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TOPICAL REVIEW

The hungry fetus? Role of leptin as a nutritional signal before birth

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In adult animals, leptin is an adipose-derived hormone that is important primarily in the regulation of energy balance during short- and long-term changes in nutritional state. Expression of leptin and its receptors is widespread in fetal and placental tissues, although the role of leptin as a nutritional signal *in utero* is unclear. Before birth, leptin concentration correlates with several indices of fetal growth, and may be an endocrine marker of fetal size and energy stores in the control of metabolism and maturation of fetal tissues. In addition, leptin synthesis and plasma concentration can be modified by insulin, glucocorticoids, thyroid hormones and oxygen availability *in utero*, and therefore, leptin may be part of the hormonal response to changes in the intrauterine environment. Evidence is emerging to show that leptin has actions before birth that are tissue-specific and may occur in critical periods of development. Some of these actions are involved in the growth and development of the fetus and others have long-term consequences for the control of energy balance in adult life.

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In adult animals, the role of leptin in the control of energy balance and a range of other physiological systems has become increasingly well characterised (Harris, 2000; Margetic *et al.* 2002). Leptin is primarily synthesised by white adipose tissue and acts as an endocrine signal of energy reserves to the hypothalamus and other tissues in the coordination of appetite and metabolism with nutrient availability (Ahima & Flier, 2000). In adult life, leptin has a variety of actions in the control of energy balance, both in the long-term regulation of body weight and in the short-term regulation of metabolic and other endocrine responses to fasting (Ahima & Flier, 2000; Harris, 2000). It has also been shown to be involved in the activity of the immune system, and the onset and maintenance of reproductive function (Caprio *et al.* 2001; Lago *et al.* 2008). Before birth, however, the role of leptin as a nutritional signal, and the concept of 'appetite' in the intrauterine environment, is less clear when the fetus normally receives a continuous transplacental supply of glucose and other nutrients for growth and metabolism. This review will focus on the expression, and regulation, of leptin *in utero*, and the contribution of leptin to the hormonal control of fetal growth and development, with particular emphasis on the sheep fetus as an experimental animal model.

Expression of leptin in fetal and placental tissues

Leptin has been measured in the fetal circulation of different animal species, including human beings and sheep, from mid-gestation (Matsuda *et al.* 1999; Chen *et al.* 2000; Ogeuh *et al.* 2000; Ehrhardt *et al.* 2002). In the ovine fetus, plasma leptin concentration and adipose leptin mRNA abundance increase towards term which suggests that fetal adipose tissue is a major source of circulating leptin *in utero* (Yuen *et al.* 1999; Forhead *et al.* 2002). However, plasma leptin may also originate from a range of other fetal and placental tissues. In all species studied to date, leptin and leptin receptor gene expression have been found to be widespread in fetal and placental tissues (Table 1). Leptin may, therefore, have local as well as endocrine actions in the fetus which may be important for normal growth and development before birth.

The extent to which leptin is transported, and synthesised and secreted, by the placenta, and the contribution that maternal and placental leptin make to circulating levels in the fetus, appears to vary between animal species and with the stage of gestation studied. In human and non-human primate pregnancy, the placenta expresses significant amounts of leptin mRNA

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Table 1. Expression of leptin and leptin receptors in fetal and placental tissues in different animal species

	Leptin		Leptin receptor		
Species	Protein	mRNA	Protein	mRNA	References
Human	Placenta Adipose tissue Stomach	Placenta Adipose tissue Stomach	Placenta Oesophagus Stomach Small and large intestine	Placenta Adipose tissue Anterior pituitary Stomach Small intestine	Hassink *et al.* 1997 Hoggard *et al.* 1997 Shimon *et al.* 1998 Lea *et al.* 2000 Lepercq *et al.* 2001 Aparicio *et al.* 2005
Baboon		Placenta Lung		Lung	Henson *et al.* 1999, 2004
Sheep	Placenta Adipose tissue	Placenta Adipose tissue Brain Heart Liver Kidney Skeletal muscle	Placenta Adipose tissue Liver Skeletal muscle	Placenta Adipose tissue Heart Liver Kidney Skeletal muscle	Hoggard *et al.* 1997 Yuen *et al.* 1999 Buchbinder *et al.* 2001 Thomas *et al.* 2001 Ehrhardt *et al.* 2002 O'Connor *et al.* 2007 Forhead *et al.* 2008
Pig	Placenta	Adipose tissue	Placenta	Adipose tissue Umbilical cord Brain Intestines Heart Liver Muscle	Ashworth *et al.* 2000 Chen *et al.* 2000 Lin *et al.* 2000
Mouse	Placenta Cartilage and bone Heart Liver Hair follicles	Placenta Cartilage and bone Heart Liver Hair follicles	Placenta Cartilage and bone Hair follicles Brain Lung Kidney	Placenta Cartilage and bone Hair follicles Brain Lung Kidney Testis	Hoggard *et al.* 1997 Hoggard *et al.* 2000
Rat	Placenta		Placenta Brain	Placenta Pancreatic islets	Hoggard *et al.* 1997 Matsuda *et al.* 1999 Islam *et al.* 2000 Smith and Waddell, 2002

(Henson *et al.* 1999; Lea *et al.* 2000), although studies *in vitro* using the dually perfused human placenta at term show that 98% of placental leptin is secreted into the maternal circulation (Linnemann *et al.* 2000). Furthermore, leptin transfer across human choriocarcinoma BeWo cells occurs at a relatively low rate (Wyrwoll *et al.* 2005), and no relationship exists between plasma leptin concentration in maternal and umbilical blood at delivery (Schubring *et al.* 1997). In rodent and ovine species, leptin mRNA is detected in the placenta albeit at relatively low levels (Hoggard *et al.* 1997; Ashworth *et al.* 2000; Thomas *et al.* 2001; O'Connor *et al.* 2007). In contrast to human pregnancy, a positive correlation has been observed between plasma leptin concentrations in the ewe and fetus in well-fed and undernourished conditions during late gestation (Yuen *et al.* 2002). Further studies are required, however, to establish whether this relationship is due to placental transfer of leptin from the maternal to fetal circulation, or whether maternal body composition has other, indirect, effects on the secretory capacity of adipose tissue in the fetus. The rat placenta appears to be permeable to leptin, as significant transfer of radiolabelled leptin to the fetus has been demonstrated after injection into the mother (Smith & Waddell, 2003). In some species, therefore, leptin in the fetal circulation may have originated from the mother and/or the placenta.

Leptin as a signal in response to the intrauterine environment

Leptin expression in the fetus is altered by different intrauterine conditions, and these responses vary according to the nature of the stressor. Table 2 summarises the

Table 2. Effect of manipulation of the intrauterine environment on leptin expression in the ovine fetus

Intrauterine manipulation	Effect on leptin expression	Reference
Maternal undernutrition (70% for 139 days)	No change in plasma leptin	Edwards *et al.* 2005
Maternal undernutrition (55% for 13 days)	No change in plasma leptin	Ehrhardt *et al.* 2002
Maternal undernutrition (50% for 30 days)	No change in adipose leptin mRNA	Yuen *et al.* 2002
Maternal overnutrition (155% for 25 days)	↑ adipose leptin mRNA and no change in plasma leptin	Mühlhäusler *et al.* 2002, 2007
Chronic fetal hypoglycaemia and hypoinsulinaemia (36–76 days)	↓ adipose leptin mRNA	Devaskar *et al.* 2002
Chronic fetal hyperglycaemia and hyperinsulinaemia (14–20 days)	↑ adipose leptin mRNA	
Acute fetal hyperinsulinaemia and euglycaemia (24 h)	↑ adipose leptin mRNA	
Acute fetal hyperglycaemia and euinsulinaemia (24 h)	No change in adipose leptin mRNA	
Chronic 50% reduction in uterine blood flow (23 days)	↑ plasma leptin	Buchbinder *et al.* 2001
Placental carunclectomy	↓ adipose leptin mRNA and no change in plasma leptin	Duffield *et al.* 2008
Chronic hypoxia at high altitude (100 days)	↑ plasma leptin and ↑ adipose and placental leptin mRNA	Ducsay *et al.* 2006
Fetal cortisol infusion (5 days)	↑ plasma leptin and ↑ adipose leptin mRNA	Forhead *et al.* 2002 O'Connor *et al.* 2007
Maternal dexamethasone treatment (2 doses at 24 h intervals)	↑ plasma leptin and ↑ adipose leptin mRNA	O'Connor *et al.* 2007
Fetal hypothyroidism by thyroidectomy	↑ plasma leptin and ↑ adipose leptin mRNA	O'Connor *et al.* 2007

effects of a variety of experimental manipulations on plasma leptin concentration and adipose leptin gene expression in the ovine fetus. Moderate changes in maternal nutrition do not appear to affect tissue leptin expression or circulating leptin in fetal sheep. While maternal undernutrition influences plasma leptin in the pregnant ewe, there is little change in plasma leptin or adipose leptin mRNA abundance in the fetus (Yuen *et al.* 2002; Ehrhardt *et al.* 2002; Edwards *et al.* 2005). Maternal overnutrition increases leptin gene expression in fetal adipose tissue, without affecting plasma leptin concentration (Muhlhausler *et al.* 2002, 2007). In this study, adipose leptin mRNA abundance was positively correlated with plasma insulin concentration *in utero* (Muhlhausler *et al.* 2007). Indeed, leptin gene expression in adipose tissue is clearly regulated by circulating insulin in the fetus as in the adult animal. In fetal sheep, chronic hyperglycaemia and hyperinsulinaemia causes an increase in adipose leptin mRNA, while hypoglycaemia and hypoinsulinaemia leads to a reduction in adipose leptin mRNA levels (Devaskar *et al.* 2002). Similarly, in acute studies, hyperinsulinaemia with euglycaemia causes a two-fold increase in leptin gene expression in fetal adipose tissue, whereas hyperglycaemia with euinsulinaemia has no effect on adipose leptin mRNA abundance (Devaskar *et al.* 2002).

Placental insufficiency induced in sheep by carunclectomy causes a decrease in leptin mRNA expression in perirenal adipose tissue of the fetus with no change in circulating leptin concentration (Duffield *et al.* 2008). Suppression of leptin gene expression in this model of intrauterine undernutrition and growth retardation may be due to low plasma concentrations of insulin and glucose *in utero* (Duffield *et al.* 2008). In contrast, chronic undernutrition of the ovine fetus by occlusion of the uterine artery and a reduction in uterine blood flow leads to a rise in plasma leptin concentration (Buchbinder *et al.* 2001). Likewise, elevated plasma leptin, when expressed on a weight-specific basis, has been reported in growth-retarded human fetuses with lactacidaemia and abnormal Doppler imaging of the umbilical cord (Cetin *et al.* 2000). Stimulation of plasma leptin during fetal distress may be related to changes in oxygen availability and/or adrenocortical activity since plasma leptin in sheep fetuses has been shown to correlate inversely with the arterial partial pressure of oxygen and positively with plasma cortisol concentration (Forhead *et al.* 2002). Long-term hypoxia induced in sheep at high altitude for most of gestation increases plasma leptin in the fetus, and gene expression of leptin in placenta and fetal adipose tissue, without any change in plasma glucose or insulin concentrations (Ducsay *et al.* 2006). Glucocorticoids modify leptin expression before and after birth: in fetal sheep, leptin mRNA abundance in adipose tissue, and circulating leptin concentration, are increased by cortisol and dexamethasone treatment, and suppressed by fetal adrenalectomy (O'Connor *et al.* 2007). Interestingly, however, maternal dexamethasone administration in pregnant rats decreases leptin concentration in the fetal circulation in association with changes in placental leptin receptor expression and reductions in placental content and transfer of leptin (Sudgen *et al.* 2001; Smith & Waddell, 2002, 2003). Thyroid hormones also affect circulating and adipose levels of leptin before birth. Hypothyroidism

in the ovine fetus near term, induced by thyroidectomy, increases plasma leptin and leptin mRNA abundance in fetal adipose tissue (O'Connor *et al.* 2007). Moreover, leptin synthesis by fetal adipose tissue shows negative feedback control to regulate circulating concentrations. Intravenous infusion of recombinant ovine leptin in fetal sheep reduces leptin mRNA abundance in perirenal adipose tissue (Yuen *et al.* 2003). It is also apparent that circulating leptin concentration *in utero* may depend upon the breed, and genetic background, of the sheep used in experimental studies. The Welsh Mountain fetus has lower plasma leptin concentration to the Merino fetus, and the developmental increase in adipose leptin mRNA abundance seen in both breeds near term is accompanied by a rise in plasma leptin in the fetuses of the Welsh Mountain, but not Merino breed (Yuen *et al.* 1999, 2004; Forhead *et al.* 2002; O'Connor *et al.* 2007). These differences may reflect the amount, and secretory capacity, of adipose tissue in the fetuses of different sheep breeds and the physiological consequences of breeding sheep for different environmental conditions. Therefore, leptin synthesis and circulating concentration *in utero* respond to a range of nutrient, hormonal and genetic influences, although little is known about how these factors affect the expression of leptin receptors in fetal tissues. Leptin may be one of a number of hormones, including insulin, glucocorticoids and thyroid hormones, that signal changes in the intrauterine environment and, in turn, govern appropriate responses in growth and development in fetal tissues.

Leptin and growth of the fetus

The widespread localisation of leptin receptors in the developing fetus, especially in bone and cartilage, has led to the proposal that leptin is involved in the control of fetal growth. In human infants at term, umbilical leptin concentration has been correlated with placental weight and with a number of indices of fetal growth including body weight and length, head circumference, ponderal index, adiposity and bone mineral content and density (Hassink *et al.* 1997; Varvarigou *et al.* 1999; Javaid *et al.* 2005; Valuniene *et al.* 2007). Low concentrations of circulating and placental leptin have been reported in babies that are small for their gestational age while high concentrations occur in the macrosomic offspring of diabetic mothers (Lea *et al.* 2000). Similarly, in sheep fetuses, adipose leptin mRNA abundance correlates with fetal bodyweight at mid and late gestation (Yuen *et al.* 1999). However, in human infants at delivery, positive relationships have also been identified between umbilical leptin and other hormones known to be associated with nutritional status and intrauterine growth, such as insulin and insulin-like growth factor-I (Maffeis *et al.* 1999). It is difficult, therefore, to determine the extent to which circulating leptin *in utero* is an important physiological regulator of fetal growth or simply reflects adipose and placental tissue mass, and/or the prevailing insulin concentration in the fetal circulation.

Clinical and experimental studies of leptin gene mutations have provided no evidence to support leptin as a major growth factor in fetal life. Human and murine neonates with genetic leptin deficiency are reported to be of normal morphology and birth weight (Montague *et al.* 1997; Mounzih *et al.* 1998). In *ob*/*ob* mice with a mutation in the leptin gene, the establishment of pregnancy is leptin dependent, but withdrawal of leptin replacement from 0.5 days of gestation has no effect on litter size or fetal weights (Mounzih *et al.* 1998). Furthermore, in fetal sheep during late gestation, intravenous administration of recombinant ovine leptin for 4–5 days does not influence body or organ weights, or the rate of linear spinal growth (Yuen *et al.* 2003; Forhead *et al.* 2008). Many of these studies have measured growth in terms of body weight and gross morphology, and more detailed analyses at the tissue and cellular level are required to determine fully the importance of leptin as a growth factor in fetal life. Studies *in vitro* have demonstrated that leptin stimulates proliferation of pancreatic islet cells from fetal rats (Islam *et al.* 2000). Furthermore, leptin is important for the normal development and migration of neuronal and glial lineage cells in the cerebral cortex of fetal mice (Udagawa *et al.* 2007). In perirenal adipose tissue of fetal sheep, leptin infusion upregulates insulin-like growth factor-I receptor expression and causes a shift in the relative proportions of unilocular and multilocular cells (Yuen *et al.* 2003; Forhead *et al.* 2008). The effects of leptin on growth and development in the fetus, therefore, may be cell- and tissue-specific rather than on general body growth and size. While the evidence for leptin as a growth-promoting factor before birth remains inconclusive, the relationship between circulating leptin and fetal size, and specifically adipose mass, suggests that leptin signals energy reserves *in utero* as it does in adult life.

Leptin derived from the placenta may have an important role in the control of placental growth and function, and consequently, the growth of the fetus. Placental leptin concentration is elevated in pregnant mice heterozygous for a mutation in the leptin receptor, and this is associated with an increase in fetal weight near term, both in mutant and wild-type pups (Yamashita *et al.* 2001). Furthermore, administration of leptin to wild-type pregnant mice decreases placental leptin content and leads to reductions in placental and fetal weights (Yamashita *et al.* 2001). In human trophoblast cells *in vitro*, exogenous leptin treatment has mitogenic and anti-apoptotic effects, while inhibition of endogenous placental leptin expression, using an anti-sense oligonucleotide, reduces cell proliferation and increases apoptotic cell number and caspase-3 activity (Margarinos *et al.* 2007). Studies *in vitro* have also shown that leptin

upregulates nitric oxide production and lipolysis in the human and rodent placenta at term (White *et al.* 2004, 2006) with possible consequences for placental blood flow and transfer of free fatty acids to the fetus. Furthermore, leptin stimulates activity of the amino acid transporter system A in human placental villous fragments at term (Jansson *et al.* 2003). This sodium-dependent transporter is responsible for the placental transfer of neutral amino acids to the fetus, and, coincident with placental leptin content (Lea *et al.* 2000), is known to be down-regulated in intrauterine growth retardation and upregulated in diabetic pregnancies (Jansson *et al.* 2003).

Leptin and energy balance of the fetus

In adult animals, leptin is a key regulator of feeding behaviour via actions on hypothalamic neural pathways (Trayhurn & Bing, 2006). Before birth, the neuropeptides involved in these pathways are present in the developing hypothalamus (Muhlhausler *et al.* 2004; Beloosesky *et al.* 2006), but the control and physiological importance of appetite-regulatory neural networks in the fetus are unclear. In rodents, milk intake over the immediate newborn period is relatively insensitive to leptin, primarily due to immaturity in the neural connections of the arcuate nucleus (Mistry *et al.* 1999; Bouret & Simerly, 2006). Indeed, it may be crucial that feeding behaviour in the newborn is resistant to the satiating effects of leptin at a time when levels are relatively high, and when leptin may have alternative actions in the maturation of tissues and physiological systems important for neonatal survival. Leptin does appear, however, to be involved in establishing the neural networks that regulate feeding behaviour in postnatal life (McMillen *et al.* 2005, Bouret & Simerly, 2006). In rodents, these hypothalamic pathways are established in the first 2 weeks of life, and are dependent on the postnatal surge in plasma leptin over this period (Bouret *et al.* 2004). Leptin-deficient *ob*/*ob* mice show abnormal development of neural projections from the arcuate nucleus, which can be corrected by leptin treatment in neonatal but not adult life (Bouret *et al.* 2004). Furthermore, in rats born to mothers undernourished during pregnancy, leptin administration in the neonatal period has been shown to prevent the programmed development of obesity in later life (Vickers *et al.* 2005, 2008). Since the rodent brain develops later than the human and ovine brain, leptin-sensitive formation of the hypothalamic appetite-regulatory network may occur before birth in more precocial species (McMillen *et al.* 2005, Bouret & Simerly, 2006). Exposure of the fetus to leptin at critical periods of development may, therefore, have important programming consequences for the formation and activity of hypothalamic networks responsible for appetite regulation and energy balance in adult life (McMillen *et al.* 2005, Bouret & Simerly, 2006).

Relatively few studies have investigated the effect of leptin on metabolism and energy balance in the fetus. In fetal sheep during late gestation, intravenous administration of leptin reduces glycogen content and the activities of the gluconeogenic enzymes, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, in the liver without influencing plasma insulin or hepatic insulin signalling molecules (Forhead *et al.* 2008). Furthermore, intracerebroventricular leptin administration has no effect on plasma glucose or insulin concentrations, or on glucose clearance or insulin responsiveness to a glucose challenge (Howe *et al.* 2002). Therefore, in normal conditions, leptin may be responsible, in part, for suppression of endogenous glucose production *in utero* when adipose energy stores are increasing towards term and transplacental nutrient delivery is sufficient to meet the energy requirements of the fetus. In macrosomic babies of diabetic mothers, however, hyperleptinaemia may contribute to neonatal hypoglycaemia by impairing glycogenolytic and gluconeogenic capacities at birth.

Leptin and maturation of the fetus near term

Towards term, a number of structural and functional changes occur in fetal tissues in preparation for the transition from intrauterine to extrauterine and independent life. Many of these changes are triggered by the rise in glucocorticoid concentration that occurs in the fetal circulation near term (Fowden *et al.* 1998). In fetal sheep, both endogenous and synthetic glucocorticoids cause an increase in adipose leptin mRNA and circulating leptin concentration (Forhead *et al.* 2002; O'Connor *et al.* 2007), which has led to the suggestion that some of the maturational effects of glucocorticoids may be mediated by leptin. One example is the developmental and glucocorticoid-dependent onset of surfactant production in fetal lungs near term. Expression of leptin and leptin receptors has been demonstrated in fetal lungs of rodent and primate species (Hoggard *et al.* 1997; Henson *et al.* 2004), and, in baboon fetuses, pulmonary leptin receptor mRNA abundance increases between mid and late gestation (Henson *et al.* 2004). In addition, both dexamethasone and pulmonary stretch have been shown to stimulate leptin expression by fetal rat lung fibroblasts in cell culture (Torday *et al.* 2002; Torday & Rehan, 2002). *In vitro* studies using fetal tissue suggest that leptin may be an important regulator of pulmonary surfactant synthesis before birth. Leptin increases surfactant protein mRNA and protein levels in lung explants from fetal rats (Kirwin *et al.* 2006), and promotes surfactant phospholipid synthesis in type II pneumocytes isolated from fetal rats and rabbits (Bergen *et al.* 2002; Torday *et al.* 2002). Furthermore, stretch-induced production of surfactant

phospholipids by fetal rat type II pneumocytes *in vitro* is abolished by leptin antagonism using a leptin antibody (Torday & Rehan, 2002). The role of leptin in pulmonary maturation has not been investigated in detail in the whole animal, although relative lung weights and immunostaining for surfactant proteins B and C are increased in rat fetuses whose mothers were treated with leptin during late gestation (Kirwin *et al.* 2006). Taken together, these observations suggest that leptin may act as a paracrine and/or endocrine regulator of surfactant production in the fetal lungs near term, although further studies are required to confirm the importance of leptin *in vivo*.

While glucocorticoids promote synthesis and secretion of leptin in the ovine fetus, in turn, leptin appears to regulate the activity of the fetal hypothalamic–pituitary–adrenal axis near term. In sheep fetuses during late gestation, intravascular or intracerebroventricular infusions of leptin suppress the normal prepartum increase in pulsatile adrenocorticotrophic hormone and cortisol secretion, without any change in pituitary sensitivity to exogenous arginine vasopressin or corticotrophin-releasing hormone (Howe *et al.* 2002; Yuen *et al.* 2004). Although no change in gestational length has been observed in leptin-treated animals (Yuen *et al.* 2004), the existence of a negative feedback loop between leptin and the hypothalamic–pituitary–adrenal axis in the ovine fetus may have implications for the onset of parturition, known to depend on fetal glucocorticoids in this species.

Conclusions

Circulating leptin *in utero* is an endocrine signal of both fetal and placental size, and may indicate the nutritional status and energy reserves of the fetus to the mother, the placenta and to a range of fetal tissues. Although the role of leptin as a growth factor before birth remains inconclusive, the widespread expression of leptin in fetal and placental tissues, and the increasing evidence of tissue-specific actions, suggest that leptin has physiological significance in fetal life. Leptin concentration in the fetus responds to a range of nutritional and endocrine stimuli, and therefore, it may signal changing nutrient availability, particularly in the control of glucogenesis and tissue maturation during late gestation and the establishment of neural pathways important for energy balance in later life.

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