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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 high leptin levels have been correlated with symptomatology. Schizophrenia is also associated with both low and high leptin levels. However, as anti-psychotics 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 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.

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 an 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, there is evidence 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

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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 (37%) and overweight (67%) women in the United States (Ogden et al., 2014) 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.

Leptin's role in pregnancy

Leptin's role in human pregnancy

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