

# Chapter 12

## Early Origins of Obesity and Developmental Regulation of Adiposity

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**Abstract** Whilst overweight and obesity result in significant health problems in childhood and adulthood, their origins may lie in earlier life experiences from the nutritional environment of the periconceptional, in utero and postnatal periods. Epidemiological data from human populations show that changes in maternal nutrition during different phases of pregnancy affects the long term health of offspring. Importantly in the context of contemporary populations, maternal overnutrition and obesity also influence offspring health and may induce long term changes which predispose offspring to insulin resistance, obesity and metabolic syndrome in later life. Although changes in maternal nutrition can alter fetal adiposity without overall changes in birthweight, obese mothers are more likely to have large for gestational age babies and these offspring are more prone to becoming overweight and obese in later life. In addition to the effects of the maternal nutritional environment, accelerated growth in the early postnatal period, particularly when preceded by fetal growth restriction, can be detrimental to long term health and increase the risks of obesity and Type 2 diabetes, consequences similar to those following rapid and early increases in body mass index in childhood. Key pathways of fetal programming include those mediated through glucocorticoids, with their vital role in developmental regulation of adipose tissue, appetite regulation and energy homeostasis regulated by the hypothalamus, and the neurohormones insulin and leptin influencing the actions of neuropeptides in the hypothalamic nuclei. A better understanding of these processes may provide opportunities for the prevention of obesity and improved public health.

**Keywords** Obesity • Adipose tissue • Nutritional programming • Pregnancy nutrition • BMI • Growth • Metabolic syndrome

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Overweight and obesity are defined by abnormal or excessive fat accumulation which may impair health and obesity and have significant repercussions on health, being related to various cardiovascular causes of mortality, cancer, Type 2 diabetes, musculoskeletal disorders, work disability and sleep apnoea (Visscher and Seidell 2001).

Obesity, once established, is infamously difficult to reverse and, therefore, the solution to obesity related health problems may lie in its prevention. Traditionally, obesity has been thought to result from an imbalance of energy intake and expenditure, resulting if the intake of energy exceeds its expenditure over a significant period of time. It is intriguing to consider why energy balance occurs in some individuals despite the same obesogenic environmental conditions prevalent in the developed world which in others leads to obesity (Ojha et al. 2015).

It can be hypothesized that the control of body weight and composition depends on an axis with interrelated, and possibly self-controlled, components of food intake, metabolic rate, body fat stores and physical activity. Whilst it is assumed that body weight is ultimately determined by the interaction of genetic, environmental and psychosocial factors acting through several physiological mediators of food intake and energy expenditure (Martinez 2000), the debate over whether obesity is caused by over-eating, lack of physical activity or genetic predisposition remains.

Although the energy balance equation between food intake and energy expenditure may appear deceptively simple, it seems that these variables have a much more complex relationship (Budge et al. 2005). Moreover, recently there is increasing evidence that factors in the periconceptual period, in utero and in early neonatal life may determine later obesity. This may be mediated by their influence on food intake via appetite regulation, nutrient turnover and thermogenesis or by modulation of fat deposition and adiposity. In this chapter, we will discuss the early determinants of adiposity and the current insights into preconceptional, in utero and early life developmental factors which influence later obesity (Ojha et al. 2013). We will discuss how the nutritional environment during the development of the organism impacts upon the physiology of appetite regulation, energy homeostasis, adipose tissue biology and the development of obesity.

## **12.1 The Theories of the Developmental Origins of Adult Diseases and the Link Between Development and Later Adiposity**

Longstanding epidemiological evidence suggests that early life experiences have important implications for long term health. In a Norwegian population, Forsdahl showed that significant poverty in childhood and adolescence, followed by prosperity, is a risk factor for arteriosclerotic heart disease (Forsdahl 1977). Later, in England and Wales, Barker and colleagues demonstrated that ischemic heart disease was strongly correlated with both neonatal and post-neonatal mortality and

suggested that poor nutrition in early life increases susceptibility to the effects of an affluent diet (Barker and Osmond 1986). They further postulated that coronary heart disease is associated with specific patterns of disproportionate fetal growth which result from fetal undernutrition between middle to late gestation (Barker et al. 1993). It is recognised that there are critical windows in fetal development when the process is “plastic” i.e. during periods in which the fetus is undergoing rapid cell proliferation and is very susceptible to environmental influences (McCance and Widdowson 1974). This plasticity provides organisms with the ability to change structure and function in response to environmental cues. Data from the Dutch “Hunger Winter” (the Famine of 1944–45) exemplifies this, documenting the various long term outcomes from significant maternal undernutrition during different periods of gestation (Roseboom et al. 2001). In those exposed to famine in early gestation, even though there was no effect on birth weight, there was an increased risk of later obesity (Ravelli et al. 1999) and metabolic diseases including a three-fold increase in incidence of cardiovascular diseases (Roseboom et al. 2000a).

Hales and Barker have proposed the “thrifty phenotype hypothesis” (Hales and Barker 2001) which postulates that poor fetal nutrition sets in a chain of responses which alters growth and permanently changes the structure and function of the offspring. They proposed that the poorly nourished mother essentially forecasts a poor nutritional environment into which the fetus will be born. Fetal adaptations enable it to survive in the adversity of poor nutrition. However, this becomes detrimental when the postnatal environment changes, with increased abundance of nutrients leading to obesity. Furthermore, the concept of “programming”, introduced by Lucas, describes a more general process, whereby a stimulus or insult at a critical period of development has lasting or lifelong significance (Lucas 1991). Gluckman and colleagues (Gluckman et al. 2005) defined predictive adaptive responses (PARs) as a form of developmental plasticity which evolved as adaptive responses to environmental cues acting early in the life cycle. The advantages gained from these adaptations help the offspring survive if the environment remains similar. In these ways, contemporary concepts of the developmental origins of disease have been reached, namely that fetal growth is determined by interaction between fetal environment and fetal genome which, in turn, determines the risk of postnatal disease as well as the individual’s capacity to cope with the postnatal environment (Gluckman and Hanson 2004).

The risk of obesity in later life may be determined by both extremes of early nutrition, the risk increasing with early life nutritional deprivation as well as with early life excess due to overnutrition. The Nurses’ Health Study in the United States showed an increase in body mass index in midlife in those who weighed more than 10 lb at birth as well as in those who were born with low birth weight (Curhan et al. 1996). Furthermore, increased maternal weight and decreased insulin sensitivity are correlated with fetal growth and, particularly, with increased fat mass at birth (Catalano et al. 1995). In pregnancy, obese women, particularly when they also have Type 2 or gestational diabetes mellitus, make excess nutrients available to the fetus, leading to fetal macrosomia which, in turn, is linked to adolescent and adult obesity. The U.K. Centre for Maternal and Child Enquires reported in 2010 that 5% of U.K.

women who gave birth at  $\geq 24$  weeks of gestation had a body mass index (BMI)  $\geq 35$  (CMACE 2010). The report also found that the perinatal mortality rate for singleton infants born to mothers with BMI  $\geq 35$  was almost double that of the general population and that their babies are at greater risk of being born large for gestational age and/or preterm. Not only were infants of obese mothers more likely to be born large for gestational age, this was amplified when maternal obesity was accompanied by diabetes (CMACE 2010).

Whilst being born large for gestational age presents an obstetric risk to infant and mother, the effects of maternal obesity on the infant persist beyond the newborn period. Maternal obesity prior to pregnancy predisposes offspring to insulin resistance and inflammation (Retnakaran et al. 2003) and increases the risk of overweight in adolescence. The associations between maternal obesity and overnutrition and between obesity and metabolic syndrome in the offspring has been described as the “developmental overnutrition hypothesis” (Armitage et al. 2008) which states that high maternal glucose, free fatty acid and amino acid concentrations result in permanent changes in appetite control, neuroendocrine functioning and/or energy metabolism in the developing fetus which cause obesity and other manifestations of metabolic syndrome in later life. In the face of the obesity epidemic, with increasing prevalence of adolescent obesity and increasing incidence of Type 2 diabetes among young women, there is a vicious cycle of propagation of obesity by the effects of early overnutrition on the fetus and onwards through successive generations (Catalano 2003).

## 12.2 Evidence from Animal Models

Data from epidemiological studies in human populations such as the British cohorts (Law et al. 1992; Sayer et al. 2004) and the “Dutch Hunger Winter” have provided invaluable evidence suggesting links between early life experiences and later obesity. Although prospective investigations in human cohorts would be of enormous value, these are complex, expensive and confounded by the influences of uncontrollable variables of genetic and environmental origin (Taylor and Poston 2007). Randomised trials to elucidate the relative contributions of different factors and interventions such as sedentary behaviour and maternal nutrition and their modulation by postnatal diet are not practically possible in human populations while in observational studies the effects of the behaviours and other factors of interest are complicated by too many confounding variables. Well-defined experimental studies with the necessary controls can examine precise hypotheses in humans but are usually limited by small numbers and are often ethically impossible (Symonds et al. 2000). The alternative is large observational studies without appropriate controls. In such situations, there are too many confounders and reliance on food diaries or food frequency questionnaires which are not adequately validated. Furthermore, individuals who are under- or over-eating make imprecise records, increasing the likelihood of Type II errors (Symonds et al. 2000; Edington 1999).

The use of animal models is, therefore, essential if the relative contributions of maternal nutrition during fetal development, post-weaning nutrition and sedentary behaviour are to be explored. Animal studies also permit more detailed elucidation of the cellular changes which occur during the evolution of obesity and the changes induced by altered environments (Budge et al. 2005). Several animal models have been used for this purpose, the most common being rodent and sheep models. Like the human, the sheep is a precocial species, carrying one or two fetuses born, at term, after a long gestation (Symonds et al. 2007). However, they have a different pattern of placentation—sheep placentae are cotyledonary synepitheliochoria whilst humans have a discoid haemochorial placenta. Rats, on the other hand are litter bearing with immature offspring born after a short gestation. The rat placenta is more similar to human placenta, although placental differences have not been shown to have substantive modulating effects on nutritional programming. Responses to changes in maternal nutrition at different periods of fetal and early neonatal development can also be better elucidated in the sheep as its diet can be manipulated to coincide with precise periods of fetal organogenesis which are comparable with those during human fetal development (Festing 2006). Sheep are also comparable to humans in a variety of metabolic functions, including brown adipose tissue (BAT) physiology. Both sheep and humans are precocial thermoregulators. BAT is most abundant at the time of birth (Clarke et al. 1997a) which triggers non-shivering thermogenesis (Symonds et al. 2003). On the contrary, rats are altricial species where there is postnatal maturation of uncoupling protein (UCP)1 abundance and the hypothalamo-pituitary axis.

Important long-term impacts also result from changes in organ growth rates, fetal metabolic rate and protein turnover which are similar in sheep and humans, but different in rodents. The hypothalamic–pituitary–adrenal axis, a major player in endocrine control of feeding and adipose tissue metabolism, has a similar maturity pattern in sheep and humans (Fowden et al. 1998) as does the central neural network for the regulation of appetite (Muhlhausler et al. 2004). In rats, these developments occur in the early postnatal period and are dependent on the influence of a neonatal surge in leptin (Bouret et al. 2004). These differences highlight important discrepancies in the pattern of development in various animals. The neuroendocrine mechanisms which modulate appetite and energy homeostasis are largely developed in late gestation in both sheep and humans whilst substantial maturation occurs in the early postnatal period in rodent species. Therefore, sheep models may be a closer estimate of the “programming” effects of nutritional variations and possible interventions in human fetus and neonate.

### 12.3 The Programming of Adipose Tissue

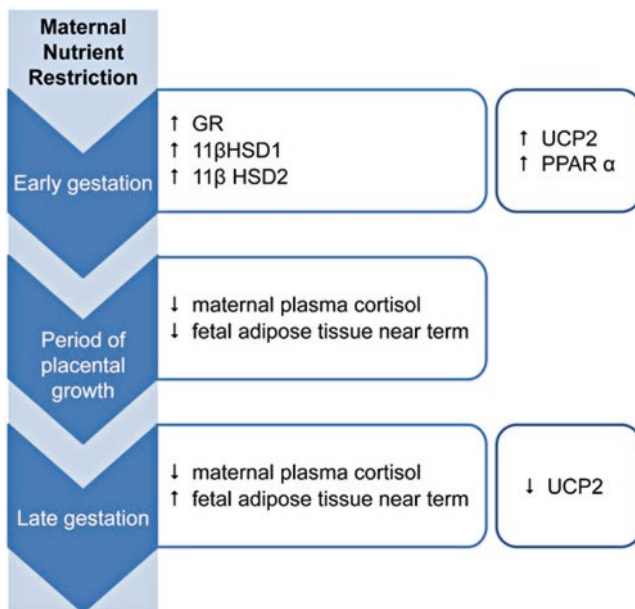
Adipose tissue is present from very early in fetal development but, for larger animals such as humans and sheep, the majority of adipose tissue deposition occurs in the last one-third of gestation (Clarke et al. 1997a). Fetal adipose tissue exhibits characteristics

of both brown and white adipose tissue, demonstrating an ontogenic rise in the BAT specific uncoupling protein 1 (UCP1) as well as leptin secretion, characteristic of white adipose tissue (Budge et al. 2003; Symonds et al. 2004). It consists of a combination of multilocular and unilocular adipocytes (Yuen et al. 2003). Birth results in a surge of UCP1 synthesis in precocial species such as sheep (Budge et al. 2003), followed by a gradual loss of UCP1 to undetectable levels by 1 month of age (Clarke et al. 1997b). Therefore, in precocial thermoregulators such as humans and sheep, brown fat is most abundant at birth and then in sheep disappears to undetectable levels in the postnatal period. In altricial species such as rodents, maximal UCP1 concentrations occur in the postnatal period and functional brown fat is retained throughout life (Budge et al. 2003), as is now known to be the case in humans (Sacks and Symonds 2013).

In large animals, BAT is present mainly around the core organs such as in perirenal fat depots and constitutes only 2% of birth weight (Symonds and Lomax 1992), as well as in the neck region (Symonds et al. 2012). Although BAT is primarily utilised for thermoregulation following the exposure to the extra-uterine environment, it also plays an important role in energy homeostasis (Symonds et al. 2003). When stimulated, BAT produces up to 300 W/kg tissue of heat compared with 1–2 W/kg tissue by most other tissues (Power 1989). In utero, adipose tissue growth is under marked nutritional constraints, unsurprisingly given that the metabolic demand for fat deposition is higher than that for protein deposition. Therefore, in the persistently hypoxic and hypoglycaemic fetal milieu, adipose tissue is kept firmly regulated (Symonds et al. 2003). However, despite this, fetal adipose tissue is significantly altered by changes in maternal nutrition during fetal development and these changes have the potential to substantially increase the risk of offspring becoming obese in later life (Budge et al. 2005).

At the beginning of the third trimester, only a small amount of adipose tissue is present and, at this stage, leptin and UCP1 appear in the fetus (Yuen et al. 1999; Budge et al. 2004; Casteilla et al. 1987). Leptin synthetic capacity of fetal tissue then increases in late gestation (Yuen et al. 1999). After appearing around mid-gestation, UCP1 becomes more abundant in perirenal fat, gradually increasing to peak soon after birth (Budge et al. 2004). This development of fetal adipose tissue in late gestation appears to be stimulated by an increase in sympathetic innervation,  $\beta$ -adrenergic receptor density and plasma catecholamine concentrations which are likely to be the primary stimuli for appearance of UCP1 (Symonds et al. 2003). Endocrine adaptations also take part in this process of adipose tissue development. Increases in the abundance of prolactin receptors and in plasma prolactin and are seen along with rise in the metabolically active forms of thyroid hormones in the fetal adipose tissue (Symonds et al. 2003). All these are implicated in upregulation of UCP1 gene expression.

Changes in maternal nutrition during various phases of fetal development can alter fetal adiposity as summarised in Fig. 12.1. These responses may not always manifest as differences in fetal body or adipose tissue weight (Budge et al. 2003). The timing of maternal nutritional manipulation is also critical. Maternal nutrient restriction during the time of placental growth does not affect adipose tissue growth initially but the fetus subsequently deposits more adipose tissue with increased



**Fig. 12.1** Effects of maternal nutrient restriction on the development of adipose tissue. Nutrient restriction at different phases of development alters the abundances of glucocorticoid receptors (GR), 11β-hydroxy steroid dehydrogenases, (11βHSD), uncoupling protein (UCP) 2 and peroxisome proliferator-activated receptor (PPAR) α in fetal adipose tissue deposition

expression for insulin like growth factor (IGF) I and II receptors (Gardner et al. 2005). In comparison, although offspring of sheep which are nutrient restricted in late gestation may be of similar body weight to those whose mothers were adequately nourished during this period, they develop glucose intolerance, insulin resistance and more fat in young adulthood (Bispham et al. 2005). Similarly, maternal overnutrition also affects adipose tissue deposition and UCP1 expression. Increased maternal nutrition in the latter half of gestation results in heavier offspring with less BAT per kilogram of body weight. However, the BAT in these offspring is richer in UCP1 and has greater thermogenic activity (Budge et al. 2000). Increased maternal nutrition is also associated with the emergence of a strong reciprocal relationship between UCP1 and leptin expression in fetal adipose tissue in late gestation (Muhlhauser et al. 2003).

### 12.3.1 Role of Glucocorticoids in Programming Obesity

Adipose tissue is the only adult organ which is capable of almost unlimited growth. Glucocorticoids appear to play a vital role in regulation of adipose tissue during fetal development and in later life (Gnanalingham et al. 2005a). They are essential



for the terminal differentiation of adipocytes as seen by the expression of late markers such as glycerol-3-phosphate dehydrogenase (GPDH) activity and triacylglycerol accumulation which are indicative of terminal differentiation in adipocytes (Gaillard et al. 1991). Glucocorticoids also have an action in both the hypertrophic and hyperplastic growth of adipose tissue and influence differentiation, metabolism and gene expression in these cells (Gaillard et al. 1991; Gnanalingham et al. 2005b).

The action of glucocorticoids on adipose tissue is mediated by glucocorticoid receptors (GR) and 11- $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ HSD) types 1 and 2. 11 $\beta$ HSD1 behaves predominantly as an 11-oxoreductase, utilising nicotinamide adenine dinucleotide phosphate (NADP) as a cofactor to catalyse the conversion of inactive cortisone to bioactive cortisol and as an intracellular amplifier of glucocorticoid excess to the GR (Bamberger et al. 1996; Budge et al. 2005). The reverse action is catalysed by 11 $\beta$ HSD2 which acts as a nicotinamide adenine dinucleotide (NAD)—dependent dehydrogenase, catalysing the conversion of cortisol to inactive cortisone, a process which maintains the specificity of the mineralocorticoid receptor for aldosterone (Stewart and Krozowski 1999; Budge et al. 2004). Both GR and 11 $\beta$ HSD1 expression increase with fat mass, whilst 11 $\beta$ HSD2 expression decreases (Gnanalingham et al. 2005b; Budge et al. 2005). In sheep offspring, both GR and 11 $\beta$ HSD1 mRNA abundance increase with postnatal age and are maximal at 6 month of age when they demonstrate an inverse relationship with adipose tissue weight (Gnanalingham et al. 2005b). This appears to be exclusive to perirenal adipose tissue, which is the major fat store in the animal, suggesting a differential regulation of glucocorticoid action in adipose tissue and, hence, the possibility that it may be the pathophysiological mediator of later obesity (Gnanalingham et al. 2005b). In addition, 11 $\beta$ HSD1 gene expression increases in adult women with central obesity (Engeli et al. 2004). Further support for its role comes from transgenic mice where those that overexpress 11 $\beta$ HSD1 in adipose tissue have increased corticosterone and develop visceral obesity and glucose intolerance (Masuzaki et al. 2001) whilst those lacking 11 $\beta$ HSD1 are resistant to obesity (Kotelevtsev et al. 1997).

The environment of the fetus, particularly the maternal diet, has a strong influence on glucocorticoid metabolism (Budge et al. 2005) and this may be an important pathway for regulation of fetal and later obesity. Maternal early to mid-gestation nutrient restriction in sheep increases the expression of GR, 11 $\beta$ HSD1 and attenuates the expression of 11 $\beta$ HSD2 in adrenal and kidney in the neonatal offspring even in the absence of changes in birth weight (Whorwood et al. 2001). In perirenal tissue, such changes persist beyond the period of nutrient restriction, despite increased feed intake, suggesting that the gene expression changes have been programmed in the offspring (Whorwood et al. 2001). Furthermore, an increase in glucocorticoid action persists to at least 6 months of age (Gnanalingham et al. 2005b). Maternal nutrient restriction in sheep during the phase of maximal placental growth results in lower maternal plasma cortisol with an increase in fetal adipose tissue deposition near to term (Bispham et al. 2003), whilst undernutrition in late gestation transiently increases maternal cortisol concentrations when combined with fetal surgery (Edwards and McMillen 2001). In the offspring, early- to



mid-gestational nutrient restriction increased glucocorticoid action both near term and at 6 months of age, whilst it was decreased at both 1 and 30 days of postnatal age by late-gestational undernutrition (Gnanalingham et al. 2005b). As this does not correspond with the changes seen in maternal glucocorticoid concentrations, they are likely to reflect alterations in the mitochondria (Gnanalingham et al. 2005b). These modifications in glucocorticoid sensitivity following maternal nutritional variations could be a pivotal adaptation leading to later obesity, fitting with current theories of fetal programming of adult diseases (Budge et al. 2005). These and other studies have illustrated the role of glucocorticoids and 11 $\beta$ HSD in the regulation of adipose tissue, implicating this developmental pathway as a possible mechanism for later obesity.

### ***12.3.2 Uncoupling Protein 2 in the Regulation of Obesity***

Whilst UCP1 is specific to brown adipose tissue, UCP2 is expressed more widely in adult human tissue and is upregulated in white fat in response to fat feeding (Fleury et al. 1997). UCP2 has a role in the control of reactive oxygen species production, regulation of ATP synthesis and the regulation of fatty acid oxidation (Boss et al. 2000) and has been linked to hyperinsulinemia and obesity, suggesting a vital role in energy balance and body weight regulation (Fleury et al. 1997). In adipose tissue, UCP2 levels peak at 30 days of postnatal age and decline up to the age of 6 months (Gnanalingham et al. 2005b) and its expression is positively correlated with total and relative adipose tissue weight. This peak at 30 days of age may be a marker of transition from brown to white adipose tissue (Gnanalingham et al. 2005b; Clarke et al. 1997b). The changes in UCP2 expression with maternal nutrient restriction are similar to the effects on glucocorticoid action as its abundance increases with early- to mid-gestational nutrient restriction and decreases with late gestation nutrient restriction (Gnanalingham et al. 2005b). These changes in UCP2 expression are also implicated in the programming effects of maternal nutrition via UCP2 actions in the acquisition of white adipose tissue characteristics and the accumulation of macrophages, which has been implicated in the development of visceral obesity (Gnanalingham et al. 2005b; Weisberg et al. 2003).

### ***12.3.3 Peroxisome Proliferator-Activated Receptors in the Programming of Obesity***

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors which have three isotypes present in various tissues including adipose tissue (Grimaldi 2001). Although PPAR- $\alpha$  in the liver has a role in fatty acid oxidation (Reddy and Hashimoto 2001), in BAT it does not appear to participate in

adipogenesis. In contrast, PPAR- $\gamma$  is a master transcription factor of the adipocyte lineage and is critical for adipogenesis (Grimaldi 2001). PPAR- $\gamma$  regulates adipose tissue mass through stimulation of lipoprotein lipase (LPL) and glycerol-3-phosphate dehydrogenase (G3PDH) and is involved in the regulation of adipokines such as leptin and adiponectin (Muhlhausler et al. 2007). In response to maternal nutritional restriction between early- to mid-gestation, PPAR- $\alpha$  and UCP2 gene expression increase with adipose tissue mass, particularly when mothers are fed to requirements in the third trimester (Bispham et al. 2005). As both PPAR- $\alpha$  and UCP2 are characteristic of white adipose tissue, this might indicate the potential significance of PPAR- $\alpha$  in regulating early adipose tissue development, particularly in white adipocytes. PPAR- $\alpha$  upregulates fatty acid oxidation and when accompanied by an increase in UCP2 (Bispham et al. 2005) can promote substrate availability to adipose tissue. As IGF- I and II receptors are also upregulated in these circumstances (Bispham et al. 2003), increasing the uptake of glucose, lipid deposition could be promoted.

Maternal overnutrition also impacts on fetal adiposity and its markers. Increased nutrient supply in late gestation results in an increase in the expression of PPAR- $\gamma$ , lipoprotein lipase, adiponectin and leptin expression in fetal perirenal adipose tissue, suggesting that elevated nutrient supply before birth may result in premature activation of the expression of genes which accelerate the transformation of adipose tissue from a neonatal thermogenic organ to an adult lipid storage organ, laying down the foundations of obesity (Muhlhausler et al. 2007). Periconceptual overnutrition followed by embryo transfer in sheep results in a significant increase in total fat mass in female offspring, with the greatest impact on visceral fat depots, but does not alter the expression of PPAR- $\gamma$ , G3PDH, LPL or leptin (Rattanatray et al. 2010).

### ***12.3.4 Role of Prolactin***

Prolactin has a role in fetal adipose tissue growth and maturation before birth when there is a rise in prolactin receptor (PRLR) expression during the phase of rapid perirenal BAT deposition in sheep (Symonds et al. 1998). In rats, prolactin receptors are widely expressed and increase in PRLR expression is seen in late gestation in a number of fetal tissues (Royster et al. 1995). Administration of prolactin to pregnant rats increases UCP1 abundance in both fetus and newborn offspring, accelerating BAT maturation and enhancing its function, suggesting the role of prolactin in development of BAT (Budge et al. 2002).

Both PRLR 1 and PRLR 2 levels peak between 90 and 125 days of gestation in sheep (Symonds et al. 1998), a time when UCP1 is first detected in BAT (Clarke et al. 1997c). A reduction in fetal nutrition alone does not affect PRLR expression but hypoxia combined with fetal undernutrition (achieved by removal of endometrial caruncles before mating) downregulates PRLR1 gene expression (Symonds

et al. 1998). With an increase in maternal nutrition, fetal plasma prolactin is raised (Stephenson et al. 2001) along with increase in the long isoform of PRLR in BAT (Budge et al. 2000). Interestingly, in the same study, PRLR abundance was not altered in hepatic tissue, a finding which indicates that prolactin has an adipose tissue specific role at this stage of development (Stephenson et al. 2001). This specific relationship between PRLRs and adipose tissue development is also suggested by the effects of experimental placental restriction which significantly reduces fetal plasma prolactin concentrations in late gestation without altering PRLR gene expression in the liver or kidney of the fetus (Phillips et al. 2001).

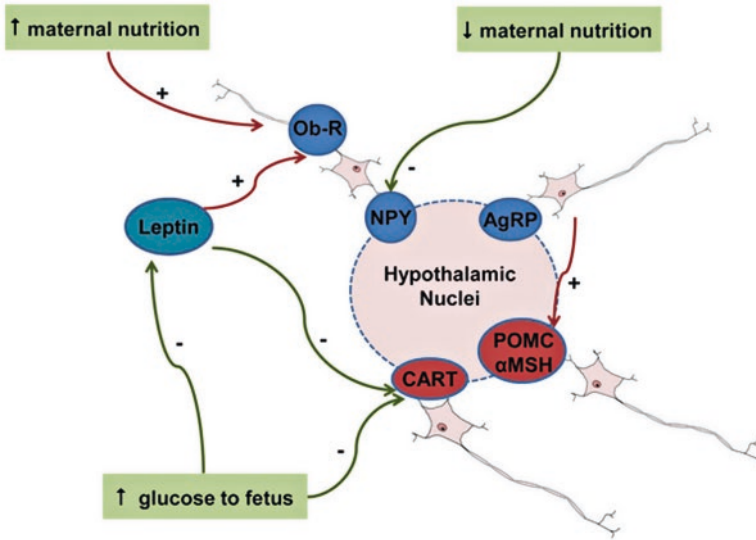
## 12.4 Programming of Appetite Regulation and the Hypothalamus

The hypothalamus regulates feeding and energy balance (Bouret 2009) and is a site of action for the central regulatory effects of leptin on energy balance (Elmquist et al. 1999). The arcuate nucleus of the hypothalamus (ARC) receives and integrates signals from peripheral hormones such as leptin and insulin and has a role in peripheral glucose homeostasis.

The central neurohormonal regulation of appetite is also controlled via the action of neuropeptides in hypothalamic nuclei (Fig. 12.2). The major appetite stimulators are neuropeptide Y (NPY) and agouti-related protein (AgRP), whilst the appetite inhibitory factors include pro-opiomelanocortin (POMC), a precursor of  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), and cocaine-and amphetamine-regulated transcript (CART) (McMillen et al. 2005). NPY neurons are activated by signals from peripheral markers such as glucose, insulin and leptin. These neurons, in turn, project onto other hypothalamic nuclei. Leptin concentrations increase with food intake, decreasing hypothalamic NPY expression, leading to suppression in appetite and hence reduced energy intake (Schwartz 2001). AgRP is co-expressed with NPY and acts as an antagonist for hypothalamic melanocortin receptors. Derived from POMC,  $\alpha$ -MSH decreases food intake and its anorexigenic action is increased by leptin which upregulates POMC expression (Schwartz 2001).

Animal studies have suggested that developmental programming of obesity may be due to the influence of the perinatal environment on the developing hypothalamus. This could lead to programming of energy balance “set points”. The effects of maternal nutritional modifications (both under- and overnutrition) may be mediated via time-critical influences which alter the expression and actions of specific neuropeptides involved in appetite regulation along with changes in the metabolic regulation of energy homeostasis.

The hypothalami of altricial species, such as rodents, continue to develop until day 20 of postnatal life (Grove et al. 2005). The early neonatal period of precocial species, such as humans, may also be important as although hypothalamic circuits appear to develop in utero in primates (Grayson et al. 2006), maturation may con-



**Fig. 12.2** Effects of maternal nutrition on appetite regulation. Decreased maternal nutrition increases the neuropeptide Y (NPY) action on hypothalamic nuclei (HN) whilst leptin acts an appetite suppressant by inhibiting NPY neurons. Increased maternal nutrition reduces leptin receptors in the HN. Increased glucose administration to the fetus (as in diabetic mothers) increases leptin concentrations and stimulates the action of cocaine and amphetamine related transcript (CART). Agouti-related protein (AgRP); pro-opiomelanocortin (POMC);  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH); leptin receptor (Ob-R)

tinue into early postnatal life. Therefore, the perinatal environment, including early neonatal nutrition, can influence hypothalamic programming with implications for later obesity.

Insulin and leptin are the most important peripheral hormone signals of the central nervous system. In early life, leptin acts as a trophic agent and promotes the formation of metabolic pathways. Rodents have gradually increasing leptin concentrations during the first week of life in parallel with the recruitment of non-shivering thermogenesis (Cottrell et al. 2009), even though leptin does not regulate food intake during this period. This has been demonstrated in  $Lep^{ob}/Lep^{ob}$  mice (mice lacking leptin), where administration of leptin does not affect food intake, oxygen consumption, body weight or adiposity until weaning (Proulx et al. 2002). Instead of altering metabolism, neonatal leptin appears to be an important signal for the development of hypothalamic circuits controlling food intake and body weight (Bouret and Simerly 2006). This postnatal leptin surge in rodents may originate in adipose tissue (Devaskar et al. 1997), stomach (Oliver et al. 2002), or come from mother's milk (Casabiell et al. 1997). Animal data also indicate that this early critical period for the neurodevelopmental action of leptin seems to be restricted to the first few weeks of life. The existence of a critical period for the developmental effects of leptin suggests changes in leptin concentrations during key periods of

hypothalamic development may induce long-lasting, and potentially irreversible, effects on metabolism (Bouret 2009).

A role for leptin has been shown in the scenario of mismatched in utero and postnatal environments. In a mouse model in which offspring born to mothers with gestational undernutrition were fed a high-fat diet, there was pronounced weight gain and adiposity (Yura et al. 2005). These offspring show a premature onset of the neonatal leptin surge compared to offspring of mothers fed a standard diet. The same authors further demonstrated that exogenous leptin administration to offspring with normal in utero nutrition and a high fat postnatal diet also leads to accelerated weight gain (Yura et al. 2005). Blockage of leptin action during the critical period of early life in rodents has long-term consequences by altering the capacity to respond to leptin during adulthood (Attig et al. 2008), a pattern of long-term leptin insensitivity implicated in adult humans with obesity (Arch et al. 1998). Administration of leptin to offspring of undernourished mothers reverses some of the programming effects of poor nutrition in utero (Vickers et al. 2005). Neonatal rats given leptin during the critical neonatal period show limited neonatal weight gain, and in adulthood caloric intake, locomotor activity, body weight, fat mass, and fasting plasma concentrations of glucose, insulin and leptin are all normalised.

Studies in sheep may be closer to humans as the appetite regulatory network develops before birth in both the species. NPY is present in the sheep hypothalamus prior to birth and fetal undernutrition and glucocorticoids increase NPY gene expression in the fetus (Warnes et al. 1998). Glucose administration to fetal sheep (a surrogate for increased nutrient availability) increases expression of POMC (Muhlhausler et al. 2005), whilst increased maternal nutrition in late pregnancy results in transiently higher relative milk intake, glucose concentration and relative subcutaneous fat mass in early postnatal life (Muhlhausler et al. 2006). The offspring of the well-fed mothers (primarily singletons) have alterations in the expression of the long form of the leptin receptor ORBb in ARC such that there is an inverse relationship between ORBb expression and relative fat mass compared to controls (primarily twins). Increased adiposity is associated with reduced expression of leptin receptors in the ARC. This suggests that exposure to overnutrition in late pregnancy, or fetal number, can cause decreased sensitivity to the actions of leptin (Muhlhausler et al. 2006).

Leptin has also been studied in humans. In pregnancies complicated by maternal diabetes, the fetus is hyperglycaemic and hyperinsulinaemic and cord blood leptin concentrations are increased in parallel with infant adiposity (McMillen et al. 2005). Adults with lower birth or infant weight have higher leptin concentrations than those of higher birth weight with similar degrees of obesity (Phillips et al. 1999). If birth weight is taken as a marker of in utero nutrition, this may be a reflection of the effects of in utero nutrient restriction on adipocyte metabolism and energy homeostasis mediated by serum leptin. Body mass index (BMI) measured at 2 years of age, of infants with intrauterine growth restriction (IUGR), remains significantly lower than those born normal weight (Jaquet et al. 1999). However, although serum leptin was low in IUGR infants at birth, it was raised when measured at 1 year of age compared with those of normal birth weight and there was a loss of the regulatory

effect of BMI and gender. This could be an adaptive leptin resistance to enable so called “catch up” growth. Alternatively, such leptin resistance could be a marker for adipocyte dysfunction.

Leptin concentrations later in life can also be influenced by early neonatal nutrition. In preterm babies, dietary manipulation for an average of only 1 month markedly influences leptin concentrations relative to fat mass up to 16 years later (Singhal et al. 2002). Importantly, the consumption of human milk is associated with a lower leptin to fat mass ratio in comparison to nutrient-enriched preterm formula milk and may represent one possible mechanism of programming by early diet (Singhal et al. 2002).

Animal models and supportive human epidemiological data suggest a fundamental role for leptin in the development and maturation of hypothalamic feeding circuits for long term energy balance. These can be modulated by both in utero and early neonatal nutrition and a premature surge in leptin concentrations can alter weight regulation and energy homeostasis, indicating a time-critical role for leptin. However, although exogenous leptin administered to “programmed” animals can potentially reverse some of the effects, in human studies to date, leptin’s potential role as a therapeutic target has not proved to be the much awaited “magic bullet” for preventing obesity (Mantzoros and Flier 2000).

Epidemiological, clinical and experimental results suggest that gestational diabetes or even slightly impaired glucose tolerance during pregnancy are important risk factors for the development of an increased risk of Type 2 and even Type 1 diabetes in the offspring (Dorner and Plagemann 1994) implicating a potential role for insulin in hypothalamic programming. Both perinatal undernutrition and overnutrition can cause hyperinsulinism and lead to permanent dysregulation of the hypothalamus. Malformation of the ventromedial hypothalamic nucleus (Plagemann et al. 1999), suppression of fetal brain NPY concentrations (Singh et al. 1997) and an increase in NPY-positive neurons in the ARC (Plagemann et al. 1998) (a possible marker of acquired hypothalamic insulin resistance) have all been shown in association with alterations in perinatal insulin concentrations.

The effect of untreated maternal diabetes during pregnancy and its consequences for differentiation of hypothalamic nuclei and levels of orexigenic and anorexigenic neurons in the offspring has been demonstrated in an elaborate study on rats (Franke et al. 2005). Exposure to a diabetic intrauterine environment and its prevention by treatment of maternal hyperglycaemia by islet transplantation during gestation has effects on neuronal organisation and expression of orexigenic and anorexigenic neuropeptides in the ARC. There is increased immunopositivity of NPY and AgRP in offspring of mothers with untreated diabetes whilst immunopositivity is decreased for MSH. The change in MSH indicates that exposure to maternal diabetes can alter the processing of POMC to MSH which is an important anorexigenic pathway. Treatment of maternal diabetes by islet cell transplantation (which induces to normoglycaemia) reverses all these effects suggesting that perinatally acquired hypothalamic neuropeptidergic responses are preventable by normalisation of gestational hyperglycaemia (Franke et al. 2005). Animal studies indicate that insulin, particularly fetal or neonatal hyperinsulinism, could induce permanent alterations in hypothalamic organisation affecting energy homeostasis and metabolism throughout life.

In utero nutrition also affects feeding behaviour possibly via the programming of hypothalamic circuits. Offspring hyperphagia in IUGR rats born to nutrient restricted mothers occurs as a result of increased orexigenic hypothalamic signals and reduced anorexigenic physiologic responses (Desai et al. 2007). Programming of central appetite regulation and glucose and lipid metabolism are also affected both by maternal obesity and postnatal overnutrition (Chen et al. 2008). In rats, although maternal obesity does not alter the body or organ weight of newborn offspring, plasma leptin concentrations and hypothalamic NPY, POMC, melanocortin 4 receptor (MC4R), leptin receptor (Ob-Rb), signal transducer and activator of transcription 3 (STAT3), SOCS3 (suppressor of cytokine signaling 3) and mammalian target of rapamycin (mTOR) are all reduced (Morris and Chen 2009). Subsequently, postnatal overnutrition leads to greater weight gain, reduced NPY, increased POMC expression and downregulation of hypothalamic glucose transporter (GLUT) 4 and mTOR expression (factors involved in brain glucose sensing) (Chen et al. 2008). Maternal and postnatal overnutrition also reduces muscle GLUT 4 expression which may explain the resulting glucose intolerance (Chen et al. 2008). This pattern of alterations in glucose handling and in regulators of appetite in response to maternal and postnatal overnutrition could be the foundation of leptin and insulin resistance associated with later obesity and highlights that amplified effects occur when maternal obesity is combined with exposure of the offspring to an obesogenic environment.

## 12.5 Programming of Level of Physical Activity

Whether reduced physical activity, or increased food intake driven by appetite, is the primary driver for obesity remains an area of continued debate. In evolutionary terms, man was dependent on physical activity for procurement of food and genes evolved to regulate efficient intake and utilisation of fuel stores to ensure survival in an environment of inconsistent food supply (Chakravarthy and Booth 2004). In the current era, the continuous supply of food without any requirement for overt physical activity produces an imbalance in energy intake and expenditure and leads to weight gain. Nevertheless, few studies have analysed the programming effects of physical activity and its effects on later obesity.

When obese individuals lose weight or lean individuals gain weight, their movements associated with routine life (nonexercise activity thermogenesis or NEAT) is unchanged (Levine et al. 2005), suggesting that they may be biologically determined. In rats, an adverse prenatal environment can lead to development of both abnormal eating and exercise behaviour. In this rat model, offspring of undernourished mothers were more sedentary in postnatal life than those born to mothers fed *ad libitum* and, although present in both genders, males were more inactive than females (Vickers et al. 2003). Therefore, it appears that there may be some effect of the in utero environment of the physical activity of offspring that contributes to obesity in later life.



## 12.6 Effects of Maternal Undernutrition

Maternal undernutrition can significantly alter the physiology and metabolic course of the offspring. This has been classically demonstrated in humans exposed to the Dutch “Hunger Famine” cohort. Several animal studies have also explored the effects of maternal undernutrition. In a rat model, offspring whose mothers were randomly assigned to received 30% of the ad libitum amount consumed by controls exhibited fetal growth retardation (Vickers et al. 2000). Fetal undernutrition induces inappropriate hyperphagia in adult life and postnatal hypercaloric nutrition further amplifies the abnormalities induced by fetal undernutrition (Vickers et al. 2000). Although offspring of undernourished mothers have markedly increased fasting plasma leptin and insulin concentrations which should decrease appetite, exposure to a postnatal hypercaloric diet, amplifies the hyperphagia, suggesting an inappropriate response due to insulin and leptin resistance induced by early programming. However, it should be noted that these animals were severely nutrient restricted and the model may not be applicable to contemporary human situations. In another rat model where pregnant mothers fed half of the daily intake of controls during the last week of gestation until weaning maternal undernutrition induced both short and long term effects on the hypothalamo-pituitary-adrenal axis (Vieau et al. 2007). There was chronic hyperactivity of the HPA axis leading to high glucocorticoid levels in adulthood. Similarly, large animal studies also indicate that it is only when there is a very severe and prolonged reduction in maternal food intake that birth-weight is consistently compromised (Mostyn and Symonds 2009).

Behaviour and lifestyle choices which exacerbate obesity and associated conditions may also have a prenatal origin. Rodent offspring of mothers who were undernourished in pregnancy are significantly more sedentary in postnatal life than those born to ad libitum-fed mothers, independent of postnatal diet (Vickers et al. 2003). Furthermore, this sedentary behaviour is exacerbated by postnatal hypercaloric nutrition. Such findings imply that that “programmed” adults may be more resistant to public health policies and interventions aimed at increasing physical exercise and reducing food intake.

### *12.6.1 Effect of Undernutrition in Various Stages of Development*

The Dutch Famine studies have also demonstrated that there are different consequences of exposure to undernutrition in different trimesters of pregnancy (Roseboom et al. 2001). These differential effects are not surprising in view of the chronological development and growth of fetal organ systems, with cardiovascular growth occurring early in gestation, that of the kidney occurring in mid-gestation and adipose and muscle development occurring late in fetal development. Exposure to the Dutch Famine during early gestation had no effect upon birthweight. However,

as adults, these offspring exhibited a more atherogenic lipid profile (Roseboom et al. 2000b) and increased risks of obesity (Ravelli et al. 1999) and metabolic diseases, including a threefold increased incidence of cardiovascular disease (Roseboom et al. 2000a).

In animal models of maternal undernutrition, peri-implantation undernutrition in sheep (between 0 and 30 days of gestation, where term is around 145 days) does not affect birth weight or offspring growth to 1 year of age although baroreflex sensitivity, which may be precursor of hypertension in later life (Gardner et al. 2004), and the hypothalamo-pituitary-adrenal axis are altered (Gardner et al. 2006). When maternal nutrient restriction is targeted at the period of maximal placental growth (i.e. 28–80 days gestation in sheep), not only is placental growth altered (Dandrea et al. 2001) but maternal plasma cortisol, leptin, thyroxine, and IGF-I are reduced without effects on birth weight, prolactin or glucose concentrations. Interestingly, maternal undernutrition in early-mid gestation increases fetal adipose tissue deposition as measured near to term, a response that is independent of maternal food intake in late gestation (Bispham 2003). These maternal adaptations to undernutrition in pregnancy may act to reduce maternal requirements for nutrients, particularly glucose, therefore partitioning it to the fetus (Symonds et al. 2007). Enhanced fetal fat stores achieved by promoting nutrient supply to the fetus will be beneficial in the short term, promoting metabolic adaptations at birth (especially when in utero nutrient restriction is “predicting” poor nutrition availability after birth), but may set the fetus for excess fat deposition after birth if nutrients are no longer limited (Symonds et al. 2007).

In both sheep and humans, fetal adipose tissue is primarily deposited during the final third of gestation. Over this period, there is an increased abundance of circulating hormones within the fetal circulation which are important in regulating fetal adipose tissue development, and include IGF-I and leptin. The increases in their concentrations are determined by maternal nutrition between early to mid-gestation. Maternal nutrient restriction during this period results in increased expression of both the IGF-I and IGF-II receptors, in conjunction with enhanced adipose tissue deposition, irrespective of the level of maternal nutrition in late gestation (Symonds et al. 2004). As these previously nutrient restricted fetuses have an increased abundance of GLUT 1 (Dandrea et al. 2001), the enhanced responsiveness to IGF may promote the anabolic effects of glucose on fetal adipose tissue growth. Therefore, maternal nutrient restriction in mid-gestation results in enhanced fetal fat deposition in combination with enhanced IGF receptor abundance and glucose supply, which could exacerbate the deposition of fat following the restoration of the maternal diet (Bispham et al. 2003; Symonds et al. 2004).

For sheep, whilst nutrient restriction up to 110d gestation promotes adipose tissue deposition, nutrient restriction in late gestation, decreases it (Gopalakrishnan et al. 2001). Adipose tissue deposition in offspring can also be reduced by manipulating the maternal metabolic and hormonal environment by increasing food intake in late gestation (Symonds et al. 2003). Indeed, late gestation appears to be the period when maternal nutrition restriction has the greatest effect on birth weight (Symonds et al. 2007). These effects are similar to the findings from the Dutch

studies where exposure to famine in late gestation had the greatest effect upon fetal growth, with offspring at birth being lighter, shorter and thinner with small head circumferences (Roseboom et al. 2001).

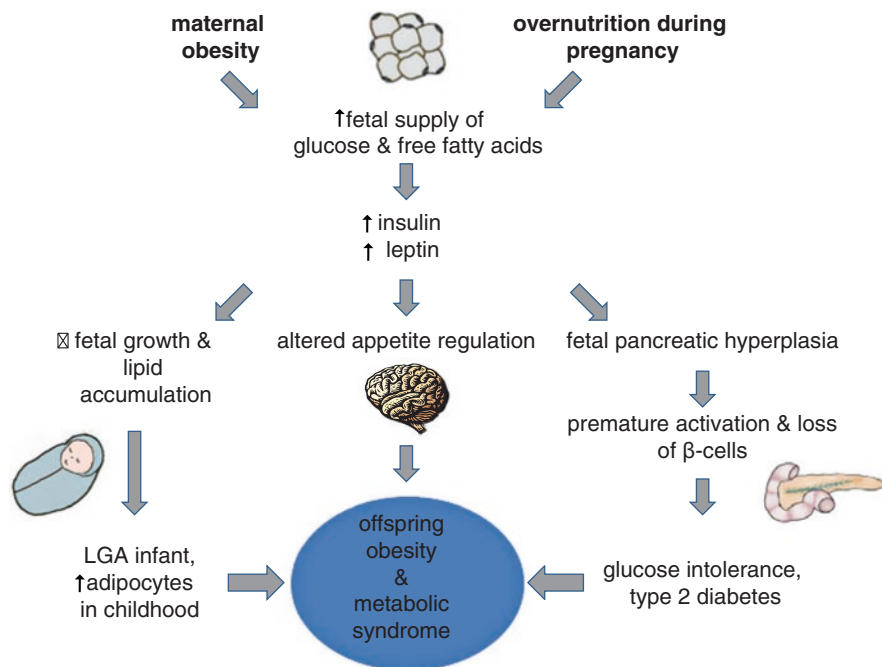
Sheep studies have demonstrated that although more fat is present at term when mothers are nutrient restricted during the period of maximal placental growth (Bispham et al. 2003), the offspring of mothers who are nutrient restricted in late gestation go on to have greater adiposity as young adults, along with glucose intolerance and insulin resistance (Gardner et al. 2005). This insulin resistance occurs in conjunction with altered glucose uptake in adipose tissue but not in skeletal muscle and there is an increase in adipose tissue insulin receptors in nutrient restricted offspring (Gardner et al. 2005). There is also a reduction in GLUT 4, the major insulin responsive glucose transporter, in adipose tissue suggesting that impaired glucose tolerance is related to the ability of adipose tissue to take up glucose in an insulin responsive manner with a reduction in its abundance is closely associated with insulin resistance (Budge et al. 2005).

In summary, animal studies support evidence from the Dutch “Hunger Winter” that specific periods of famine exposure may impact upon specific physiological control systems in adult life producing differential effects on regulation of adiposity (Budge et al. 2005). These differential effects of maternal nutritional restriction on fetal adiposity suggest that intervention strategies aimed at these critical periods of development have the potential to reduce an individual’s predisposition to obesity in adult life (Symonds et al. 2004).

## 12.7 Effects of Maternal Overnutrition

Starting with the Dutch “Hunger Winter”, many studies have focussed on studying the effects of maternal undernutrition on long term outcomes for the fetus. However, the Western World and possibly, in very near future, developing nations (Yajnik 2004), are in the midst of an obesity epidemic. This results in more women being obese both at time of conception and throughout pregnancy. The infants of these obese women are nurtured in the same obesogenic environment as their parents, making them susceptible to postnatal excesses and amplifying effects of in utero overnutrition as summarised in Fig. 12.3.

A study of pregnant women in nine US states showed a 69% increase in pre-pregnancy obesity in one decade (Kim et al. 2007). Studies in the UK also show a similar trend where the number of women who are obese at the start of the second trimester have doubled (Yu et al. 2006). In addition to pre-pregnancy obesity, weight gain during pregnancy can also be excessive. A study of pregnancy outcomes in obese women in Missouri found that 46% gained more than 25 lb of weight during pregnancy (Kiel et al. 2007) and that all pregnancy complications studied were reduced when less weight was gained. With significant implications for maternal and fetal outcomes (Catalano and Ehrenberg 2006), maternal obesity is being increasingly recognized as a major public health issue. In addition to the ill-effects



**Fig. 12.3** Maternal obesity and overnutrition can programme the fetus to adult obesity and metabolic syndrome

of obesity itself, high maternal weight is associated with a substantially higher risk of gestational diabetes mellitus (Chu et al. 2007), exposing the fetus to further risks due to hyperglycemia and hyperinsulinemia during development.

Maternal obesity has been reported to have varying influences on birth weight in animals. Whilst several studies have not established a link (Chen et al. 2008; Gorski et al. 2006; Caluwaerts et al. 2007; Shankar et al. 2008), some have reported a decrease (Howie et al. 2009). Studies in sheep showed no effect on birth weight when mothers were fed 160% of metabolisable energy requirements during pregnancy (Muhlhausler et al. 2006).

Mechanisms linking maternal and offspring obesity include high maternal glucose, free fatty acid and amino acid concentrations causing permanent programming of energy homeostasis in the fetus (Armitage et al. 2008). A maternal diet rich in energy, fat, sugar and salt during gestation and lactation in rats, induces a preference for similar diet in offspring and increases their body weight (Bayol et al. 2007). Offspring of obese mothers who are cross-fostered to lean mothers fed on a normal diet gain greater body weight and higher percentage of body fat when fed a high-fat diet (Shankar et al. 2008). Effects of maternal obesity are also seen on body composition (Bayol et al. 2009), inflammatory markers (Yan et al. 2010), insulin signalling and mitochondrial activity in muscles (Shelley et al. 2009).

Some influence may be due the composition of the diet rather than the absolute calorie content. In rats, female offspring of mothers who are fed high fat diets have raised blood pressure at 6 and 12 months of age (Khan et al. 2003). This increase is seen with a saturated fat supplemented diet but not with increased maternal polyunsaturated fatty acid intake (Armitage et al. 2004). A high fat diet in rats also affects glucose homeostasis with increased insulin: glucose ratio, higher glucose and triglyceride levels and higher adiposity in the offspring (Guo and Jen 1995). Rats fed a diet rich in omega-6 fatty acids produce offspring with increased proportion of total body and abdominal fat with increase in hepatic triglyceride concentrations and hepatic insulin resistance (Buckley et al. 2005). In contrast, other studies emphasize the effects of essential fatty acid deficiency in the maternal diet on altered leptin expression and adiposity in the offspring (Korotkova et al. 2001). Furthermore, prenatal and suckling exposure to a diet rich in animal fat results in insulin resistance and pancreatic beta cell dysfunction, preceded by altered mitochondrial gene expression (Taylor et al. 2005). Maternal high carbohydrate diets may have a different influence to high fat diets—offspring of rats fed high fat diet have greater appetite stimulation in response to intraventricular-NPY injection (Kozak et al. 2000). These studies suggest that the proportion and quality of fat and other macronutrients in maternal diet, rather than merely the total calorie intake, may be important for metabolic programming.

These animal studies support human observational data that maternal obesity and overnutrition can program the offspring for later obesity and glucose intolerance. Furthermore, children of obese women are more likely to become overweight and develop insulin resistance later in life, if their mothers had diabetes during pregnancy (Taylor and Poston 2007). Therefore, obesity and its related consequences may be a self-perpetuating problem passed through generations and progressively worsened by the facilitative obesogenic environment.

In humans, the increasing prevalence of maternal obesity and overweight (both pregravid weight and weight gain during pregnancy) have been implicated in the causation of the excess of large for gestation age (LGA) and macrosomic babies (Catalano and Ehrenberg 2006; CMACE 2010). Each kilogram of maternal weight gain during pregnancy significantly increases birth weight except in mothers whose prepregnancy weight is more than 135% of ideal for height (Abrams and Laros 1986). As the relationship between birthweight and adult BMI is U- or J shaped (Curhan et al. 1996; Fall et al. 1995), LGA infants are more likely to become obese as adults. The programmed individual may become obese by increasing the number of adipocytes and by producing pancreatic beta-cell hyperplasia which results in hyperinsulinaemia, insulin-resistance and increased deposition of lipids in adipose tissue stores (Levin 2006). High insulin levels seen in overnourished mothers (Taylor et al. 2005) along with alterations in leptin concentrations may impact on neuronal differentiation, synapse formation and maturation in the hypothalamus which may increase the body weight “set point” with increased appetite, reduced basal metabolic rate and altered energy balance resulting in the metabolic syndrome phenotype (Armitage et al. 2004). Among low-income families in Ohio, maternal obesity in early pregnancy doubled the risk of obesity at 2–4 years of age (Whitaker

2004). Maternal pregravid weight and diabetes also increases the risk of obesity in adolescence (Catalano and Ehrenberg 2006). With the substantially increased morbidity associated with maternal obesity and the possible trans-generational cycle it perpetuates, there is an imperative need to understand the mechanisms behind this programming effect and aim to establish successful obesity prevention strategies.

## 12.8 Early Postnatal Growth and Adiposity Rebound

In the Avon longitudinal study in the UK, children who have intrauterine restraint of fetal growth have more so called “catch-up” growth and go on to be fatter with more central fat distribution at 5 years of age compared with controls (Ong et al. 2000). Such accelerated postnatal growth is also associated with raised blood pressure (Huxley et al. 2000; Adair et al. 2009) and death from coronary heart disease (Eriksson et al. 1999). In a Swedish cohort, the highest death rates from coronary heart disease occurred in boys who were thin at birth but who gained weight centiles in childhood such that they had an average or above average body mass from the age of 7 years (Eriksson et al. 1999).

The programming effects of overfeeding immediately after fetal growth retardation have been studied in animal models. In rats, growth retarded offspring of undernourished mothers recoup their weight when fed adequately (by reducing the litter size) during lactation (Bieswal et al. 2006). After weaning, they continue to gain weight and become significantly heavier than control animals. This weight difference is exaggerated if a high calorie diet is provided to the previously growth restricted animal, an effect more prominent if the gestational undernutrition is achieved with a low calorie diet rather than with an isocaloric protein restricted diet.

Male offspring of mice, who are undernourished during pregnancy, live longer if they are growth restricted during the suckling period. This slowing of postnatal growth also appears to protect against an obesity-inducing diet later on (Ozanne and Hales 2004). Conversely, male mice which are poorly nourished in utero but cross-fostered to normally fed dams exhibit rapid “catch-up” growth and die at a younger age. Life expectancy further reduces with subsequent consumption of a high calorie and high fat diet (Ozanne and Hales 2004).

There is a link between in utero nutrient and growth restriction followed by accelerated postnatal growth and later emergence of insulin resistance, glucose intolerance and visceral obesity. Insulin receptors in the skeletal muscle of sheep are more abundant in response to growth restriction, an effect that persists in postnatal life (Muhlhausler et al. 2009). When nutrition availability improves in postnatal life, this abundance of insulin receptors, along with upregulation of insulin signalling molecules (Muhlhausler et al. 2009), results in accelerated growth of the previously growth restricted animal (Morrison et al. 2010). However, the increased insulin sensitivity changes into insulin resistance, a pattern recognizable as early as 1 year of age (Soto et al. 2003).

Adiponectin, an adipokine, is paradoxically reduced in obese subjects (Arita et al. 1999) and appears to play a central role in development of Type 2 diabetes. A high concentration of adiponectin is associated with reduced relative risk of Type 2 diabetes (Spranger et al. 2003). Children who are born small for gestational age (SGA) have lower adiponectin concentrations compared with those who are short but of appropriate weight for gestational age and with those who are obese (Cianfarani et al. 2004). Additionally, adiponectin is significantly lower in SGA children whose height is appropriate for age, sex and genetic potential (as indicated by mean parental height) when compared to those who are short (Cianfarani et al. 2004), possibly signifying that accelerated postnatal growth increases the risk of obesity and Type 2 diabetes in later life.

Children who are born SGA continue to gain body fat and abdominal fat mass between 2 and 4 years of age despite having largely achieved height and weight similar to children born appropriate for gestation age by 2 years of age (Ibanez et al. 2006). This is accompanied by increases in insulin resistance and IGF1 (Ibanez et al. 2006). Total and abdominal fat mass is further increased between 4 and 6 years of age and visceral fat is already present at 6 years of age (Ibanez et al. 2008), even in non-obese children.

In the process of growth during childhood, BMI increases rapidly during the first year of life followed by a decline. It reaches a minimum in early childhood and then starts to increase up to the end of growth. Adiposity rebound has been defined as the point of least BMI at which the sustained increase begins (Rolland-Cachera et al. 1984). The difference in body composition during “adiposity rebound” has been shown to be due to alterations in body fat rather than changes in lean body mass, children who have early adiposity rebound gaining fat faster (Taylor et al. 2004). The mean age of adiposity rebound was 5.5 years in a US retrospective cohort study (Whitaker et al. 1998) whilst a New Zealand cohort reported 6 years for boys and 5.6 years for girls (Williams et al. 1999). However, the timing of adiposity rebound may be an important factor for the development of obesity, reflecting the changing BMI pattern of the individual. In obese subjects, adiposity rebound occurs around 3 years of age (Rolland-Cachera et al. 1987). An early adiposity rebound has been associated with Type 2 diabetes (Eriksson et al. 2003), higher BMI in adolescence (Rolland-Cachera et al. 1984; Siervogel et al. 1991), early adulthood (Prokopec and Bellisle 1993) and in later adult life (Whitaker et al. 1998) and suggests determinants are established in early life (Rolland-Cachera et al. 2006).

## 12.9 Conclusion

The high prevalence and health consequences of obesity require urgent preventative strategies. There is ample evidence to show that the origins of adiposity lie in early development, from the periconceptual period through to early childhood. An increasing understanding of these processes and their contribution to later obesity and its accompanying diseases may provide opportunities for long term prevention and prove vital to improving public health.



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