful tool for the investigation of mechanisms that might underlie metabolic programming, and potentially for the determination of intervention strategies.

Within the authors' laboratory the low-protein intervention involves feeding either a standard control diet

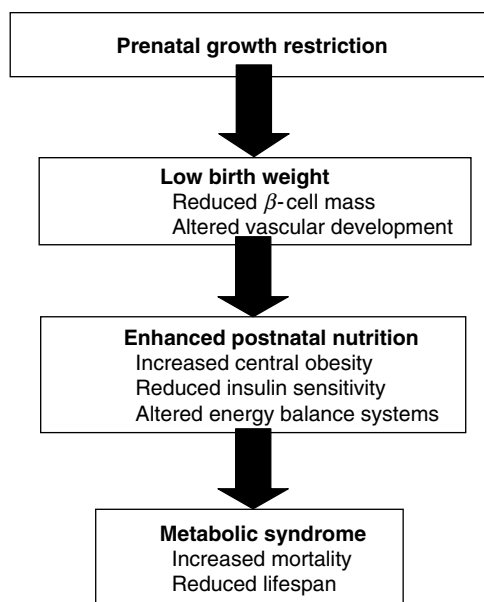


Fig. 2. Thrifty phenotype development of the metabolic syndrome.

containing 200 g protein/kg or an isoenergetic diet having reduced protein (80 g/kg) to female rodents during pregnancy and/or lactation. Growth restriction during gestation gives rise to offspring having a reduced body weight, and if the low-protein diet is continued throughout lactation these animals remain permanently smaller even when weaned onto a control diet (Desai *et al.* 1996; Ozanne *et al.* 1997, 2005). Initial studies have shown a wide range of programmed metabolic disturbances arising from these early-life dietary manipulations. In general, offspring of low-protein-fed dams show improved glucose-handling capabilities in early adult life, but undergo a greater age-related decline in glucose tolerance, and have alterations in insulin-signalling pathways in muscle and adipose tissue (Hales *et al.* 1996; Ozanne *et al.* 1996, 1997).

In an extension of this low-protein protocol cross-over groups have been included to assess the differential effects of reduced growth at different stages of early development. The crossing of low-protein offspring to control-fed dams for the period of lactation ('recuperated' offspring) results in a rapid growth during this period, and conversely crossing control offspring to low-protein-fed females during lactation (postnatal low-protein animals) slows growth and permanently reduces body size (Hales *et al.* 1996; Ozanne *et al.* 2004a). One of the most striking findings of these studies is that rapid growth during lactation significantly reduces lifespan in male rats, whereas a slowing of growth during this period increases longevity (Hales *et al.* 1996). More recently, the low-protein cross-over model has been applied in mice (Ozanne *et al.* 2004b), and again these findings on lifespan have been replicated. In addition, it has been shown that postnatal low-protein animals are resistant to weight gain when given access to a highly-palatable diet from weaning, suggesting changes in energy balance systems. In another animal model (Vickers *et al.* 2000) severe maternal energy restriction (to 30% control diet) results in the development

of hyperphagia, obesity and hypertension in adult offspring, and additionally that these animals are hypometabolic. Furthermore, and in agreement with the authors' findings, these detrimental effects of impaired early growth are amplified in the presence of excessive postnatal nutrition (Vickers *et al.* 2003). Although the mechanisms underlying the phenotypic responses in this model remain to be defined, recent evidence suggests that a reduction in sensitivity to the appetite-reducing and metabolic effects of leptin may play an important role (Krechowec *et al.* 2006).

Conclusions

Impaired fetal growth is associated with increased risks of later metabolic disease, and these risks are amplified in the presence of accelerated growth during the early postnatal period and/or increased energy intake in later life (Fig. 2). Of importance in determining the ultimate outcome, the extent of disparity between early growth cues and subsequent level of nutrition are thought to be crucial (Gluckman *et al.* 2005). It appears that a lower plane of nutrition during the early postnatal period is protective in terms of later development of obesity and other metabolic complications. However, there is at present insufficient evidence to advocate a reduction in nutritional intake in human infants during the early life period as a means of reducing chronic disease, and clearly an intervention of this nature would be difficult to implement. Epigenetics, an expanding field investigating changes in gene expression as a result of alterations in DNA methylation and histone modifications, is receiving greater attention in terms of programming of the metabolic syndrome and other diseases (Gallou-Kabani & Junien, 2005). There is a need for further investigation as to the way in which different organ systems develop in relation to altered growth trajectories and the mechanisms contributing to coordinated adaptations to nutrient supply. The relative contribution of changes in appetite pathways, body composition and metabolic rate are unclear at present. Future studies involving the low-protein model aim to further investigate these potential mechanisms, and it will also be of interest to determine the extent to which metabolic adaptations might remain plastic in later life. Ultimately, studies in this field will work toward the development of intervention strategies aimed at reducing the incidence of metabolic disease and alleviating the associated health and economic burdens.

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