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Interaction of perinatal and pre-pubertal factors with genetic predisposition in the development of neural pathways involved in the regulation of energy homeostasis

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Abstract

A majority of human obesity is inherited as a polygenic trait. Once obesity develops, over 90% of individuals repeatedly regain lost weight after dieting. Only surgical interventions offer long lasting weight loss. Thus, clinical data suggest that some individuals have a predisposition to develop and maintain an elevated body weight set-point once they are provided with sufficient calories to gain weight. This set-point is mediated by an integrated neural network that controls energy homeostasis. Unfortunately, currently available tools for identifying obesity-prone individuals and examining the functioning of these neural systems have insufficient resolution to identify specific neural factors that cause humans to develop and maintain the obese state. However, rodent models of polygenically inherited obesity allow us to investigate the factors that both predispose them to become obese and that prevent or enhance the development of such obesity. Maternal obesity during gestation and lactation in obesity-prone rodents enhances offspring obesity and alters their neural pathways involved in energy homeostasis regulation. Early postnatal exposure of obesity-resistant offspring to the milk of genetically obese dams alters their hypothalamic pathways involved in energy homeostasis causing them to become obese when fed a high fat diet as adults. Finally, short-term exercise begun in the early post-weaning period increases the sensitivity to the anorectic effects of leptin and protects obesity-prone offspring from becoming obese for months exercise cessation. Such studies suggest that early identification of obesity-prone humans and of the factors that can prevent them from becoming obese could provide an effective strategy for preventing the world wide epidemic of obesity.

Keywords

obesity; hypothalamus; leptin; exercise

Introduction

The idea that the perinatal nutritional environment can affect the metabolic status of offspring arose from epidemiological studies carried out on survivors of the Dutch Hunger Winter which followed World War II (Ravelli et al., 1998; Ravelli et al., 1976; Ravelli and Belmont, 1979; Stein et al., 1995). Although the results varied with regard to outcome, these

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studies and others (Barker, 1995; Barker, 1998) suggested that undernutrition during various stages of gestation was associated with an increased risk of adverse metabolic outcomes in offspring. These include obesity, diabetes, hypertension and stroke. Additional observations made it clear that the postnatal environment was also important in the determination of metabolic outcome (Gillman et al., 2001; O'Tierney et al., 2009; Plagemann et al., 2002) (Ravelli et al., 2000). However, as might be expected from a heterogeneous population, the outcomes of these perinatal effects varied considerably. This is not surprising with regard to obesity since up to 70% of human obesity is inherited as polygenic traits (Bouchard and Tremblay, 1990; Stunkard et al., 1986) and the most common forms of human obesity arise from the interactions of multiple genes, environmental factors, and behavior (Comuzzie and Allison, 1998). This would predict different outcomes depending upon the perinatal environment and the genetic background of the individual. Although it is known that parental obesity has a high correlation with offspring obesity (Maffeis et al.; Schaefer-Graf et al., 2005), the inability to identify individual obesity-prone humans accurately makes interpretation of such data difficult with regard to the role of environment x gene interactions. Finally, although strides with sophisticated imaging techniques have been made to link obesity with altered brain function (Baicy et al., 2007; Batterham et al., 2007; Del Parigi et al., 2002; Farooqi et al., 2007; Matsuda et al., 1999; Wang et al., 2001), these techniques still lack sufficient resolution to assess the function of complex brain regions such as the hypothalamus and brainstem that regulate energy homeostasis. Thus, many of the advances in our understanding of how genotype interacts with the brain-body-external environment interface to alter the regulation of energy homeostasis have utilized animals models. These interactions will be the subject of this review with a specific focus on the perinatal and pre-pubescent periods since this is the time during which the development of these systems are highly susceptible to environmental perturbations.

Neural control of energy homeostasis

Energy homeostasis is the balance between intake on the one hand and expenditure on the other. Any excess caloric intake over expenditure is stored primarily as adipose tissue and this storage depot is utilized as a primary source of energy during periods of energy deficit. The regulation of energy homeostasis reflects an ongoing dialogue among the internal and external environments and the brain. The brain is capable of sensing and integrating a multitude of hormonal, metabolic and hard wired neural signals from peripheral sensors and organs to regulate both the control of individual meals and the long-term balance between intake and expenditure. Leptin, which is produced by adipose depots in proportion to their size, acts as the prototypic signal for keeping the brain informed about the status of peripheral adipose stores (Zhang et al., 1994). As depot size increases due to excess intake over expenditure, leptin levels increase to provide a tonic, negative feedback on anabolic, and a positive feedback on catabolic neural circuits. Insulin, although produced by the pancreas, indirectly reflects adipose levels (Bagdade et al., 1967; Polonsky et al., 1988) and acts as an additional negative feedback signal. Various gut neuropeptides are produced in response to both pre- and postingestive factors to modulate short-term regulation of individual meals (Shin et al., 2009). Many of these are sensed by vagal and sympathetic afferents which terminate in critical brainstem areas (Shin et al., 2009). In addition, a variety of metabolic substrates such as glucose, fatty acids, ketone bodies and lactate, as well as cytokines produced in the periphery, signal the brain via these same autonomic afferents and by transport across the blood-brain barrier (Levin et al., 2004b; Levin, 2006; Patterson and Levin, 2008). These signals are sensed and integrated by a distributed network of "metabolic sensing" neurons located in key areas of the hindbrain and forebrain, including critical hypothalamic nuclei such as the arcuate (ARC) and ventromedial (VMN) nuclei (Levin et al., 2004b; Levin, 2006; Patterson and Levin, 2008). The integrated signals from this network are relayed to efferent neuroendocrine and autonomic areas of the hypothalamus

(paraventricular nucleus (PVN) and lateral hypothalamic area (LHA)) and hindbrain. In addition, neurons in areas of the brain involved in motivation, reward and memory are engaged by many of the same afferent signals from the periphery (Levin et al., 2004b; Levin, 2006; Patterson and Levin, 2008).

Development of the nervous system

Progenitor cells arise in a number of sites throughout the nervous system and differentiate during development into glial and neural elements. In the hypothalamus, new neuron formation (neurogenesis) takes place in the neuroepithelial lining of the third cerebral ventricle (Altman and Bayer, 1978; Cottrell et al., 2009; Kokoeva et al., 2005; Kokoeva et al., 2007; Xu et al., 2005). These neurons migrate to their final positions and then send out axonal sprouts to target areas. Those axons that form functional connections with their targets survive and those that do not undergo apoptotic cell death (Botchkina and Morin, 1995; Fujioka et al., 1999). One of the problems in using rodent models as surrogates for human conditions in this research area is that there are critical differences in the timing of central nervous system development between humans and the rodents. For example, whereas the human hypothalamus is completely developed at birth (Ackland et al., 1983; Bugnon et al., 1982; Burford and Robinson, 1982; Koutcherov et al., 2002; Mai et al., 1997), most hypothalamic neurons differentiate into mature neurons at embryonic day 12–16 (E12–16) (Markakis, 2002), where birth of the pup occurs at ~E22. Furthermore, hypothalamic projections from the ARC to the PVN are not completed until P12–14 in rodents (Bouret et al., 2004a; Grove et al., 2003; Grove and Smith, 2003). Such disparities unfortunately make it difficult to equate the timing of interventions and their effects on brain development in rodents and humans. Also, it is now clear that some hypothalamic neurogenesis continues into early postnatal, and possibly into adult life in rodents (Cottrell et al., 2009; Kokoeva et al., 2005; Kokoeva et al., 2007) but it is unknown whether similar continued neurogenesis occurs in humans. Finally, other brain areas undergo different temporal patterns of this developmental sequence and these patterns are different in human vs. rodent brains.

Regardless of the temporal sequences, there are numerous factors that can influence neural development. Importantly, both leptin and insulin have properties that affect neuronal survival (neurotropic) and process outgrowth (neurotrophic) of developing neurons (Bouret et al., 2004b; Bouret et al., 2008; Puro and Agardh, 1984; Recio-Pinto et al., 1984; Tanaka et al., 1995; Udagawa et al., 2006). Mice lacking leptin or with deficient leptin signaling have abnormal development of ARC-PVN axonal projections of anabolic neuropeptide Y (NPY/agouti-related peptide (AgRP) and catabolic proopiomelanocortin (POMC) neurons involved in the regulation of energy homeostasis (Bouret et al., 2004b). On the other hand, injection of insulin into the dam during the last week of gestation (Jones and Dayries, 1990; Jones et al., 1995; Jones et al., 1996) or directly into the hypothalamus on or before P8 produces obesity in association with altered hypothalamic development (Plagemann et al., 1992; Plagemann et al., 1999b). It is unclear whether the alterations produced by differences in leptin and insulin signaling involve epigenetic modifications (see below) or, as is more likely, cause their effects by directly altering physical properties of the developing nervous system. Finally, amylin has recently been reported to influence the development of pathways from the area postrema to the nucleus of the solitary tract (Lutz, 2010). This is particularly interesting since amylin administration increases binding of leptin to its receptors in the hypothalamus and produces a synergistic effect on leptin sensitivity both biochemically and in the treatment of human and rodent obesity (Roth et al., 2008; Trevaskis et al., 2009; Turek et al., 2010).

Perinatal factors that alter offspring energy homeostasis

Based on the type of intervention and its timing, there are two broad categories of possibly interrelated change which can occur in offspring during the perinatal and pre-pubertal periods, genetic imprinting and altered organ development. First, non-Mendelian, or epigenetic modifications of genes can occur by methylation or acetylation. Such imprinting can markedly alter the ways in which those genes are expressed in the formation of organs and metabolic pathways involved in the regulation of energy homeostasis. Prader-Willi syndrome is a prototypic example of a disease caused by imprinting which affects both energy homeostasis and neural development. It is caused by inhibition of genes at the 15q11-q13 locus which undergo histone methylation on the maternal chromosome (Xin et al., 2003). It is characterized by pre- and postnatal hypotonia, feeding difficulties in early life, subsequent hyperphagia with obsessive/compulsive food searching, obesity, short stature and hypogonadism (Gurrieri and Accadia, 2009). In addition to such well described syndromic disorders, alterations in the perinatal nutritional environment can also cause epigenetic changes that alter the phenotypic characteristics of offspring. For example, supplementation of the maternal diet of yellow agouti mice with a diet high in methyl donors increases methylation of so called CpG islands resulting in altered coat color of the offspring (Waterland and Jirtle, 2003). Also, offspring of mothers that show high levels of licking and grooming and arched-back nursing alter offspring histone acetylation and transcription factor NGFI-A binding to a hippocampal glucocorticoid receptor gene promoter region. This can be reversed and the stress responsivity of offspring altered either by cross-fostering to dams exhibiting low levels of these behaviors or by central infusion of a histone deacetylase inhibitor (Weaver et al., 2004).

A second way in which perinatal interventions can alter offspring function is to affect the development of specific organ systems through changes in the metabolic and hormonal milieu of the perinatal environment. This idea was first enunciated by Barker (Barker, 1990) who proposed that fetal or early life environmental perturbations can act to program risks for adverse health conditions in adult life. This was later extended to apply to type 2 diabetes (Hales and Barker, 1992). While imprinting might be involved in these processes, it is not necessarily required. In experimental animals, such effects can be parsed out by altering the metabolic and hormonal milieu of offspring during gestation and/or the postnatal period. Interestingly, undernutrition (caloric or protein), maternal obesity or offspring overnutrition during various stages of gestation and/or lactation can lead to obesity and/or diabetes in adult offspring of both humans and rodents (Buckley et al., 2005; Faust et al., 1980; Fernandez-Twinn et al., 2004; Guo and Jen, 1995; Jones and Friedman, 1982; Jones et al., 1984; Jones et al., 1986; Kennedy, 1957; Levin et al., 2005; Ozanne et al., 2004; Ravelli et al., 1998; Ravelli et al., 1999; Samuelsson et al., 2008). These conditions are particularly aggravated by allowing offspring either normal postnatal nutrition, in the case of undernourished dams, or by feeding a high fat diet after weaning. Importantly, such perinatal dietary manipulations have lasting effects on the development and function of hypothalamic pathways and systems involved in the regulation of energy homeostasis (Cripps et al., 2009; Heideil et al., 1999; Irani et al., 2009; Jones et al., 1995; Le Foll et al., 2009; Plagemann et al., 1998a; Plagemann et al., 1998b; Plagemann et al., 1999a). While the development of obesity in offspring of obese mothers, or mothers who were overnourished during the early postnatal period, would appear to be a logical outcome, the reason for obesity following gestational undernutrition is less obvious. Hales and Barker (Hales and Barker, 2001) proposed that poor fetal and infant growth and the subsequent development of the metabolic syndrome are a direct result of early life undernutrition due to the attempts of the fetus to compensate for limited nutritional resources by increasing metabolic efficiency to aid survival both pre- and postnatally.

Gene x environment interactions in the development of obesity

All of the studies quoted above were carried out either retrospectively in humans or in animal models where possible genetic predispositions towards obesity could not (in the case of humans) or were not considered (in the case of rodents). Aside from one study demonstrating important postnatal effects of maternal obesity on inbred strains of mice (Reifsnyder et al., 2000), the subject of gene x environment interactions predisposing to obesity has largely been ignored. The lack of such studies led us to develop substrains of rats which we selectively bred for their propensity to develop diet-induced obesity (DIO) or to be diet-resistant (DR) when fed a 31%, 25% sucrose high energy (HE) diet. These rats were originally derived from the outbred line of Sprague-Dawley rats from Charles River Laboratories (Levin et al., 1997). Perpetuation of these phenotypic traits has been remarkably stable over more than 40 generations. Although the genotype is unknown, we were able to transmit the DIO phenotype to the inbred, obesity-resistant Fischer F344 rat strain by crossing DIO males with F344 females (Levin et al., 2003a). These studies, as well as many others phenotyping the DIO rat, demonstrate that the DIO phenotype is transmitted as a polygenic trait which is associated with hyperphagia, obesity, insulin resistance, hypertension and hyperlipidemia when, and only when, they are exposed to HE diets (Ricci and Levin, 2003). Thus, this rat strain has many of the characteristics of a majority of obese humans (Bouchard and Perusse, 1993; Stunkard et al., 1986).

Importantly, the DIO rats appear to have an inborn reduction in their sensitivity to the behavioral and physiological effects of leptin on energy homeostasis. From as early as P10, they have reduced signaling downstream of the long, signaling form of the leptin receptor (Lepr-b) in the ARC (Bouret et al., 2008). This is associated with a reduced anorectic and thermogenic effect of leptin before they are made obese on HE diet (Gorski et al., 2007) and reductions in the expression of the Lepr-b gene (Levin et al., 2003b; Levin et al., 2004a), binding of leptin to its receptor in the ARC, VMN and DMN (Irani et al., 2007) and the excitatory effects of leptin on their VMN neurons (Irani et al., 2009). Importantly, leptin resistance during the postnatal period is associated with a reduced trophic effect of leptin which is likely to be responsible for the maldevelopment of their ARC-PVN AgRP and α -MSH neuronal projections (Bouret et al., 2008). DIO rats also have reduced dendritic arborization of VMN neurons (Labelle et al., 2009) and a reduced areal extent of VMN cellular elements (Levin, 1996). In addition to inherent leptin resistance, DIO rats are also centrally resistant to insulin's anorectic effects (Clegg et al., 2005). This is paralleled by reduced hypothalamic binding of insulin to its receptor (Irani et al., 2009). DIO rats also have altered hypothalamic norepinephrine, dopamine and serotonin function before they become obese (Hassanain and Levin, 2002; Levin, 1995; Levin, 1996; Wilmot et al., 1988). Finally, DIO rats have increased sensitivity to the inhibitory effects of both glucose and long chain fatty acids on VMN neurons (Le Foll et al., 2009) and this is associated with reduced physiological responses to the central effects of glucose (Dunn-Meynell et al., 1997; Levin, 1992; Levin and Planas, 1993).

Having extensively characterized these models of genetically inherited predispositions to become obese or resist obesity on moderately high fat diets, we then utilized them to investigate the perinatal factors that contribute to these predispositions. Our first study demonstrated that making DIO dams obese during gestation and lactation caused their adult offspring to become obese and insulin resistant, even when fed only a low fat diet from weaning (Levin and Govek, 1998). Importantly, neither feeding DR dams HE diet nor making them obese on a highly palatable liquid diet during gestation and lactation altered the resistance of the DR offspring rats to obesity on HE diet as adults (Levin and Govek, 1998). In association with their increased predisposition to become obese, offspring of obese DIO dams also had a reduction in PVN (as well as ARC and VMN) norepinephrine reuptake

transporters (Levin and Dunn-Meynell, 2002). Since the majority of norepinephrine is removed from the synapse by reuptake into axons terminals by these transporters, a reduction in their number would be expected to increase synaptic norepinephrine content, a condition known to increase food intake and cause obesity (Leibowitz et al., 1984; Levin and Dunn-Meynell, 2002). Interestingly, maternal obesity per se was associated with enlargement of the areal extent of both the VMN and DMN in DIO and DR offspring. Also, despite the fact that their offspring did not become obese as adults, offspring of obese DR dams did have increased norepinephrine transporters in the PVN (which should reduce synaptic norepinephrine) and a generalized increase in serotonin reuptake transporters in all hypothalamic areas (Levin and Dunn-Meynell, 2002).

At the cellular level, offspring of lean DIO dams have fewer VMN neurons that are excited and more that are inhibited by leptin than do offspring of lean DR dams. While maternal intake of HE diet during gestation and lactation is associated with a reduced number of such leptin-excited neurons in both DIO and DR offspring, this reduction is much greater in offspring of obese DIO dams which also have a selective reduction in the number of leptin-inhibited neurons (Irani et al., 2009). The VMN is also enriched in metabolic sensing neurons which respond to both glucose and long chain fatty acids. Whereas 3–4 wk old offspring of lean DIO dams have 2 fold more VMN neurons that are inhibited by glucose (GI neurons) than do those of lean DR dams, this difference is eliminated in offspring of obese DIO dams (Le Foll et al., 2009). Similarly, while offspring of lean DIO dams have more GI neurons that are either excited or inhibited by oleic acid than do lean DR offspring, maternal obesity exaggerates this difference in DIO offspring (Le Foll et al., 2009). Thus, VMN neurons in DIO rats are generally less responsive to both hormonal and metabolic signals from the periphery than are those from DR rats and this difference is exaggerated by maternal intake of HE diet and the development of obesity in DIO dams.

Since axonal outgrowth of ARC NPY/AgRP and POMC neurons occurs largely postnatally in rodents, manipulation of the postnatal environment can have major effects on this development in genetically predisposed animals. For example, the leptin deficient ob/ob mouse, like the DIO rat, has a reduced plexus of both AgRP and α -MSH axon terminals in the PVN. This deficit can be almost fully correct by administration of leptin during the first 2 wk of postnatal development (Bouret et al., 2004b). Similarly, cross-fostering genetically obesity-prone mice to genetically lean dams at birth ameliorates their obesity, while fostering lean mice to obesity-prone dams makes the genetically lean mice more obesity-prone (Reifsnnyder et al., 2000). Similarly, fostering offspring of lean DR dams to obese (but not lean) DIO dams causes the offspring to become obese and insulin resistant when fed HE diet as adults (Gorski et al., 2006). Their obesity is associated with increases of 45% in ARC AgRP, 46% in VMN Lepr-b and 38% insulin receptor mRNA expression (Gorski et al., 2006). This effect appears to be mediated in part by the fact the milk from obese DIO dams has very low levels of both poly- and mono-unsaturated fatty acids and, despite the fact that their plasma insulin levels are not elevated during lactation, their milk has a marked increase in insulin levels (Gorski et al., 2006). Since rat pups absorb both insulin and leptin from maternal milk during the early postnatal period (Koldovsky et al., 1995; Sanchez et al., 2005), and increased hypothalamic insulin levels during this period can cause obesity in adult offspring (Plagemann et al., 1992), this elevation in maternal milk insulin could contribute to the accentuated obesity of offspring of obese DIO dams. Disappointingly, fostering offspring of either lean or obese DIO dams to lean DR dams has essentially no protective effect on their propensity to become obese on HE diet as adults (Gorski et al., 2006). Thus, there is a genotype specific effect of altering the pre- and early postnatal environment on the propensity of selectively bred DIO and DR rats to become obese and on the underlying neuronal responsiveness of hypothalamic neurons to hormones and metabolic substrates that regulate energy homeostasis.

Exercise has a variable effect on weight loss in obese and previously obese humans (Klem et al., 1997; McGuire et al., 1999; Patterson and Levin, 2008; Wyatt et al., 1999). In rodents, exercise generally produces weight loss only in obese males since lean males and obese females tend to compensate for increased energy expenditure and weight loss by increasing their caloric intake (Levin and Dunn-Meynell, 2004; Levin and Dunn-Meynell, 2006; Mayer et al., 1954; Patterson et al., 2008; Patterson et al., 2009). Even when obese adult rats do lose weight during exercise, they regain it when exercise ceases (Applegate et al., 1984). However, since the rat brain continues to develop well into the pre-pubescent stage, we hypothesized that early onset exercise might have a more long-lasting effect on lowering body weight in DIO rats. We found that, when male DIO rats are fed HE diet but also provided with a running wheel from 4 wk of age, they gain less weight than sedentary DIO rats. Moreover, when the wheels are removed, they maintain their lower body weight and adiposity gain for up to two and a half months (Patterson et al., 2008). Three, but not two weeks, of running wheel exposure is sufficient to maintain this post-exercise protection from becoming obese despite continued intake of HE diet (Patterson et al., 2008). Importantly, sensitivity to the anorectic effects of leptin, binding of leptin to its receptor and signaling downstream of the leptin receptor are all increased after 3 wk of exercise and these increases persist for at least another 4 wk after wheel removal (Patterson et al., 2009). In these same studies, a control group of rats were calorically restricted to 85% of the intake of sedentary DIO rats for comparison to the exercising rats. Strikingly, as opposed to the rats which had been in running wheels and were protected from becoming obese after wheel removal, calorically restricted DIO rats immediately overate and became even more obese than the sedentary rats when they were allowed to eat ad libitum (Patterson et al., 2008). Also, while exercise had no effect on the outgrowth of axons from ARC neurons to their PVN targets, only 3 wk of caloric restriction produced a further inhibition of outgrowth of α -MSH axons to the PVN (Patterson et al., 2009). Thus, short-term post-weaning exercise increased both leptin sensitivity and resistance to obesity beyond the exercise period, despite continued HE diet intake. However, caloric restriction during this same period had the opposite effect; it increased obesity in association with further deterioration of the already defective outgrowth of catabolic α -MSH fibers to the PVN. Thus, interventions beginning in this critical pre-pubertal period can have either positive and negative effects on re-setting the body weight set-point in genetically obese DIO rats.

Summary and conclusions

Once it develops, obesity becomes an intractable problem for which only surgical intervention has proven effective as a treatment in humans. For that reason, prevention is likely to be the best strategy to fight the now, world-wide epidemic of obesity. Because energy homeostasis is regulated by the brain and because the development of neural systems that regulate energy homeostasis are affected by a number of perinatal and early pre-pubertal interventions, a focus on identifying factors that favorably affect the development of obesity during this period is an obvious target for preventing obesity. Since human obesity has a strong underlying genetic predisposition, research which identifies factors that can influence the development of obesity in a genotype-specific fashion are likely to have the biggest impact upon developing strategies to prevent obesity. Of course, this presupposes that we can prospectively identify humans who are at high risk for becoming obese before they actually become obese. While there statistical correlations between parental and/or ethnic predispositions to obesity that provide some hints as to who will become obese, for effective intervention we will first need to find an effective way of identifying specific individuals in the general population who are at risk for becoming obese. Thus, research in this field should focus on early identification of both obesity-prone individuals and on factors that alter the likelihood that such individuals will become obese. Our studies suggest that a profitable area for exploration is the identification of specific factors produced by alterations

of the perinatal nutritional and metabolic environments and physiological interventions such as exercise that increase the inhibitory feedback of signals such as leptin as a strategy for producing pharmacological interventions to prevent and/or treat early onset obesity.

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