

Modeling the impact of growth and leptin deficits on the neuronal regulation of blood pressure

Baiba Steinbrekera and Robert Roghair

Stead Family Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA

Correspondence should be addressed to R Roghair

Email
robert-roghair@uiowa.edu

Abstract

The risk of hypertension is increased by intrauterine growth restriction (IUGR) and preterm birth. In the search for modifiable etiologies for this life-threatening cardiovascular morbidity, a number of pathways have been investigated, including excessive glucocorticoid exposure, nutritional deficiency and aberration in sex hormone levels. As a neurotrophic hormone that is intimately involved in the cardiovascular regulation and whose levels are influenced by glucocorticoids, nutritional status and sex hormones, leptin has emerged as a putative etiologic and thus a therapeutic agent. As a product of maternal and late fetal adipocytes and the placenta, circulating leptin typically surges late in gestation and declines after delivery until the infant consumes sufficient leptin-containing breast milk or accrues sufficient leptin-secreting adipose tissue to reestablish the circulating levels. The leptin deficiency seen in IUGR infants is a multifactorial manifestation of placental insufficiency, exaggerated glucocorticoid exposure and fetal adipose deficit. The preterm infant suffers from the same cascade of events, including separation from the placenta, antenatal steroid exposure and persistently underdeveloped adipose depots. Preterm infants remain leptin deficient beyond term gestation, rendering them susceptible to neurodevelopmental impairment and subsequent cardiovascular dysregulation. This pathologic pathway is efficiently modeled by placing neonatal mice into atypically large litters, thereby recapitulating the perinatal growth restriction–adult hypertension phenotype. In this model, neonatal leptin supplementation restores the physiologic leptin surge, attenuates the leptin-triggered sympathetic activation in adulthood and prevents leptin- or stress-evoked hypertension. Further pathway interrogation and clinical translation are needed to fully test the therapeutic potential of perinatal leptin supplementation.

Key Words

- ▶ adipose tissue
- ▶ developmental origins
- ▶ prematurity
- ▶ sex
- ▶ sympathetic nervous system

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Introduction

Leptin is a pleiotropic hormone with early neurotrophic effects on the hypothalamus (Bouret *et al.* 2004, Pinto *et al.* 2004). Later in life, leptin acts as a homeostatic agent by balancing appetite and sympathetic activity with energy stores such that increased adiposity increases circulating

leptin levels, reducing appetite and increasing sympathetic tone. In addition to promoting energy expenditure, this sympathetic activation increases blood pressure (Rahmouni & Morgan 2007). According to the developmental origins of adult disease construct, physiologic challenges early in

life can skew the developmental processes during critical windows of susceptibility. This potentially can leave long-standing pathologic repercussions if the altered regulatory processes are rigidly established. This review presents the evidence of an attenuated late gestation leptin surge in intrauterine growth-restricted (IUGR) or preterm infants. With IUGR and prematurity each affecting at least ten percent of all pregnancies, this perinatal leptin deficiency influences nearly a quarter of all infants (WHO 1995, Beck *et al.* 2010), supporting the development of translational models. We review the clinical and preclinical data leading to murine models designed to test the hypothesis that neonatal leptin deficiency leads to permanent alterations in hypothalamic leptin signaling, predisposing to leptin-evoked hypertension in adulthood (Fig. 1).

Perinatal growth restriction, prematurity and adult hypertension

Clinical investigations

Intrauterine growth restriction is a strong, independent risk factor for adult cardiovascular disease. International investigations over the past three decades have reaffirmed the landmark epidemiological observations of Barker and coworkers (1989). In those seminal studies, an inverse relationship was noted between birth weight and ischemic heart disease. Although dyslipidemia and obesity often coexist, hypertension remains a modifiable risk factor for life-threatening heart disease. Subsequent studies have thus focused on the association between IUGR and adult hypertension.

Consistent with the earlier investigations, a number of studies over the following decades demonstrated an inverse correlation between birth weight and adult blood pressure (Curhan *et al.* 1999, Eriksson *et al.* 2007). In a large twin cohort study, Bergvall and coworkers (2007) found decreased birth weight associated with increased risk of hypertension independent of genetic factors, shared familial environment and adult body mass index. Although relatively few human studies have been powered for sex-specific effects, the available data are consistent with sex differences in the developmental origins of hypertension (Intapad *et al.* 2014). Jones and coworkers (2008) and Miles and coworkers (2011) have each shown that former IUGR men but not women have increased baseline blood pressure that is exacerbated by psychological stress, and this sexual dimorphism has been a consistent theme in preclinical animal models (Intapad *et al.* 2014).

Clinical investigations into the potential etiology of IUGR-associated hypertension have consistently demonstrated increased sympathetic tone in formerly or persistently growth-restricted adults, including heightened peroneal nerve traffic, urinary catecholamine excretion and stress-evoked cardiovascular alterations (Boguszewski *et al.* 2004, Johansson *et al.* 2007, Jones *et al.* 2008). Intriguingly, the stress hypertension seen in IUGR infants correlates with a lack of salivary cortisol response to painful procedures, suggesting programmed alterations in hypothalamic function (Schäffer *et al.* 2009). This contrasts with the increased cortisol response typically seen in adults with stress-evoked hypertension (Grant *et al.* 2009). Studies on autonomic blood pressure regulation in adults generally

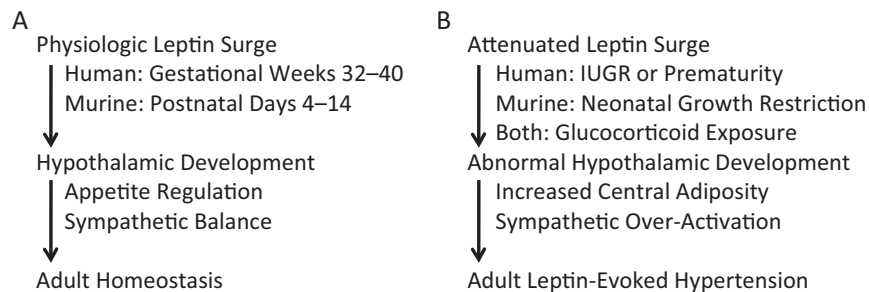


Figure 1

The importance of the perinatal leptin surge as a stimulus for hypothalamic development. (A) During normal human pregnancy, fetal leptin levels rapidly increase from gestational week 32 to delivery. Mice have a relative delay in adipogenesis, and an analogous increase in leptin does not occur until postnatal days 4–14. In both species, the physiologic increase in perinatal leptin is critical for normal hypothalamic development. In adulthood, cardiometabolic homeostasis is facilitated by well-tuned appetite regulation and sympathetic tone. (B) Perinatal leptin deficiency can occur after intrauterine growth restriction (IUGR) or prematurity in humans, neonatal growth restriction in mice or exaggerated perinatal glucocorticoid exposure in both species. The attenuated leptin surge increases the risk of hypothalamic hypoplasia and dysregulation with the potential for hypersensitivity to leptin-triggered sympathetic activation in the presence of selective resistance to leptin-mediated anorexia. Individuals with obesity-related hyperleptinemia in the presence of heightened leptin-mediated sympathetic activation are at dramatically increased risk of adult hypertension.

do not report birth weight or gestational age at delivery. Longitudinal assessment of premature or growth-restricted populations will be necessary to identify the temporal relationship between sympathoadrenal activation and the development of hypertension.

The impact of IUGR on adult blood pressure is significantly influenced by the rate of postnatal growth. Central adiposity is seen in a subpopulation of growth-restricted individuals who otherwise remain smaller than their normal birth weight peers (Hack *et al.* 2003, Crume *et al.* 2014). Neonatal growth acceleration increases the risk of adult obesity and hypertension (Ben-Shlomo *et al.* 2008), whereas continued growth restriction throughout infancy increases the risk of hypertension and ischemic heart disease more than that seen after IUGR alone (Barker *et al.* 1989, Eriksson *et al.* 2007). More so than term infants, premature infants are at substantial risk for neonatal growth restriction, with 90% of preterm infants developing postnatal weights below the 10th percentile by the time of hospital discharge (Dusick *et al.* 2003). Extremely low birth weight children remain smaller than their peers in regard of height and weight at age 8 years, and by 14 years, boys catch up, but girls continue to remain smaller (Hack *et al.* 2014). In part related to this near universal prematurity-associated neonatal growth restriction, preterm birth trumps IUGR as a risk factor for hypertension (Johansson *et al.* 2005).

As seen in IUGR infants, preterm infants have additional cardiovascular risk factors consistent with sympathetic over-activation, including increased catecholamine excretion, increased resting heart rates, and exaggerated pressor responses to psychological stress (Ward *et al.* 2004, Johansson *et al.* 2007, Jones *et al.* 2007, Pyhälä *et al.* 2009). Up to 70% of preterm infants demonstrate elevated systolic blood pressure as early as 1 year of age, and hypertension remains a significant health concern into adulthood, especially in the presence of adult obesity (Johansson *et al.* 2005, Pyhälä *et al.* 2009, Dagle *et al.* 2011, Duncan *et al.* 2011, Sipola-Leppänen *et al.* 2015). The fact that prematurity-related hypertension persists into adulthood puts significant afterload on the heart for decades (de Jong *et al.* 2012, Kerkhof *et al.* 2012), potentially contributing to the abnormal cardiac dimensions seen even in infancy (Lewandowski *et al.* 2013, Sehgal *et al.* 2013). Unfortunately, this hypertensive phenotype is present among infants born as late as during 37-week gestation (Gunay *et al.* 2014), and unlike the sexual dimorphism seen in IUGR infants, both preterm boys and girls appear

to be at a heightened risk of adult hypertension (Bonamy *et al.* 2012). Notably, the same neurodevelopmental consequences that follow preterm delivery have been increasingly reported in IUGR infants, including reduced brain volumes and impaired neuronal connectivity (Miller *et al.* 2016), suggesting a potential common etiology linking neurodevelopment and the neuronal regulation of blood pressure.

Murine model

Animal models have been indispensable in elucidating the physiologic and cellular processes that are altered by perinatal growth restriction. Interspecies differences are important considerations in identifying appropriate preclinical models to test critical hypotheses. We continue to collaborate with others in the pursuit of answers in sheep, rats and mice with notable sex-specific phenotypes observed (Roghair & Aldape 2007, Roghair *et al.* 2009, Katkhuda *et al.* 2012). Important investigations in rats have already shown that late-gestation uterine artery ligation elicits intrauterine growth restriction, increased sympathetic tone and postmenopausal hypertension that can be normalized by estrogen replacement or bilateral renal denervation (Ojeda *et al.* 2007, Intapad *et al.* 2013). Likewise, maternal malnutrition-induced IUGR programs sympathetic nerve overactivity in response to physical stress (Mizuno *et al.* 2013). Interestingly, it has been shown that the effects of uterine artery ligation may be mediated, in part, by placental hypoxia-related perinatal leptin deficiency (Nüsken *et al.* 2016). We in turn developed a mouse model to test the mechanistic hypothesis that central neuronal pathways are involved in the perpetuation of programmed hypertension.

As a foundation for the mechanistic studies to come, we assessed the physiologic implications of natural variation in perinatal growth. Those initial studies replicated human observations that IUGR with persistent neonatal growth restriction increases the risk of hypertension and neurodevelopmental impairment (Hermann *et al.* 2009) and that estrogen replacement mitigates the hypertensive phenotype otherwise seen in postmenopausal growth-restricted mice (Haskell *et al.* 2016). Our follow-up investigations revealed that neonatal leptin supplementation prevents the neuropsychiatric impairment and hypertensive response to psychological stress that otherwise follow neonatal growth restriction (Erkonen *et al.* 2011, Meyer *et al.* 2014). This therapeutic use of leptin was informed by clinical data showing both

IUGR and preterm infants undergo critical phases of neuromaturation in the presence of low circulating levels of the neurotrophic hormone leptin.

Perinatal growth restriction, prematurity and circulating leptin levels

Clinical investigations

Leptin is primarily secreted by mature adipocytes and circulating leptin levels highly correlate with body mass index. In the fetus, adipose development begins in the 2nd trimester, and by 28-week gestation, adipose tissue has appeared in the major deposition areas (Poissonnet *et al.* 1988). Considering the key role leptin plays in organogenesis, it is understandable that redundant systems are in place to ensure the adequacy of circulating leptin levels throughout gestation. Among the contributors to fetal plasma leptin levels, the mother and the placenta play a major role in the first and second trimesters, and the fetus itself becomes a main contributor in the final trimester.

Studies describing the strong association between maternal adiposity, maternal leptin levels and cord blood leptin levels support an important role for transplacental (maternal to fetal) leptin delivery (Varvarigou *et al.* 1999, Toprak *et al.* 2004, Ho *et al.* 2010, Luo *et al.* 2013). Arguing for alternative leptin sources to support fetal development, other investigations have not observed the same association (Hassink *et al.* 1997, Clapp & Kiess 1998, Helland *et al.* 1998, Hytinen *et al.* 1999, Sooranna *et al.* 2001, Yildiz *et al.* 2002, Pighetti *et al.* 2003), and direct maternal-to-fetal leptin transfer has not been identified.

Many investigators have demonstrated a direct correlation between placental weight and cord blood leptin levels (Koistinen *et al.* 1997, Clapp & Kiess 1998, Jaquet *et al.* 1998, Varvarigou *et al.* 1999, Valūniene *et al.* 2007). Hassink and coworkers (1997) signaled the potential of the placenta as a contributor to fetal leptin by showing that placental trophoblastic cells secrete leptin, and Yura and coworkers (1998) demonstrated higher leptin levels in umbilical venous blood compared with umbilical arterial blood. Lea and coworkers (2000) subsequently demonstrated that leptin mRNA and protein can be found in the placenta as early as the 1st trimester. In the same study, leptin mRNA and protein were localized to the syncytiotrophoblast and the villous vascular endothelium (Lea *et al.* 2000). These data suggest that placental leptin is released into both the fetal and

maternal circulations. Lepercq and coworkers (2001) later showed that nearly 95% of placental leptin is secreted into maternal circulation with only 5% delivered to the fetus. Evidence supporting the physiologic relevance of placental leptin production includes the increased plasma leptin levels seen in pregnant vs non-pregnant women (Matsuda *et al.* 1999, Schubring *et al.* 1999, Yokota 2003), and the positive correlation of maternal leptin levels with advancing gestational age (Helland *et al.* 1998, Visentin *et al.* 2014). Although the increase in plasma leptin level during pregnancy often correlates with gestational weight gain (Castellano Filho *et al.* 2013, Marino-Ortega *et al.* 2015), that association is not observed in obese women (Misra & Trudeau 2011, Franco-Sena *et al.* 2015), suggesting that increased fat mass is not the only contributor to the rise in maternal leptin levels during pregnancy. Further support for an adipose-independent source for leptin is found in the studies by Highman and coworkers (1998) showing that the increase in maternal leptin precedes pregnancy-related weight gain, and maternal leptin levels promptly decrease after delivery (Highman *et al.* 1998, Schubring *et al.* 1998, Lage *et al.* 1999).

Placental leptin production and release appear to be regulated by factors including synthetic and endogenous glucocorticoid exposure. Antenatal betamethasone acutely increases maternal leptin but decreases fetal leptin (Marinoni *et al.* 2008). Those results were replicated by third trimester dexamethasone administration to pregnant rats (Sugden *et al.* 2001), supporting glucocorticoid-induced reduction in maternal-to-fetal and placental-to-fetal leptin passage (Smith & Waddell 2003). Consistent with those data, growth-restricted fetuses that are exposed to increased endogenous glucocorticoids typically have reduced leptin levels with decreased placental leptin expression, whereas maternal plasma leptin levels are increased (Lepercq *et al.* 2001, Pighetti *et al.* 2003, Nezar *et al.* 2009, Visentin *et al.* 2014). Similar changes are seen in twin pregnancies with lower placental leptin expression in IUGR-affected twin placenta compared with normal growth twin placenta (Lea *et al.* 2000). It is notable that other studies have failed to demonstrate a consistent relationship between antenatal glucocorticoid exposure and fetal leptin levels (Shekhawat *et al.* 2000, Ng *et al.* 2001, Spear *et al.* 2001). Beyond adrenal steroids, sex steroids appear to influence leptin levels with male infants having lower levels than females (Hassink *et al.* 1997, Helland *et al.* 1998, Ertl *et al.* 1999, Jaquet *et al.* 1999, Matsuda *et al.* 1999, Ong *et al.* 1999, Ng *et al.* 2000, 2001, Yokota 2003, Toprak *et al.* 2004, Valūniene *et al.* 2007, Chiesa *et al.* 2008), and an indirect relationship has been

observed between testosterone and leptin levels (Ertl *et al.* 1999, Ng *et al.* 2001, Su *et al.* 2002). Of note, this sexual dimorphism does not emerge until the final 6 weeks of gestation (Koistinen *et al.* 1997, Jaquet *et al.* 1998, Spear *et al.* 2001, Stoll-Becker *et al.* 2003). The dependence of leptin levels on maternal-independent factors suggests the fetus helps regulate its own leptin level in the later stages of gestation. It has not been determined clinically whether growth restriction itself reduces adipocyte leptin production independent of fetal fat mass accrual.

Although fetal adipocytes produce leptin as early as 20-week gestation (Lepercq 2001), fetal fat mass more than doubles from 32 to 41 weeks of gestation (Lapillonne *et al.* 1997). Umbilical cord blood leptin levels thus slowly increase from 18 to 32 weeks of gestation and then increase rapidly until birth (Jaquet *et al.* 1998, Ertl *et al.* 1999, Matsuda *et al.* 1999, Cetin *et al.* 2000, Park *et al.* 2001, Lo *et al.* 2002, Stoll-Becker *et al.* 2003, Yokota 2003, Fonseca *et al.* 2004). The importance of fetal fat mass accumulation is supported by the fact that neonatal fat mass has a stronger association with newborn leptin levels than birth weight (Clapp & Kiess 1998, Jaquet *et al.* 1998, Fonseca *et al.* 2004, Toprak *et al.* 2004). Not surprisingly, by 34-week gestation, intrauterine growth-restricted (IUGR) infants tend to have lower cord blood leptin levels than those appropriate for gestational age infants (Koistinen *et al.* 1997, Lapillonne *et al.* 1997, Jaquet *et al.* 1998, Cetin *et al.* 2000, Yildiz *et al.* 2002, Pighetti *et al.* 2003, Valūniene *et al.* 2007, Chiesa *et al.* 2008, Martos-Moreno *et al.* 2009, Nezar *et al.* 2009), although some investigations have not observed the same results (Geary *et al.* 1999, Stoll-Becker *et al.* 2003, Aydin *et al.* 2015). Furthermore, leptin levels do not vary between appropriate for gestational age and small for gestational age early preterm infants (Jaquet *et al.* 1998, Stoll-Becker *et al.* 2003, Ohkawa *et al.* 2010, Hellgren *et al.* 2015). Overall, depending on the population and gestational stage of assessment, cord blood leptin positively correlates with a mix of factors including maternal weight gain during pregnancy, maternal BMI, gestational age, birth weight, ponderal index, infant skin fold thickness and ultrasound-measured adiposity (Cetin *et al.* 2000, Su *et al.* 2002, Yildiz *et al.* 2002, Mantzoros *et al.* 2009, Brynhildsen *et al.* 2013, Karakosta *et al.* 2013). The finding that infant BMI has a greater association with infant plasma leptin levels than birth weight (Fonseca *et al.* 2004, Toprak *et al.* 2004) again supports the premise that the development of adipose tissue and the accumulation of fat mass drive the late gestation surge in serum leptin.

Consistent with the importance of transplacental leptin passage even in the later stages of gestation, the physiologic leptin surge is abruptly terminated by delivery for both preterm and term infants (Helland *et al.* 1998, Hytinantti *et al.* 1999, Jaquet *et al.* 1999, Valūniene *et al.* 2007, Kawamata *et al.* 2014). After this initial drop, leptin levels remain low for the first week of life (Harigaya *et al.* 1997, Ertl *et al.* 1999, Matsuda *et al.* 1999, Ng *et al.* 2000, Park *et al.* 2001, Yokota 2003, Valūniene *et al.* 2007). Not surprisingly, this postnatal leptin decline does not correlate with the extent of neonatal weight loss (Hytinantti *et al.* 1999, Jaquet *et al.* 1999, Matsuda *et al.* 1999, Park *et al.* 2001, Valūniene *et al.* 2007) because a majority of initial weight loss reflects fluid shifts rather than changes in fat mass.

Premature infants face the challenge to grow and develop in the presence of profound leptin deficiency. They are born before the third trimester leptin surge and suffer from a lack of placental and transplacental leptin delivery. There are reports showing a correlation between infant plasma leptin levels and infant gestational age and anthropometric measures (Ng *et al.* 2000, 2001, Lo *et al.* 2002, Toprak *et al.* 2004, Valūniene *et al.* 2007, Chiesa *et al.* 2008), but there are also reports suggesting a lack of correlation in preterm infants (Jaquet *et al.* 1998, Spear *et al.* 2001, Ho *et al.* 2010, Ohkawa *et al.* 2010, Hellgren *et al.* 2015). The correlation between preterm infant leptin and weight typically becomes significant after infants begin to accrue adipose tissue mass (Enzi *et al.* 1981). Depending on the gestational age at birth, leptin levels remain below term infant values for 3–8 weeks (Ertl *et al.* 1999, Ohkawa *et al.* 2010). Ng and coworkers (2001) studied 61 premature infants and did not observe a statistically significant leptin level increase through day of life 35. Likewise, Toprak and coworkers (2004) showed that an increase in body weight and thickness of subcutaneous adipose tissue eventually led to an increase in leptin levels with adipose tissue appearing to be the main contributor to leptin levels after 30 days of life.

To further quantify the leptin deficiency of prematurity, Hellgren and coworkers (2015) compared 4-week-old preterm infants at 32-week adjusted gestational age to newborn infants at 32-week gestation and noted that former 28-week preterm infants had leptin levels far below the reference cohort. To our knowledge, this was the first study comparing postnatal leptin levels of preterm infants with 'reference fetus' levels. Those data highlight the concern that preterm infants develop persistent postnatal leptin deficiency during a

window of developmental vulnerability with potential neurodevelopmental implications. The duration of the postnatal leptin deficiency has not been fully quantified, but recent investigations have confirmed the persistent growth deficiency consistently reported in longitudinal studies (Rochow *et al.* 2016). For example, Spear and coworkers (2001) followed weekly leptin levels for infants born before 32-week gestation until discharge and did not observe leptin level increase in these infants, and their levels remained significantly below those seen in term infants, even after the preterm cohort reached 40-week corrected gestational age. Likewise, Toprak and coworkers (2004) showed that infants born on average at 34-weeks gestation needed three months to reach serum leptin levels near those of full-term infants. This prolonged low leptin state might represent functional immaturity, a lack of sufficient adipose tissue or the suboptimal nutrition that is frequently seen in premature infants. Further studies are needed to define postnatal leptin changes and the cause–effect relationship between circulating leptin and postnatal growth.

In addition to preterm infants, IUGR infants have decreased postnatal leptin levels (Harigaya *et al.* 1997, Jaquet *et al.* 1999). Twin studies by Lea and coworkers (2000) and Sooranna and coworkers (2001) have shown that leptin levels are lower in the growth-restricted twin compared with the normal growth twin, further supporting the theory that leptin is either a cause or consequence of growth deficiency. Similar to the abrupt postnatal leptin decline observed in preterm infants, leptin levels decrease below already low fetal levels in IUGR infants throughout the first week of life (Jaquet *et al.* 1999, Duncan *et al.* 2011). With many IUGR infants showing significant catch-up growth during the first year of life, Jaquet and coworkers (1999) evaluated their leptin level changes over 2 years and observed a peak at 6 months.

Beyond caloric intake, the nutritional source influences postnatal leptin levels. Parenteral nutrition and infant formulas do not contain leptin (Resto *et al.* 2001, O'Connor *et al.* 2003), but breast milk does (Casabiell *et al.* 1997, Resto *et al.* 2001, Miralles *et al.* 2006). Savino and coworkers (2013) evaluated leptin levels among healthy term infants and then performed follow-up at a median age of 8.8 years. They reported that the infants who were breast fed had higher leptin levels than formula-fed infants. At follow-up, breast-fed infants had lower BMI contributing to the inverse relationship seen between leptin levels in infancy and childhood BMI. The encouragement of breast feeding may help curtail transgenerational obesity as maternal BMI and

Table 1 Factors that increase the risk of perinatal leptin deficiency and programmed hypertension.

Decreased breast milk intake
Male sex
Perinatal growth restriction
Perinatal glucocorticoid exposure
Placental insufficiency or hypoxia
Preterm birth

maternal serum leptin correlate with breast milk leptin levels, and increased breast milk leptin is associated with reduced neonatal growth velocity (Schuster *et al.* 2011). Studies in rats have confirmed absorption of enterally administered leptin (Casabiell *et al.* 1997, Sánchez *et al.* 2005). Unfortunately, at 15 days of life, breast milk leptin is decreased in mothers of growth-restricted infants in comparison with the breast milk provided by mothers of appropriately grown infants (Dundar *et al.* 2005). Table 1 summarizes the risk factors in common for perinatal leptin deficiency and programmed adult hypertension.

Murine model

Consistent with their relative short gestation, mice are born with a paucity of adipose tissue and thus have low leptin levels throughout the first 3–4 postnatal days; with increasing adipose deposition and advancing breast milk intake, leptin levels then rise and peak between day 4 and 14 (Ahima *et al.* 1998, Yura *et al.* 2005, Delahaye *et al.* 2008). In the initial investigation of Ahima and coworkers (1998), female mice with normal birth weights were fostered in litters of 5 pups, and leptin levels surged between days 4 and 16. When Yura and coworkers (2005) instead fostered normal birth weight mice into mixed sex litters of 8 or 9 pups, and they observed a smaller leptin surge spanning from day 8 to 16. In that study, intrauterine growth restriction was induced in additional mice by maternal caloric restriction, and the postnatal leptin surge was skewed toward higher values on days 8–10 with decreasing values on day 16, leading to the conclusion that IUGR may provoke a ‘premature leptin surge’. However, the peaked leptin levels seen in IUGR mice on days 8–10 mirrored the timing of the leptin surge in the study by Ahima and coworkers (1998), as well the investigations by Delahaye and coworkers (2008) showing a postnatal peak on days 4 to 10 in control male rats fostered in litters of 8 pups. In that latter study, maternal perinatal undernutrition did not alter the timing of the leptin surge, but did significantly decrease neonatal leptin levels with parallel interference with hypothalamic development (Delahaye *et al.* 2008).

Leptin's role in adult hypertension

Clinical investigations

The first insights into the hemodynamic effects of leptin emerged from epidemiological investigations showing that individuals with rare leptin gene mutations were morbidly obese but paradoxically normotensive (Montague *et al.* 1997, Ozata *et al.* 1999, Rahmouni *et al.* 2005). Controversy ensued because early clinical trials of leptin in patients with obesity or lipodystrophy primarily evaluated metabolic outcomes but cursorily reported an absence of leptin-induced cardiovascular manifestations (Heymsfield *et al.* 1999). The concept of leptin-mediated hypertension gained traction when leptin levels were shown to independently correlate with blood pressure in both postmenopausal women and otherwise healthy men (Ma *et al.* 2009, Allison *et al.* 2013, Smith *et al.* 2015). Elegant preclinical and clinical investigations finally demonstrated the retention of sympathetic activation and hypertension despite selective obesity-related resistance to leptin-induced anorexia (Simonds *et al.* 2014). Further investigations continue to uncover downstream pathways that can be exploited to target the various effects leptin elicits in the normal physiologic state. For example, hypothalamic leptin receptor expression is found to play a critical role in leptin-induced sympathetic activation and hypertension (Rahmouni & Morgan 2007, Harlan *et al.* 2011) with signal transducer and activator of transcription 3 (STAT3) phosphorylation within proopiomelanocortin neurons particularly important in leptin- or stress-evoked hypertension (do Carmo *et al.* 2011, Dubinion *et al.* 2013).

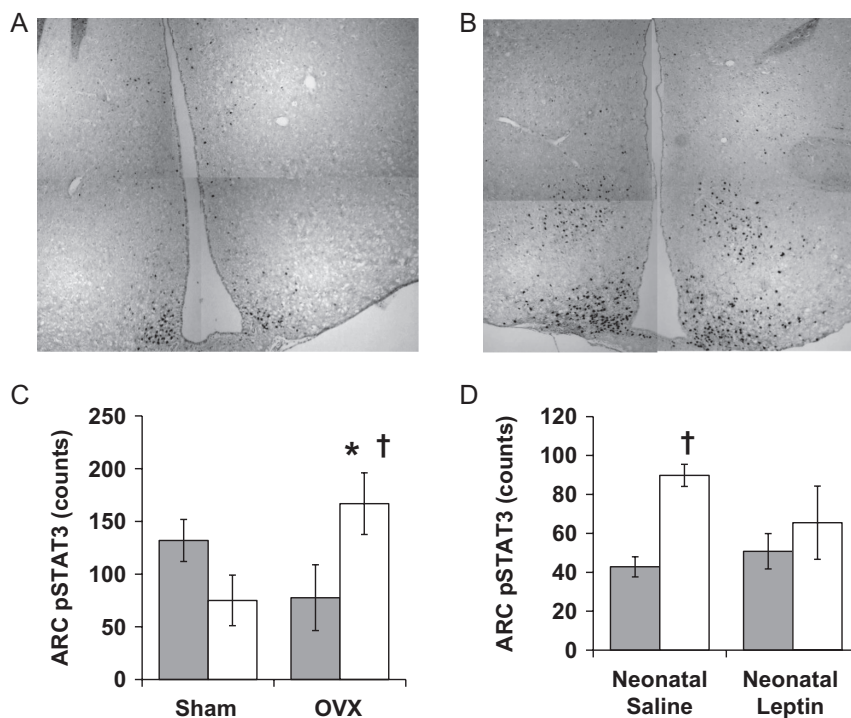
Murine models

We developed a murine model to specifically test the hypothesis that leptin is involved in both the inception and the propagation of perinatal growth restriction-related hypertension. After validating the model by demonstrating adult hypertension in intrauterine and/or neonatal growth-restricted mice (Hermann *et al.* 2009), we went on to test leptin's therapeutic potential. Given the relative developmental immaturity of newborn mice, the critical third trimester of human adipogenesis and neurodevelopment is analogous to the first two postnatal weeks in mice (Romijn *et al.* 1991, Grove *et al.* 2005). Likewise, the leptin surge that occurs in the final months of human gestation coincides with the postnatal day 4 to 14 leptin surge that occurs in well-grown mice. To focus

on that critical window of vulnerability, we developed a neonatal growth restriction model by placing pups into litters of 12 to elicit neonatal growth restriction, defined by a weaning weight below the 10th percentile in a manner consistent with WHO guidelines. Mice with incipient growth restriction then receive daily parental leptin supplementation from day 4 to 14 at a dose (80 ng/g) that recapitulates the leptin levels measured in control mice that are fostered in typical litters of 6 pups. This is a multifactorial model with likely contributions from the same factors operating in preterm humans, including neonatal stress as well as relative neonatal undernutrition. Beyond leptin's neurodevelopmental effects, exogenous leptin can attenuate the adrenal response to neonatal stress (Salzmann *et al.* 2004). Future studies are needed to determine the acute effect of neonatal leptin supplementation on adrenal function and glucocorticoid levels to test the hypothesis that leptin protects against the hypertensive effects of glucocorticoids.

In adulthood, mice with a history of neonatal growth restriction displayed psychological stress-exacerbated hypertension, neuropsychiatric impairment and altered brain morphology (Erkonen *et al.* 2011, Meyer *et al.* 2014). Neonatal leptin supplementation exerted trophic effects on the hypothalamus and normalized all of those findings (Erkonen *et al.* 2011, Meyer *et al.* 2014). Mechanistically, neonatal leptin normalization corrected the exaggerated pressor response seen after intracerebroventricular leptin administration, normalized the heightened renal sympathetic nerve response seen after parenteral leptin administration and normalized the increased leptin receptor expression seen in the arcuate nucleus of the hypothalamus (ARC) (Peotta *et al.* 2016).

Regarding the potential effects of neonatal leptin on adult cardiovascular outcomes; the dose and timing of the intervention are critically important. When neonatal leptin is administered to well-grown mice and rats at supraphysiologic doses (2.5–6 mg/kg/day), long-term impairment in leptin-triggered anorexia is observed (Yura *et al.* 2005, Samuelsson *et al.* 2013). Vickers and coworkers (2005, 2008) have shown that supraphysiologic leptin administration (2.5 mg/kg/day) leads to selective leptin resistance in adult mice, with loss of leptin's anorectic effects but retention of leptin-induced hypertension. This inverse correlation between leptin sensitivity and neonatal leptin levels is consistent with the investigations of Rahmouni and coworkers (2005) showing obesity-related (supraphysiologic) hyperleptinemia is associated with selective resistance to leptin's metabolic effects. Finally, the timing of the leptin replacement must match the

**Figure 2**

The influence of perinatal growth, ovarian status and neonatal leptin administration on leptin-stimulated hypothalamic signaling in adult mice. These original experiments with C57BL/6J mice (Jackson Laboratory) were approved by the University of Iowa Office of Animal Resources. Neonatal growth restriction (GR) was induced by placing mice into litters of 12 rather than 6 pups on postnatal day 1, and GR was confirmed by weanling weights below the 10th percentile for the colony on postnatal day 20. At 2–4 months, female mice underwent bilateral ovariectomy (OVX) or sham surgery (incisions without ovary removal) under inhaled isoflurane anesthesia (4%, Phoenix Scientific, St Joseph, MO, USA). After 2–3 months of postoperative recovery, a 3-h fast was followed by intraperitoneal injection of murine leptin (1 mg/kg, Biomyx Technology, San Diego, CA, USA) 1 h before transcardiac perfusion fixation during anesthesia with intraperitoneal ketamine (262.5 mg/kg, Sigma-Aldrich) and xylazine (37.5 mg/kg, Sigma-Aldrich). Coronal cryosections were obtained through the arcuate nucleus of the hypothalamus (ARC), and pSTAT3 immunoreactivity was quantified with anti-phospho-STAT3 (9145, Cell Signaling) followed by detection with ImmPRESS/DAB (MP-7401, Vector Laboratories, Burlingame, CA, USA). Representative immunostains (A, Control-OVX; B, GR-OVX) are composites of 4 higher magnification images. (C) Leptin-stimulated pSTAT3-positive cells counts were influenced by a significant interaction between GR and adult ovarian status (control: closed bars, GR: open bars, $n=4$ or 5). OVX significantly increased leptin-evoked pSTAT3 signaling in GR mice ($^{\dagger}P<0.05$ by ANOVA) such that GR-OVX mice had significantly more pSTAT3 reactive nuclei than control-OVX mice ($^*P<0.05$ by ANOVA), suggesting that adult ovarian function suppresses GR-associated leptin responsiveness. Compared with control-OVX mice, GR-OVX mice also tended to have more pSTAT3-reactive nuclei in the ventral medial hypothalamus, but the difference did not reach statistical significance (control-OVX 11 ± 6 , GR-OVX 31 ± 7). (D) Unlike the significant increase in ARC, pSTAT3 seen in control (neonatal saline) mice that received leptin (open bars) vs saline (closed bars) before perfusion fixation ($^{\dagger}P<0.05$ by ANOVA), neonatal leptin-treated mice did not have significantly different responses to pre-fixation injection of leptin vs saline, suggesting that neonatal leptin administration decreased adult leptin responsiveness ($n=3$ or 4).

phase of leptin-sensitive neurodevelopment. For example, physiologic leptin administration to lactating rats confers protection from diet-induced obesity in association with favorable alterations in hypothalamic gene expression (Picó *et al.* 2007, Stocker *et al.* 2007, Palou *et al.* 2011). Likewise, placing pups in large litters to elicit neonatal undernutrition leads to a lean, leptin-responsive adult phenotype, whereas placement in small litters to elicit overnutrition predisposes to obesity in association with impaired leptin-triggered hypothalamic STAT3 signaling (Rodrigues *et al.* 2009). Complementary models once again show that intrauterine growth restriction followed more importantly by accelerated neonatal growth, suppresses adult leptin signaling (Coupé *et al.* 2012).

Further investigations are required to dissect relevant signaling partners with leading candidates including leptin-induced co-activation of the renin–angiotensin system (Hilzendeger *et al.* 2012). There are also known interactions between estrogen and leptin, with both hormones acting in part through phosphorylation of STAT3 (Clegg *et al.* 2006, Gao *et al.* 2007, Shi & Brooks 2015). Regarding brain site-specific regulation, the ARC is exquisitely sensitive to environmental modulation of leptin sensitivity and sympathetic tone increases after ARC-targeted leptin microinjections (Münzberg *et al.* 2004, Harlan *et al.* 2011, Tanida *et al.* 2015). Our initial investigations have confirmed interactions among neonatal growth restriction, ovarian function and

neonatal leptin administration in the establishment of leptin-induced STAT3 signaling in the ARC (Fig. 2).

Conclusion

In conclusion, the cumulative evidence indicates that leptin plays a critical role in the perinatal development and that perinatal leptin levels are insufficient to optimize neuroregulatory pathways in both IUGR and preterm infants. In translational mouse models, leptin supplementation targeted to otherwise leptin-deficient growth-restricted mice is sufficient to prevent the development of neurocardiovascular dysfunction and normalize the neural control of renal sympathetic activity and arterial pressure. In addition to mice, leptin supplementation elicits neurotrophic effects in growth-restricted piglets and genetically leptin-deficient humans (Matochik *et al.* 2005, Attig *et al.* 2008). Although the neuroanatomic and molecular interactions in the pathways leading to programmed adult hypertension are incompletely understood, the important role that leptin plays in key developmental and regulatory pathways support ongoing investigations into the impact of leptin on the inception and perpetuation of perinatal growth restriction or prematurity-related hypertension.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

B Steinbrekera and R Roghair drafted and revised the article. R Roghair was involved in the design, analysis and interpretation of the primary experiments.

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