Leptin in pregnancy and development: a contributor to adulthood disease?

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Briffa JF, McAinch AJ, Romano T, Wlodek ME, Hryciw DH. Leptin in pregnancy and development: a contributor to adulthood disease? *Am J Physiol Endocrinol Metab* 308: E335–E350, 2015. First published December 17, 2014; doi:10.1152/ajpendo.00312.2014.—Emerging research has highlighted the importance of leptin in fetal growth and development independent of its essential role in the maintenance of hunger and satiety through the modulation of neuropeptide Y and proopiomelanocortin neurons. Alterations in maternal-placental-fetal leptin exchange may modify the development of the fetus and contribute to the increased risk of developing disease in adulthood. In addition, leptin also plays an important role in reproductive functions, with plasma leptin concentrations rising in pregnant women, peaking during the third trimester. Elevated plasma leptin concentrations occur at the completion of organogenesis, and research in animal models has demonstrated that leptin is involved in the development and maturation of a number of organs, including the heart, brain, kidneys, and pancreas. Elevated maternal plasma leptin is associated with maternal obesity, and reduced fetal plasma leptin is correlated with intrauterine growth restriction. Alterations in plasma leptin during development may be associated with an increased risk of developing a number of adulthood diseases, including cardiovascular, metabolic, and renal diseases via altered fetal development and organogenesis. Importantly, research has shown that leptin antagonism after birth significantly reduces maturation of numerous organs. Conversely, restoration of the leptin deficiency after birth in growth-restricted animals restores the offspring's body weight and improves organogenesis. Therefore, leptin appears to play a major role in organogenesis, which may adversely affect the risk of developing a number of diseases in adulthood. Therefore, greater understanding of the role of leptin during development may assist in the prevention and treatment of a number of disease states that occur in adulthood.

leptin; maternal obesity; intrauterine growth restriction; organogenesis; adulthood diseases

LEPTIN'S PHYSIOLOGICAL ROLES

Maintenance of Hunger and Satiety

LEPTIN, the 16-kDa product of the obese (*ob*) gene, is secreted predominantly by white adipose tissue and under certain circumstances may be produced in other tissues, including the human placenta, mammary epithelium, and gastric mucosa (8, 63, 93). Under normal physiological conditions, plasma leptin concentrations reflect adiposity, with elevated plasma leptin detected in obese individuals (57). Leptin's main physiological role is to regulate hunger and satiety (40, 48). It does this by being transported across the blood-brain barrier by the scavenger receptor megalin (41) and signaling via the leptin receptors (ObR) in the arcuate nucleus (ARC) of the basomedial hypothalamus (BMH). In the BMH, leptin has actions on two sets of neurons whose axons project into the paraventricular hypothalamus, which contains the satiety center, with both neurons eliciting different effects (55). Specifically, leptin binding to ObR on both neuropeptide Y (NPY) neurons and agouti-related protein (AgRP) neurons inhibits their orexigenic effects by preventing their inhibition on anorexigenic proteins (corticotropin-releasing hormone and oxytocin) and preventing the expression of orexin neurotransmitters (115, 158). Additionally, leptin binding to ObR on proopiomelanocortin (POMC) neurons activates these neurons and increases the expression of the norexigenic proteins α-melanocyte stimulating hormone and thyrotropin-releasing hormone, further inhibiting the secretion of orexigenic proteins (melanin-concentrating hormone) (115, 158). Leptin's effects on these two neuron types ultimately results in a decrease in food intake, an increase in satiety, and an increase in energy expenditure (Fig. 1) (48).

Reproductive Function

Leptin can act on the periphery to modulate normal physiological function. For example, leptin plays an essential role in reproductive function. Specifically, research has shown that an injection of leptin is essential for conception in leptin-deficient (*ob/ob*) mice who are infertile (31), since leptin initiates the

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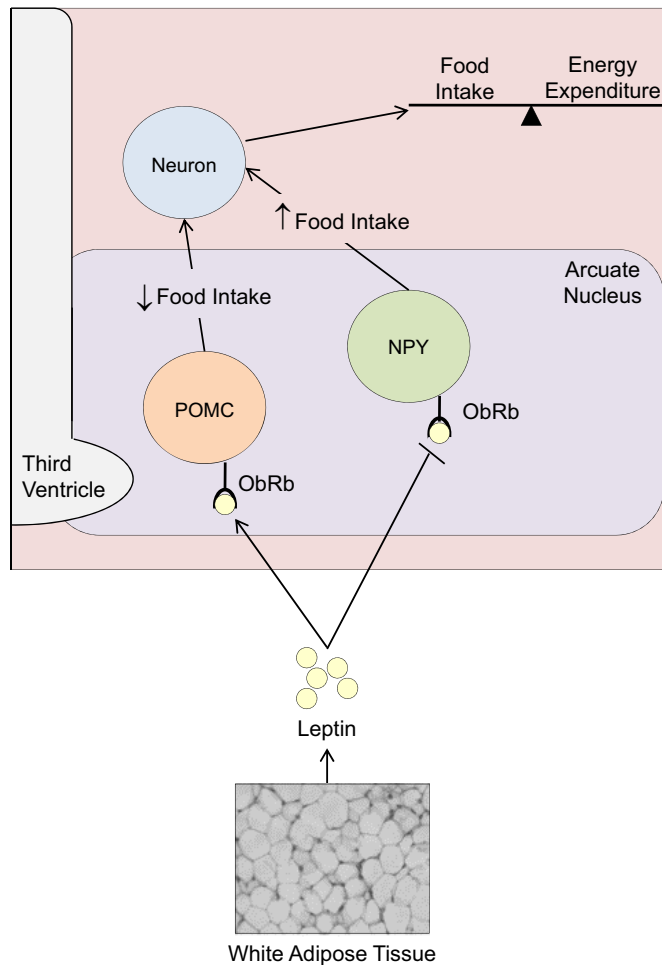
Fig. 1. Leptin's actions in regulating food intake in the brain. White adipose tissue produces and secretes leptin, which crosses the blood-brain barrier and acts on neurons in the arcuate nucleus (ARC). Leptin binding to the leptin receptor (ObRb) on proopiomelanocortin (POMC) neurons reduces food intake, and leptin binding to ObRb on neuropeptide Y (NPY) neurons inhibits NPY's actions in increasing food intake, resulting in an increase in energy expenditure. Figure adapted with permission from Barsh and Schwartz (13).

onset of puberty, as demonstrated in human females (67). This is presumably via leptin's stimulation of luteinizing hormone (LH) secretion (170). In addition, leptin can stimulate the production of gonadotropin-releasing hormone (GnRH) from the GnRH neurons via the modulation of other neurons (such as NPY, POMC, and AgRP) in the ARC that are also associated with GnRH neurons (38, 74). Interestingly, a study exploring leptin in ovary development in *ob/ob* mice identified that *ob/ob* mice have a smaller vaginal opening, smaller uteri, and have fewer primordial follicles (64), demonstrating that leptin is critical in reproductive development. Potentially, this may be via the modulation of apoptosis, as leptin deficiency also resulted in increased markers of apoptosis, in addition to increased apoptosis in the ovary (64), and increased apoptosis in germ cells via the upregulation of proapoptotic gene expression in the testis (21). In turn, these data suggest that leptin may impair secretion of GnRH, which decreases follicle-stimulating hormone and LH secretion, impairing oocyte maturation and sperm production.

LEPTIN IN PREGNANCY

Leptin Production

During pregnancy, maternal plasma leptin concentrations rise in the first and second trimesters and peak during the third trimester, with plasma leptin concentrations then returning to prepregnancy concentrations prior to parturition (132). Several studies have demonstrated a positive correlation between human umbilical cord blood leptin concentration and birth weight (66, 82, 104, 135). Research by Lea et al. (95) identified in human placentas, using in situ hybridization and immunohistochemistry, that leptin mRNA and protein are colocalized to the syncytiotrophoblast (in direct contact with the maternal blood) and the villous vascular endothelial cells (in contact with the fetal blood), suggesting that the placenta is a source of both fetal and maternal leptin. Despite this, research in human embryos (at 6–10 wk gestation) has shown that leptin is expressed in differentiating preadipocytes, suggesting that fetal adipose tissue is capable of producing leptin at the beginning of lipidogenesis and differentiation (5). Thus, these data suggest that fetal leptin concentrations are directly correlated to fetal fat mass (similar to adults), with negligible contributions by the mother (34, 82). In support of this, research has demonstrated that despite the human placenta being a site for both maternal and fetal leptin production, most of the placental leptin is transported into the maternal circulation (96), with research by Lepercq et al. (96) identifying that, in isolated human placentas, <5% of placentally derived leptin enters the fetal circulation in humans. However, this study only demonstrates the transferability of leptin via the placenta; it did not measure the maternally produced protein and its abundance in the offspring. Therefore, at this time the amount of maternal leptin that is produced by maternal adipose and subsequently transferred to the offspring in vivo is unknown.

Leptin Transportation Across the Placenta

To alter intracellular signaling and function, leptin must bind to either the ObR or the scavenger receptor megalin (2, 63). There are six different isoforms of ObR (a–f) that are produced by alternative RNA splicing (22). The only isoform that has a transmembrane domain that is capable of activating signal transduction pathways is ObRb, whereas the other five short ObR isoforms have either a truncated or no transmembrane domain and are unable to activate signaling pathways (22). Activation of ObRb results in an upregulation of a number of signal transduction pathways, including the janus kinase/signal transducers and activators of the transcription pathway (JAK/STAT), as well as the mitogen-activated protein kinase pathway (9).

Research in ex vivo human placental organ baths has demonstrated that placental leptin is transported to both the fetal and maternal interfaces (75). It has also been determined that leptin transportation can occur in both the apical-to-basolateral and basolateral-to-apical directions in human choriocarcinoma (BeWo) cells in vitro. Despite the limitations associated with the differences between in vitro studies and in vivo research, these findings do indicate that there may be fetal-to-maternal leptin exchange across the placenta (169). Importantly, to date, it is not known which receptor is mediating this transportation or whether this phenomenon is occurring in vivo. Research has

identified that both ObR and megalin (along with its associated receptor cubilin) are expressed in the human placenta and are localized to the syncytiotrophoblast (95), with megalin and cubilin also located in the cytotrophoblast (28). Megalin and cubilin endocytose a number of ligands (32), including leptin in the kidney (63), and during pregnancy their expression increases with advancing gestation (28), suggesting that these receptors are important to both maternal and fetal systems. Recent research has demonstrated that megalin-mediated leptin signaling can alter targets in renal cell proliferation (26); however, the role megalin plays in leptin transport in the placenta has not yet been clearly established. Interestingly, recent research suggests that megalin may also be responsible for gene transcription modulation in the placenta (99, 136). Specifically, research in a placentally derived cell line (L2 rat yolk sac cells) identified that megalin is trafficked to the endocytic recycling compartment for proteolytic processing (136). Once cleaved, the intracellular domain of megalin modulates gene expression, which may lead to the activation of signal transduction pathways (99).

Leptin Resistance in Pregnancy

In response to the high energy demand associated with human pregnancy, there is elevated maternal plasma leptin concentrations compared with nonpregnant women, which is in part due to an accumulation of body fat as well as leptin production by the placenta (96, 145). This elevation in plasma leptin concentration is maintained by an increase in leptin bound to the soluble ObRe leptin receptor that delays the clearance of leptin (150). In contrast to leptin's normal effect on satiety, human pregnancy is associated with increased food intake, which prevents maternal nutrient depletion, allowing for an increased nutrient delivery to the growing fetus (145). This discrepancy is due to central leptin resistance that occurs during the second trimester of human pregnancy (59, 151), which may be due to the reduction in hypothalamic ObRb expression (59). In support of this, research by Ladyman and Grattan (91) has identified that injection of leptin directly into the brains of pregnant Sprague-Dawley rats has no effect on reducing food intake. Therefore, during pregnancy, increased leptin concentrations and signaling play an important role in the modulation of food intake.

Leptin in Maternal Milk

After parturition, it is not known whether the main source of infant leptin is infant leptin production or from the maternal milk supply. Recent research has identified that leptin concentrations are elevated in mature milk (21–30 days) compared with colostrum leptin concentrations, with infant weight and height also increasing during this period (42). Thus, maternal milk leptin may play a role in regulating infant growth. Research has clearly demonstrated that leptin is present in the maternal milk; however, it is unclear whether milk leptin is absorbed into the offspring bloodstream and is biologically active. A study in rodents has shown that the stomach is able to reabsorb maternally derived leptin into the bloodstream (29). Although not directly demonstrating that milk leptin is biologically active, it does support this hypothesis. However, there is no research to date that specifies exactly how much leptin is

able to be reabsorbed from the stomach and whether maternal leptin can elicit effects in the offspring.

LEPTIN IN FETAL DEVELOPMENT

The role of leptin in fetal development has not been investigated extensively. The majority of existing research focuses on the role of leptin in brain development, with very few studies investigating leptin's role in organogenesis in other systems. Table 1 lists the current research relating to leptin and ObR expression in the placenta, brain, heart, pancreas, and kidney across the different species, and Table 2 lists the length of gestation in these animals. Notwithstanding the number of studies performed in this area, there are major limitations in this research, as most studies are based on gene expression in animal models, with very few studies investigating phenotypic changes associated with altered leptin concentrations. Furthermore, in a number of animal models organ development continues after birth, compared with humans, whose development is completed largely before birth, indicating a potential limitation in the translational outcomes from studies in animals. In all species, there is a plasma leptin surge that occurs during pregnancy (humans) or postnatally during the suckling period (other mammals) that is associated with organ maturation and development (1, 6, 70, 101, 132, 133, 141). Table 2 also lists the timing of the leptin surge in the different species used to investigate the role of leptin in pregnancy.

Central Nervous System

As described previously, the main physiological role of leptin is to maintain hunger and satiety. These pathways are clearly outlined in Fig. 1 (40, 48). In addition, leptin has also been demonstrated to play a role in brain development. In the mouse, ObRb is detected in the rhobencephalon (in the ventricular zone), telencephalon (in the ventricular zone and cortical plate), mesencephalon, cerebellar primordium, thalamus (in the ventricular zone), premamillary hypothalamic nucleus, superficial gray matter of the superior colliculus of the cerebellum (external germinal and Purkinje cell layers), facial nucleus, ARC, and ventromedial hypothalamic nucleus at various embryonic days (E; E10.5–E18.5; term = 20 days) (156). Interestingly, ObRb expression has also been identified in the ventricular layer of the brain in rats at E14 (term = 22 days), which contains premature neuronal cells, with ObRb detected in the paraventricular nucleus (PVN) and ependymal cells on E18 (107). These findings suggest that leptin, and more importantly ObRb, may play an important role in the development or function of the brain in rodents. However, direct research has not been performed to determine this.

Much of our understanding of leptin's role in the brain has come from animal models where leptin signaling is altered. Research in neuronal ObR knockout mice has identified that obesity is negatively correlated with the amount of hypothalamic ObR expression, which is consistent with findings in *ob/ob* mice whereby both animals develop obesity (35). The cause of obesity in these ObR knockout mice is likely increased hypothalamic expression of NPY and AgRP mRNA, which increases food intake (35). In support of this, *ob/ob* mice have reduced hypothalamic development characterized by reduced neuronal fiber density in the PVN that is restored with leptin treatment during the early postnatal period [postnatal day

Table 1. *Leptin and leptin receptor locations in the different species used to investigate leptin in pregnancy*

Species	Leptin		Leptin Receptor		Ref. No(s).
	mRNA	Protein	mRNA	Protein	
Human	Placenta	Placenta	Placenta	Placenta	24, 66, 73, 95, 106, 110, 134, 137
	Heart	Heart	Heart	Heart	
		Brain	Brain	Brain	
			Pancreas	Pancreas	
Nonhuman primate*	Placenta		Placenta	Placenta	46, 60, 72, 78, 121
			Brain		
			Heart		
			Kidney		
Sheep	Placenta	Placenta	Placenta	Placenta	27, 47, 152, 165
	Brain		Brain		
	Heart		Heart		
	Kidney		Kidney		
Pig	Placenta	Placenta	Placenta	Placenta	85, 100, 138, 143, 144
	Brain	Brain	Brain	Brain	
			Heart		
			Kidney		
			Pancreas		
Rabbit	Brain	Brain		Brain	105
Rat	Placenta	Placenta	Placenta	Placenta	81, 107, 108, 118, 142, 171
	Heart	Heart	Heart	Heart	
	Brain		Brain	Brain	
	Kidney		Pancreas		
Mouse	Placenta	Placenta	Placenta	Placenta	49, 76, 77
	Heart	Heart	Heart	Kidney	
			Brain	Brain	
			Kidney		
			Pancreas		

*Baboon or rhesus monkey.

(PN)12] (25). Furthermore, in vitro leptin treatment in ARC explants of *ob/ob* offspring shows that leptin treatment specifically promotes axon elongation and proliferation (25). In addition, *ob/ob* fetuses have significantly fewer cells on E16 and E18 in the neuroepithelium and reduced expression of NPY mRNA in the cortical plate (155). A intracerebroventricular leptin injection in *ob/ob* mice on E14 increases the number of neuroepithelium cells on E16 (155) and restores differentiation of these cells into astrocytes and neurons (39, 155). Thus, these data collectively highlight that leptin is an important factor in neural development in the embryo and that leptin concentrations are critical for the establishment of neuronal pathways required for the maintenance of satiety.

A number of studies investigating the role of leptin in brain development have employed specific agonist and antagonist treatments. In Wistar Kyoto rats injected with a rat-pegylated

Table 2. *Gestation length and leptin surge in the various species used to investigate leptin in pregnancy*

Species	Gestation Length, days	Leptin Surge	Ref. No(s).
Human	266 days	24–40 wk gestation	84, 132
Nonhuman primate	154–266*	NS	
Sheep	152	PN4–PN11	101
Pig	114	NS	
Rabbit	31	NS	
Rat	22	PN5–PN15	1, 36, 141
Mouse	20	PN4–PN15	1

PN, postnatal day; NS, not studied. *Depending on the nonhuman primate family.

leptin antagonist on PN9 (2 × 5 mg/kg), there was surprisingly no change in body weight, with only female offspring having altered hypothalamic signaling mediator expression on PN13 (111). In addition, the female offspring also had increased hypothalamic cell death and a shift toward an antiapoptotic balance (111), providing evidence of sex-specific effects of leptin signaling. In Wistar Kyoto rats injected with the rat leptin antagonist L39A/D40A/F41A (7.5 μg·g^{-1}·day^{-1}) from PN2 to PN13 (7, 18), there were no changes in female body weight, but leptin resistance developed at 4 mo (7, 18). Interestingly, when these females were fed a high-energy diet for 3 mo, there was a significant increase in body weight, adiposity, and hyperleptinemia (7). However, in male offspring, leptin antagonism resulted in a significant increase in body weight gain (PN2 to PN125) that was maintained with 1 mo of high-fat feeding (PN125 to PN153) (18). Furthermore, leptin antagonism increased hypothalamic leptin receptor (ObRa and ObRb), insulin receptor, and adiponectin receptor 2 mRNA expression at PN28 in the males (18). However, these animals' sensitivity to leptin were not investigated, with previous research identifying that reduced hypothalamic ObR expression is associated with leptin resistance (102), indicating that these animals are not likely to be leptin resistant. Thus these studies demonstrate that leptin's role in central nervous system development is sex specific. However, a clear limitation in all of the leptin antagonist studies described is that these studies employ a reduction in litter size [8 (111) or 10 pups (7, 18)] or cross-fostering pups (7). Because leptin can be transferred from the mother to offspring, the altered milk quality and quantity would likely affect the outcomes of these studies

(120). Conversely, several in vivo studies in rodents have also identified that leptin agonism during the early postnatal period also alters brain development. Specifically, Sprague-Dawley offspring administered leptin intracerebroventricularly from PN2 to PN7 have a reduction in body weight from PN2 to PN21, which is sustained to PN120 in females (162). The reduction in body weight may be the consequence of a reduction in NPY and ObR expression in the PVN (PN8, PN21, and PN120) and an increase in α-melanocyte-stimulating hormone in the dorsomedial nucleus (PN21 and PN120) and ARC (PN120) (162). One limitation that was not acknowledged in this study is that they utilized Sprague-Dawley rats that are prone to developing obesity, which would elevate plasma leptin concentrations (14). Further compounding this is that litter sizes were also reduced (10 pups/litter), impacting on the results. These in vivo studies highlight that maintenance of physiological levels of leptin plays an important role in normal brain development in a sex-specific manner.

Cardiovascular System

A number of studies have demonstrated that leptin may play a role in cardiac development. In embryonic development, leptin stimulates proliferation in cardiac muscle HL-1 cells in vitro (148). Furthermore, in CD1 mouse embryos, leptin is strongly expressed in the myocardium of the heart on E8.5 (118). Once the transition of epithelial cells to mesenchymal cells begins on E9, leptin expression in the myocardium begins to diminish, and leptin expression is enhanced in the newly formed mesenchymal cells, with a decrease in leptin in the myocardium during the later stages of morphogenesis (E9.5–E12.5). Thus, this suggests that leptin's expression in the endocardium and mesenchymal cells is required for the epithelial to mesenchymal cell transition, proliferation, and early remodeling of the heart. In parallel, ObR expression is also detected on E9 in mesenchymal cells and decreases during the later stages of morphogenesis (118).

In rats, the plasma leptin surge occurs from PN5 to PN15 (Table 2) (6, 141), which coincides with the final stages of organogenesis (70). To identify the role leptin plays in cardiac development during the postnatal period, Attig et al. (6) injected Wistar Kyoto rats with 7.5 $\mu g \cdot g^{-1} \cdot day^{-1}$ leptin antagonist (rat leptin mutant L39A/D40A/F41A) from PN2 to PN13 and identified no changes in heart weight or alterations in histological appearance in the leptin antagonist-treated rats (6). In the postnatal period, when development is continuing in a number of animal models, including rodents (70), leptin administration in vivo alters cardiovascular development. Specifically, in female Sprague-Dawley offspring injected with leptin (3 mg/kg twice daily) from PN9 to PN15, there are no alterations to offspring body weight (128). However, on PN30 these offspring are leptin resistant and have a heavier heart mass and increased cardiomyocyte number, with increased heart rate, systolic blood pressure, and mean arterial pressure (128). These female offspring also have left ventricular remodeling on PN30 and at 12 mo have impaired cardiac function, as indicated by a reduced ejection fraction and fractional shortening, which was absent in males (128). In contrast, the male offspring have altered left ventricular structure at 12 mo and impaired contractile function at 5 mo (128), suggesting that leptin's role in cardiac development has a sex-specific pheno-type. In further support of a sex-specific effect of leptin in cardiac development, we have shown sex-specific alterations in JAK/STAT signaling in Wistar-Kyoto rats (160). Specifically, males have decreased JAK2 (PN1 and PN7), increased STAT3 (E20 and PN35), increased STAT5 on E20 that decreased thereafter (PN7 and PN35), increased SOCS3 (E20 and PN1) that decreased on PN7, and increased phosphatidylinositol 3-kinase expression on E20 and PN1 that decreased at PN7 compared with female offspring (160). Thus, despite the limitation that alterations in ObR were not determined in our study, it was clearly demonstrated that maintenance of normal leptin signaling is critical for development.

Renal System

Currently, there is only limited research investigating the effect leptin has on renal development. Specifically, research by Attig et al. (6) determined that Wistar-Kyoto rats exposed to the leptin antagonist L39A/D40A/F41A during the period of the leptin surge (PN2 to PN13), had a significantly reduced glomerular number and size, with an increased presence of immature glomeruli (6). However, this analysis was based on histological measurements and not via the physical fractionator/dissector method of unbiased serology, which is the gold standard in determining glomerular number (116, 172). Despite this, assuming that leptin antagonism reduces glomerular number and size, these data have implications in a role for leptin in nephrogenesis, and the presence of the leptin surge (PN5 to PN15) may be important for normal kidney development. Because both megalin and ObR are expressed in the kidney (63), it is clear that leptin plays a role in renal development. However, at this time the exact mechanism and pathways involved are unknown.

Endocrine System and Metabolic Disease

There is a well-established link between leptin and insulin (161), with maintenance of normal leptin concentrations essential to achieve normoglycemia via the modulation of neuronal pathways (POMC and AgRP) (161). Research has shown that leptin may modulate blood glucose concentrations through maintaining normal physiological function of the pancreas. The loss of normal leptin signaling in both *ob/ob* and leptin receptor-deficient (*db/db*) mice leads to hyperinsulinemia and the development of type 2 diabetes (88). At a cellular level, research by Kieffer et al. (88) in primary *ob/ob* islets demonstrated that leptin (100 ng/ml) suppresses insulin secretion. Furthermore, leptin treatment of primary pancreatic islet cells from Sprague-Dawley rats isolated from E21 fetuses stimulates pancreatic islet proliferation, indicating that leptin plays an important role in regulating normal function in the pancreas (81).

Research has established a role for leptin in the early development of the pancreas. In Wistar-Kyoto rats treated with 7.5 $\mu g \cdot g^{-1} \cdot day^{-1}$ of leptin antagonist L39A/D40A/F41A during the leptin surge (PN2 to PN13), there is hypertrophy of the islet cells and an increased α-cell/β-cell ratio despite no changes in total pancreas weight (6). Conversely, in healthy C57BL/6 mice, leptin treatment (PN2 to PN7) results in hyperglycemia (PN120), glucose intolerance (PN60), and hyperinsulinemia (PN8) that preceded hyperglycemia in the female offspring only (162). To support a role for elevated leptin in

metabolic disease, Trotta et al. (154) injected healthy Wistar-Kyoto pups with leptin or saline for 10 days during the leptin surge (PN1 to PN10). Animals were then treated with either saline or anti-leptin antibody on PN29 and PN30, giving rise to four groups (control/saline, leptin/saline, control/antibody, and leptin/antibody). The Wistar-Kyoto rats from the leptin/saline group were obese (high visceral and total fat mass) and had hyperleptinemia, hypertriglyceridemia, and hypoadiponectinemia, all of which are consistent with changes observed in obesity (154). Interestingly, control/antibody Wistar Kyoto rats have the same metabolic changes as the leptin/antibody group, with a higher insulin resistance index (154). However, again, both of these studies reduced the litter sizes, which may alter the leptin phenotype of these animals. Despite this, these data suggest that both hyperleptinemia and hypoleptinemia program obesity and metabolic disease in adulthood.

ALTERATIONS IN LEPTIN AS INDICATIONS OF DISEASE RISK

The role of leptin in growth and development can best be demonstrated by growth restriction and obesity, which alter offspring leptin, increasing the risk of deficits in organ maturation and disease. These two conditions are described below and detail changes in fetal and infant development and their impact on diseases in adulthood.

Fetal Growth Restriction

Despite leptin playing an important role in both maternal adaptations to pregnancy and fetal development, there are conditions where maternal and/or fetal plasma leptin concentrations are significantly lower compared with normal pregnancies. Growth restriction occurs in ~10% of all human pregnancies (12) and is characterized by a birth weight of <2.5 kg (157). Epidemiological studies have identified that growth-restricted infants have an increased risk of developing a number of diseases in adulthood, including cardiovascular (12, 16, 50, 87, 159) and metabolic diseases (33, 131). In Western cultures, the main cause of growth-restricted babies is utero-placental insufficiency, whereby the placenta is not able to transport nutrients and wastes effectively to and from the growing fetus (37). In third-world countries, the main cause of growth-restricted babies is maternal malnutrition (37). Of note is that both causes of growth-restricted pregnancies alter placental function (37). Specifically, intrauterine growth restriction is frequently associated with inflammation and infarcts within the villi, resulting in lesion formation or in severe cases a reduction of the villous surface area, implying abnormal villous development (37). Conversely, maternal malnutrition results in an increased villous surface area, with no changes in placental volume, potentially suggesting an attempt to compensate for the maternal malnutrition by increasing villi branching (37). Based on these findings, the potential effects on programming in these different groups are likely to vary significantly. Research investigating maternal plasma leptin concentrations in human pregnancies complicated with growth restriction is contradictory, with some studies reporting that maternal plasma leptin concentrations are significantly lower (30, 92), whereas others are significantly elevated (97, 113, 124), and some studies report no changes (4). These results must be interpreted in the context of the previous discussion

about the contribution of maternal leptin to offspring leptin in utero. Despite these varied results in the maternal plasma leptin concentrations, there is a significant reduction in the fetal leptin concentrations in growth restriction that is associated with both maternal malnutrition and placental insufficiency (4, 90, 119, 124). Thus, there is either reduced leptin transportation or reduced placental leptin production, which decreases offspring leptin concentrations. To further compound this, in growth-restricted babies the maternal milk quality is also reduced, with a reduction in milk leptin concentrations observed in mothers of growth-restricted babies (45). These findings suggest that both the in utero and postnatal environments play crucial roles in modulating infant plasma leptin concentrations.

The literature reporting the effect growth restriction has on rat offspring plasma leptin concentrations is quite limited. Furthermore, much of the current knowledge is focused on models where there is maternal malnutrition, which would reduce maternal adiposity and thus leptin. For example, in a maternal model of malnutrition, research by Bautista et al. (17) in pregnant Wistar-Kyoto rats fed a low-protein (10% casein) diet identified no changes in postnatal leptin on PN2, but maternal malnutrition delayed the offspring leptin surge (PN21 compared with PN14). In animal models that more closely follow Western society, namely placental insufficiency, no studies to date have investigated maternal or offspring plasma leptin concentrations. Because leptin plays a role in the development of a number of fetal organ systems, any condition that reduces fetal leptin concentrations is likely to reduce fetal growth and development, predisposing these offspring to a number of diseases in adulthood.

Central nervous system development in growth restriction. Several epidemiological studies have established that fetal growth restriction increases fat mass and percent body fat and reduces lean body mass (80, 83), collectively increasing the risk of developing obesity in adulthood. However, these findings are contradictory, as other studies have found a reduction in adiposity (69) and BMI (65) across the ages in growth-restricted humans. These discrepancies may be due to the cause of growth restriction (placental insufficiency or maternal malnutrition), and as such, future studies are required to identify whether there is an association between growth restriction due to placental insufficiency, adiposity, and obesity in adulthood. As the brain regulates hunger and satiety, it is possible that the low leptin concentrations that these individuals are exposed to during fetal development and early childhood can alter brain development. As mentioned previously, leptin and ObRb are expressed in the brain during various embryonic stages, suggesting that leptin plays an important role in brain development and potentially in food seeking/reward behavior (Fig. 1) (25, 39, 107, 155, 156), although these findings have not been investigated specifically. To add to this knowledge, studies in growth-restricted Sprague-Dawley rats, induced by placental insufficiency, have demonstrated the specific leptin pathways that contribute to normal development of neuronal function (126, 127). Specifically, these studies report reduced brain STAT3 (126) and POMC mRNA and protein expression (126) and increased NPY (127) and corticotropin-releasing factor mRNA and protein expression (127) at various fetal and postnatal days (E20, birth, PN4, and PN21); however, no differences in ObR mRNA expression are reported (126). Furthermore, immunohistochemical analysis of the growth-

restricted Sprague-Dawley rat brains identified an increase in NPY immunoreactivity in the hypothalamus across all ages analyzed (E20 to PN21) (127). These findings suggest that growth restriction results in changes in leptin signaling mediators that may reduce energy homeostasis, causing hyperphagia and ultimately leading to obesity in adulthood (Fig. 1). However, in both Sprague-Dawley studies there was a significant reduction in offspring weight (20–30%) that is likely to result in a more severe phenotype, compared with models that have a modest growth restriction (10%) (166), which is comparable with the growth restriction observed in human uteroplacental insufficiency and resultant growth restriction. However, the validity of these studies should be repeated in other animal models to determine whether the phenotype is due to growth restriction and not to the genetic variation in the Sprague-Dawley rats. Furthermore, little is known about the changes in brain development in humans born with growth restriction.

Cardiovascular development in growth restriction. Research in humans has demonstrated that growth-restricted infants have increased rates of cardiovascular disease (hypertension and coronary artery disease) (10, 12) due to altered cardiac function and vascular dysfunction (133). Specifically, growth-restricted infants have elevated systolic and diastolic blood pressure, reduced left ventricular output, diastolic dysfunction, increased abdominal aorta stiffness, and reduced arterial distensibility 3 days postbirth (90, 133). Importantly, these alterations in cardiovascular development and function may give rise to cardiovascular disease in adulthood. Research has shown that male fetuses grow faster than females and are more dependent on their mothers' diet for increasing energy supplies to maintain their growth, indicating that they are more susceptible to alterations in maternal nutrient delivery (50). Not surprisingly, placental influence on hypertension development between sexes varies. Specifically, males have an increased risk of developing hypertension that may be associated with a smaller placenta diameter (50, 159), whereas females have an increased risk of developing hypertension due to a smaller placental weight (50). However, both of these studies are in models of maternal malnutrition that occurred during periods of famine. Because of the reduced applicability of these studies to Western society, future studies should investigate these associations in children that are growth restricted due to placental insufficiency.

In rats, growth restriction (~10% body weight reduction) is associated with left ventricular hypertrophy (167), hypertension (23, 109, 116, 167), and vascular dysfunction (109, 123) in adulthood. In male growth-restricted Wistar-Kyoto rats, this is likely to be the result of a reduced absolute heart weight (PN1 and PN7) and reduced cardiomyocyte number (PN7) compared with control rats (23). Because leptin can induce cardiomyocyte proliferation (148), the reduced fetal leptin concentrations that are associated with growth restriction may be in part responsible for the reduced cardiomyocyte number; however, such studies have not yet been performed. Interestingly, in growth-restricted male Wistar-Kyoto rats induced by uteroplacental insufficiency (~10% reduction in body weight), there is an increased expression of cardiac growth factors (*Igf1* and *Igf2*) on E20 and increased expression of the proliferation marker *Cymc* and the antiapoptotic factor *Bcl2* on E20 and PN7, suggesting that these genes may be attempting to com-

pensate for the reduced cardiomyocyte number observed (23). Additionally, there are sex-specific alterations in JAK/STAT signaling mediators (E20, PN1, PN7, and PN35) (160), which may suggest that altered ObR signaling is in part responsible for the development of cardiovascular disease in these rats. However, such experiments have not been performed in growth-restricted humans, and a number of other molecular pathways may lead to the differences in the JAK/STAT signaling mediators that were reported. These male growth-restricted Wistar-Kyoto rats also have a significant increase in blood pressure at 6 mo (23, 167), which is not detected in the female growth-restricted rats (even at 18 mo) (109, 116). The male growth-restricted Wistar-Kyoto rats also have increased left ventricular weight and increased ventricle expression of angiotensin receptor 1A, TIMP metallopeptidase inhibitor 1, and collagen 3 mRNA at 6 mo (167). Together, these findings suggest that growth restriction in males results in cardiac hypertrophy and dysregulated ventricular collagen deposition, which may indicate cardiac fibrosis (167). The apparent sexual dimorphism in the hypertensive phenotype in the growth-restricted Wistar-Kyoto rats is in part due to vascular dysfunction, with the males having increased vascular stiffness and reactivity compared with females (109, 123, 149). Specifically, male growth-restricted rats have increased wall thickness and impaired relaxation of the mesenteric arteries (149), reduced relaxation in the femoral artery (149), and impaired relaxation of the aorta (123), whereas female growth-restricted rats have impaired uterine artery relaxation and increased wall thickness (109). This suggests that females are protected from the hypertensive phenotype observed in the males due to normal arterial structure and function, which may be due to the vasoprotective role of estrogen (61). The uterine artery dysfunction in the growth-restricted females may give rise to impaired pregnancy adaptations leading to growth restriction in the next generation. However, this is not the case, since when these female rats are pregnant their offspring are not growth restricted, suggesting that in pregnancy there is a correction in the uterine artery function via an unknown mechanism (56). These studies collectively identify that there is sexual dimorphism in the cardiovascular phenotype in growth-restricted placental insufficiency Wistar-Kyoto rats. However, the sexual differences in the cardiovascular phenotype are not observed across all species used to investigate growth restriction, with growth-restricted male and female Sprague-Dawley rats, induced by placental insufficiency, having a significantly higher systolic and diastolic blood pressure (female only) on PN140 (15), suggesting that there may be species variation in the phenotype. Collectively, these studies demonstrate sex-specific and species-specific differences in the effects of growth restriction in the cardiac phenotype. Future studies should ensure that these differences are taken into consideration when the relevance of any findings is determined.

Renal development in growth restriction. In humans, research has shown that birth weight is inversely linked to glomerular number and positively correlated with glomerular volume (79), suggesting that impaired nephron development may play a role in adult onset hypertension in growth-restricted children. Despite growth restriction altering glomerular number and volume, it does not alter kidney length (16, 44, 87) or GFR (16, 87). Additionally, epidemiological studies in both babies and adults (20 yr) have identified that growth-restricted

children have a reduced kidney volume (87, 94) and increased systolic (16, 87) and diastolic pressure during infancy and early adulthood (16). These findings indicate that these growth-restricted children do not develop kidney disease in early adulthood but may have altered renal function that gives rise to hypertension. However, this study was compounded by a low sample number, which may reduce the significance of these findings. Thus, future studies are required to identify the association between glomerular number, glomerular size, and hypertension in individuals born growth restricted.

In placental insufficiency-induced growth-restricted Wistar-Kyoto rats (~10% reduction in body weight) there is a significant reduction in glomerular number in male (166, 167) and female (116) offspring. In addition, the growth-restricted Wistar-Kyoto male rats have a significant increase in individual glomerular volume at 6 mo (166, 167), which is not apparent in the females until 18 mo (116), suggesting a potential protective mechanism in the growth-restricted females to maintain normal kidney function and blood pressure. Because leptin appears to play a role in nephrogenesis (6, 7), the nephron deficit in growth-restricted rats may be due to low fetal and postnatal leptin concentrations, although no one has investigated this association yet. However, in aging female growth-restricted Wistar-Kyoto rats, there is increased renal creatinine clearance in addition to increased mRNA expression of fibrotic markers (transforming growth factor-β1, collagen IV, and matrix metalloproteinase-9) (116). Because elevated leptin has been shown previously to cause fibrotic changes to the kidney (168), it is possible that the decline in kidney function in the aging female growth-restricted rats may be due to increased leptin concentrations. However, at this time, there is a clear gap in knowledge concerning alterations in the plasma leptin concentrations in these aged rats.

Pancreas development in growth restriction. Epidemiological studies carried out by Barker et al. (11) identified that growth-restricted children are more prone to developing metabolic disease in adulthood, indicating the potential for reduced pancreatic development or function in growth-restricted children. Histological staining of pancreas sections from human fetuses has identified a reduction in β-cell number and insulin content, indicating that the cause of glucose intolerance in adults born small is likely to be insulin deficiency (19), which may give rise to metabolic disease in adulthood. Additionally, research in children has shown that growth-restricted children have reduced plasma glucose concentrations; however, these children are not insulin resistant (33). There are also sex-specific differences between male and female growth-restricted children that increase the risk of males developing a number of diseases, including cardiovascular and metabolic disease (131). Specifically, growth-restricted elderly males have an elevated resting metabolic rate in proportion to their birth weight, which may indicate alterations in sympathetic nervous system activation (131).

To examine the mechanism behind the reduction in β-cell number that growth restriction causes, epigenetic research has identified that 7-wk-old male growth-restricted Sprague-Dawley rats, induced by placental insufficiency surgery, have changes to cytosine methylation that proceed diabetes in addition to epigenetic dysregulation and mRNA alterations near genes encoding vascularization, β-cell proliferation, insulin secretion, and cell death (153). However, interestingly, the

weight reduction observed in the growth-restricted rats was not investigated. Several studies in Sprague-Dawley rat models of growth restriction (~10% reduction in body weight) induced by either placental insufficiency or by reduced uteroplacental perfusion pressure have shown that growth restriction is associated with hyperglycemia (71, 140, 146) and hyperinsulinemia (71, 140) in addition to glucose intolerance (71, 140, 146) and insulin resistance (140) as early as 2 wk after birth. Placental insufficiency-induced growth-restricted Sprague-Dawley rats have reduced β-cell number (after 3 mo) and reduced β-cell proliferation (at 2 wk), with hyperglycemia and hyperinsulinemia occurring prior to the reduction in β-cell number (146), suggesting that these rats have impaired pancreatic function. Research from our laboratory has shown that growth-restricted Wistar-Kyoto rats (~10% reduction in body weight) induced by placental-insufficient surgery, but only the aged male rats (6 mo), have impaired glucose tolerance and insulin secretion (139). Again, the differences in the metabolic phenotypes between the Sprague-Dawley and Wistar-Kyoto rats may be due to the Sprague-Dawley rats being predisposed to developing obesity and metabolic disease (14), which may indicate that the phenotype is due to the genetic variation in the Sprague-Dawley rats and not the growth restriction. Because leptin and ObR are important in β-cell proliferation and insulin suppression, it is possible that the reduced β-cell number and insulin resistance in growth-restricted offspring are due to impaired leptin signaling, which results in metabolic disease in adulthood. However, there is a clear lack of knowledge in establishing a causal effect of leptin in these rats.

Mammary development in growth restriction. Despite the apparent developmental impairment that growth restriction has, there are also maternal adaptations that occur that may further impact offspring development (120). Specifically, as described previously, placental insufficiency impairs mammary development in pregnancy, reducing milk production and quality. This in turn may reduce offspring development by decreasing the availability of essential nutrients (120). Of note is that leptin is produced by the mammary and transported to the infant by milk, with research identifying in human mothers of growth-restricted babies that there is a reduction in milk leptin concentrations (45). Although milk leptin concentrations have not yet been quantified in maternal rats with uteroplacental insufficiency, it is likely that it is reduced just as it is in the human. This may lead to the reduced organogenesis observed in growth-restricted rats, increasing the risk of developing diseases in adulthood. In support of this, cross-fostering studies have been used to investigate whether normal lactation and maternal milk can restore postnatal growth and reverse the organ deficits observed in the growth-restricted offspring (23, 149, 166). Cross-fostering studies giving rise to four groups (control on control, control on restricted, restricted on control, and restricted on restricted) identified that growth-restricted male Wistar-Kyoto rats suckled onto control mothers restored fetal growth and reversed the hypertension and cardiomyocyte deficit and alleviated the vascular stiffness and reactivity, metabolic disease, and glomerular deficit observed (23, 139, 149, 166). These studies indicate that there may be a link between maternal contributions, such as reduced milk quality and plasma leptin, in the development of the growth-restricted phenotype.

Summary: growth restriction. Uteroplacental insufficiency is the leading cause of growth restriction in the Western world, with studies identifying that human growth-restricted fetuses have lower plasma leptin concentrations, which is likely to reduce fetal development. Growth-restricted children are more prone to developing obesity in adulthood (20, 68, 122). Research in growth-restricted rats suggests that this may be due to altered hypothalamic ObR signaling (126, 127), potentially predisposing growth-restricted children to hyperphagia and leptin resistance and ultimately contributing to the increased risk of developing obesity in adulthood (Fig. 1). In rats, growth restriction leads to offspring with cardiovascular disease (23, 109, 123, 149, 167) and altered renal function (116, 166, 167), with male growth-restricted rats being more adversely affected than females. Interestingly, cross-fostering growth-restricted pups onto control mothers with normal lactation and growth reverses the cardiovascular dysfunction (23, 149, 166), glomerular deficit (116, 166), and metabolic changes (139), which may suggest a role for maternal contributions in the growth-restricted phenotype due to reduced maternal milk leptin concentrations. Growth restriction also results in hyperinsulinemia (132) and reduced β-cell number (19, 146, 147), with research in *ob/ob* mice showing that leptin plays a role in β-cell proliferation and that leptin suppresses insulin secretion (88), suggesting that low fetal leptin concentrations may contribute to the pancreatic deficit in growth-restricted children that increases the risk of developing metabolic disease in adulthood. These studies collectively suggest that low fetal leptin concentrations increase the risk of developing metabolic syndrome in adulthood by reducing the growth and maturation of the brain, heart, kidneys, and pancreas. Figure 2 summarizes the major findings (from the human research) associated with uteroplacental insufficiency and predicts (based on animal studies) the unknown mechanisms that may occur.

Maternal Obesity

Obesity is associated with significantly elevated plasma leptin concentrations due to an increase in white adipose tissue compared with healthy individuals (57). As obesity rates in the Western world are increasing rapidly, so too are the number of obese women who are pregnant (54). Importantly, obese pregnant women have significantly elevated plasma leptin concentrations compared with nonobese pregnant women throughout pregnancy (114). Interestingly, the source of the elevated leptin throughout pregnancy in obese mothers is due to increased adipose tissue deposits, with a study by Farley et al. (52) showing no difference in placental leptin production as well as no changes in fetal plasma leptin concentrations. However, Karakosta et al. (86) demonstrated that cord leptin concentrations are elevated in obese mothers, with more recent epidemiological studies supporting this (53, 164). Despite no differences in placental leptin production, there is a downregulation of ObRb expression (in both the syncytiotrophoblast and villous stroma) in the placenta of obese mothers, which would cause placental leptin resistance (in addition to the central leptin resistance that occurs during normal pregnancy) (52, 151) that may be attempting to modulate fetal growth under high-energy conditions (52, 151). As mentioned previously, human pregnancy is associated with elevated plasma leptin concentrations that are maintained by the soluble ObRe leptin

receptor, delaying leptin clearance and attributing to the central leptin resistance observed in pregnancy. Research by Ge et al. (58), using vectors to overexpress leptin receptors ObRa and ObRb both in vitro and in vivo, identified that ObRe can be produced by ectodomain shedding of both ObRb and ObRa in addition to alternative splicing of the ObR gene. Thus, in obese humans there is reduced placental ObRb (52), which may in turn reduce circulating ObRe expression and increase the clearance rate of leptin, further compounding central leptin resistance (151). Despite the complications associated with pregnancies in obese women, the offspring may be either growth restricted, normal weight, or macrosomic. However, after birth, babies born to obese mothers are exposed to elevated leptin concentrations in the maternal milk (45), which suggests that the postnatal environment may increase infant growth and development, increasing the risk of developing a number of diseases in adulthood.

In animal models of maternal obesity, research has demonstrated alterations in the postnatal leptin surge, with conflicting results. Research in sheep has reported that maternal obesity abolishes the postnatal leptin surge (101), whereas research in Sprague-Dawley rats has identified an amplified and prolonged postnatal leptin surge (89). These differences may arise due to species variations in the fetal programming caused by maternal obesity. These variations in offspring leptin concentrations demonstrate that a clear relationship between maternal obesity and plasma leptin concentrations does not exist. Despite this, any increase in plasma leptin concentrations in offspring from obese mothers is likely to be the consequence of elevated maternal production or increased placental transportation of leptin. However, there are variations in the development effects that elevated maternal plasma leptin concentrations have on the offspring due to the lack of a relationship between maternal and fetal leptin concentrations in obesity.

Central nervous system development in maternal obesity. Most studies investigating the effect maternal obesity has on fetal development have focused on linking maternal obesity to increased rates of childhood and/or adulthood obesity and metabolic disease and the programming effects maternal obesity has on the development of the brain. In a study where pregnant ewes were fed a high-calorie diet (160%; E115–E124, term = 152 days), the offspring were hyperglycemic during their early postnatal period and had higher subcutaneous fat deposits on PN30 despite no changes in body weight or plasma leptin concentrations (117). These offspring also have an increased expression of hypothalamic POMC and reduced ObRb, NPY, and AgRP expression (117), suggesting that maternal obesity reduces fetal appetite and may alter leptin signaling. Furthermore, this study identified an inverse relationship between hypothalamic ObRb expression and subcutaneous adipose mass, which indicates that these animals likely have central leptin resistance (117). These findings are not consistent with other research that demonstrated that, in offspring of mice fed a high-fat diet, these animals are not leptin sensitive at 12 wk (163). These studies further highlight the variability observed in animals fed a high-fat diet. Presumably, the differences may be based on the underlying genetic makeup of the model and the timing of the consumption of the diet as well as the percentage of fat (and thus plasma leptin concentrations) and obesity in the mothers. Despite this, there is a clear relationship between maternal obesity and offspring
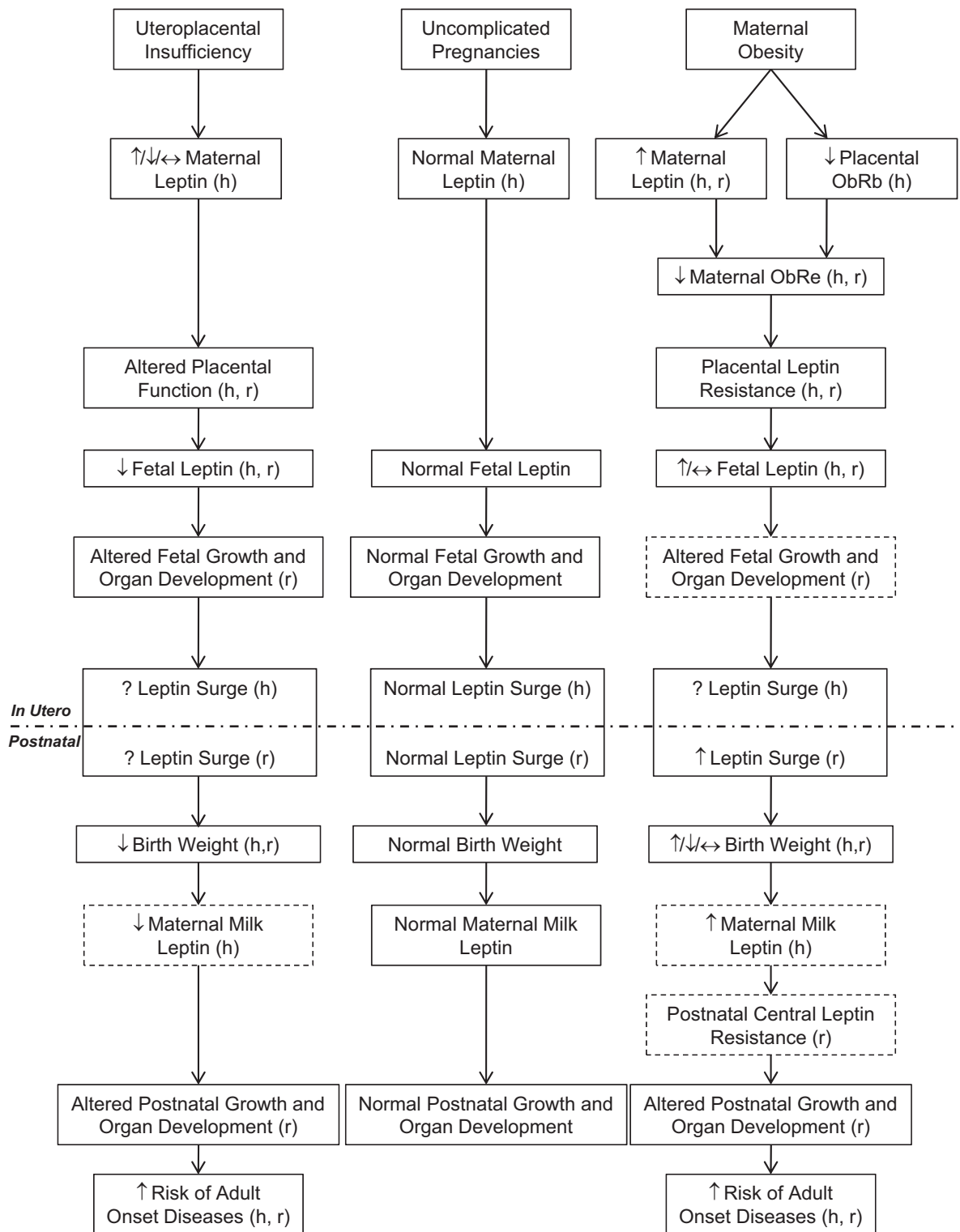
Fig. 2. Hypothesized roles of leptin in pregnancy and pathophysiological complications; the proposed roles leptin plays in pregnancy and offspring development. Pregnancies complicated by either uteroplacental insufficiency or maternal obesity have altered maternal leptin production and secretion in both humans (h) and rodents (r). Altered maternal leptin affects offspring growth and development, increasing the likelihood of these children developing diseases in adulthood. The in utero section describes changes in fetal development, and the postnatal section summarizes changes in offspring development. Findings in solid-lined boxes are associations based on information in Tables 1 and 2 (also see LEPTIN IN PREGNANCY, LEPTIN IN FETAL DEVELOPMENT, and ALTERATIONS IN LEPTIN AS INDICATIONS OF DISEASE RISK), whereas dashed-lined boxes represent hypothesized links between ideas that highlight gaps in the literature. Arrows in boxes reflect the directionality of change, and question marks highlight gaps in the literature.

health. Interestingly, reduced neuron activation in the arcuate and paraventricular nuclei after an intracerebroventricular injection of leptin into New Zealand white rabbits born to obese mothers fed a high-fat diet (13.3%) is observed despite no changes in body weight (125). Research by Kirk et al. (89) in Sprague-Dawley offspring born to obese mothers reports that leptin administration does not alter food intake on either PN30 or PN90; however, the offspring were significantly heavier than control animals from PN21, suggesting that these animals are likely to develop obesity (14) that may be species specific. Furthermore, this is associated with reduced neuron numbers in the arcuate nucleus, which is indicative of central leptin resistance. These studies suggest that maternal obesity reduces offspring leptin signaling, causing hyperphagia and obesity in adulthood, which is possibly due to leptin resistance.

Maternal obesity in other systems. Evidence supporting a role for elevated leptin in the pathology of children born to obese mothers in other systems is less clear and more speculative. Maternal obesity has been shown to increase the risk of children developing cardiovascular disease in adulthood (43), with research identifying that maternal obesity is associated with increased risks of congenital heart defects in children (103, 112). This may be due to increased basal sympathetic nerve activity, with research in Sprague-Dawley rats identifying that an injection of elevated leptin (3 μg) increases basal sympathetic nerve activity by altering baroreceptor control (98). In support of this, Sprague-Dawley offspring (PN90) born to obese mothers have persistent hypertension and reduced baroreceptor function in response to phenylephrine or sodium nitroprusside, suggesting that hypertension may be caused by the programming of persistent sympathoexcitatory hyperresponsiveness in early development (130). Additionally, recent research has reported an increase in basal renal sympathetic nerve activity as well as increased renal nerve activity responses due to stress in 4-mo-old New Zealand white rabbits born to mothers fed a high-fat diet (13.3% fat) during pregnancy (125). Sprague-Dawley rats born to obese mothers also have a significant increase in renal renin mRNA on PN30 and PN90 (130); however, at 6 mo there is a significant reduction in renal renin mRNA and Na^+/K^+ ATPase activity (3), with any changes in renin expression likely to decrease the glomerular filtration rate, further compounding hypertension and causing kidney disease. Thus these findings suggest that the increase in renal sympathetic nerve activity may be attempting to increase Na^+ retention (62), which would be lost in the urine due to the reduced Na^+/K^+ ATPase activity. Future studies are required to identify an association between the elevated maternal leptin concentrations in obese mothers and altered organ development (heart, kidneys, and pancreas) in their children.

Summary: maternal obesity. Obesity rates in Western cultures are increasing rapidly, and so, too, are the number of pregnant women who are obese. Maternal obesity is associated with increased maternal leptin concentrations throughout pregnancy. Despite the contradictory finding on cord leptin concentrations in babies of obese mothers (either unaltered or elevated), after birth these babies are exposed to elevated leptin concentrations through the maternal milk (45), which has potential implications in increasing growth and development in infancy. Collectively, the studies described above identify that children born to obese mothers have increased rates of a number of comorbidities that are associated with metabolic

disease (obesity, cardiovascular and renal diseases, and diabetes). Specifically, offspring born to obese mothers have alterations in a number of ObR signaling mediators in the brain (117) and central leptin resistance (89), which is likely to cause hyperphagia and obesity in childhood or adulthood (Fig. 1). Additionally, offspring born to obese mothers are hypertensive (125, 129, 130) and have vascular dysfunction (3, 51, 129) as well as increased renal sympathetic nervous system activation (125) and altered renin expression with time-specific differences (3, 130), all of which would ultimately contribute to cardiovascular disease. These studies collectively suggest that high maternal leptin concentrations increase the risk of their offspring developing metabolic syndrome in adulthood by increasing the growth and maturation of the brain, heart, and kidneys. Importantly, because organogenesis in humans is completed before birth, these findings demonstrated that elevated postnatal leptin can alter physiology in the offspring. Figure 2 summarizes the major findings (from the human research) associated with maternal obesity and predicts (based on animal studies) unknown mechanisms that may occur.

CONCLUSION

Leptin's main physiological role is to regulate hunger and satiety by crossing the blood-brain barrier and acting on NPY and POMC neurons, ultimately decreasing hunger and satiety and increasing energy expenditure. In addition, recent research in animal models has clearly established a role for leptin in the development of a number of organs, including the brain (155, 156), heart (6, 118), pancreas (6), and kidney (6). Further models of leptin signaling dysfunction, namely *ob/ob* mice, have reduced organ development and function (25, 39, 155), which is associated with an increased risk of a number of diseases in adulthood, including metabolic disease (88). Despite the reduced translation potential to humans, which is the result of organogenesis continuing after birth in animals and not humans, this suggests that alterations in leptin during development are likely to affect organ maturation in the human.

Uteroplacental insufficiency occurs in ~10% of all human pregnancies in the Western world (12) and is associated with an increased risk for the offspring to develop metabolic and cardiovascular disease. One potential link between adulthood diseases in growth-restricted children is leptin, whereby growth-restricted children have reduced plasma leptin concentrations (4, 90, 119, 124), which is further compounded by low leptin concentrations in the maternal milk (45). Both of these factors in utero and postnatally could impair the development and function of a number of organs in these children, ultimately giving rise to diseases in adulthood (Fig. 2). Interestingly, based on animal observations, it appears that growth restriction more severely affects males compared with females, indicating that the females are protected by a currently unidentified mechanism. These findings are typical of human outcomes where growth-restricted males have an increased risk of developing disease (131, 159). In contrast, in Western cultures the number of children born to obese mothers is increasing, with maternal obesity being linked to increased risks of their children having metabolic disease (54) and cardiovascular disease. There are currently discrepancies in the literature about the effect maternal obesity has on fetal plasma leptin concentra-

tions (52, 53, 86, 164). However, there is an increase in leptin concentrations in the maternal milk (45) that may impact postnatal growth and development (Fig. 2). Interestingly, children born to obese mothers and those suffering uteroplacental insufficiency display fetal leptin resistance and altered fetal growth, organ development, and function (Fig. 2), which in animals results in an increased risk of developing metabolic and cardiovascular diseases in adulthood. Overall, there appears to be an emerging link between leptin dysregulation in pregnancy and altered organ development and function that can give rise to diseases in adulthood.

GRANTS

DISCLOSURES

The authors declare no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

J.F.B., A.J.M., T.R., M.E.W., and D.H.H. conception and design of research; J.F.B. and D.H.H. prepared figures; J.F.B., A.J.M., T.R., M.E.W., and D.H.H. drafted manuscript; J.F.B., A.J.M., T.R., M.E.W., and D.H.H. edited and revised manuscript; J.F.B., A.J.M., T.R., M.E.W., and D.H.H. approved final version of manuscript.

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