

THEMATIC REVIEW

The role of adipokines in developmental programming: evidence from animal models

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Abstract

Alterations in the environment during critical periods of development, including altered maternal nutrition, can increase the risk for the development of a range of metabolic, cardiovascular and reproductive disorders in offspring in adult life. Following the original epidemiological observations of David Barker that linked perturbed fetal growth to adult disease, a wide range of experimental animal models have provided empirical support for the developmental programming hypothesis. Although the mechanisms remain poorly defined, adipose tissue has been highlighted as playing a key role in the development of many disorders that manifest in later life. In particular, adipokines, including leptin and adiponectin, primarily secreted by adipose tissue, have now been shown to be important mediators of processes underpinning several phenotypic features associated with developmental programming including obesity, insulin sensitivity and reproductive disorders. Moreover, manipulation of adipokines in early life has provided for potential strategies to ameliorate or reverse the adverse sequelae that are associated with aberrant programming and provided insight into some of the mechanisms involved in the development of chronic disease across the lifecourse.

Key Words

- ▶ adipokines
- ▶ developmental programming
- ▶ leptin
- ▶ nutrition

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Introduction

Data from epidemiological, clinical and experimental animal models has clearly demonstrated that the risk for developing abnormalities of metabolic and cardiovascular homeostasis and reproductive disorders in adult life is increased when developmental processes during early life have been adversely affected. In particular, changes in the nutritional environment during early life, including both undernutrition and overnutrition, can manifest as a range of cardiometabolic and reproductive disorders in offspring during adulthood. This relationship is preferentially termed 'developmental programming' or the 'Developmental Origins of Adult Health and Disease' (DOHaD).

Original observations by Professor David Barker highlighted the association between fetal growth restriction and later cardiometabolic disorders thus implying that alterations in the early life environment, including nutritional deprivation, provided a strong programming stimulus (Godfrey & Barker 2000, Barker 2007). These early observations resulted in the development and characterisation of a wide range of experimental animal models, primarily in rodents, to induce fetal growth restriction. These studies have provided empirical evidence to support the programming hypothesis and highlight the link between early life adversity and later metabolic dysregulation in offspring. Although an initial

focus was on fetal nutritional deprivation, given the rising prevalence of overweight/obesity, there has been increasing attention paid to the development of models utilising a maternal obesogenic environment and the consequences of early life nutritional excess on offspring outcomes (Elshenawy & Simmons 2016, Godfrey *et al.* 2017). Of note, these disparate models often result in a commonality in programming effects in offspring with both maternal undernutrition and a maternal obesogenic environment resulting in increased obesity and cardiometabolic dysfunction in offspring. This may, in part, be attributed to obesogenic diets and 'overnutrition' representing a form of dietary malnutrition given that many obesogenic diets are commonly characterised by micronutrient deficiencies (Via 2012). The mechanisms that underpin nutritional programming in offspring following altered maternal nutritional environments are starting to be better defined but are overlaid by clear sexual dimorphism in responsiveness to different early life nutritional environments. It is also of note that different exposure windows to altered early life nutrition may elicit similar phenotypic outcomes in offspring but these can originate via different mechanistic pathways (Thompson *et al.* 2007, Howie *et al.* 2012, 2013).

The discovery of the adipose tissue-secreting adipokines (Zhang *et al.* 1994, Ahima *et al.* 2000) led to profound changes in the field of metabolic physiology. Following the characterisation of leptin in 1994, a large number of adipokines have now been characterised including adiponectin, apelin, visfatin and omentin. A wide range of experimental animal models have now clearly highlighted an important role for adipokines in developmental programming with adipokine dysregulation, in particular that of leptin, emerging as a common phenotypic feature in the pathogenesis of many programming-mediated metabolic, cardiovascular and reproductive disorders (Kieffer & Habener 2000, Vickers *et al.* 2001, Horvath & Bruning 2006).

The most widely studied adipokine to date in the setting of developmental programming is that of leptin. The product of the obesity (*ob*) gene, leptin is a 16kDa hormone of 167 amino acids in length primarily secreted by adipose tissue (Zhang *et al.* 1994). The primary function of leptin is that of an afferent signal that acts via a negative feedback loop to maintain homeostatic control of adipose tissue mass. This then stimulates a negative energy balance controlling appetite and increasing energy expenditure (Friedman 2016). Leptin also exerts its actions across a wide number of areas including bone mass, cardiovascular health,

the immune system and reproductive function. It is now clear from a range of experimental observations that maintenance of a 'critical' leptin level during early life development is required to facilitate the normal maturation of tissues and signalling pathways involved in metabolic homeostasis and reproductive function. As such, many aberrant adaptations which underlie developmental programming have been associated with a period of relative hypo- or hyperleptinemia during early developmental windows (Vickers & Sloboda 2012a). Leptin was initially viewed as an anti-obesity hormone, preventing the storage of excess adipose tissue via a hypothalamic feedback loop acting to regulate food intake and increase energy expenditure (Hamann & Matthaei 1996, Ahima & Flier 2000). However, it has subsequently been demonstrated that most human obesity is associated with circulating hyperleptinemia, resulting from a state of leptin resistance (Considine *et al.* 1996). A number of animal models representing a range of species, strains and experimental paradigms have now provided clear evidence for a key role of leptin as a mediator of early life programming primarily via its actions as a central neurotropic factor and the potential impact of changes in the early life environment on the development of leptin circuitry related to energy balance and appetite control. Further, in addition to leptin, the impact of an altered early life environment on dysregulation of other, more recently characterised adipokines, is emerging across a range of animal studies including functional roles for these factors linking maternal adipose tissue and fetal growth via regulation of placental function.

Rodents

Rodent models have played a key role in our understanding of adipokines in the development of a range of programming-mediated disorders (Bouret 2010, Vickers & Sloboda 2012a). In the setting of intrauterine growth restriction (IUGR), the predictive adaptive response (PARs) hypothesis suggests that the foetus makes physiological adaptations in order to optimise survival in a predicted environment of nutrient deprivation (Gluckman *et al.* 2005, Bateson *et al.* 2014). When a mismatch occurs between the anticipated and actual postnatal nutritional environment, the early adaptations become maladaptive and the risk for development of metabolic disorders is increased. The adipokines fit well within the PARs framework with clear evidence for altered adipokine

profiles that arise as a consequence of perturbations in the early life environment that may confer adaptive benefits in the short term but later may be disadvantageous for example development of leptin resistance.

Leptin

Systemic leptin concentrations vary markedly during the fetal and early postnatal period, with a 5- to 10-fold increase in circulating leptin occurring in the first 2 weeks of neonatal life in female mice (Ahima *et al.* 1998). The mother's milk is an important source of leptin for postnatal rodents with greater access to milk-borne leptin to those suckled in small litters and thus exposed to early leptin-mediated neuroendocrine programming effects (reviewed in Spencer 2012).

A number of studies have reported relative hypoleptinemia in IUGR neonates arising due to a reduction in adipose mass at birth and/or decreased placental production (Desai *et al.* 2005, Briffa *et al.* 2017), but this later emerges as hyperleptinemia and increased adiposity in adulthood. Adult rat offspring subjected to severe maternal undernutrition (70% food restriction) are hypoleptinemic at birth but develop obesity and hyperleptinemia as adults (Krechowec *et al.* 2006, Lecoutre *et al.* 2017a) with alterations in leptin and leptin receptor expression in white adipose tissue (Lecoutre *et al.* 2017a). These effects occur independently of the postnatal dietary environment but can be exacerbated by a postnatal high-fat diet (Vickers *et al.* 2000) with reduced locomotor activity and hyperphagia contributing to the increased fat mass (Vickers *et al.* 2000, 2005). Offspring of low protein (LP) fed mothers exhibit an increased appetite drive as evidenced by hyperphagia that is mediated by changes in circulating leptin and ghrelin levels and higher food conversion efficiency in parallel to lower adiponectin levels (Qasem *et al.* 2012). As with the PARs framework above, it was suggested that this collection of metabolic features in the LP offspring serves to maximise the potential for survival in a postnatal environment of nutritional scarcity and therefore represents a thrifty phenotype (Hales & Barker 2001).

Studies in rodents have consistently reported that offspring of mothers fed an obesogenic diet prior to and throughout pregnancy and/or lactation are characterised by changes in energy balance and increased fat mass in adult life (Samuelsson *et al.* 2008, Kirk *et al.* 2009, Howie *et al.* 2013). The offspring phenotype is often associated with altered adipokine profiles in later life (Howie *et al.* 2009, Rajia *et al.* 2010). Rats that are overfed in the

neonatal period following litter size reduction display early increases in circulating leptin that are maintained into adulthood and is associated with corresponding increases in body weight (Sominsky *et al.* 2017). These observations include hyperleptinemia and altered leptin gene expression coupled with disturbed central regulation of appetite control leading to hyperphagia (Rajia *et al.* 2010, Lecoutre *et al.* 2016). In addition, neonatal overfeeding using this paradigm results in a hypothalamic neuronal resistance to exogenous leptin in the neonatal period, although this leptin resistance is resolved by adulthood. Of note, short-term neonatal treatment with a leptin antagonist was not able to reverse the increased body weight or hyperleptinemia in the overfed offspring, suggesting factors other than leptin contributed to development of the phenotype. Such programming of leptin gene expression has been shown to be regulated via epigenetic modifications in an adipose tissue depot-specific manner (Lecoutre *et al.* 2017b). In this work, persistent epigenetic remodelling (both methylation and histone modifications) were shown to occur at regulatory regions within intergenic sequences and associated with changes in adipose-specific leptin gene expression in adult offspring of high-fat (HF)-fed mothers.

In the setting of maternal obesity, leptin has been shown to play a role in the triggering of efferent sympathetic pathways to both thermogenic and non-thermogenic tissues (e.g. the kidney) and thus has been implicated in the developmental programming of hypertension (Taylor *et al.* 2014). Of note, in rodents a maternal obesogenic diet can result in growth restriction in offspring as a result of placental insufficiency (Mark *et al.* 2011). This is characterised by hypoleptinemia and hypoinsulinemia at birth but followed by rapid catch-up growth and hyperleptinemia and insulin resistance in adulthood (Howie *et al.* 2013). Offspring of HF-fed mothers also exhibit alterations in hypothalamic leptin-dependent STAT3 phosphorylation that are independent of the level of nutrition in the post-weaning period (Ferezou-Viala *et al.* 2007) with offspring from HF-fed mothers displaying reduced sensitivity to the anorectic effects of leptin (Walker *et al.* 2008).

In addition to HF diets, some attention has been given recently to the effects of diets high in sugar on maternal and offspring adipokine profiles. Fructose intake during pregnancy results in a diminished maternal leptin response to fasting and refeeding and is paralleled by fetal hyperleptinemia and an impairment in the transduction of the leptin signal in the foetus which may explain the

hepatic steatosis observed in offspring in this model (Rodriguez *et al.* 2013).

In rodents, the early neonatal period is characterised by a surge in circulating leptin concentrations (Ahima *et al.* 1998) that is independent of fat accretion and body weight. Despite the increased systemic leptin concentrations, neonates are able to maintain a high level of food intake with both changes in feeding behaviour and responsiveness to leptin treatment being largely absent until near the time of weaning. These elevations in leptin concentrations in early life are proposed to play a role in brain development (Bouret & Simerly 2007, Udagawa *et al.* 2007) whereby leptin acts as a potent neurotrophic factor that coordinates the establishment of the hypothalamic neuronal network responsible for the regulation of food intake (Bouret *et al.* 2004). A marked decrease in hypothalamic neuronal fibre density in leptin-deficient *ob/ob* mice was observed in early work by Bouret and Simerly. This deficit could be normalised via leptin treatment in the neonatal period (Bouret *et al.* 2004), although the period of intervention was restricted to this early neonatal period of developmental plasticity with leptin treatment in the post-weaning period having no effect. Maternal undernutrition is well known to result in changes in the neonatal leptin surge. In the rodent, a maternal LP diet can delay the leptin surge (Bautista *et al.* 2008) and global food restriction can reduce the amplification of the surge (Delahaye *et al.* 2008). Furthermore, the IUGR-mediated delay and inhibition of the leptin surge can result in disorganisation of hypothalamic circuits leading to lasting effects on appetite control and energy balance including disordered development of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (Delahaye *et al.* 2008, Coupe *et al.* 2010). In the setting of maternal HF-feeding in the rat, alterations in the leptin surge have also been reported in offspring with a prolonged and amplified neonatal leptin surge accompanied by elevated leptin gene expression in visceral fat tissue (Kirk *et al.* 2009).

Given that leptin plays a key role in the control of puberty and fertility, there is also evidence from a range of rodent studies linking altered adipokine programming to later reproduction dysfunction in female offspring. These include early-onset puberty, premature ovarian ageing and alterations in reproductive fitness (Connor *et al.* 2012, Sominsky *et al.* 2016). In the rat, maternal undernutrition has been shown to significantly impact ovarian follicle number and increase markers of ovarian oxidative stress in adult offspring and thus can potentially contribute to the premature ovarian ageing seen in this model

(Bernal *et al.* 2010). Moreover, the effects of maternal undernutrition on the ovary were dependent upon the timing of the undernutrition with undernutrition during pregnancy and/or lactation eliciting differential programming effects. These changes appeared to occur in parallel to changes in leptin profiles. In particular, given that leptin is the permissive factor in the initiation of puberty, the early-onset puberty observed in these offspring may be a result of the increased adiposity and increased relative leptin concentrations observed in these animals following rapid catch-up growth in the early post-weaning period. Further, given that central leptin sensitivity and leptin receptor expression can be enhanced via estradiol (Clegg *et al.* 2006) and ovarian-derived leptin is important for ovulation, steroidogenesis and oocyte maturation, changes in leptin receptor expression arising due to maternal undernutrition may contribute to the observed decrease in follicle number in offspring. Of note, when maternal undernutrition (50% of *ad libitum*) encompasses the period of lactation (pregnancy and lactation or lactation alone), pubertal onset is delayed in pups of both sexes (Leonhardt *et al.* 2003). This may reflect a lack of catch-up growth in these animals during the pre-weaning period and further highlights the effects of different timing of developmental exposures on offspring outcomes (Howie *et al.* 2012). Similar to that observed in models of maternal undernutrition, neonatal overfeeding in the rat results in an acceleration in reproductive maturation and a decline in ovarian reserve with reduced ovulatory concentrations of gonadotropins, increases in circulating and ovarian leptin concentrations concomitant with increased leptin receptor expression in the ovary (Sominsky *et al.* 2016). A primary focus to date has been on programming of ovarian function in female offspring and there remains a paucity of data examining the altered timing of puberty in male offspring and examination of sex-specific responses to programming stimuli. Work by Sánchez-Garrido *et al.* highlighted important sexually dimorphic responses to various early nutritional challenges on the timing of pubertal onset (Sánchez-Garrido *et al.* 2013) and thus further work comparing both sexes is required to provide mechanistic insight into the role of adipokines in underpinning the different patterns of pubertal onset and related comorbidities observed between sexes.

In addition to models of altered maternal nutrition, alterations in adipokine profiles have also been investigated in models of glucocorticoid overexposure *in utero*. Dexamethasone to pregnant rats results in fetal growth retardation and hyperleptinemia and

hyperinsulinemia in the mid-late gestation foetus (Ahmed 2016). However, adult rat offspring of mothers exposed to dexamethasone present with hyperglycemia and tissue-specific markers of insulin resistance but no changes in adipose leptin or resistin were observed across groups (Cleasby *et al.* 2003). Prenatal stress (restraint stress) in the rat has also been shown to result in basal hypoleptinemia and hyperglycemia in aged male offspring concomitant with fasting-induced hyperphagia (Lesage *et al.* 2004).

Adiponectin

Adiponectin modulates a number of metabolic processes, including fatty acid oxidation and glucose homeostasis with a reduced adiponectin expression commonly associated with impaired insulin sensitivity in animal models (Diez & Iglesias 2003). Studies in rodents have provided evidence for adiponectin acting as a link between maternal adipose tissue and fetal growth via regulation of placental function (Aye *et al.* 2013). In adult male rat offspring of LP-fed mothers, adiponectin concentrations are reduced concomitant with insulin resistance, hyperphagia and increased visceral adiposity (Silvestre *et al.* 2014, De Oliveira *et al.* 2016). In the LP model used by Silvestre *et al.*, adiponectin and adiponectin receptor expression was reduced in offspring adipose tissue, along with levels of peroxisome proliferator-activated receptor (PPAR)- α and activity of AMP-activated protein kinase (AMPK) which are downstream targets of adiponectin. Thus, altered adiponectin signalling may lead to an impaired ability to inhibit adipogenesis and lipogenesis thus predisposing offspring to obesity and metabolic dysfunction in later life (Silvestre *et al.* 2014). Maternal obesity or gestational diabetes leads to reduced circulating levels of adiponectin and these mothers frequently deliver large babies with increased adiposity, who are susceptible to a range of perinatal complications and an increased risk for the development of metabolic syndrome in later life (Aye *et al.* 2015). In an obese mouse model of programming, circulating concentrations of both adiponectin and resistin were reduced in obese dams compared to lean counterparts and were associated with increased fetal weights, but the effects on offspring adipokine profiles were not examined (Kępczynska *et al.* 2013). Neonatal nutritional programming via alterations in litter size has been shown to impair adiponectin effects on energy homeostasis in adult male rats with animals raised in either small or large litters being unresponsive to the appetite-reducing effects of central adiponectin administration (Halah *et al.* 2018). Fructose intake

through pregnancy alone induces hypoadiponectinemia concomitant with hyperinsulinemia and impaired insulin signalling in adult male, but not female, rat offspring independent of any changes in body weight (Rodriguez *et al.* 2016). In a mouse model of maternal fructose intake, female offspring exhibited reduced circulating adiponectin concentrations in parallel to hyperleptinemia, reduced insulin sensitivity and increased fat mass (Saad *et al.* 2016).

Other adipokines

In clinical studies, circulating concentrations of resistin, apelin and visfatin have been shown to be correlated with markers of bone formation in IUGR foetuses at term (Briana *et al.* 2014) but less is known about these adipokines experimentally. Resistin inhibits angiogenesis and induces insulin resistance. Data from clinical studies examining differences in resistin concentrations between IUGR and term groups suggest that resistin may not be directly involved in the regulation of adipogenesis and insulin sensitivity in the perinatal period with no differences in circulating concentrations observed between the groups (Briana *et al.* 2008).

First identified in 2004, visfatin (also known as pre-B-cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (NAMPT)) has been suggested to act as an insulin mimetic and is highly enriched in visceral adipose tissue in both humans and rodents with circulating concentrations increasing in parallel with the development of obesity (Sonoli *et al.* 2011, Stastny *et al.* 2012). However, the associations of visfatin with obesity and diabetes has been a subject of controversy (Fukuhara *et al.* 2005, Arner 2006, Korner *et al.* 2007) and the evidence remains limited for its role in the setting of developmental programming. In a rat model of IUGR using uterine artery ligation, visfatin did not appear to be involved in the disturbed glucose metabolism in offspring and may only represent a marker of fat accumulation (Bouret 2010).

The adipokine apelin, discovered in 1998 (Tatemoto *et al.* 1998), is expressed and secreted by a range of tissues including adipose tissue, liver and brain, and its production is increased during adipocyte differentiation and is stimulated by insulin (Boucher *et al.* 2005). Apelin (and its receptor APJ) has been linked to a number of disease pathologies including obesity, diabetes and cardiovascular disease with recent work highlighting an important role in the regulation of glucose homeostasis. However, relatively little has been reported around the apelinergic system in the setting of developmental programming.

Lecoutre *et al.* studied apelin regulation in adipose tissue in a model of severe maternal undernutrition and showed increased circulating apelin concentrations and adipose tissue apelin gene expression with a postnatal HF diet resulting in increased apelin receptor (APJ) and protein levels (Lecoutre *et al.* 2017a). Further work in this model revealed a role for apelin in the control of fetal and neonatal glucose homeostasis with maternal undernutrition drastically reducing apelinemia in both mothers and IUGR fetuses and altering expression of the apelinergic system at the fetal and placental interface (Mayeur *et al.* 2016). In the setting of maternal obesity in mice, the apelin system is altered at the fetal–maternal interface with placental apelin release and gene expression levels reduced by maternal obesity and maternal apelinemia increased at term in obese females. However, in contrast to the model of maternal undernutrition, no differences were observed in fetal plasma apelin concentrations between groups and longer term outcomes in offspring were not investigated (Hanssens *et al.* 2016).

Little has been reported around omentin, an adipokine with anti-inflammatory activity, in experimental models of developmental programming. Maternal circulating omentin profiles are similar between humans and rodents (Garces *et al.* 2015). In clinical studies, pre-existing maternal obesity associates with a reduction in expression of omentin-1 in placenta, adipose tissue and maternal plasma and alterations in omentin-1 in pregnancy were therefore proposed to play a role in the development of metabolic disorders in offspring in later life. However, experimental evidence remains limited (Barker *et al.* 2012).

Large animal models (ovine, pig, NHP)

There are some reported differences in the programming of adipokines and timing of critical windows between the rodent models and the large animal models. This is due, in part, to developmental events that occur in the early postnatal period in the rodent, particularly around hypothalamic development, occurring *in utero* in large animal models (Coupe *et al.* 2010, Mela *et al.* 2015, 2016). However, there is also evidence for some consistency, particularly as regards neonatal leptin, across both small and large animal models thus reflecting programming of effects on adipokines that are independent of the level of maturity at birth (Long *et al.* 2011).

Leptin

Maternal undernutrition throughout pregnancy in the sheep increases expression of the leptin receptor in the fetal hypothalamus in late gestation with levels largely normalised following improved maternal nutrition in the last trimester of pregnancy (Adam *et al.* 2015). In sheep, the impact of maternal undernutrition on circulating maternal leptin concentrations during late gestation has been shown to be dependent on fetal number with evidence that there is an increase in fetal adipose tissue in twins of ewes exposed to nutrient restriction throughout gestation (Edwards *et al.* 2005).

In the sheep, maternal obesity leads to a reduction in leptin signalling by the pituitary and altered regulation of the growth hormone (GH)/insulin-like growth factor (IGF)1 axis leading to appetite dysregulation, hyperleptinemia and increased adiposity in adult male offspring (Long *et al.* 2015, Tuersunjiang *et al.* 2017). Despite developmental timing differences of central regulatory processes between rodents and large animal models, it has been shown that maternal obesity diminishes the plasma leptin peak in lamb neonates thus suggesting that similarities in neonatal leptin action exist in species born both immature and mature (Long *et al.* 2011). Moreover, it has also been shown that such changes in the leptin surge in sheep can be transmitted over generations with the impact of maternal overnutrition/obesity affecting the neonatal leptin surge in granddaughters (Shasa *et al.* 2015). Increased maternal nutrition results in increased leptin expression in adipose tissue in the postnatal lamb that are depot specific (Muhlhausler *et al.* 2007a). It has also been shown in the sheep that maternal obesity and an increased nutritional intake prior to and during pregnancy results in increased growth and adiposity in response to a feeding challenge and that this was paralleled by hyperphagia and hyperleptinemia (Long *et al.* 2010).

The role of adipokines and the development of brain circuits involved in the regulation of energy homeostasis in higher species remains limited (Grayson *et al.* 2010). In the non-human primate (NHP), a maternal HF diet can programme energy balance and hypothalamic signalling in offspring (Rivera *et al.* 2015, Sullivan *et al.* 2015, 2017) although adipokine profiles remain poorly characterised in these models. Further, although shown to be critical for brain development in rodents, there is limited evidence supporting a role for leptin in brain development in the NHP although leptin may play a role in the refinement of arcuate projection pathways (Grayson *et al.* 2010).

Adiponectin

Recent work by Fensterseifer *et al.* reported in a sheep model that maternal obesity resulted in changes in adiponectin expression in fetal adipose tissue as well as adipogenic and circulating concentrations of total adiponectin. Although adiposity in pregnant ewes did not alter maternal adiponectin, it may have influenced fetal adipogenesis via alterations in the expression of adiponectin, PPAR- γ and sterol regulatory element-binding factor (SREBF)1 in fetal adipose tissue (Fensterseifer *et al.* 2018). Earlier work in the sheep had also reported that increased maternal nutrition (55% above maintenance) led to stimulation of leptin and adiponectin mRNA expression in fetal perirenal adipose depots (Muhlhausler *et al.* 2007b).

As with the rodent models, the timing of the nutritional insult also impacts upon adipokine programming in the sheep. As an example, maternal overnutrition in the periconceptual period alone, although resulting in increased body fat mass in the postnatal lamb, has been shown to be independent of any changes in adipose tissue leptin or adiponectin expression (Rattanatray *et al.* 2010).

Other adipokines

Evidence is limited in large animal models for programming for other adipokines with a primary focus to date being around that of leptin and adiponectin action. The link between resistin and insulin resistance in the NHP model has been reported (Lu *et al.* 2015, Qi *et al.* 2015) but no data are available around its potential role in programming-mediated outcomes. Similarly, there is limited evidence for a role of apelin in the sheep via its involvement in the development of central feeding processes (Sato *et al.* 2012), but this has not been investigated in the setting of development programming.

Intervention strategies

A number of studies in experimental animal models have now shown that some disorders induced as a consequence of aberrant developmental programming are potentially reversible by modulation of adipokines during early life windows of developmental plasticity (Vickers & Sloboda 2012a,b). In particular, manipulation of the leptin axis has shown to reverse many of the postnatal sequelae in offspring arising due to programming effects (Vickers & Sloboda 2012a,b). Neonatal leptin treatment to rat offspring born following maternal undernutrition can

ameliorate many of the effects associated with maternal deprivation including normalisation of body weight, fat mass, circulating leptin concentrations, bone parameters and locomotor activity (Vickers *et al.* 2005, Gluckman *et al.* 2007a, Firth *et al.* 2017). Of note, these effects appear to be sexually dimorphic in nature with increased benefits of leptin treatment seen in programmed female offspring compared to males. Moreover, whereas leptin treatment to male offspring of undernourished mothers conferred protection against programming-induced disorders, treatment of offspring from control pregnancies led to an increase in diet-induced body weight gain and related adverse metabolic sequelae, including hyperinsulinemia and increased total body adiposity (Vickers *et al.* 2008). This may be the result of leptin treatment to control animals creating an amplified and prolonged leptin surge as has been shown in offspring of obese mothers with similar effects observed on offspring outcomes (Kirk *et al.* 2009). This suggests that the effect of leptin treatment in the neonatal period on later offspring outcomes is dependent upon both maternal nutritional status and the sex of the offspring. This was highlighted in further work in this model whereby the effects of neonatal leptin treatment on hepatic gene expression and epigenetic status in adulthood were directionally dependent on the animal's nutritional status *in utero* (Gluckman *et al.* 2007b).

In the maternal LP rat model, leptin administration normalised the reduction in fetal IGF-1 concentrations and significantly increased fetal IGF-2 and leptin concentrations (Stocker *et al.* 2004). These effects positively impacted upon the development of key organs including the fetal pancreas and thus conferred long-term protection against the development of obesity and type 2 diabetes (Stocker *et al.* 2007). A limitation of this study was that leptin administration was not undertaken in the normal pregnancy group; as previous work has suggested that leptin treatment in the setting of normal pregnancies could elicit an adverse offspring outcome (Vickers *et al.* 2008). In the piglet, early postnatal leptin treatment following IUGR promoted organ maturation and development with notable changes in weight and structure across a range of tissues including liver, spleen, pancreas, kidney and ovaries (Attig *et al.* 2008a).

The model of neonatal leptin treatment has provided some empirical evidence to support the PARs hypothesis as developmental outcome was altered by experimentally manipulating the predicted environment that is using leptin to signal a high nutrient postnatal environment. Conversely, it has also been shown that blocking leptin

action in the early postnatal period (via treatment with a leptin antagonist) results in programming of leptin resistance and increased susceptibility to diet-induced obesity in rodents (Attig *et al.* 2008b). Further work by Mela *et al.* showed that treatment in the rat with a leptin antagonist from PND 5 to 9, coincident with peak leptin levels in the neonatal surge, resulted in changes in reproductive factors in the hypothalamus which impact upon sexual maturation including modifying the timing of pubertal onset and leading to persisting changes on hypothalamic expression on reproductive neuropeptides (Mela *et al.* 2015, 2016).

It must be noted that in addition to dose and timing of administration, some of the observed differences in outcomes of leptin treatment studies may also reflect the type of leptin used. Human leptin has been shown to have diuretic/natriuretic activity in the rodent and thus consideration needs to be made when examining programming-mediated effects around blood pressure regulation and renal function (Jackson & Li 1997).

In the setting of IUGR in male rat offspring (via uterine artery ligation), increased visceral adiposity was accompanied by a dysregulation in the expression of peroxisome proliferator activated receptor (PPAR)- γ expression. Given that activation of PPAR- γ can increase adiponectin expression in subcutaneous adipose tissue and normalise visceral adipose deposition, it was proposed that maternal supplementation with a PPAR agonist could normalise adipose regulation in IUGR offspring (Bagley *et al.* 2013). Indeed, supplementation to the maternal diet with docosahexaenoic acid (DHA), a known PPAR- γ agonist, has been shown to normalise IUGR-mediated changes in adipose tissue deposition, increased circulating adiponectin concentrations and reversed programming-induced changes in adipose tissue adiponectin and adiponectin receptor expression in male rats (Bagley *et al.* 2013). However, as with leptin, these effects appear to be sex specific with IUGR and DHA-induced changes in adipose tissue depots and altered PPAR regulation observed in male but not female offspring (Joss-Moore *et al.* 2010, Bagley *et al.* 2013).

Treatment of pregnant mice with adiponectin can prevent the adverse consequences of maternal obesity on placental function and fetal growth (Aye *et al.* 2015). In obese mouse dams, placental insulin and mammalian target of rapamycin complex 1 (mTORC1) signalling was activated, placental transport of glucose and amino acids was increased, PPAR α phosphorylation was reduced and there was an increase in fetal weights of approximately 30%. Maternal adiponectin infusion in these obese mice

led to a normalisation of maternal insulin sensitivity, nutrient transport, placental insulin/mTORC1 and PPAR α signalling and fetal growth independent of the effects on maternal fat mass (Aye *et al.* 2015). Further work by Paulsen *et al.* has also shown that normalisation of adiponectin levels of maternal obesity in the mouse prevented the development of adverse metabolic outcomes in male offspring (Paulsen *et al.* 2018) and thus suggests that low circulating maternal adiponectin may represent a critical mechanistic link between a maternal obesogenic environment and the development of metabolic disease in offspring.

Discussion

Alterations in adipokine profiles, particularly leptin, have been examined across a wide range of experimental animal models of developmental programming. It is now clear that maternal undernutrition and obesity during pregnancy and/or lactation all produce offspring characterised by obesity and leptin resistance, the effects of which can be exacerbated as a result of rapid postnatal catch-up growth and exposure to a post-weaning obesogenic dietary environment (Fig. 1). A primary focus to date on the role of adipokines has been on alterations in the early life nutritional environment with undernutrition and overnutrition both resulting in marked alterations in adipokine profiles, the timing and magnitude of the leptin surge and wiring of the hypothalamic circuits regulating appetite control and energy expenditure. There is also evidence that leptin can act as a metabolic signal to the reproductive system via direct actions at the ovarian level (Spicer & Francisco 1997, Bernal *et al.* 2010) leading to outcomes including early onset puberty and markers of early ovarian ageing.

Leptin has been the most widely studied adipokine to date. Although leptin is expressed in the placenta and in certain fetal tissues, the role of leptin as a regulator of fetal growth still remains unclear (Hoggard *et al.* 2001, Hauguel-De Mouzon *et al.* 2006). It also needs to be noted that models of maternal diabetes need to be differentiated from those models of maternal obesity *per se*. Circulating leptin concentrations can be reduced in offspring of obese pregnancies whereas offspring of diabetic mothers are often characterised by macrosomia and hyperleptinemia.

Although the leptin surge has been characterised across a range of small animal models, it is not as well defined in larger animal models such as the sheep or NHP. Most hypothalamic development in rodents occurs in

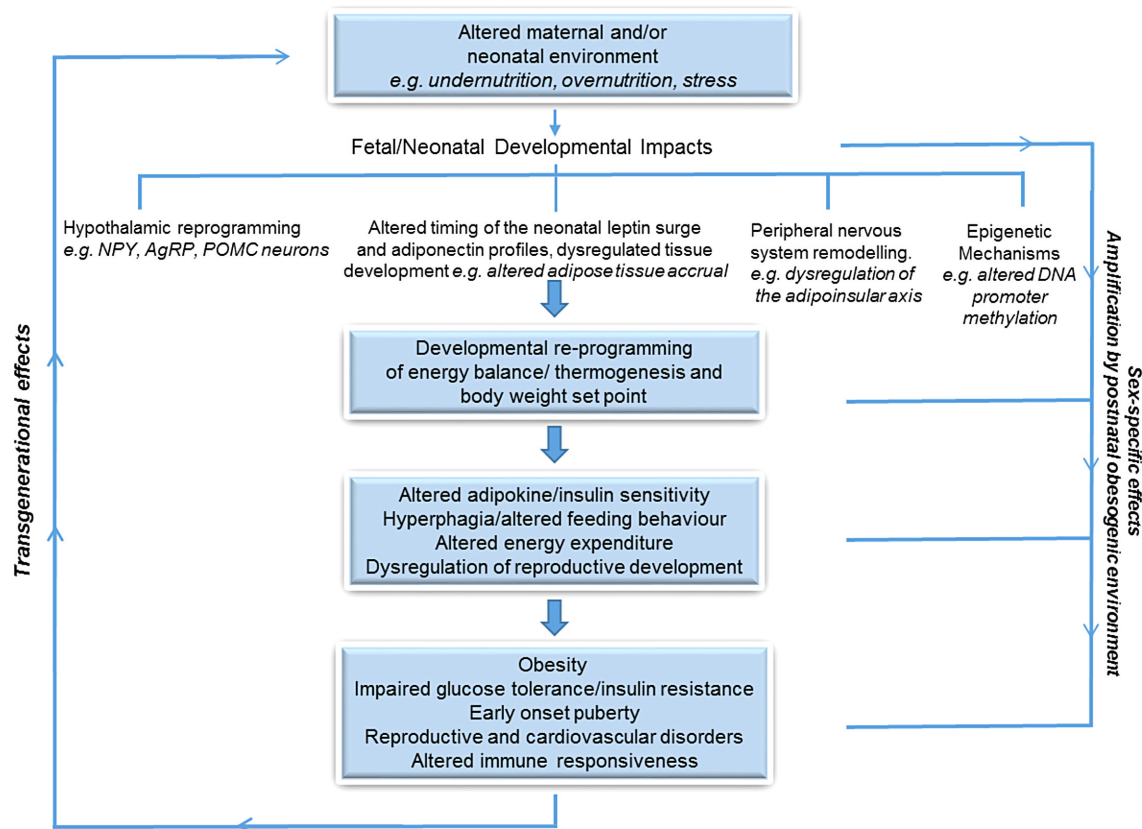


Figure 1

The impact of an altered early life environment on developmental programming of energy balance, adipokine regulation and consequences for later life metabolic, reproductive and cardiovascular health in offspring.

the early postnatal period thus aligns with the timing of the neonatal surge whereas these processes largely occur *in utero* in large animal models (Grove *et al.* 2005). It is important to note therefore that a leptin surge *in utero* may not arise from the mother, as leptin does not cross the placenta. In larger animal models and that of the human, it is more likely that insulin, which can cross the placenta and enter the fetal brain, interacts with leptin signalling via the adipoinsular axis feedback loop (Vickers *et al.* 2001, Horvath & Bruning 2006). Indeed, offspring born to women with obesity or type 2 diabetes have an increased risk of developing metabolic disorders (Grove *et al.* 2005) although whether this is the result of developmental alterations in hypothalamic circuits remains to be addressed. However, despite these differences in timing of developmental events across model species, there are reports of a neonatal leptin surge in the sheep which can be modified by maternal nutritional status thus providing some commonality across small and large animal models.

Although leptin has received the most attention, there is evidence across a wide range of models for dysregulation

of other key adipokines, particularly that of adiponectin. It is also notable that despite the variety of experimental paradigms used to disrupt the early life nutritional environment (global calorie restriction, LP, HF and high sugar diets), similar effects on adipokine dysregulation in adult life have been reported, suggesting common mechanistic pathways may underpin the programming of later disease in later life. These manipulations appear to increase susceptibility to obesity in offspring via dysregulating the normal development of central neural pathways involved in the regulation of appetite, energy expenditure and storage with central and peripheral leptin resistance a common phenotypic outcome. It is likely that leptin, given its strong neurotropic properties, is a major mediator of these early developmental changes. Experimental data also suggest that this activity is restricted to the early life period that precedes leptin's acute regulation of food intake in adults (Myers *et al.* 2008) with intervention strategies using leptin showing efficacy in the early neonatal period but largely ineffectual when used in the post-weaning period when leptin resistance is present.

Taken together, the evidence to date clearly highlights the important of the adipokines in programming-related disorders with manipulation of these factors offering key insight into mechanisms underpinning the development of obesity and disorders of energy balance and also avenues for potential interventions to reverse the programming process. However, it is important to note that neurodevelopmental events that occur in rodents in the neonatal period occur *in utero* in primates, including humans (Grove *et al.* 2005, Horvath & Bruning 2006, Sullivan *et al.* 2011). In rodents, maternally derived leptin can impact on the development of the regulatory neural networks that affect appetite control and on the subsequent regulation of leptin synthesis and the risk for obesity and related metabolic disorders in the offspring. However, in larger model species such as the NHP and sheep, there is also evidence that the synthesis and secretion of adipokines are regulated in fetal life (Mcmillen *et al.* 2006). More work needs to be undertaken around the potential epigenetic processes involved and the impact of alterations in the early periods of developmental plasticity on epigenetic regulation of adipokines. As an example, programming-mediated changes in methylation of the suppressor of cytokine signalling (SOCS)-3 may have persisting effects on the leptin-insulin feedback loop (the adipoinsular axis; Vickers *et al.* 2001) via inhibition of leptin signal transduction (Holness & Sugden 2006). As such, the use of epigenomic approaches and identification of target sites (e.g. methylation sites, miRNAs) involved in the epigenetic regulation of adipokine action is an increasingly important area of investigation.

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