Review Article

The Human Obesity Epidemic, the Mismatch Paradigm, and Our Modern "Captive" Environment

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ABSTRACT In the distant past obesity in humans was rare and likely caused by metabolic dysregulation due to genetic or disease-related pathology. External factors precluded the ability of most people to overeat or under exert. Socio-cultural obesity came about due to the rareness of obesity and its difficulty to achieve. What is rare becomes valuable and what is difficult to achieve becomes a badge of prestige. The modern human obesity epidemic would appear to represent a third class of obesity: environmental obesity. Much like the captive environments which humans construct for the captive/companion animals in our care, the modern human environment has greatly decreased the challenges of life that would restrict food intake and enforce exertion. And like us, our captive/companion animal populations are also experiencing obesity epidemics. A further concern is that maternal obesity alters maternal signaling to offspring, *in utero* through the placenta and after birth through breast milk, in ways that perpetuate an enhanced vulnerability to obesity. Molecules such as leptin, produced by adipose tissue and placenta, have significant developmental effects on brain areas associated with feeding behavior. Leptin and other cytokines and growth factors are found in breast milk. These molecules have positive effects on gut maturation; their effects on metabolism and brain development are unclear. Placenta and brain also are hotspots for epigenetic regulation, and epigenetic changes may play significant roles in the later vulnerability to obesity and to the development of a diverse array of diseases, including heart disease, hypertension, and noninsulin-dependent diabetes. Am. J. Hum. Biol. 00:000–000, 2012.

Throughout history and likely extending into prehistory there have been obese human beings. In the past, obesity was rare and represented highly unusual metabolic or cultural circumstances. External factors generally restricted the obesity phenotype from being expressed. Today obesity has become common, and in many cultures today obesity is approaching the norm. As many as one in three adult women in the United States are thought to be obese (Fleagle et al., 2010).

This change in our phenotype has been very rapid. In 1994 more than half of the states had a prevalence of obesity among adults of <15%. By 2000 only one state was below 15%, and by 2005 all states had >15% obesity prevalence and three states were over 30%. In 2009, the number of states with an obesity prevalence of 30% or higher had increased to nine. The lowest state obesity rate in 2009 was Colorado at 18.6%; the highest was Mississippi at 34.4% (Table 1; CDC, 2011). This is extraordinary rapid phenotypic change in a population. It cannot be caused by genetic change; rather, in some way the modern environment is interacting with our evolved biology in ways that create large groups of people who are vulnerable to sustained weight gain. Human cultural and technological abilities have allowed obesity to become common. The modern human environment has become obesogenic.

HUMAN OBESITY

Obesity has a deceptively simple cause: Consuming more calories in food than are expended in daily life, which results in positive energy balance over a sustained period of time. It is deceptively simple because the biology that underlies the regulation of all aspects of energy balance is extremely complex, and not well understood. The advice: eat less and exercise more, is very easy to give, but very difficult to follow.

Historically, there have been two types of human obesity: metabolic obesity and socio-cultural obesity. Metabolic obesity refers to individuals with identifiable differences in their physiology (sometimes congenital, others due to disease or other insult) that result in consistent weight gain. This was probably the most common cause of obesity in our distant past, but today <5% of obese people have an identifiable underlying metabolic/genetic disorder (Speiser et al., 2005). In the past, socio-cultural obesity was rare. It was difficult to become obese, and thus obesity was both rare and often perceived as desired. Obesity was a status symbol in some cultures, something to be obtained as a symbol of wealth and power. Now that obesity has become so prevalent perhaps we need a third category, environmental obesity, to account for the large number of otherwise physiologically normal people who become obese in modern society even though obesity has acquired a social stigma.

THE MISMATCH PARADIGM AND OUR "CAPTIVE" ENVIRONMENT

Obesity is not a uniquely human concern. Obesity is also a significant problem among animals that humans keep in captivity. Both companion animals, laboratory animals, and animals kept in zoological parks have seen increases in obesity prevalence (Klimentidis et al., 2011). My colleague Suzette Tardif and I have investigated the development of obesity in a colony of captive marmosets.

Contract grant sponsor: PHS; Contract grant number: R01 DK077639.

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Received 14 August 1996; Revision received 16 September 1996; Accepted 20 October 1996

DOI 10.1002/ajhb.22236

Published online in Wiley Online Library (wileyonlinelibrary. com).

TABLE 1. U.S. 2009 obesity prevalence by state

State	Obesity prevalence (%)	State	Obesity prevalence (%)
Colorado	18.6	Illinois	26.5
Washington DC	19.7	Delaware	27.0
Connecticut	20.6	Georgia	27.2
Massachusetts	21.4	Nebraska	27.2
Hawaii	22.3	Pennsylvania	27.4
Vermont	22.8	Iowa	27.9
Oregon	23.0	North Dakota	27.9
Montana	23.2	Kansas	28.1
New Jersey	23.3	Texas	28.7
Utah	23.5	Wisconsin	28.7
New York	24.2	Ohio	28.8
Idaho	24.5	North Carolina	29.3
Minnesota	24.6	South Carolina	29.4
Rhode Island	24.6	Indiana	29.5
Wyoming	24.6	Michigan	29.6
Alaska	24.8	South Dakota	29.6
California	24.8	Missouri	30.0
Virginia	25.0	Arkansas	30.5
New Mexico	25.1	Alabama	31.0
Florida	25.2	West Virginia	31.1
Arizona	25.5	Oklahoma	31.4
New Hampshire	25.7	Kentucky	31.5
Maine	25.8	Tennessee	32.3
Nevada	25.8	Louisiana	33.0
Maryland	26.2	Mississippi	34.4
Washington	26.4		

Early in the colony's existence most animals were lean (Power et al., 2001). However, over the next decade the number of high-weight animals increased. Small and normal sized animals (300–400 g) still exist in the colony; but now a significant proportion of the animals exceed 450 g, and animals with weights above 600 g are not uncommon. Obesity in these animals starts at an early age. By 12 months half of a set of animals followed from birth were obese (defined as percent body fat >14%.) Three quarters of the animals obese at 12 months were already obese at 6 months of age, and the animals that ended up obese at 12 months had higher body fat as early as 1 month of age (Power et al., in press).

Obesity matters because it has significant negative health consequences (Korner et al., 2009). For comparative purposes, obesity in nonhuman primates should be defined relative to metabolic dysregulation similar to obesity-related disease in humans. For example, adult marmosets with body fat above 14% have higher fasting glucose, higher glycosylated hemoglobin, and higher fasting triglycerides, similar to metabolic syndrome in obese humans (Tardif et al., 2009). Therefore, we can label such marmosets obese.

It is instructive to examine the analogies between the modern human environment and the captive environments we construct for animals in our care to illuminate the mismatches between our evolved biology and our modern circumstances. Captivity removes significant features of an animal's natural environment: temperatures are usually stable; wind and rain can be avoided; food is plentiful, dependable, and requires little effort to obtain; predators and competitors are usually absent; most activity is optional and often even is constrained. This purposefully benign environment often results in a mismatch with adaptive behavioral tendencies that leads to overeating and under exertion.

For most of our species' existence external factors largely constrained the expression of obesity. It was difficult to obtain even sufficient food, let alone excess food. Required energy expenditure could not be lowered to the same extent allowed by the modern environment. The modern environment has been designed to remove many of the challenges of the past. In many ways, the modern human environment resembles the captive environments we construct for the animals in our care. Most of the characteristics of captive environments are also true for the modern human environment, at least in developed nations. Humans have purposefully constructed a benign environment, removing many of the challenges our ancestors evolved to solve. Minimal exertion is required; food is not a constraint. Perhaps very significantly, effort has been removed from the process of obtaining food. In the past, obtaining food was intrinsically linked to exertion. If you did not exert you did not eat. We remain highly motivated by certain foods; but we no longer have to exert to eat them. Formerly successful adaptations may now be counterproductive, at least in terms of weight gain.

EVOLUTION OF MEALS

Our eating behavior differs from that of other species in a fundamental way; people eat meals. Food is brought to a particular place at a particular time and then consumed, usually with other people. A meal is defined in the dictionary (Webster's II, 1988) as: "The food served and eaten in one sitting or a customary time or occasion of eating food." But the human concept of "meal" has more meaning than that; a meal is often, even usually, a social situation. Not only do we eat with other people but also it is usually a cooperative event. People pass each other food; people don't steal off each other's plates. The basic concept of a meal probably started very early in our evolution, and has evolved and affected our evolution ever since. Meals have shaped our evolutionary history, both as an adaptation and as a selective pressure that was a key aspect of the adaptive advantages of our larger, more complex brain.

I am not trying to mythologize the concept of meals. Meals and eating have nutritional consequences. If eating in meals had not been a successful adaptation to satisfying nutrient requirements for our distant ancestors we might not be here; however, meals are not just about nutrition. Consider the powerful statement that a person makes when they refuse to eat a meal with other people, or the social and political strategy of convincing rivals to sit down together and share a meal. Meals have social significance. For humans, the act of eating has acquired substantial social/political/sexual significance in addition to its core nutritional function.

HOMEOSTASIS, ALLOSTASIS, AND ALLOSTATIC LOAD

In the words of Cannon (1935): "...the organs and tissues are set in a fluid matrix... So long as this personal, individual sack of salty water, in which each one of us lives and moves and has his being, is protected from change, we are freed from serious peril." The concept of stability, of resistance to change is fundamental to homeostasis. Restraint, negative feedback, is the hallmark of homeostatic processes. However, homeostasis is not synonymous with regulatory physiology, and stability is perhaps a misleading word when considering evolved

physiological adaptations. Much within the "internal milieu" is constantly changing and adapting. Some of the changes are programmed, such as circadian or seasonal rhythms, or the physiological changes associated with pregnancy and lactation. Others are acute responses to challenges. Many are anticipatory rather than reactive, occurring before the need has arrived. This is not an inherent contradiction of homeostasis; Cannon (1935) himself quoted Richet "We are only stable because we constantly change." But the concept of homeostasis must either be stretched, or other terms and concepts must be added to the lexicon of physiological regulation.

Physiological systems serve the survival and reproductive capabilities of the organism (fitness). Stability is not the currency of evolutionary success. Viability, defined as the capability of success or ongoing effectiveness, is a better concept. In an evolutionary context, this means the ability to pass on genetic material. Physiological regulation to maintain viability requires regulation of set points under some conditions, and abandonment of set points under others. There must be physiological processes that are not homeostatic, and that oppose, at least temporarily, stability.

Allostasis has been suggested as a complementary component to homeostasis for understanding physiological regulation (Schulkin, 2003). Homeostatic processes maintain/regulate physiology around a set point; allostatic processes change the state of the animal, including changing or abandoning physiological set points. Homeostatic processes are associated with negative restraint and resistance to perturbations. Allostatic processes are associated with positive induction, perturbing the system, and changing the animal's state. Sterling and Eyer (1988) defined allostasis as "achieving stability through change." A better definition, perhaps, is "achieving viability through change," with homeostasis defined as "achieving viability through resistance to change." Thus, neither should have primacy in regulatory physiology.

ALLOSTATIC LOAD

The activation of regulatory systems can have both short and long-term metabolic costs. Boulos and Rosenwasser (2004) state that "...implicit in Sterling and Eyer's model is the notion that allostatic regulation entails a price..." McEwen (1998) specifically extended allostasis to regulatory systems that were vulnerable to physiological overload, with the resulting development of disease. Many regulatory systems evolved to respond to acute or at least short-lived challenges to viability. Their activation generally results in a change of state that alleviates the challenge and thus allows the regulatory response to cease, at least temporarily. Sustained activation of these regulatory circuits is outside of the evolutionary experience. If these regulatory systems are chronically activated, either due to competing imperatives, conflicting signals, or the failure of the regulatory physiology to resolve the challenge, the associated costs can accumulate and lead to a lessening of health. The term allostatic state refers to chronic activation of regulatory systems either due to dysregulation/dysfunction of physiology or to conflicting, competing, or opposing demands. The term allostatic load refers to the strain on physiology and regulatory capacity due to sustained activation of regulatory systems.

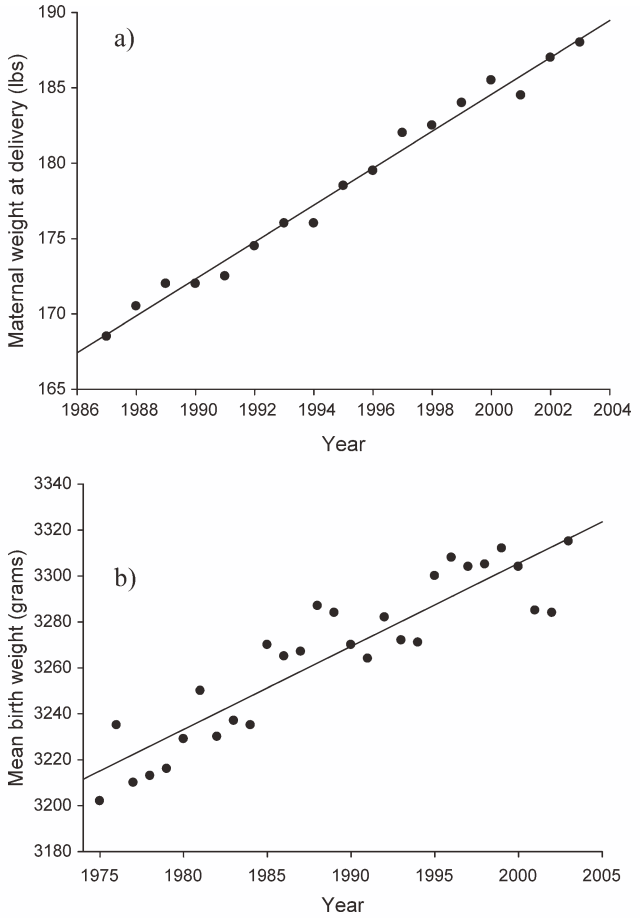

Fig. 1. Maternal weight at delivery (a) and infant birth weight (b) have steadily increased at Metro Health Medical Center, Cleveland, Ohio (From Catalano et al., Diabetes Care, Phenotypes of the infants of mothers with gestational diabetes, 2007, 30, S156–S160, reproduced by permission).

One mild criticism of the term allostatic load is that there is no particular reason why the regulatory circuits being inappropriately or chronically activated have to be allostatic in nature (Power, 2004). Homeostatic systems that become chronically activated due to sustained external pressures, or simply because the regulatory system is failing to achieve the desired homeostatic state, will potentially have the same general long-term consequences, slowly degrading physiology and lessening health. Allostatic load might be more properly termed regulatory load or metabolic load. The basic concept rests upon the fact that any regulatory system that remains continuously activated or activated to a level outside of its norm will eventually break down.

OBESITY DEVELOPS EARLY

There has been a significant increase in childhood and adolescent obesity in developed nations (Ogden et al., 2006). In US, both mean maternal weight and mean birth weight have been steadily increasing (Catalano et al., 2007; Fig. 1). Maternal obesity is a strong predictor of childhood obesity (Reilly et al., 2005), higher fetal fat mass (Sewell et al., 2006), fetal insulin resistance

(Catalano et al., 2009), and eventual metabolic syndrome in her offspring (Boney et al., 2005). Overweight/obese mothers have decreased insulin sensitivity, which results in increased lipid availability for fetal growth. Gene microarray analysis profiles of tissue from placentas from women who are overweight and have GDM show increased gene expression related to lipid metabolism as opposed to glucose metabolism (Radaelli et al., 2003). Maternal adiposity predicts infant fat mass, but not infant lean mass (Sewell et al., 2006), indicating that maternal obesity changes the quality and pattern of growth as opposed to merely increasing growth. Although increased risk of macrosomia is more strongly linked to maternal weight than diabetes status, GDM is related to significantly increased fat mass and body fat percentage in neonates, and significantly larger skin folds at all areas of measurement (tricep, subscapular, flank, thigh, abdomen) (Catalano et al., 2003).

ADIPOSE TISSUE AND ENDOCRINE FUNCTION

Obesity is excess fat, primarily stored in adipose tissue. Our understanding of the biology of adipose tissue has matured so that now it is no longer considered simply a passive store of fat, useful in avoiding lipotoxicity and providing an energy store for times when food is not available. Rather, it forms an active endocrine organ that is actively engaged in regulating physiology and metabolism (Kershaw and Flier, 2004). The dramatic expansion of adipose tissue in obesity is best considered as an expansion of an endocrine organ. Just as a dramatic increase in the size of a person's liver would have dramatic metabolic effects, so too does a dramatic increase in adipose tissue. Adipose tissue produces and secretes numerous cytokines and peptide hormones, such as leptin, adiponectin, and many of the interleukins (e.g., IL-6, IL-8, and IL-10) and immune function molecules. Many of these information molecules have direct and indirect effects on energy metabolism and appetite, and thus affect feeding behavior. Adipose tissue also produces and secretes numerous steroid hormones and the enzymes involved in steroid hormone metabolism (Fain, 2006; Kershaw and Flier, 2004). For example, estrone is converted to estradiol in adipose tissue. Indeed, most if not all circulating estradiol in postmenopausal women comes from adipose tissue (Kershaw and Flier, 2004). Adipose tissue expresses aromatase, 3α-hydroxysteroid hydrogenase type 3 (3α-HSD3) and 17β-HSD5, which are involved in androgen metabolism. These enzymes are increased in obesity (Wake et al., 2007). Adipose tissue also expresses 11β-HSD1 which converts cortisone to cortisol (Seckl and Walker, 2001) and 5α-reductase enzymes (Tomlinson et al., 2008; Wake et al., 2007) which convert cortisol to 5α-tetrahydrocortisol (5α-THF). Thus adipose tissue regulates the local concentrations of glucocorticoids (Stimson et al., 2009; Tomlinson et al., 2008) and contributes to metabolic clearance of glucocorticoids (Rask et al., 2002). Obesity is associated with both increased adrenal glucocorticoid production and higher glucocorticoid metabolic clearance, which appears to result in normal plasma concentrations. In obese individuals, 11β-HSD1 activity is reduced in liver and the inactivation of cortisol by 5α-reductase is enhanced (Rask et al., 2002; Stewart et al., 1999). However, 11β-HSD1 activity is enhanced in adipose tissue of both obese men and women (Rask et al., 2001, 2002). Obese individuals have increased hepatic inactivation of cortisol, which is generally balanced by increased regeneration of cortisol in adipose tissue. Production of cortisol from cortisone via 11β-HSD1 can make a significant contribution to both local and circulating cortisol concentrations. The effect appears stronger in women compared with men (Rask et al., 2002), possibly due to the higher fat mass in women for a given body mass index.

Metabolic diseases (e.g., obesity, Type 2 diabetes, hypertension and associated cardiovascular disease) have proportionately increased in the modern human population. Partly this is due to the decline in infectious disease and increases in life expectancy caused by modern medical advances; but the interaction of human biology with the modern human environment appears to have led to an absolute increase in metabolic disorders as well. Metabolic diseases are increasing in prevalence, but also they are being diagnosed at earlier ages. Diseases that were associated with middle-to-older age are becoming increasing common in younger adults and even children.

Metabolic diseases, such as diabetes and hypertension, represent conditions where the regulatory physiological processes have broken down. A true understanding of the pathophysiology of the metabolic syndrome requires an integration of physiology with an evolutionary perspective. Normal, adaptive metabolic responses are, in effect, causing disease because these metabolic responses are inappropriate, ineffective, or merely sustained for an excessive length of time due to environmental inputs that are outside of our historical norms. Metabolic syndrome is a disease of chronic insult, not acute insult.

OBESITY DURING PREGNANCY

The placenta is also an endocrine organ intimately involved in regulating metabolism, signaling to both maternal and fetal tissue. The placenta serves as a central regulator of maternal-placental-fetal metabolism and produces perhaps the broadest array of information molecules (hormones, cytokines, and all other classes of signaling molecules) of any other organ except for brain (Petraglia et al., 2005). There is a significant placental-brain axis for both fetal and maternal physiology. The late, eminent reproductive endocrinologist Samuel Yen referred to the placenta as the "third brain" in pregnancy (Yen, 1994) in recognition of the regulatory nature of placental function.

In many ways, pregnancy may be the canonical normally occurring allostatic state for human beings (Power and Schulkin, in press). A new organ (placenta) is developing and taking over many of regulatory functions from maternal brain. A key brain function is to allocate resources within the body to defend its own viability (Peters et al., 2004). Oxygen and glucose flow to brain is tightly regulated compared with the flow to other organs. Placenta also acts to allocate resources, in this case from the maternal to the fetal compartment. A well regulated flow of oxygen and glucose is vital to healthy placental function and fetal growth and development as well. Regulatory control is fundamentally altered during pregnancy, in part because metabolism and physiology must account for two organisms instead of one; but also because the regulatory signaling has been allocated to maternal brain and placenta. Circulating levels of glucose, insulin, cortisol and leptin all increase. Pregnant women are termed

TABLE 2. Placental weights (grams) have increased in the US (From Naeye, Human Pathology, 1987, 18, 387–391 and Swanson and Bewtra, J Matern Fetal Neonatal Med, 2008, 21, 111–113, reproduced by permission)

Year	10th percentile	Mean	90th percentile	source
1959–1966	350	446	545	Naeye, 1987
1995	390	499	537	Swanson and Bewtra, 2008
2004	410	537	710	Swanson and Bewtra, 2008

hyperglycemic, hypercortisolemic, hyperinsulemic, and hyperleptinemic. From the terminology, one might be forgiven for thinking pregnancy was a metabolic disease. However, maternal insulin resistance can be considered an example of adaptive, allostatic regulation, in which physiology is continually adapting to changing circumstances to maintain viability.

It is thus not surprising that obesity during pregnancy can lead to metabolic dysregulation. Placenta and adipose tissue both are signaling to maternal metabolism; but their signaling is not coordinated toward a common goal. Interestingly, there is a recent trend toward increasing placental weight in human pregnancy (Table 2), which is in parallel with the increase in maternal adipose tissue (Swanson and Bewtra, 2008). Both these potent endocrine organs are, on average, larger now than they have been in our past. It is reasonable to hypothesize that placenta size is increasing at least in part due to the interactive signaling between placenta and adipose tissue.

For example, leptin, a molecule intimately linked with fat and feeding behavior, is produced not only by adipose tissue but also by the placenta in many mammalian species, including humans, baboons, bats, rodents, pigs, cows, and sheep. Leptin is linked to the insulin resistance of both pregnancy and obesity. Leptin appears to have important functions in fetal growth and developmental processes (Henson and Castracane, 2002). Placental weight is correlated with placental leptin mRNA; cord serum leptin is correlated with placental leptin mRNA, maternal serum leptin, and with fetal mass (Jakimiuk et al., 2003). Large for gestational age fetuses have higher than normal leptin, small for gestational age fetuses have lower leptin.

EPIGENETICS AND IN UTERO PROGRAMMING OF DISEASE

Regulation is the key to survival. Animals are constantly adjusting their physiology and metabolism to remain within the bounds of viability. The new and exciting understanding of genetics is that, at the level of DNA, regulation is also the key to viability. Our new understanding of genomics brings it closer to that of regulatory physiology. There is metabolism at all levels in an organism: the organism level, the organ level, the cellular level, and the genome level. Many of the changes to fetal metabolism in response to the *in utero* environment of maternal obesity are likely due to epigenetic changes; i.e., changes in DNA expression via DNA methylation or demethylation, histone modifications, or other changes to the structure of the chromosomal DNA without any actual change of DNA sequence. These epigenetic changes can activate or silence genes by such mechanisms as recruiting methyl-CpG binding proteins which then block transcription factor from binding to the promoter sites or change chromatin structure enhancing heterochromatin formation (Jones and Takai, 2001). The placenta is a hot spot for epigenetic regulation, being generally the tissue with the lowest overall levels of DNA methylation. Placenta and brain also express a large number of imprinted genes, another form of epigenetic regulation.

Prebirth, clues about the nutritional environment come from the mother, through the placenta. Fetuses may have to adapt to the supply of nutrients crossing the placenta, either a deficit or an overabundance, and these adaptations may permanently change their physiology and metabolism (de Boo and Harding, 2006). These programmed changes can have a significant impact on offspring later in life, and may be the origins of a diverse array of diseases, including heart disease, hypertension, and noninsulin-dependent diabetes. Because of fetal programming, obesity may become a self-perpetuating problem. Daughters of obese mothers may themselves be vulnerable to becoming obese and more likely to have offspring that share this vulnerability, a form of "inheritance of acquired characteristics" from mother to child.

OBESITY AND BRAIN

These epigenetic changes likely affect brain development. Many of the information molecules produced by adipose and placenta may act on the fetus as potent modulators of behavior in later life. For example, leptin has significant developmental effects on neural circuits related to feeding behavior; the same circuits that leptin activates later in life. Interestingly, leptin has no affect on appetite in neonatal rats or mice, at least for the first two weeks of life (Bouret and Simerly, 2004). However, circulating leptin increases dramatically in the first and second weeks of life in rodents. This time period corresponds to a key brain developmental period; during this time the arcuate nucleus makes connections with other hypothalamic nuclei. These connections appear to be stimulated by leptin. Leptin deficient mice have poorly developed connections between the arcuate and other hypothalamic nuclei, and develop hyperphagia (Bouret and Simerly, 2004). A post natal peak in circulating leptin is also observed in lambs born to normal weight ewes, but this peak is missing in lambs born to ewes fed to obesity (Long et al., 2011). Compared with lambs from normal weight ewes, lambs from obese ewes had higher cortisol and leptin at birth, indicating disruption of the normal developmental pattern. Lambs of obese ewes are vulnerable to hyperphagia and obesity as adults (Long et al., 2011).

Rats and mice are born in an altricial state; the first 2 weeks post partum are the equivalent of the final weeks of gestation in humans. Thus, in humans it is likely that any leptin-associated neural developmental events occur *in utero*. In humans, leptin is secreted by placenta into both maternal and fetal compartments. Maternal circulating leptin increases in pregnancy, but is still reflective of maternal adipose (Butte et al., 1997). Thus, obese pregnant women will have higher circulating leptin than will normal weight pregnant women. Leptin expression by placenta does not appear to be affected by the increased maternal leptin due to obesity; however, expression of leptin receptor by placenta is decreased in obese women (Farley et al., 2010). Maternal leptin levels are correlated with cord blood levels; thus fetuses of obese mothers on average will be exposed to higher leptin levels. In addition

to peripheral metabolic changes associated with increased cord blood leptin, such as fetal insulin resistance (Catalano et al., 2009), human infants of obese mothers may have altered appetite circuits due to the effects of altered placental signaling on fetal brain development. Maternal adipose, in conjunction with placental signaling, may work to alter her child's future feeding behavior. Obesity in the elderly is associated with increases of amygdalar and hippocampal volume (Widya et al., 2011), regions of the brain associated with motivation and memory.

Maternal biochemical signaling to offspring continues after birth, as milk contains many growth factors and signaling molecules (Garofalo, 2010; Savino and Liguori, 2008; Walker, 2010). Many of the growth factors found in milk [e.g., epidermal growth factor (EGF) and transforming growth factor β (TGF-β)] are also found in amniotic fluid (Wagner et al., 2008). Gut maturation is significantly affected by EGF and TGF-β, both in utero and then through early lactation. Giving human breast milk to preterm infants greatly reduces the risk of necrotizing enterocolitis, a leading cause of morbidity and mortality in preterm babies (Dvorak, 2010).

Interestingly, breast milk provides a post natal source of exogenous leptin to infants (Smith-Kirwin et al., 1998). Leptin concentration of breast milk is negatively correlated with infant growth; however, there does not appear to be a strong association with maternal adiposity (Dundar et al., 2005). Breastfeeding is associated with a reduced risk for childhood obesity (Savino et al., 2009). However, maternal obesity is associated with a decreased rate of initiation of breastfeeding and shorter breastfeeding duration (Amir and Donath, 2007). Maternal overweight and obesity diminishes the prolactin response to suckling (Rasmussen and Kjolhede, 2004), suggesting a biochemical explanation for the difficulties in lactation onset and reduced milk production in obese women. Whether maternal obesity affects the cytokine, growth factor and immune factor components in milk is not known; however, breast milk is a potential source of early life metabolic and brain programming that could be playing a role in the modern human obesity epidemic. Evolved signaling systems may be inappropriately programming our offspring due to the changes in maternal physiology brought about by the mismatch between our modern environment and our evolutionary history.

SUMMARY

The modern human obesity epidemic represents a complex interaction between the human epigenome and the modern environment. This same type of interaction appears, not surprisingly, to be happening among captive animals in zoos and laboratory colonies. Obesity among captive nonhuman primates has many of the same negative metabolic consequences as in humans. Thus, obesity can be defined in relation to metabolic dysregulation associated with an excess of adipose tissue. Adipose tissue acts as an endocrine organ, with regulatory signaling that affects metabolism; placenta also acts as a regulatory organ. Maternal obesity complicates metabolic regulation during pregnancy with potentially serious consequences for offspring. Altered signaling due to maternal obesity may continue after birth via the growth factor constituents in milk. A vulnerability to obesity may be programmed via altered maternal signaling *in utero* and pre weaning. Maternal obesity in humans and in captive animals may be predisposing the next generation to obesity and obesity-related metabolic diseases.

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