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The Impact of Leptin on Perinatal Development and Psychopathology

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Abstract

Leptin has long been associated with metabolism as it is a critical regulator of both food intake and energy expenditure, but recently, leptin dysregulation has been proposed as a mechanism of psychopathology. This review discusses the evidence supporting a role for leptin in mental health disorders and describes potential mechanisms that may underlie this association. Leptin plays a critical role in pregnancy and in fetal growth and development. Leptin's role and profile during development is examined in available human studies and the validity of applying studies conducted in animal models to the human population are discussed. Rodents experience a postnatal leptin surge, which does not occur in humans or larger animal models. This suggests that further research using large mammal models, which have a leptin profile across pregnancy and development similar to humans, are of high importance. Maternal obesity and hyperleptinemia correlate with increased leptin levels in the umbilical cord, placenta, and fetus. Leptin levels are thought to impact fetal brain development; likely by activating proinflammatory cytokines that are known to impact many of the neurotransmitter systems that regulate behavior. Leptin is likely involved in behavioral regulation as leptin receptors are widely distributed in the brain, and leptin influences cortisol release, the mesoaccumbens dopamine pathway, serotonin synthesis, and hippocampal synaptic plasticity. In humans, both high and low levels of leptin are reported to be associated with psychopathology. This inconsistency is likely due to differences in the metabolic state of the study populations. Leptin resistance, which occurs in the obese state, may explain how both high and low levels of leptin are associated with psychopathology, as well as the comorbidity of obesity with numerous mental illnesses. Leptin resistance is likely to influence disorders such as depression and anxiety where both high and low leptin levels have been correlated with symptomatology. Schizophrenia is also associated with both low and high leptin levels. However, as antipsychotics pharmacotherapy induces weight gain, which elevates leptin levels, drug-naïve populations are needed for further studies. Elevated circulating leptin is consistently found in childhood neurodevelopmental disorders including Autism Spectrum Disorders and Rhett

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disorder. Further studies on the impact of leptin and leptin resistance on psychopathology and neurodevelopmental disorders are important directions for future research. Studies examining the mechanisms by which exposure to maternal obesity and hyperleptinemia during fetal development impact brain development and behavior are critical for the health of future generations.

Keywords

Leptin; pregnancy; psychopathology; inflammation; obesity; neurodevelopment

1. Introduction

Leptin, a protein product of the Ob gene, is a hormone secreted primarily by adipocytes. Leptin circulates in the blood in proportion to the amount of adipose tissue present in the body (Ostlund et al., 1996) and thus acts as important signal of the body's long-term energy state. Leptin acts as a signal to regulate food intake and therefore also reflects short-term changes in energy intake (Considine *et al.*, 1996; Saladin *et al.*, 1995; van Aggel-Leijssen *et al.*, 1999). Leptin is also produced, though at a much lower level, in the skeletal muscle, stomach, and placenta (Ahima and Osei, 2004; Senaris *et al.*, 1997; Sobhani *et al.*, 2000; Wolsk *et al.*, 2012). In addition, evidence exists that the brain produces leptin where it is postulated to act as a paracrine and/or autocrine regulator, however the role of brain-derived leptin is still unclear (Ahima and Osei, 2004; Morash *et al.*, 1999; Wiesner *et al.*, 1999). There are six known isoforms of the leptin receptor (LEPR), one long form (LEPRb) which has fully active signaling capabilities, four short forms (LEPRa, LEPRc, LEPRd, LEPRf) which have limited signaling capabilities, and one form (LEPRe) that circulates as a soluble receptor (Ahima and Osei, 2004; Lee *et al.*, 1996). Since its discovery in 1994 (Zhang et al., 1994), leptin has been associated with metabolism as a critical regulator of both food intake and energy expenditure (Ahima and Osei, 2004; Bates *et al.*, 2003; Halaas *et al.*, 1995; Prieur *et al.*, 2008; Zhang *et al.*, 1994). Leptin also plays an important role in maintaining normal reproductive function (Bluher and Mantzoros, 2007) and in fetal growth and development during pregnancy (Mellati et al., 2010). It is well known to moderate the inflammatory response by increasing production of inflammatory cytokines (Agrawal *et al.*, 2011; Aleffi *et al.*, 2005; Fantuzzi and Faggioni, 2000; Lappas *et al.*, 2005; Loffreda *et al.*, 1998; Lord *et al.*, 1998). Leptin is in the same protein family as interleukin (Il)-6, an inflammatory cytokine, and its long-form receptor mediates intercellular signals similarly to the Il-6 receptor (Baumann *et al.*, 1996; Fantuzzi and Faggioni, 2000; Zhang *et al.*, 1997). Recently, leptin dysregulation has been associated with psychopathology, and evidence suggests that this relationship is related to leptin's inflammatory function. This review will present evidence for the association between dysregulation in leptin signaling and various forms of psychopathology including depression, anxiety, schizophrenia, and autism, and discuss the potential mechanisms for these relationships.

Evidence for leptin's role in psychopathology largely comes from the high comorbidity of obesity with numerous mental illnesses including major depression, bipolar disorder, and panic disorder (Simon et al., 2006). Obesity is associated not only with high circulating leptin concentrations, but also with a reduced diurnal rhythm, decreased pulsatility, and

leptin resistance (Ahima and Osei, 2004; Levin and Dunn-Meynell, 2002; Mingrone *et al.*, 2005; Saad *et al.*, 1998). In leptin resistance, high leptin levels have diminished actions on the cell similar to that of low leptin levels. There are several proposed mechanisms for leptin resistance including polymorphisms causing leptin receptor dysfunction (Quinton et al., 2001), impaired downstream signaling (El-Haschimi et al., 2000; Munzberg and Myers, 2005), and inadequate transport of leptin across the blood-brain-barrier (BBB) (Banks et al., 1999; El-Haschimi et al., 2000) resulting in a decrease in the cerebrospinal-fluid/serum leptin ratio (Caro et al., 1996). Many possible factors may impair transport of leptin across the BBB in obese individuals. One of the most promising findings is that triglycerides, which are elevated in obesity, inhibit this transport (Banks *et al.*, 2004). Hypertriglyceridemia occurs in starvation states as well, giving evolutionary merit to triglyceride induced leptin resistance (Banks *et al.*, 2006). The amplitude of pulsatile leptin secretion increases in the obese state, which may cause down-regulation of cerebral microvascular leptin receptors, thereby decreasing transport of leptin across the BBB (Kalra, 2008). Obesity also creates endoplasmic reticulum stress in the hypothalamus, which reduces leptin signaling (Ozcan *et al.*, 2009). Lower levels of the circulating soluble leptin receptor are found in obese humans, which also may lead to decreased leptin action (Ogier *et al.*, 2002). Both high and low levels of leptin have been implicated in psychiatric disorders, such as depression (Lu, 2007), suggesting that leptin resistance accompanying high leptin levels is a possible factor in the development of psychopathology.

Another important issue to be addressed is the gender dimorphism in circulating leptin levels with women having a threefold higher level of serum leptin than men (Ostlund et al., 1996). The increased level of circulating leptin in women remains higher than men even when body fat percentage is controlled for (Ostlund et al., 1996). This gender difference in leptin is thought to be due to sex steroids. Testosterone has been shown to have an inhibitory effect on leptin (Ahima and Osei, 2004; Alexander *et al.*, 2010; Fallah *et al.*, 2012; Gambino *et al.*, 2010; Jockenhovel *et al.*, 1997; Machinal *et al.*, 1999; Soderberg *et al.*, 2001). Combined oral contraceptive pills containing levonorgestrel and ethinyl-estradiol increase circulating leptin levels (Fallah et al., 2012). Ovariectomization of female rats causes a decrease in ob gene mRNA expression in fat cells, and exposure to 17beta-estradiol reverses this (Machinal *et al.*, 1999; Yoneda *et al.*, 1998). In human women, 17beta-estradiol increases ob gene mRNA expression and leptin secretion in fat cells (Machinal-Quelin *et al.*, 2002). Moreover, in women, leptin levels vary across the menstrual cycle, peaking during the luteal phase when estrogen and progesterone levels are elevated (Hardie et al., 1997). Interestingly, women that are average weight or overweight have a higher prevalence of lifetime depression and anxiety than men, whereas underweight women do not (Zhao et al., 2009) which suggests that differences in circulating leptin may contribute to gender differences in the occurrence of mental health disorders. Given the high prevalence of obese (35%) and overweight (64%) women in the United States (Flegal et al., 2012) research into the role of leptin and other obesity-related mechanisms in psychopathology are very important. Moreover, as pre-pregnancy obesity rates are continuing to rise (Fisher et al., 2013), and exposure to elevated leptin levels along with maternal obesity during development have a long-lasting impact on prenatal development and long-term risk of psychopathology, studies

elucidating the mechanisms by which this maternal state impacts brain development and behavior are critical for the health of future generations.

2. LEPTIN'S ROLE IN PREGNANCY

2.1 Leptin's Role in Human Pregnancy

2.1.1 Leptin Production During Pregnancy—Leptin plays a critical role in gestation, as evidenced by elevated circulating leptin levels and leptin synthesis by the placenta. During pregnancy, maternal serum leptin concentrations increase in the first and second trimesters independent of changes in body mass index (BMI), plateau during the third trimester, and decrease significantly within days of giving birth (Sivan et al., 1998). Most studies show a two- to three-fold increase in leptin levels over the course of pregnancy (Sattar et al., 1998; Schubring et al., 1997; Sivan et al., 1998). By six weeks postpartum, leptin levels are comparable to early pregnancy and pre-pregnancy levels (Schubring et al., 1998). The rate of increase in circulating leptin levels during pregnancy does not correlate with the increase in maternal body fat, thus the increase in leptin cannot be explained solely by the increase in adipose tissue during pregnancy. The placenta synthesizes leptin, as indicated by the presence of high amounts of leptin mRNA (Lepercq et al., 1998; Senaris et al., 1997). Estrogen is elevated during pregnancy, and 17beta-estradiol has an excitatory effect on leptin expression in the placenta (Gambino et al., 2010). This leptin produced by the placenta likely causes the increase in circulating maternal leptin levels. In fact, over 98% of leptin produced by the placenta is released into maternal circulation and less than 2% is released into fetal circulation (Linnemann et al., 2000). Along with leptin, leptin receptors are expressed in the trophoblast in human placentas (Challier *et al.*, 2003; Henson *et al.*, 1998), suggesting leptin may have autocrine and paracrine mechanisms within the placenta. The increased levels of leptin in the maternal circulation suggest that leptin plays a role in pregnancy, but the small amount of placental leptin that crosses to the fetus does not completely explain leptin's role in fetal development.

Other possible sources of leptin for the fetus include amnion cells that secrete leptin into the circulating amniotic fluid (Masuzaki et al., 1997), and fetal membranes and the umbilical cord that co-express leptin and leptin receptor genes during human pregnancy (Akerman et al., 2002). This demonstrates that leptin is not only synthesized by maternal tissue during pregnancy but also by fetal tissue, signifying a role in fetal development. It is interesting to note that umbilical cord leptin levels are significantly higher in pregnancies with girls than boys (Tome et al., 1997), again suggesting sexual dimorphism in leptin regulation. Leptin is detected in fetal circulation starting in the second trimester and continues to increase throughout pregnancy (Cetin et al., 2000). Newborn infant serum leptin concentrations are much higher than in children and adults when adiposity is controlled for (Hassink et al., 1997) and the levels decrease significantly after birth (Sarandakou et al., 2000). This indicates that the high levels of circulating leptin in the fetus are not solely produced by the fetus, but also come from sources such as the umbilical cord, placenta, and amniotic fluid. Consequently, high maternal leptin levels in obesity may adversely impact fetal growth and development.

2.1.2 Leptin's Impact on Fetal Growth and Development—The increase in maternal leptin levels during pregnancy and the synthesis of leptin by the placenta suggest that leptin plays an important role in fetal development. Women who are obese are more likely to have high leptin levels (Considine et al., 1996), complications during pregnancy such as preterm births (Cnattingius et al., 2013; Wang et al., 2011) and infants born both large and small for gestational age (Djelantik et al., 2012). The literature consistently finds an association between high maternal leptin levels and high fetal leptin levels (Hauguel-de Mouzon et al., 2006). High maternal pre-pregnancy BMI and excessive weight gain during pregnancy are predictive of elevated leptin levels in the umbilical cord (Mellati et al., 2010). Elevated cord leptin levels are associated with physiological changes in offspring, such as increased adiposity and hyperleptinemia (Karakosta et al., 2013), as well as higher birth weight, BMI, and Ponderal Index, which is a mass to height measurement commonly used in pediatrics (Mellati et al., 2010). Fetuses from pregnancies complicated by gestational diabetes also have higher leptin levels than those from normal pregnancies (Lea et al., 2000). Maternal glycated hemoglobin (HbA_{1c}), a measure of the average level of circulating glucose over a three month period, is also correlated with infant leptin levels (Ng et al., 2000). In normally developing and intrauterine growth restricted fetuses, elevated fetal plasma leptin levels are predictive of higher birth weight; but this is not the case in offspring of mothers with gestational diabetes (Cetin et al., 2000). This may mean that there is a leptin concentration ceiling effect, in which at very high levels of fetal leptin there is no longer a linear increase in birth weight.

The literature clearly demonstrates that maternal obesity and hyperleptinemia correlate with increased leptin levels in the umbilical cord, placenta, and fetus. Is important to study how this may cause epigenetic changes that affect the offspring later in life. Maternal glucose levels correlate with methylation of placental DNA that encodes for the leptin gene in pregnancies with impaired glucose tolerance but not in normal pregnancies (Bouchard et al., 2010). This indicates that once maternal plasma glucose concentrations reach a specific threshold they influence epigenetic regulation of leptin gene expression in the placenta. In addition to epigenetic changes occurring in-utero, Chen et al. suggest that elevated circulating leptin levels in both mother and infant may cause leptin withdrawal in the infant after birth (Chen et al., 2011). Their hypothesis is that the fetal brain down-regulates leptin receptors and signaling as an adaption to a fetal environment high in leptin. In rodent models, intrauterine growth restriction has been shown to impair leptin signaling, causing leptin resistance (Coupe *et al.*, 2012), supporting this hypothesis. After birth, leptin levels decline severely, and reduced leptin signaling may result in compromised brain development that occurs in intrauterine growth restriction. Children from diabetic mothers who experience intrauterine growth delay exhibit dysfunctions with language and speech development, social development, and gross motor skill development (Petersen *et al.*, 1988). Whether these delays are related to leptin, insulin, or other factors is difficult to determine, which is why animal models are so critical in determining mechanisms behind fetal brain development and future behavioral abnormalities.

2.2 Leptin's Role in Nonhuman Pregnancy

There is evidence that leptin impacts development in many vertebrate species including zebrafish (Liu *et al.*, 2012), frogs (Crespi and Denver, 2006), rodents (Ahima *et al.*, 1999; Erkonen *et al.*, 2011; Hassink *et al.*, 1997; Udagawa *et al.*, 2006), sheep (Ehrhardt *et al.*, 2001; Thomas *et al.*, 2001), and primates (Castracane *et al.*, 2005; Henson *et al.*, 1999). The majority of studies on leptin during pregnancy use rodent models, particularly rats and mice. Thus, it is important to understand how leptin acts during rodent pregnancy when considering the validity of applying these studies to the human population. Leptin levels rise during pregnancy in rats and mice (Ladyman, 2008) as they do in humans, but the magnitude of the increase in rodents is much higher (30–40 fold versus 2–3 fold increase over non-pregnant levels) (Gavrilova et al., 1997). This hyperleptinemia is not associated with increased leptin production by adipose tissue, but with placental production of leptin which is secreted into maternal circulation (Gavrilova et al., 1997). Besides the differences in the magnitude of the pregnancy-associated increase in maternal leptin, rodent neonates also experience a postnatal leptin surge that does not occur in human infants. In a study by Ahima and colleagues, female mice had a five to ten-fold increase in leptin during the second postnatal week, independent of food intake and body fat (Ahima et al., 1998). A possible reason for the leptin surge is decreased leptin receptor sensitivity; however future research is needed to further investigate this and other possible mechanisms for this hyperleptinemia. In rats, leptin levels are also elevated between days four and fourteen in male neonates, and decrease to adult levels by fourteen days after birth (Delahaye et al., 2008). Both rats from diet-induced obese mothers and rats from control mothers that were administrated leptin during the second postnatal week develop leptin resistance that persists into adulthood (Samuelsson et al., 2013). The postnatal leptin surge that occurs in rodents is at odds with the profile of leptin across human development, as elevated leptin levels are seen in human fetuses at the end of the prenatal period, and leptin levels decline quickly after birth. Rodent models are useful for mechanistic and exploratory studies, but other animal models and human studies are needed to fully understand the role of leptin in human development.

A few studies have examined leptin during sheep pregnancy, which, like humans, is a species in which adipose tissue is deposited before birth, and higher leptin levels exist at birth than at postnatal day thirty (Muhlhausler et al., 2007). Serum leptin in ewes increases similarly to human mothers at about a two-fold increase by mid-pregnancy, then declines throughout late pregnancy and early lactation (Ehrhardt et al., 2001). A study with 15 pregnant baboons showed that leptin mRNA was present in the placenta and that there was a 100-fold increase in maternal serum leptin compared to non-pregnant cycling baboons (Henson et al., 1999). Maternal leptin declined to normal levels by 15 days postpartum (Henson et al., 1999). Other old world primates, such as rhesus and cynomolgus macaques, also experience increases in leptin during similar stages of pregnancy as humans (Castracane et al., 2005). In Japanese macaques, circulating leptin and 17-beta estradiol are correlated. Both hormones increase slightly in the first quarter, largely in the second and third quarters, peak in the fourth quarter, and return to first quarter levels by 10 days post-partum (Wang *et al.*, 2005), closely resembling the pattern found in human pregnancy. However, the increase in these primates is a much higher magnitude than what is seen in humans (Castracane et al.,

2005; Henson et al., 1999). Studies which use animals with a more similar leptin profile during pregnancy and development, such as large mammals and nonhuman primates, are critical in understanding leptin's role in human development.

3. LEPTIN'S ROLE IN PSYCHOPATHOLOGY

3.1 Leptin in the Brain

Leptin receptors are widely distributed in the human brain—including expression in the cortex, amygdala, hippocampus, and thalamus—with highest levels in hypothalamic nuclei such as the arcuate nucleus (ARC) and paraventricular nucleus (PVN) (Couce et al., 1997; Meister, 2000). The earliest and most robust role of leptin in the brain is its anorexigenic action in the hypothalamus (Meister, 2000). Leptin regulates feeding behavior and body weight homeostasis by inhibiting orexigenic neuropeptide Y (NPY) and stimulating anorexigenic proopiomelanocortin (POMC) neurons in the ARC, which project to the lateral hypothalamus (Elias et al., 1999) and PVN (Oomura *et al.*, 2006a). Decreased leptin levels that occur during fasting upregulate agoutirelated peptide (AgRP) in the hypothalamus, which increases food intake (Korner et al., 2001). Additionally, leptin activates signal transducer and activator of transcription-3 (STAT3) signaling in AgRP neurons in the ARC, promoting increased locomotor activity (Mesaros et al., 2008). Leptin also increases energy expenditure and thermogenesis by stimulating the sympathetic nervous system (Shanley et al., 2001). Moreover, leptin has a well-documented role in regulating the neuroendocrine system, reproductive system, immune system, bone development, and brain development (Ahima and Osei, 2004). Important evidence for leptin's role in the human brain comes from the rare condition of human leptin deficiency. In leptin deficient humans, leptin supplementation increases grey matter concentration in areas such as the anterior cingulate gyrus, inferior parietal lobule, and the cerebellum which have roles in emotion, attention, and motivation (Matochik et al., 2005). As leptin action is explored in additional brain regions, the knowledge of leptin's effects on behavior will continue to increase.

Though it is widely accepted that the majority of leptin that acts on these receptors in the brain comes from adipose tissue and then crosses the BBB, there is also evidence that leptin is produced by the brain. Leptin is secreted by the brain and pituitary gland (Morash et al., 1999) and appears to be released by brain tissue into the plasma (Wiesner et al., 1999). As the pituitary is highly vascularized, it is likely that pituitary produced leptin is also released into plasma, though this has not yet been demonstrated. Women have higher levels of leptin production in the brain than men (Wiesner et al., 1999), which could contribute to the higher levels of circulating leptin found in women. The role of centrally derived leptin has been largely understudied and its role in behavioral regulation and psychopathology has not yet been explored.

The amygdala is well known for its role in anxiety and stress response and the presence of leptin receptors and their projections to this brain region indicate that leptin may play a role in the mediation of emotions and behaviors. Leptin receptors are located in the basolateral amygdala (BLA) (Han et al., 2003), but their impact on behaviors outside of feeding—such as emotion, learning, and behaviors such as fear, aggression, and addiction—remain unclear. In a congenital leptin deficient patient, leptin treatment decreased activation of the amygdala

in response to pictures of food (Frank et al., 2011). This suggests that leptin regulates the emotional response to food. Neurons expressing the long form of the leptin receptor that originate in the ventral tegmental area of the midbrain send projections to the central amygdala and regulate the expression of cocaine and amphetamine regulated transcript (CART) neurons (Leshan et al., 2010). As CART expression within the central amygdala correlates with symptoms of depression and anxiety in rodents (Dandekar et al., 2009), this may be one mechanism in which leptin impacts risk for mental health disorders. Additionally, leptin receptors are localized throughout the hippocampus, which plays an important role in learning and memory. In the hippocampus, leptin enhances the induction of synaptic plasticity (Oomura *et al.*, 2006b; Shanley *et al.*, 2001) by increasing the motility and density of dendritic filopodia (O'Malley *et al.*, 2007), which are protrusion on neurons that receive synaptic input and can develop into dendritic spines. Future studies are needed to further examine leptin's role in the amygdala and hippocampus, and to examine the impact of leptin in these brain regions on behavioral regulation.

Leptin and leptin receptors are also located throughout the hypothalamic-pituitary-adrenal (HPA) axis (Roubos *et al.*, 2012), which is a critical regulator of stress response and emotional disorders. Leptin receptor mRNA is found widely through the hypothalamus, including the ARC, PVN, dorsomedial, ventromedial and ventral premammillary nuclei, and lateral hypothalamic area (Elmquist *et al.*, 1998; Roubos *et al.*, 2012). Interestingly, adrenocorticotropic hormone (ACTH) and cortisol levels are inversely correlated with leptin levels (Licinio et al., 1997) and leptin can directly inhibit cortisol production in adrenocortical cells (Glasow and Bornstein, 2000; Walker *et al.*, 2004). Leptin acts directly in the pituitary by binding to leptin receptors in endocrine cells in the anterior lobe (Roubos *et al.*, 2012). Leptin is also expressed in anterior pituitary cells and, most commonly, in ACTH cells (Jin *et al.*, 1999). Abnormalities with leptin can cause HPA axis dysregulation which may lead to increased anxiety and related emotional disorders.

Leptin regulates several neurotransmitter systems and brain regions critical in behavioral regulation including the dopaminergic (Burghardt et al., 2012; Fulton et al., 2006) and serotonergic (Collin *et al.*, 2000; Yadav *et al.*, 2009) systems. The lateral hypothalamic area which is heavily populated by leptin receptors sends projections to the mesolimbic dopamine system, which is important in the regulation of motivation, addiction, and reward (Leinninger, 2011). Leptin regulates the mesoaccumbens dopamine pathway in rodents and humans (Burghardt et al., 2012; Fulton et al., 2006), and administration of leptin in rodent models has been shown to reduce the firing of dopaminergic neurons (Fulton et al., 2006). Leptin action causes presynaptic inhibition of dopamine neurons in the ventral tegmental area, which modulate reward-seeking behavior found in food consumption and addiction (Thompson and Borgland, 2013). Circulating leptin levels increase during withdrawal from alcohol, which may act on dopamine to enhance cravings (Aguiar-Nemer *et al.*, 2013). Moreover, enhanced activity of the mesolimbic dopamine system has been implicated in schizophrenia and a number of other psychiatric disorders (American Psychiatric Association, 2000). Leptin deficient Ob/Ob mice have down regulated serotonin transporter mRNA in the dorsal raphe nucleus and exhibit depressive-like behaviors (Collin et al., 2000). This may be a compensatory response to increased serotonin (Harris *et al.*, 1998; Lin

et al., 1992), as leptin has also been shown to inhibit serotonin synthesis in the brain (Yadav et al., 2009). Reduced central serotonin synthesis is consistently reported in humans diagnosed with anxiety (Spindelegger et al., 2009), depression (Kiyohara and Yoshimasu, 2009; Sullivan et al., 2006), Attention Deficit Hyperactivity Disorder (ADHD) (Oades et al., 2008), and Autism Spectrum Disorder (ASD) (Challier et al., 2008; Chugani et al., 1999) and these disorders are commonly treated with selective serotonin reuptake inhibitors, which increase serotonin concentration in synapses. Thus, leptin suppression of serotonin synthesis is a possible mechanism behind the comorbidity between obesity and mental health disorders.

3.2 Maternal Leptin's Role in Psychopathology

Given the current epidemic of obesity in women of childbearing age, and the association between obesity and high leptin levels, it is critical to examine the role of high maternal leptin on offspring's risk of developing psychopathology. Most studies examining the connection between maternal leptin levels and offspring psychopathologies have used a rodent model. Ob/ob mice are useful in examining the developmental effects of leptin because they have a genetic mutation causing deficiency in the synthesis of leptin. This deficiency results in decreased brain size (Steppan and Swick, 1999) and behavioral abnormalities such as increased anxiety and depression like behaviors (Collin et al., 2000). Treating ob/ob mice with leptin causes an increase in brain volume and total brain DNA, demonstrating that leptin insufficiency has a number of negative impacts on brain development (Steppan and Swick, 1999). Db/db mice, which do not express the long isoform of the leptin receptor (Tartaglia *et al.*, 1995), provide another model for leptin dysfunction. Db/db mice show increased leptin levels along with neurobehavioral disturbances such as depression and anxiety behavior and psychosis-like symptoms (Sharma et al., 2010). These mice show increased immune and inflammation-related molecules, as well as perturbations in 14-3-3 protein family in the hippocampus that are also found in schizophrenia, ASD, and bipolar disorder (Ernst et al., 2013). In humans, umbilical cord leptin levels are positively correlated with head circumferences in monozygotic twins with discordant fetal growth (Gohlke et al., 2006). This suggests that leptin levels impact fetal brain development in both humans and animal models. Indeed, leptin receptors are prevalent throughout the fetal brain and leptin has been shown to have long lasting effects on prenatal and postnatal brain development (Bouret, 2010).

Maternal undernutrition, which causes reduction in maternal leptin, has previously been examined in relation to offspring leptin levels and behavior. Rat dams that are moderately or severely calorie restricted during gestation and lactation have offspring that as adults have higher leptin levels, heavier body weights, and increased anxiety behaviors compared to controls (Levay et al., 2008). Multiple factors may feed into these offspring outcomes, one of which is the decreased leptin levels in calorie-restricted dams. Few studies have examined the effects of maternal hyperleptinemia on offspring psychopathology. Aguilar-Valles and colleagues conducted a study to examine the direct effects of maternal leptin on the development of psychopathology. Using a rat model of maternal inflammation, circulating Il-6 and leptin levels contributed to increased activity of dopamine neurons in the nucleus accumbens of adult offspring, as well as elevated spinophilin, a protein that increases

synaptic activity by regulating dendritic spines (Aguilar-Valles et al., 2012). In this model of prenatal inflammation, the increased levels of baseline dopamine, spinophilin, and associated heightened locomotor responses to amphetamines were prevented by neutralization of leptin (Aguilar-Valles et al., 2012). More studies examining the direct effects of maternal leptin on the development of psychopathology during fetal development are needed to expand on these findings.

The timing and magnitude of the postnatal leptin surge that rodents experience have a long-term impact on brain development, physiology, and behavior. In mice, administration of leptin during the early postnatal period—particularly in the first ten days of lactation—causes an increase in body weight, food intake, and leptin levels in the adult (de Oliveira Cravo et al., 2002). Leptin administration during this point in development improves function of the glucocorticoid receptor and the adrenocortical axis (Proulx et al., 2001). This function is important in moderating the adrenocortical response to stressors, and suggests that leptin administration reduces anxiety levels and response to stress. In contrast, neonatal mice that were administered leptin during the first ten days of lactation were reported to display increased anxiety levels in adulthood (Fraga-Marques et al., 2009). This result was the opposite of what the researchers predicted when they gave acute administration of leptin, because mice deficient in leptin have also been reported to demonstrate increased anxiety (Collin et al., 2000). Fraga-Marques and colleagues explain their result by postulating that neonatal hyperleptinemia resulted in a mechanism of leptin resistance that affects behavior later in life. The differing results may also be explained by the amount of leptin administered, as Proulx et al. administered a much lower dose (8 ug/100 g), which is within physiologic levels. This suggests that small doses of leptin may have beneficial effects, but large doses induce leptin resistance. These investigations on leptin's role during the early neonatal period in rodents illustrate several potential mechanisms for leptin in the development of psychopathology. However, it is important to examine whether these mechanisms are consistent in larger animal models, which experience similar changes in leptin levels across development and similar timing of brain development to humans.

3.3 Leptin and Inflammation

Circulating leptin is elevated by acute infections, inflammatory cytokines, and in response to endotoxins (Ahima and Osei, 2004). Inflammatory cytokines, like leptin, correlate strongly with BMI; consequently, overweight and obese adults demonstrate a chronic increase in systemic inflammation (Visser et al., 1999). Elevated leptin levels are likely contributing to this increase in inflammation associated with obesity. Leptin receptor activation initiates release of proinflammatory cytokines in rodents and humans (Aleffi et al., 2005; Deng et al., 2012; Pessin and Kwon, 2013) and stimulates the expression of proinflammatory cytokines in the human placenta (Lappas et al., 2005). This has been directly demonstrated in a rodent model of prenatal inflammation, in which neutralization of leptin prevented several inflammation-induced effects on mesolimbic dopamine activity in the adult offspring (Aguilar-Valles et al., 2012). As leptin has such an evident impact on inflammation, it is important to look at possible effects of inflammation during pregnancy on fetal development and psychopathology.

Increased inflammation in pregnancy predicts poor obstetric outcomes such as low birth weight, premature birth, and pregnancy complications (Blackmore et al., 2011). Along with these outcomes, gestational inflammation is implicated in neurodevelopmental psychiatric disorders in the offspring such as schizophrenia, psychotic episodes (Buka et al., 2001), and ASD (Angelidou et al., 2012). Proinflammatory cytokines, regulated by leptin, are able to cross the placenta and the BBB, enter the fetal brain, and contribute to a variety of neurodevelopmental dysfunctions. The administration of the inflammatory cytokine Il-6 during rodent pregnancy alters gene expression in the frontal cortex and causes behavioral abnormalities such as deficits in prepulse inhibition and latent inhibition (Smith et al., 2007). This study focused on overall changes in the transcriptome of the brain and follow up studies will examine the specific gene that were impacted, however the observed deficits in prepulse inhibition and latent inhibition suggest that the inflammation-induced gene alterations could contribute to disorders such as schizophrenia and ASD. In rats, peripheral inflammation caused by maternal obesity resulted in elevated markers of inflammation in the hippocampus of the offspring along with increased anxiety and decreased spatial learning (Bilbo and Tsang, 2010). These results continued into adulthood, despite offspring being switched to a control diet at weaning, suggesting that exposure to inflammation causes irreversible programming of the brain. Interferon (INF)-alpha, which increases proinflammatory cytokines, causes dysfunction in the development of the serotonergic system in rats (Ishikawa et al., 2007). Also, a study using embryonic rat cells showed that cytokines decrease survival of serotoninergic neurons in both the substantia nigra and the rostral raphe (Jarskog et al., 1997). Thus, exposure to maternal inflammation may increase risk of depression, anxiety, and ASD by a mechanism of serotonergic dysfunction.

Adults in the obese state experience leptin resistance, in which high circulating leptin levels fail to decrease food intake and increase energy expenditure. But this state of hyperleptinemia can still cause an increase in inflammatory cytokines. Indeed, obesity may be considered a state of chronic inflammation. Leptin has many roles in modulating inflammation, including inducing release of inflammatory cytokines such as TNF-alpha and Il-6 by binding to leptin receptors found on monocytes (Zarkesh-Esfahani *et al.*, 2001). Leptin also effects T cell (Th) immunity by increasing Th1, which secretes proinflammatory cytokines such as Il-2 and IFN-γ, and suppresses Th2 which secretes regulatory cytokines such as Il-4 (Lord *et al.*, 1998). A meta-analysis showed that increased inflammatory cytokines, such as TNF-alpha and Il-6 are higher in depressed patients than controls (Dowlati *et al.*, 2010). Increased inflammation has also been found in many other mental health disorders such as post-traumatic stress disorder (Gill *et al.*, 2009; Hoge *et al.*, 2009), generalized anxiety disorder (Bankier *et al.*, 2008), panic disorder (Hoge *et al.*, 2009), schizophrenia (Korschenhausen *et al.*, 1996), and ASD (Vargas *et al.*, 2005). Inflammatory cytokines—increased by high circulating leptin—acting on various brain regions may explain the association between obesity and psychopathology.

3.4 Depression

The relationship between leptin levels and depressive disorders is not consistent across studies. In many studies, lower levels of leptin are associated with an increase in symptoms of depression. Kraus and colleagues published that significantly lower leptin levels were

found in depressed patients compared to healthy controls when the groups were matched for BMI (Kraus et al., 2001). Another study revealed that leptin levels were inversely correlated with Hamilton Rating Scales for Depression and Anxiety and Perceived Stress Scale scores independent of weight or body fat in adult women (Lawson et al., 2012). In a study that did not control for BMI, lower levels of leptin and cholesterol were observed in depressed patients (Jow et al., 2006). Also, individuals that attempted suicide have been observed to have lower leptin levels compared to healthy controls (Atmaca et al., 2002b). Likewise, bipolar disorder is also associated with low leptin levels, particularly among those with manic episodes (Atmaca et al., 2002a). But not all studies show this inverse correlation between leptin and depression. An epidemiologic study determined that women with a history of major depressive disorder had higher serum leptin levels, independent of body mass (Pasco et al., 2008). A study examining depression in a population with metabolic syndrome found that higher leptin levels correlated with depression, particularly somatic depressive symptoms (Chirinos et al., 2013), which are physical symptoms including fatigue and dysfunction in sleep, appetite, and digestion. The association between leptin concentration and depression could be a u-shaped curve in which both high and low leptin levels are associated with depression, which would explain the discrepancies between studies.

One explanation for these inconsistent findings between studies is that leptin resistance interacts with circulating leptin levels to contribute to depression. Obese individuals have increased lifetime diagnosis of depressive disorders compared to individuals of normal weight (Simon et al., 2006). But obesity and higher body fat percentage are also correlated with higher levels of leptin (Considine et al., 1996). It is well accepted that leptin resistance explains why increased leptin levels fail to reduce appetite and promote weight loss in the obese population (El-Haschimi et al., 2000; Munzberg and Myers, 2005). This resistance to leptin may also explain why obesity, which is a condition with higher levels of circulating leptin, is correlated with depression—despite the majority of studies associating low levels of leptin with depression. Leptin resistance may be similar to having low levels of leptin in its influence on depressive symptoms. The previously mentioned study by Chirinos and colleagues deals with a population with metabolic syndrome, one of the defining characteristics of which is obesity. If leptin resistance were a factor in depression, it would follow that those with higher leptin levels would be more leptin resistant and therefore have more depressive symptoms. In a study on the onset of depression in older men and women, men with higher leptin levels had an increased risk of depression onset (Milaneschi et al., 2012). This association was observed in men with abdominal obesity, but not in those with normal visceral adiposity, lending credence to the leptinresistance hypothesis. When examining the association between adiposity, leptin levels, and depression, individuals that were low to normal weight were more likely to have depression when accompanied by lower circulating leptin levels (Morris et al., 2012). But when looking at overweight and obese participants the opposite was found to be true, with depressed participants having higher leptin levels than their non-depressed counterparts (Morris et al., 2012). Leptin resistance contributing to depression would explain how studies could find either high leptin levels or low leptin levels associated with depression.

Rodent studies are able to further elucidate the association between leptin and depression, in part due to a lack of confounding factors that are observed in human studies such as cyclical changes in leptin in women (Hardie et al., 1997), effects of prior medication (Kraus et al., 2002), current fasting state (Haluzik *et al.*, 2001), and other environmental and genetic variables. Ob/Ob mice, which are entirely leptin deficient, exhibit depression-like behaviors and have down regulated serotonin transporter mRNA in the dorsal raphe (Collin et al., 2000). Db/db mice, which lack the long isoform of the leptin receptor and have high levels of circulating leptin, also show increased depression and anxiety behaviors (Sharma *et al.*, 2010). Studies consistently find that reduced plasma leptin levels accompany depression-like behavior induced by chronic stress (Garza et al., 2011; Ge et al., 2013; Lu et al., 2006). Rats with low leptin levels and depression-like symptoms experienced amelioration of these symptoms and increased neuronal activation in the hippocampus in response to leptin treatment (Garza et al., 2011; Lu et al., 2006). This was also found to be true in control diet fed mice (Yamada et al., 2011). But administration of leptin in diet induced obese mice did not induce antidepressant-like effects or increase hippocampal brain-derived neurotropic factor concentrations, suggesting that impaired leptin signaling in the central nervous system may be a mechanism for the connection between obesity, high leptin levels, and depression (Yamada et al., 2011). In another mouse study, depression-like behaviors were induced by deletion of specific leptin receptors in the hippocampus (Guo et al., 2013). Together, these rodent studies indicate that leptin may be an effective antidepressant for individuals that are normal weight with low leptin levels, but would not improve depressive symptoms in those that are leptin resistant due to hyperleptinemia. Individuals with low leptin mRNA expression, decreased leptin serum levels, and polymorphisms in the leptin gene are more likely to be unresponsive to treatment by currently available antidepressants (Kloiber et al., 2013). This suggests that leptin may be a novel antidepressant used alone or in combination with existing antidepressants in individuals with low or normal leptin levels.

3.5 Anxiety

Anxiety disorders are associated with activation of the HPA axis increasing cortisol and ACTH release (Graeff, 2007). As leptin receptors are prevalent throughout the HPA axis, studies on the association between leptin levels and anxiety disorders are needed. In a study examining the association between phobic anxiety and adipokine and cytokine levels in women, those who scored higher on the Crown-Crisp phobic anxiety subscale had higher levels of leptin, even after adjusting for BMI (Brennan et al., 2009). In a male population, high leptin levels were associated with higher perceived psychological stress (Otsuka et al., 2006). Liao and colleagues discovered higher leptin levels in those with subsyndromal posttraumatic stress disorder after a major earthquake, with anxiety levels being positively correlated with leptin (Liao et al., 2004). Though there are few human studies looking at the association between anxiety disorders and leptin levels, those that exist correlate higher leptin levels with increased anxiety.

The aforementioned human studies seem to be at odds with animal studies examining the effect of leptin administration on anxiety. In a mouse study, leptin reduced the stress-induced activation of the HPA axis by inhibiting corticotrophin-releasing factor (Heiman et al., 1997). Hyperactivity of corticotrophin-releasing factor is associated with depression and

anxiety disorders (Arborelius et al., 1999). Leptin treatment is also known to reduce anxiety in leptin-deficient Ob/Ob mice (Asakawa et al., 2003). As Ob/Ob mice have higher corticosterone levels than regular mice, it follows that leptin acts on the HPA axis to alleviate anxiety. In a female rhesus macaque model, chronic administration of leptin was found to reduce activation of the HPA axis in response to an unpredictable situation (Wilson et al., 2005). Because none of these studies used leptin resistant animals, conclusions cannot be drawn as to whether leptin resistance could explain the conflicting results between animal studies and human studies. In a high-fat diet-induced maternal obesity nonhuman primate model, offspring from high-fat diet fed mothers show increased anxiety, which may be the result of being exposed to high prenatal leptin levels (Sullivan *et al.*, 2010). More studies with diet-induced obese animals may clarify the association between leptin and anxiety in the future.

3.6 Schizophrenia

Schizophrenia is a chronic mental health disorder distinguished by disturbances in perception, thoughts, and cognition (Amercan Psychiatric Association, 2000). Although disease onset typically occurs in late adolescence, the prenatal environment is strongly implicated (Piper et al., 2012) in the etiology of schizophrenia. There are very few studies on leptin levels and schizophrenia that do not have the confounding factor of antipsychotic medication. Kraus and colleagues found levels of leptin in schizophrenic patients to be lower than healthy controls and depressed patients (Kraus et al., 2001). This was independent of psychotropic medication, and BMI did not differ between groups. Another study also found low levels of leptin to be associated with unmedicated schizophrenic patients, particularly in those who previously attempted suicide (Atmaca et al., 2003b). Those with violent suicide attempts, as opposed to attempt by overdose, had even lower serum leptin levels (Atmaca et al., 2003b). A study involving an antipsychotic-free group and an olanzapine-treated group identified lower leptin levels associated with more severe positive symptoms of schizophrenia (Takayanagi et al., 2013). This finding remained when adjusting for age, gender, body mass index, and olanzapine medication at baseline. The majority of studies that control for BMI observe these lower circulating leptin levels in patients with schizophrenia compared to controls.

On the other hand, Jow and colleagues observed high levels of leptin in schizophrenic patients after excluding those who had treatment with psychotropic medication within the last 4 weeks (Jow et al., 2006). This study did not control for body weight, and the patients with schizophrenia had significantly higher BMIs than the control group, which likely contributed to the observed higher leptin levels in schizophrenic patients. Leptin levels also positively correlated with the duration of illness in schizophrenic patients, and because most of the patients had been previously treated with antipsychotics these results suggest more about the effects of antipsychotic treatment on leptin levels than the correlation between schizophrenia and leptin. A different study found higher levels of leptin in schizophrenic patients undergoing antipsychotic treatment than healthy controls (Tsai et al., 2011). This result has been duplicated many times and is related to antipsychotic drug induced weight gain (Atmaca et al., 2003a; Herran et al., 2001; Jin et al., 2008; Kraus et al., 2001). Because

of the confounding factor of antipsychotic treatment, it may only be useful to look at leptin levels in drug naïve populations to examine leptin's possible role in schizophrenia.

Rodent models of schizophrenia are widely used to investigate brain mechanisms and possible treatments. Using a social isolation developmental model of schizophrenia, leptin treatment improved prepulse inhibition of acoustic startle in rats (Dashti et al., 2013). Poor prepulse inhibition is thought to be due to increased dopaminergic activity and is common in schizophrenia. Among other brain abnormalities, dysregulation of dopamine neurotransmission is strongly associated with schizophrenia (Abi-Dargham et al., 2000). A different study using the same social isolation model of schizophrenia treated the rats with an intracerebroventricular injection of leptin, which decreased the level of dopamine in the nucleus accumbens (Krügel et al., 2003). As studies using rodents or drug naïve humans show that low leptin levels are associated with schizophrenia, and antipsychotic drugs increase leptin levels, it may be that leptin itself could be a possible treatment for schizophrenia.

3.7 Autism Spectrum Disorders (ASD) and Rett Syndrome

According to the DSM-IV-TR, ASD are a group of developmental brain disorders that include a wide range of symptoms and levels of impairment characterized by communication difficulties, social impairment, and repetitive or stereotyped behaviors (Amercan Psychiatric Association, 2000). A study with 70 children diagnosed with ASD and 99 age-matched control children demonstrated a significant increase in leptin levels in autism (Ashwood et al., 2008). Children with early onset autism also had higher leptin levels than those with regressive autism (Ashwood et al., 2008). These results remained significant when age, IQ, BMI, and whether patient was medicated or untreated was controlled for. In another study, higher leptin levels were observed in autistic children with no comorbid disorders than in controls and leptin levels increased in autistic patients over a one year period (Blardi et al., 2010). A study with brain tissue, showed leptin, along with a multitude of proinflammatory and modulatory cytokines, at a higher concentration in the anterior cingulate gyrus of patients with autism than that of controls (Vargas et al., 2005). There is an increased risk for ASD in children from both underweight and obese mothers (Moss and Chugani, 2014), which may be due to abnormal maternal leptin levels. As the few studies examining leptin and autism display an association, further studies should continue investigating prenatal leptin exposure and leptin levels in those with ASD.

Rett syndrome is a severe developmental–neurological disorder, which occurs almost exclusively in females, and is defined by diminishing intellectual functioning after a period of normal development, stereotypy, nervous system dysfunction, and growth failure (Amercan Psychiatric Association, 2000). Leptin is of interest to Rett syndrome researchers, because of the associated growth failure and low BMI. Similar to ASD, leptin is elevated in patients with Rett syndrome compared to controls of similar BMI (Blardi et al., 2009; Blardi et al., 2007). Leptin levels are also significantly increased in patients with Rett syndrome over the course of a two-year study (Blardi et al., 2009). Some patients in this study were treated with carbamazepine which has no effect on leptin levels (Himmerich et al., 2005), but others were treated with valproate which may increase leptin levels (Greco et al., 2005).

Higher plasma leptin levels are also correlated with overactivity of the sympathetic nervous system, as established by high sympatho-vagal balance (Acampa et al., 2008). This suggests that hyperleptinemia may contribute in part to the cardiac dysautonomia observed in Rett syndrome. Investigators may want to explore whether higher leptin levels are correlated with decreased intellectual functioning or increased stereotypy and autism-like behaviors in future Rett syndrome research.

4. Conclusion

The mechanisms and causal factors underlying psychopathologies are a complex combination of genetic, environmental, and intrauterine programming. Effects of the prenatal environment on fetal brain development, epigenetics, and future mental illness are still largely unknown. More studies using large animal models such as sheep and nonhuman primates—which have similar pregnancy profiles to humans—need to be conducted, in order to draw firm conclusions on the effects of maternal leptin on the offspring's future psychopathology. The roles of leptin and inflammation must be parsed out from other metabolic and behavioral complications arising in the obese state. More BMI controlled, drug-naïve human studies are needed to examine leptin levels in various mental health disorders. Examining leptin resistance as a mechanism of mental illness is critical as treatment with leptin may be effective in patients with low circulating leptin but is unlikely to help those with elevated levels. Studies only measuring circulating leptin levels may not be as useful as those determining CSF leptin levels and leptin receptor action. In conclusion, although there is a large body of evidence associating states of leptin dysregulation such as obesity and alterations in leptin levels in various psychopathologies, much additional work is needed to determine if leptin dysregulation directly impacts risk for mental health and neurodevelopmental disorders.

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Highlights

- Leptin dysregulation is associated with many common mental health disorders
- Offspring brain development is impacted by maternal obesity and hyperleptinemia
- Leptin initiates release of inflammatory cytokines
- Leptin resistance may explain the comorbidity of obesity and psychopathologies