REVIEW

Endocrine and nutritional regulation of fetal adipose tissue development

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Abstract

In the fetus, adipose tissue comprises both brown and white adipocytes for which brown fat is characterised as possessing the unique uncoupling protein (UCP)1. The dual characteristics of fetal fat reflect its critical role at birth in providing lipid that is mobilised rapidly following activation of UCP1 upon cold exposure to the extra-uterine environment. A key stage in the maturation of fetal fat is the gradual rise in the abundance of UCP1. For species with a mature hypothalamic–pituitary axis at birth there is a gradual increase in the amount and activity of UCP1 during late gestation, in conjunction with an increase in the plasma concentrations of catecholamines, thyroid hormones, cortisol, leptin and prolactin. These may act individually, or in combination, to promote UCP1 expression and, following the post-partum surge in each hormone, UCP1 abundance attains maximal amounts.

Adipose tissue grows in the fetus at a much lower rate than in the postnatal period. However, its growth is under marked nutritional constraints and, in contrast to many other fetal organs that are unaffected by nutritional manipulation, fat mass can be significantly altered by changes in maternal and, therefore, fetal nutrition. Fat deposition in the fetus is enhanced during late gestation following a previous period of nutrient restriction up to mid gestation. This is accompanied by increased mRNA abundance for the receptors of IGF-I and IGF-II. In contrast, increasing maternal nutrition in late gestation results in less adipose tissue deposition but enhanced UCP1 abundance. The pronounced nutritional sensitivity of fetal adipose tissue to both increased and decreased maternal nutrition may explain why the consequences of an adverse nutritional environment persist into later life.

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Introduction

Brown fat is characterised as possessing a unique uncoupling protein (UCP)1 that when maximally activated is able to produce up to 300 W/kg tissue of heat compared with 1–2 W/kg tissue by most other tissues (Power 1989). A primary function of fetal fat development, particularly in precocious thermoregulators, is to ensure that sufficient UCP1 is synthesised to enable effective thermoregulation following cold exposure to the extra-uterine environment (Clarke *et al.* 1997*c*). This adaptation is determined by the pre-partum development of the fetal endocrine mechanisms that ensure the maturation of a range of fetal organs for life after birth. The activation of UCP1 at birth is accompanied by a dramatic increase in lipolysis and mobilisation of lipids within fat depots (Power 1989) that also show white adipose tissue characteristics (Bispham *et al.* 2002). For both sheep and humans, brown fat is located primarily around the core organs and constitutes 2% of birth weight (Symonds & Lomax 1992). Despite the relatively small amount of adipose tissue present in the fetus, its growth is under marked nutritional constraints. In contrast to many other fetal organs that are unaffected by nutritional manipulation, fat mass can be significantly altered by changes in maternal and, therefore, fetal nutrition (Budge *et al.* 2003). The present review will therefore consider the following critical aspects of fetal adipose tissue development:

1. The normal ontogenic development of the endocrine systems necessary for ensuring maximal UCP1 abundance around the time of birth.

2. Can specific endocrine stimulation of the fetus or newborn promote UCP1 abundance and thus mimic in part the endocrine stimulation that occurs around the time of birth?

3. The extent to which targeted nutritional manipulations may act to increase or decrease fetal fat deposition and the potential consequences for UCP1 function after birth.

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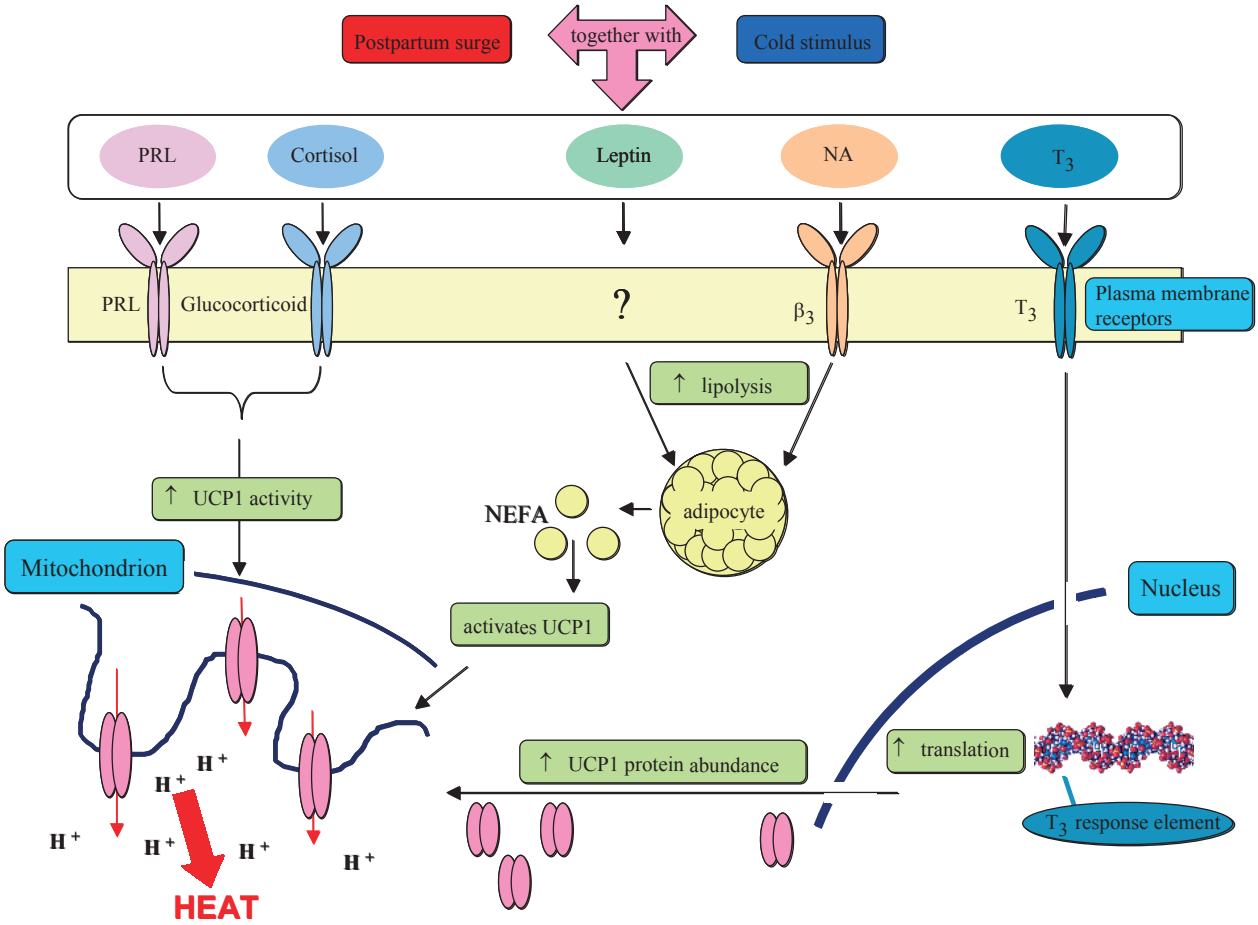

Figure 1 Summary of the endocrine regulation of fetal adipose tissue maturation in preparation for life after birth. PRL, prolactin; NA, noradrenaline; β_3, β_3-adrenergic receptor; NEFA, non-esterified fatty acids; T_3, triiodothyronine; UCP, uncoupling protein.

Ontogeny of fetal adipose tissue

The fetus grows and develops in an environment in which substrate availability is limited. Compared with the mother, the fetus is subjected to persistent hypoxia and hypoglycaemia. It is not therefore unexpected that as a consequence of the much higher metabolic demands for fat compared with protein deposition that fetal adipose tissue growth is much lower compared with after birth (Clarke *et al.* 1997*b*). Fetal fat possesses the dual characteristics of brown and white adipocytes (e.g. Casteilla *et al.* 1987, Devasker *et al.* 2002) from which leptin secretion may provide a 'lipostatic' role before birth (McMillen *et al.* 2004). In species such as humans and sheep that are born with a mature hypothalamic–pituitary axis and are precocial thermoregulators, brown fat abundance is maximal around the time of birth (Clarke *et al.* 1997*a*) and is then not normally detectable after the postnatal period (Lean 1989, Finn *et al.* 1998). For altricial species, such as rodents, in which the newborn maintain their body temperature by huddling together in a nest, maximal UCP1 abundance occurs postnatally coincident with maturation of the hypothalamic–pituitary axis (Cannon *et al.* 1988). Functional brown fat is then retained throughout the life cycle in rodents.

For humans and sheep, fetal adipose tissue deposition occurs primarily over the final third of gestation. In fetal sheep at least 80% of this fat is located around the kidneys (i.e. perirenal-abdominal adipose tissue) with very little, if any, fat present in the omental region which only develops after birth. During late gestation, as fetal fat mass expands, there is a concomitant increase in hormone receptor populations which, together with the development of the sympathetic nervous system, acts to ensure that UCP1 abundance peaks at birth (Symonds & Stephenson 1999). The following adaptations, therefore, occur within adipose tissue during late gestation as summarised in Fig. 1:

1. Rise in sympathetic innervation (Gemmel & Alexander 1972), β-adrenergic receptor density (Casteilla *et al.* 1994) and plasma catecholamine concentrations

(Eliot *et al.* 1981), which are likely to be the primary stimulus for the initial appearance of UCP1.

2. Increase in plasma prolactin (Houghton *et al.* 1995) and prolactin receptor abundance (Symonds *et al.* 1998) that may directly stimulate further expression of UCP1.

3. Increase in plasma thyroid hormones (Fraser & Liggins 1989) and enhanced capacity to convert thyroxine to the metabolically active tri-iodothyronine (T_3) via the enzyme 5′-monodeiodinase (Clarke *et al.* 1997*a*). This may result in a localised rise in T_3 within the adipocyte that would be predicted to up-regulate and stabilise UCP1 expression (Stein *et al.* 1994, Guerra *et al.* 1996) and abundance (Heasman *et al.* 2000) via T_3-responsive sequences on the UCP1 gene (Rabelo *et al.* 1995, Cassard-Doulcier *et al.* 1998).

The sensitivity of fetal adipose tissue to stimulation from endocrine factors appears to be greater than in the adult, when opposite effects can occur. For example, in the juvenile and adult rat, prolactin administration down-regulates UCP1 abundance (Chan & Swaminathan 1990, Pearce *et al.* 2003*a*) compared with up-regulation in the fetus (Budge *et al.* 2002). This distinct difference is likely to reflect the critical role of adipose tissue in the neonatal period as the newborn is subjected to physical and environmental stresses of an intensity seldom encountered again through life. The process of normal parturition at term, and concomitant squeezing through the birth canal, act to ensure maximal endocrine stimulation of the newborn (Clarke *et al.* 1997*c*). The peak in UCP1 on the inner mitochondrial membrane is accompanied by a high abundance of other mitochondrial proteins involved in energy metabolism (Mostyn *et al.* 2003*b*). These include voltage-dependent anion channel (VDAC), located on the outer mitochondrial membrane, which has a role in regulating the supply of mitochondrial ATP and ADP (Gottlieb 2000). VDAC abundance in fetal adipose tissue is not nearly as responsive to endocrine stimulation as UCP1 (Budge *et al.* 2002, Yuen *et al.* 2002, 2003, Mostyn *et al.* 2003*a*).

Endocrine stimulation of fetal adipose tissue function

During late gestation, a range of metabolic hormones have significant effects on fetal adipose tissue maturation. These roles have been established primarily in the sheep, which is arguably the optimum animal model for conducting this type of study. In the ovine fetus, therefore, specific endocrine manipulations have been shown to prematurely activate fetal UCP1. Chronic fetal infusion of the β-adrenergic receptor agonist ritodrine promotes the thermogenic potential of UCP1 and enhances lipolysis within the fetus (Bassett & Symonds 1998). The same response is not observed when endogenous ligands of the adrenergic receptors, adrenaline and noradrenaline are infused, which could reflect greater receptor stimulation by synthetic agonists compared with the natural ligands. A 5-day period of continuous leptin infusion, sufficient to raise fetal plasma leptin five-fold, also results in raised UCP1 abundance, in conjunction with an increase in the proportion of multilocular compared with unilocular adipocytes whose size is reduced (Yuen *et al.* 2003). This is accompanied by a down-regulation of leptin mRNA abundance and could indicate that it is the relative size of an adipocyte which determines its capacity to synthesise leptin.

The adrenal gland is essential for the pre-partum rise in UCP1 (Mostyn *et al.* 2003*a*) but the extent to which cortisol alone, or in conjunction with parallel changes in plasma T_3, affects adipose tissue development remains to be established. An intact thyroid is necessary for the maximal appearance of UCP1 at birth (Schermer *et al.* 1996), with the weight of the thyroid gland being positively correlated with UCP1 abundance in the neonate. A compensatory fetal response to the lack of thyroid hormones and reduced UCP1 is an increase in lipid content of fat, indicating that these two characteristics of fetal adipose tissue can be inversely correlated.

Endocrine manipulation of the mother has also been shown to promote UCP1 maturation in the rat fetus. Prolactin administration throughout gestation to the mother which results in substantial transfer of prolactin into the fetus (Yang *et al.* 2002) promotes UCP1 abundance at the same time as reducing lipid locule size (Budge *et al.* 2002). Taken together, the above findings strongly suggest that an increased abundance of stimulatory endocrine factors are of greater importance in regulating fetal adipose tissue development than placental inhibitory factors such as adenosine and prostaglandin (Gunn & Gluckman 1995). Placental factors have not been shown to have any direct maturational effects on UCP1 and only act to limit the rate of lipolysis (Gunn & Gluckman 1995), which is not necessary for UCP1 expression (Mostyn *et al.* 2003*a*).

The post-partum surge in catecholamines and T_3 are critical for the maximal activation of UCP1 in the newborn (Symonds *et al.* 2000), but it has not been elucidated whether cortisol, prolactin or leptin can have similar roles. Both prolactin and leptin are able to elicit a transient thermoregulatory effect in the newborn (Mostyn *et al.* 2002, Pearce *et al.* 2003*b*), which acts to delay the decline in colonic temperature over the first 2 days of neonatal life. This response is mediated by an increase in the activity of pre-existing UCP1 rather than a further increase in UCP1 expression. Given the critical role that UCP1 has in preventing hypothermia in the newborn, particularly in sheep (Clarke *et al.* 1997*c*), it is not unexpected that a number of complementary control mechanisms act to ensure maximal recruitment. These may, however, be less efficient in preterm

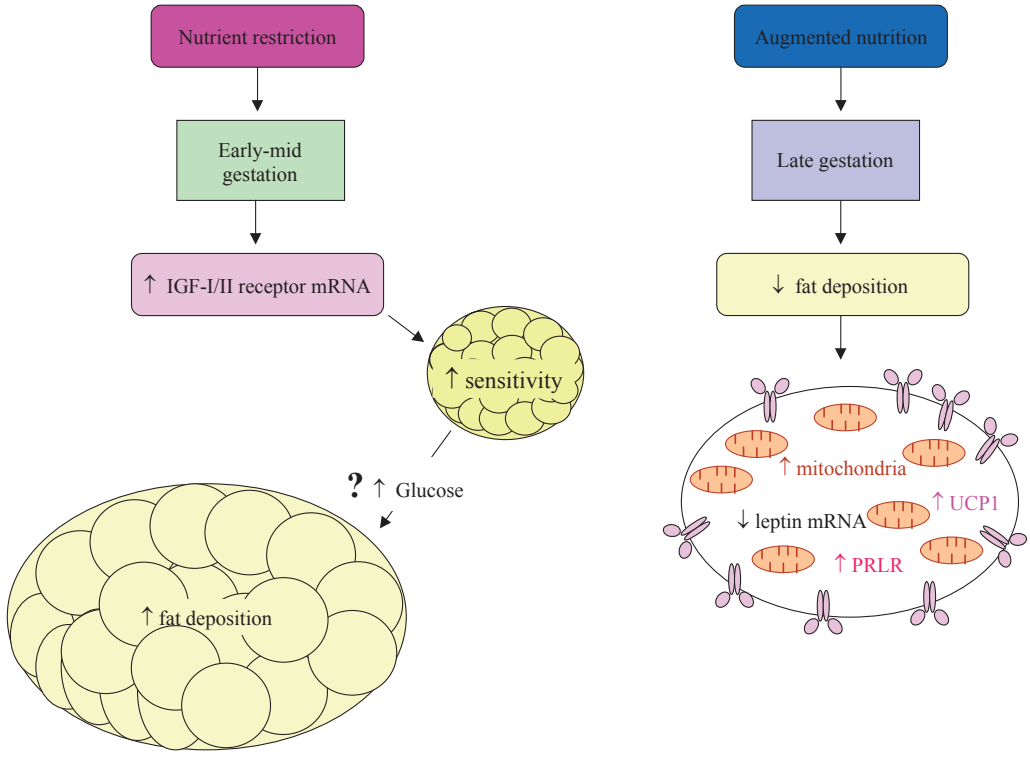

Figure 2 Summary of the differential effects of maternal nutritional manipulation of fetal adipose tissue growth. PRLR, prolactin receptor; IGF, insulin-like growth factor; UCP, uncoupling protein.

deliveries in which hormone receptor abundance can be reduced.

Nutritional regulation of fetal adipose tissue deposition

It is not only the abundance of UCP1 that is critical in determining heat production at birth – it is also the amount of fat (Symonds *et al.* 1992). Prolonged manipulation of maternal nutrition has pronounced effects on fetal adiposity (Fig. 2), which can occur in the absence of any change in the weight of other fetal organs (Budge *et al.* 2003). The consequences of maternal nutritional manipulation of the fetus with respect to fat deposition are strongly dependent on the time of the nutritional intervention. For sheep, maternal nutrient restriction between 28 and 80 days' gestation (term = 147 days), which is coincident with the time of uterine attachment (~28 days) to the stage at which placental growth ceases (~80 days), has no initial effect on adipose tissue growth (Clarke *et al.* 1998). These fetuses do, however, subsequently deposit more adipose tissue up to term following the restoration of maternal diet to the same level as controls (Bispham *et al.* 2003). This adaptation is accompanied by an increased abundance of mRNA for insulin-like growth factors (IGF)-I and II receptors, which is likely to increase adipose tissue sensitivity to the potential anabolic effects of IGFs (Teruel *et al.* 1996). A combination of enhanced responsiveness to IGFs in conjunction with increased abundance of glucose to previously nutrient-restricted fetuses (Dandrea *et al.* 2001) may act to promote the anabolic effect of glucose on fetal fat deposition (Stevens *et al.* 1990). No effect was found on mitochondrial protein abundance, suggesting a divergence of endocrine control between adipose tissue deposition and functional consequences in terms of UCP1 expression. An increase in the amount of adipose tissue alone would, however, be sufficient to promote total UCP1 abundance in the newborn.

Surprisingly, increasing maternal nutrition in late gestation can have reciprocal effects on adipose tissue deposition and UCP1 abundance. When maternal food intake is unrestricted, this results in proportionately less adipose tissue per kilogram of fetus but increased UCP1 abundance (Budge *et al.* 2000). At the same time there is an inverse relationship between mRNA for UCP1 and leptin in adipose tissue samples from well-fed, but not control, fetuses (Mühlhäusler *et al.* 2003) suggesting a change in both brown and white adipocyte characteristics

with increased nutrition. These adaptations may reflect the modest rise in both fetal plasma glucose and insulin in well-fed animals, although these were not of sufficient magnitude to promote fat deposition. Raised maternal food intake also results in higher fetal plasma prolactin (Stephenson *et al.* 2001) in conjunction with increased abundance of the long, but not short, form of the prolactin receptor (Budge *et al.* 2000). The long and short forms of prolactin receptor result from differential splicing of a single gene transcript (Bignon *et al.* 1997) and although these splice variants differ in their intracellular signalling regions they have identical extracellular domains. Nutritional enhancement of the long form of the prolactin receptor, in conjunction with raised prolactin, may be important in promoting UCP1 abundance in the fetus (Budge *et al.* 2000, 2002).

Reduced maternal nutrition in late gestation results in smaller fat depots with less UCP1 (Symonds *et al.* 1998, Budge *et al.* 2001), in conjunction with lower fetal plasma glucose and insulin, but has no effect of fetal leptin or prolactin receptor mRNA abundance (Symonds *et al.* 1998, Yuen *et al.* 2002). After birth, however, there appears to be a compensatory increase in VDAC abundance in nutrient-restricted offspring (Budge *et al.* 2003) that is maintained up to at least 1 month of age (Mostyn *et al.* 2003*b*). This is accompanied by an increase in UCP2, which, in contrast to UCP1, only appears to be present after birth. A higher abundance of UCP2 may have adverse consequences as this can result in enhanced susceptibility to infection and death from toxoplasmosis (Arsenijevic *et al.* 2000). It has also been shown that in obese women UCP2 gene exon 8 may affect susceptibility to obesity through an interaction with leptin (Cassell *et al.* 1999). Enhanced abundance of both UCP2 and VDAC could result in an accelerated rate of apoptosis (Voehringer *et al.* 2000). Clearly, the longer-term consequences of these different nutritional models of adipose tissue manipulation need to be established.

In conclusion, fetal adipose tissue growth is a co-ordinated process that involves the accumulation of lipid and synthesis of the brown adipose tissue specific UCP1. In species with a mature hypothalamic–pituitary axis, a major end point of endocrine regulation is to maximise UCP1 synthesis that can then be activated rapidly at birth to ensure effective adaptation to cold exposure of the extra-uterine environment. The apparent nutritional sensitivity of adipose tissue growth to both increased and decreased maternal nutrition may not only have consequences in the immediate peri-partum period but could persist into later life.

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