Metabolic imprinting: critical impact of the perinatal environment on the regulation of energy homeostasis

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Epidemiological studies in humans suggest that maternal undernutrition, obesity and diabetes during gestation and lactation can all produce obesity in offspring. Animal models have allowed us to investigate the independent consequences of altering the pre- versus post-natal environments on a variety of metabolic, physiological and neuroendocrine functions as they effect the development in the offspring of obesity, diabetes, hypertension and hyperlipidemia (the ‘metabolic syndrome’). During gestation, maternal malnutrition, obesity, type 1 and type 2 diabetes and psychological, immunological and pharmacological stressors can all promote offspring obesity. Normal post-natal nutrition can reduce the adverse impact of some of these pre-natal factors but maternal high-fat diets, diabetes and increased neonatal access to food all enhance the development of obesity and the metabolic syndrome in offspring. The outcome of these perturbations of the perinatal environmental is also highly dependent upon the genetic background of the individual. Those with an obesity-prone genotype are more likely to be affected by factors such as maternal obesity and high-fat diets than are obesity-resistant individuals. Many perinatal manipulations appear to promote offspring obesity by permanently altering the development of central neural pathways, which regulate food intake, energy expenditure and storage. Given their strong neurotrophic properties, either excess or an absence of insulin and leptin during the perinatal period are likely to be effectors of these developmental changes. Because obesity is associated with an increased morbidity and mortality and because of its resistance to treatment, prevention is likely to be the best strategy for stemming the tide of the obesity epidemic. Such prevention should begin in the perinatal period with the identification and avoidance of factors which produce permanent, adverse alterations in neural pathways which control energy homeostasis.

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1. INTRODUCTION

There are several possible explanations for the relatively recent increase in the prevalence of obesity and the metabolic syndrome (diabetes, hypertension, hyperlipidaemia; Bjorntorp 1992) with which it is associated in both the adult (Popkin & Doak 1999; van der Sande *et al.* 2001; Ford *et al.* 2004; Al-Almaie 2005; Andersen *et al.* 2005; Keinan-Boker *et al.* 2005; Kim *et al.* 2005; Sanchez-Castillo *et al.* 2005) and childhood populations (Rosenbloom *et al.* 1999; Wang 2001; Ogden *et al.* 2002). Epidemiological studies in humans suggest that undernutrition during various phases of gestation can predispose some individuals to become obese and insulin-resistant (Ravelli *et al.* 1976; Dorner *et al.* 1984; Phipps *et al.* 1993; van der Sande *et al.* 2001; Al-Almaie 2005; Kim *et al.* 2005; Sanchez-Castillo *et al.* 2005). Barker suggested that the adaptations required to survive in an energy deficient gestational environment produced individuals who

were more prone to develop diseases such as coronary heart disease, stroke, type 2 diabetes mellitus (T2DM) and hypertension (Barker 1995*a,b*). However, another outcome of gestational undernutrition not mentioned by Barker is an enhanced metabolic efficiency, which predisposes the individual to become obese. It is likely that he did not mention obesity because it had not yet been widely recognized as an important predisposing cause to all of the other diseases on which he originally focused (Bjorntorp 1992).

But gestational undernutrition is not the only perinatal condition which predisposes individuals to develop obesity. Obesity has reached epidemic proportions in the United States without major periods of famine (Ogden *et al.* 2002; Ford *et al.* 2004) and some studies suggest that maternal obesity itself is associated with a higher risk of obesity in offspring (Plagemann *et al.* 1997; Whitaker 2004). The apparent paradox whereby both a surfeit and deficiency of energy supply during gestation are linked to obesity is mirrored in the fact that insulin deficiency (type 1 diabetes mellitus, T1DM) and insulin excess (T2DM) during pregnancy both increase the risk that offspring will develop obesity

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and T2DM (Silverman *et al.* 1995; Berenson *et al.* 1997; Pettitt *et al.* 1988). Although these results are not necessarily mutually exclusive, they do demonstrate the problems of interpreting the results of retrospective studies in humans, which lack proper controls for dietary content and quantity or the severity of obesity or diabetes in mothers and offspring. Neither can one discern the relative importance of pre- versus post-natal factors from most of these human studies. Most importantly, it is virtually impossible to identify potential underlying mechanisms for the increase in offspring obesity from such studies. For these reasons, animal models have become a mainstay of research, which seeks to identify the impact of manipulating the perinatal environment on the metabolic, neural and hormonal systems, which normally regulate energy homeostasis and their role in the development of obesity and the metabolic syndrome. Even so, studies carried out in the controlled environment of the research laboratory still leave a number of important unanswered questions as to the types of perinatal conditions which predispose offspring to develop obesity and the mechanisms by which these conditions produce this outcome.

This review will focus on the impact of perinatal factors on the control of energy homeostasis where energy homeostasis is defined as the balance among energy intake, expenditure and storage. In lean individuals, these competing forces are balanced within very narrow limits and do not vary appreciably over long periods of time (Levin *et al.* 1985; Weinsier *et al.* 1995). However, in obese individuals the 'set-point' or 'settling-point' about which they are balanced tends to rise throughout life and, at each successively higher level, cannot be lowered permanently by any conventional therapy in the majority of individuals (Scarpace *et al.* 2000*a,b*). There is a controversy about whether body weight and adipose stores are actually regulated variables (Wirtshafter & Davis 1977; Davis & Wirtshafter 1978; Stunkard 1982; Keesey & Corbett 1984; Flatt 2000). Regardless, of whether these are actively or passively regulated, it is clear that specific levels are actively defended when attempts are made to drive them off a given baseline. This is specifically the case in caloric restriction where the system actively resists all attempts to drive energy homeostasis below a basal level of adiposity (MacLean *et al.* 2004*a-c*). On the other hand, the defended body weight can easily be moved permanently upward in some individuals (Levin & Keesey 1998; Levin & Dunn-Meynell 2002*a-c*). This unidirectional movement of the defended body weight would ensure maximal preservation of energy stores during times of plenty but allow for more leeway for overfilling of stores in anticipation of times of deficit. This metabolic 'strategy' predisposes some individuals to become obese in times of plenty and becomes problematic because such individuals avidly defend each new, higher level of adiposity. This upward but not downward movement of the defended body weight suggests that some permanent change can occur in the pathways involved in the regulation of energy homeostasis. One possibility is that neuronal plasticity occurs within the central nervous systems with formation of new neural connections much as

occurs during the formation of long-term memories (Levin & Keesey 1998; Levin 2000). While evidence for such naturally occurring, permanent changes in neural connectivity are lacking, a variety of lesions within the complex network of neurons and metabolic sensors within the brain and periphery can markedly and permanently alter the level about which body weight is defended (Mitchel & Keesey 1977; Keesey & Corbett 1984; Vilberg & Keesey 1984, 1990; King *et al.* 1993*a,b*; Bellinger & Bernardis 2002). Thus, a variety of alterations in the connectivity and function of pathways regulating energy homeostasis, whether naturally occurring or experimentally imposed, can lead to major changes in the level of defended body weight and adiposity.

Lean individuals appear to accurately monitor their caloric intake within very narrow limits and make appropriate corrections in subsequent intake and energy expenditure to maintain their defended body weights within relatively narrow limits over long periods of time (Levin *et al.* 2003*a,b*). Such tight regulation of adipose stores is not necessarily the best survival strategy in times of intermittent famine. Based on work in rodent models of diet-induced obesity (DIO), we have proposed that the best survivors might be those with an elevated threshold for sensing and responding to many of the hormonal and metabolic cues which normally limit food intake (Levin & Dunn-Meynell 2002*a-c*; Levin *et al.* 2003*a,b*; Ricci & Levin 2003; Levin 2004). Such an elevated threshold might allow such individuals to ingest and store more energy as fat than lean individuals in times of excess food availability to act as a buffer against times when the food supply becomes limited. During periods of low energy availability, catabolic processes are minimized and the anabolic drive to eat and conserve stored calories by reducing metabolic rate is maximized (Hill *et al.* 1985; Levin & Dunn-Meynell 1997; Mizuno *et al.* 1998; Ahima *et al.* 1999*b*; Levin 1999; MacLean *et al.* 2004*a-c*). It is likely that, much of the control of energy homeostasis is mediated by central neural systems, which are genetically determined. However, these systems are also highly plastic and readily modified by environmental inputs. Because much of the normal plasticity within these systems occurs during their developmental stages, the perinatal period is the most important time during which extrinsic factors can permanently alter the set-point about which body weight is regulated. The term 'metabolic imprinting' has been used to denote the long-term effects that the perinatal environment has on the developing foetus and neonate (Waterland & Garza 1999). This review will focus on the imprinting effects that perturbations of the perinatal environment have on the development of obesity and the metabolic syndrome and the way in which such perturbations alter the neural systems which regulate energy homeostasis.

2. EFFECTS OF ALTERING THE MATERNAL ENVIRONMENT THROUGHOUT GESTATION AND LACTATION

The perinatal environment is an important determinant of future weight gain, adiposity and other

physiological properties. In rats, life long patterns of food intake and body weight are essentially established by events, which occur prior to the second week of life as long as dietary content is held constant thereafter (Kennedy 1957; Widdowson & McCance 1960). Maternal obesity throughout gestation and lactation in rats is clearly associated with the development of the obesity and the metabolic syndrome in offspring (Guo & Jen 1995; Langley-Evans *et al.* 1996; Levin & Govek 1998; Palinski *et al.* 2001; Levin & Dunn-Meynell 2002a–c; Khan *et al.* 2003; Levin *et al.* 2005; Taylor *et al.* 2005). Feeding dams diets with moderate or high-fat content throughout the perinatal period produces obesity in all offspring (Guo & Jen 1995; Wu *et al.* 1998). But genotype also has an important influence on this outcome. In rats selectively bred to be either prone or resistant to the development of DIO, maternal obesity throughout gestation and lactation leads to increased obesity only in the offspring of dams which have a genetic predisposition to develop DIO (Levin & Govek 1998; Levin & Dunn-Meynell 2002a–c). Maternal diabetes also has a deleterious effect on offspring regardless of their genetic background. Mothers with T2DM produce offspring which become obese and have abnormalities of insulin secretion (Boloker *et al.* 2002), while T1DM during pregnancy produces both cardiovascular dysfunction (Holemans *et al.* 1999) and accelerated growth through the first 6–10 weeks of adult life (Oh *et al.* 1988).

Macronutrient composition of the maternal diet is also a critical determinant of outcome in offspring. While maternal high-fat diets generally promote offspring obesity (Guo & Jen 1995; Wu *et al.* 1998), all fats are not created equal in this respect. Maternal diets high in omega-6 fatty acids produce obese offspring with increased hepatic lipid content and hepatic insulin-resistance (Buckley *et al.* 2005). However, feeding dams diets high in essential fatty acids throughout late gestation and lactation produces offspring which eat less, are leaner and have improved insulin sensitivity as adults (Korotkova *et al.* 2001, 2002a,b). High-carbohydrate diets can also alter metabolic function in offspring. In some cases they can be protective. Maternal diets high in carbohydrates produce offspring which remain lighter in weight, become more sensitive to the effects of orexigenic neuropeptides (Kozak *et al.* 2000) and have alterations in their preference for sucrose as adults (Kozak *et al.* 2005).

As in human beings (Ravelli *et al.* 1976; Dorner *et al.* 1984; Phipps *et al.* 1993), maternal malnutrition can also produce obesity and the metabolic syndrome in rodents. Offspring of rat dams subjected to protein malnutrition throughout gestation and lactation become obese, insulin-resistant, hyperlipidemic and hypertensive as adults and these effects are magnified when the offspring are fed a highly palatable diet from weaning (Petry *et al.* 1997; Fernandez-Twinn *et al.* 2004). This outcome is also dependent upon gender. Female offspring of dams which were protein restricted throughout gestation and lactation actually have lower body weights, food intake and increased insulin sensitivity as adults (Zambrano *et al.* 2005).

In summary, high-fat diets and maternal obesity during gestation and lactation promote obesity and insulin-resistance in rat offspring, while high carbohydrate diets may have a protective effect. However, these outcomes are dependent upon the type of fatty acids in the diet, genetic background and gender. On the other hand, maternal undernutrition during gestation also produces obese, insulin-resistant offspring. The fact that both over- and undernutrition during gestation and weaning can lead to the same outcome of obesity and insulin-resistance suggests that different mechanisms underlie the two processes. Undernutrition during gestation and lactation may cause the foetus to become more metabolically efficient to deal with the reduced supply of nutrients during development (Ravelli *et al.* 1976; Barker 1995a,b; Vickers *et al.* 2000; McMillen *et al.* 2005). Such alterations predispose individuals to gain more adiposity and develop insulin-resistance when provided with sufficient calories during the post-natal period (Ozanne & Hales 2005). On the other hand, over-nutrition during gestation and lactation may program the individual to become obese and insulin-resistant by increasing the number of adipocytes and by producing pancreatic β -cell hyperplasia which results in hyperinsulinaemia, insulin-resistance and increased deposition of lipids in adipose stores (Knittle & Hirsch 1968; Johnson *et al.* 1973). Changes in the metabolic milieu during gestation and lactation in obese dams may also affect the development of offspring central systems involved in the regulation of energy homeostasis, possibly because of exposure to high insulin or leptin levels during the period of brain development (Jones & Dayries 1990; Plagemann *et al.* 1992a,b; Dorner & Plagemann 1994; Jones *et al.* 1995, 1996; Ahima *et al.* 1999a; Levin & Dunn-Meynell 2002a–c).

3. PRE-NATAL FACTORS

A number of factors in the gestational environment have important effects on offspring development. Cross fostering studies of mice derived from two different strains suggest that the pre-natal environment accounts for 61–96% of the variance in body weight gain in male and 35–92% in female offspring (Kurniati *et al.* 1998). When rat dams were fed high-fat diets during gestation and their pups were cross-fostered to dams on low-fat diets at birth, the pups became more obese as adults than those whose dams were fed low-fat diets during gestation, even if the latter group of pups were fostered to dams fed a high-fat diets during lactation (Wu *et al.* 1998, 1999). As with humans, maternal malnutrition during gestation also produces offspring obesity in rodents. Jones *et al.* (1984, 1986) were the first to utilize the maternal undernutrition model to simulate the conditions suggested by the famine studies following World War II. They found that up to 50% caloric restriction during the first two trimesters of pregnancy in rat dams produced male (but not female) offspring which spontaneously increased their intakes of low-fat diet, gained more weight beginning at weaning (Jones *et al.* 1986) and developed DIO as adults (Jones *et al.* 1984, 1986). On the other hand, others found that gestational undernutrition produced male offspring,

which had reduced body weight while female offspring had increased body weight and adiposity as adults (Anguita *et al.* 1993). It is unclear what accounts for the differences in these results but it is likely that the gender-based differences in outcome are dependent upon sex hormones and/or sexually dimorphic development of central pathways regulating energy homeostasis. However, no studies have directly tested this hypothesis. Although human studies and the rat studies of Jones *et al.* suggest that malnutrition during early gestation is the most important for the development of offspring obesity, we found that last trimester malnutrition produced obesity in offspring of dams with an obesity-prone, insulin-resistant genotype (Levin *et al.* 2005). Also, severe maternal undernutrition (70% caloric restriction) throughout the entire pregnancy produced offspring, which were underweight at birth, had stunted linear growth but had increased food intake throughout early development. These offspring ended up being obese, hyperinsulinemic, hypertensive and hypoactive as adults (Vickers *et al.* 2000, 2003). Finally, specific maternal protein malnutrition throughout gestation shortens offspring life span if the dams are allowed to overfeed during lactation (Ozanne & Hales 2005). Thus, both caloric or protein undernutrition can produce obesity and T2DM in both human and rodent offspring although it is unclear what the critical period is during gestation for development of these outcomes.

A variety of stressors imposed on the mother during gestation can also effect the metabolic development of offspring. Offspring of dams exposed to endotoxin (Nilsson *et al.* 2001), tumor necrosis factor- α or interleukin-6 (Dahlgren *et al.* 2001) during the first two trimesters of gestation became obese as adults. Paradoxically, injections of dams during the first two trimesters with dexamethasone, an immunosuppressant corticosteroid, produced effects on offspring similar to those whose dams were injected with pro-inflammatory agents (Dahlgren *et al.* 2001). Also, when obesity-prone, insulin-resistant dams were injected with dexamethasone during the last trimester of pregnancy, the growth of their offspring was stunted but they became obese and insulin-resistant as adults (Levin *et al.* 2005). Thus, depending upon the type and timing, a variety of stresses during gestation can promote obesity and insulin-resistance in adult offspring although it is less than clear what mechanisms underlie these outcomes.

Both insulin and leptin have important effects on the metabolic and neural development of the foetus. Insulin is a key regulator of glucose homeostasis but it also acts as an index of carcass adiposity (Bagdade *et al.* 1967; Polonsky *et al.* 1988), a trophic factor for neural development (Puro & Agardh 1984; Recio-Pinto & Ishii 1984; Heidenreich & Toledo 1989) and an antilipolytic agent (Brown *et al.* 1988). While insulin was originally thought not to cross the placenta (Freinkel 1980), there is evidence suggesting that it can actually enter the foetal circulation from the mother in humans (Menon *et al.* 1990). If so, this might explain why offspring of mothers injected with insulin daily during the last trimester of pregnancy develop obesity as adults (Jones *et al.* 1996). Maternal

hyperinsulinaemia might also act by increasing glucose transport across the placenta to the foetus (Osmond *et al.* 2001). Maternal hyperinsulinaemia and hyperglycaemia could thus cause foetal hyperglycaemia with attendant hyperinsulinaemia (Kainer *et al.* 1997). This could contribute to the elevated foetal weight in offspring of mothers with gestational diabetes (Taricco *et al.* 2003). On the other hand, the low-birth weight of offspring of mothers with T2DM might be due to insulin-resistance which develops in the foetus causing reduced effectiveness of insulin as a trophic factor with resultant *in utero* growth retardation (Hattersley & Tooke 1999).

A significant amount of leptin is produced by the placenta (Hoggard *et al.* 1997; Senaris *et al.* 1997). Insulin treatment of T1DM mothers increases placental leptin production (Lepercq *et al.* 1998) leading to increased cord blood leptin levels (Persson *et al.* 1999). In rats, leptin can also cross the placenta and serve as a significant source of leptin in the foetus. In fact, the transport and resultant foetal plasma leptin levels are increased 10-fold during the last trimester of gestation (Smith & Waddell 2003). This finding predicts that foetuses of obese dams should be hyperleptinemic. Since leptin has neurotrophic properties, such hyperleptinaemia might have a major impact on brain development and the central pathways involved in energy homeostasis (Ahima *et al.* 1999a; Bouret *et al.* 2004a,b; Pinto *et al.* 2004).

In summary, maternal undernutrition, high-fat diet feeding and maternal stress during gestation can all predispose offspring to become obese although it is unclear which period of gestation is most critical for such manipulations to lead to this outcome. Since both leptin and insulin have trophic effects on the nervous system, either high or low levels of either in the maternal environment might alter brain development in the foetus.

4. POST-NATAL FACTORS

A number of post-natal factors can alter the development of ingestive behaviour in neonates and predispose them to develop obesity and the metabolic syndrome as adults. Metabolic, hormonal and behavioural interactions of pups with their dams are critical factors in this regard. The composition of milk understandably has a major impact on the developing neonate. Because maternal milk contains more fat than carbohydrate (Grigor *et al.* 1986; Rolls *et al.* 1986; Del Prado *et al.* 1997), neonates utilize fatty acids and ketone bodies as their primary energy substrates. During suckling, neonates transport ketone bodies preferentially over carbohydrates across the blood-brain barrier and ketone bodies serve as the primary energy substrate for neuronal and glia metabolism (Vannucci *et al.* 1991; Pellerin *et al.* 1998). Blockade of both fatty acid oxidation (lipoprivation; Horn & Friedman 1998) and glucose oxidation (glucoprivation; Smith & Epstein 1969) increase food intake in adults. But, despite the high lipid content of their diets, independent feeding in response to such lipoprivation does not develop in rat pups until 12 days of age and independent glucoprivic feeding does not occur

throughout the period of suckling (Swithers 1997; Swithers 2000; Weller *et al.* 2001). Neither are gastric filling or postabsorptive metabolic signals major determinants of intake in neonates. Rather osmotic load appears to be the most important regulator (Weller *et al.* 2001; Davis *et al.* 2003) and this regulation may be mediated by cholecystokinin which can cause satiety in neonates as early as the second week of life (Weller *et al.* 1990).

As would be expected, maternal diet is a primary determinant of milk composition. Feeding dams a 'cafeteria diet' composed of highly palatable junk foods increases the long-chain and decreases the medium-chain fatty acid content of their milk. Intake of such a diet has an additive effect to the presence of maternal obesity in lowering the protein content and raising the long-chain fatty acid content of the milk (Rolls *et al.* 1986). Feeding dams a high-fat diet also accelerates the onset of independent feeding in neonates by 1–2 days (Doerflinger & Swithers 2004) in association with increased weight gain (Swithers *et al.* 2001) and the development of hypertension and abnormal glucose homeostasis as adults (Khan *et al.* 2005). Furthermore, feeding successive generations of dams a high-fat diet leads to progressive increases the level of obesity of their offspring (Lim *et al.* 1991). Under conditions somewhat comparable to bottle feeding, high carbohydrate diets can produce obesity in pups. When pups are artificially raised away from their dams and fed by gastric tube, those fed a diet high in carbohydrate content develop obesity and insulin-resistance as compared to those fed either a low-fat, low carbohydrate or high-fat diet (West *et al.* 1982, 1987; Hiremagalur *et al.* 1993; Vadlamudi *et al.* 1995). This effect is most marked in female offspring (Vadlamudi *et al.* 1995; Diaz & Taylor 1998). This predominant effect in female offspring may account for the carry-over effect such artificial rearing has on the development of obesity in their offspring, even when the next generation is normally reared (Vadlamudi *et al.* 1995). Finally, whereas maternal protein malnutrition during pregnancy lowers offspring birth weight, this effect can be overcome by fostering those offspring with dams fed a normal diet postnatally. Unfortunately, such 'recovered' offspring also become more obese than offspring of normal pregnancies when both are subsequently fed a cafeteria diet (Ozanne *et al.* 2004). As with artificial rearing on high carbohydrate diets, this effect of protein malnutrition carries over into subsequent generations. Male pups become obese and insulin-resistant when their grandmothers (but not their mothers) were protein malnourished during gestation (Zambrano *et al.* 2005).

The quantity of food available during suckling is also a determinant of the development of obesity in pups. Kennedy first used large and small litter sizes as a strategy to alter the intake of neonates (Kennedy 1957). He and others showed that rat pups raised in small litters were heavier at weaning and gained more weight as adults, while those raised in large litters gained less weight than pups raised in normal size litters (Kennedy 1957; Widdowson & McCance 1960; Johnson *et al.* 1973; Oscai & McGarr 1978; Faust *et al.* 1980; Levin *et al.* 1984). These differences in

weight gain appeared to be due to early differences in milk availability and intake (Kennedy 1957; Oscai & McGarr 1978). The increased weight gain of adults raised in small litters is associated with the development of obesity (Knittle & Hirsch 1968; Johnson *et al.* 1973; Faust *et al.* 1980; Levin *et al.* 1984), hyperleptinaemia (Schmidt *et al.* 2001), abnormal insulin secretion (Waterland & Garza 2002), insulin-resistance (Levin *et al.* 1984) and dyslipidaemia (Hahn 1984). Interestingly, the post-weaning weight gain seen in the original Kennedy study was not associated with increased intake as a function of body weight (Kennedy 1957) suggesting that reduced energy expenditure rather than actual hyperphagia was responsible for the subsequent development of obesity (Wiedmer *et al.* 2002). Thus, the amount of milk consumed during the suckling period and the content of that milk, as determined by maternal diet, can have an enormous impact on the subsequent development of obesity.

Maternal obesity and gestational diabetes can also promote the development of obesity and insulin-resistance in offspring. However, cross-fostering studies demonstrate that alterations in the post-natal maternal environment can overcome even genetic predispositions to become obese or lean. Raising pups, which have inherited an obesity-prone genotype with an obesity-resistant dam can attenuate their development of obesity, while raising obesity-resistant pups with obesity-prone dams causes them to develop obesity and insulin-resistance (Reifsnnyder *et al.* 2000; Gorski & Levin 2004). Also, pups born to mothers made diabetic during gestation are heavier and hyperinsulinemic at weaning (Plagemann *et al.* 1999a–d; Boloker *et al.* 2002) while offspring of normal dams fostered to diabetic dams develop early post-natal growth delay and decreased body weight gain (Fahrenkrog *et al.* 2004). Whereas stressing the dam during the last trimester of gestation produces smaller, obese offspring (Levin *et al.* 2005), this effect can be reversed by handling the pups repeatedly during the post-natal period (Vallee *et al.* 1996).

Both leptin and insulin can affect development during the post-natal period. Rat pups have little body fat and produce very little leptin over the first 7–10 days of life (Ahima *et al.* 1998). Depending upon the doses given, pups may (Kraeft *et al.* 1999; Yuan *et al.* 2000) or may not (Ahima & Hileman 2000) respond to exogenous leptin administration by reducing their weight gain during this period, probably by increasing metabolic rate rather than reducing food intake (Mistry *et al.* 1999). Elevated leptin levels in the milk of obese dams might alter the metabolism of their pups through a similar mechanism since leptin can be absorbed from the milk and enter the pup's circulation during this early post-natal period (Stehling *et al.* 1996; Casabiell *et al.* 1997; Lyle *et al.* 2001). Aside from altering metabolic rate, leptin might act on the developing neonatal nervous system through its neurotrophic properties. Thus, leptin can correct the abnormal development of neural pathways mediating energy homeostasis in the leptin-deficient *ob/ob* mouse (Bouret & Simerly 2004; Bouret *et al.* 2004a,b) and actually alter its own signalling pathways in normal neonates when administered during the first two weeks

of life (Proulx *et al.* 2002). Insulin may also play an important neurotrophic role during this critical period. Direct injections into the rat hypothalamus on the 8th day of life significantly alter the development of hypothalamic areas involved in the control of energy homeostasis in normal rats (Plagemann *et al.* 1999a–d).

In summary, manipulations of the early post-natal environment can have profound effects on the development of obesity and insulin-resistance of developing offspring. The mechanisms underlying these effects are currently unknown. Changes in the composition and amount of maternal milk may be among the most important of these although maternal-pup behavioural interactions are also likely to affect outcome. Because they are secreted in the milk and can be ingested and assimilated by offspring, leptin and insulin may exert effects on the developing brain by virtue of their neurotrophic properties.

5. PERINATAL ENVIRONMENT AND BRAIN DEVELOPMENT

A basic assumption of this review is that the brain is the master controller of energy homeostasis. It can perform this task adequately only when it receives neural, hormonal and metabolic signals from the body and external environment. Mammals have evolved a unique set of 'metabolic-sensing' neurons which receive these multiple inputs from the periphery. These neurons are arrayed in multiple interconnected sites throughout the brain (Levin 2001; Berthoud 2002; Levin 2002a–c). Originally described as 'glucose-sensing' because they alter their firing rate when ambient glucose levels change (Anand *et al.* 1964; Oomura *et al.* 1964), it is now clear that many of these same glucose-sensing neurons also utilize metabolites such as lactate (Yang *et al.* 1999, 2004; Song & Routh 2005), ketone bodies (Minami *et al.* 1990) and fatty acids (Oomura *et al.* 1975; Wang *et al.* 2006) as signalling molecules. They also have receptors for and respond to hormones such as leptin and insulin (Harvey *et al.* 1997; Routh *et al.* 1997; Spanswick *et al.* 1997; Cowley *et al.* 2001; Kang *et al.* 2004). Because of their ability to use metabolic substrates, as well as hormones and peptides associated with adiposity, gut function and feeding, we have called them metabolic-sensing neurons (Levin 2002a–c; Levin *et al.* 2004a,b). Whereas most neurons use metabolites to fuel the metabolic needs generated by changes in their activity, metabolic-sensing neurons use them as signalling molecules to alter their firing rate in proportion to changes in metabolite and hormone availability. Hindbrain areas such as the nucleus tractus solitarius, area postrema, raphe pallidus and obscurus and A1/C1 and C3 areas contain such metabolic-sensing neurons (Adachi *et al.* 1984; Dallaporta *et al.* 1999; Ritter *et al.* 2000; Sanders & Ritter 2000; Moriyama *et al.* 2003; Levin *et al.* 2004a,b; Sanders *et al.* 2004). Some of these receive direct neural inputs from sensors in peripheral organs such as the gastrointestinal tract and hepatic portal vein (Nijima 1969, 1982; Adachi *et al.* 1984; Hevener *et al.* 1997). Metabolic-sensing neurons within the hindbrain express the monoamines noradrenaline

(norepinephrine) (NA), adrenaline (epinephrine) (Adr) and serotonin (5HT) (Ritter *et al.* 2000; Sanders & Ritter 2000; Moriyama *et al.* 2003) and neuropeptides such as the neuropeptide Y (NPY) and proopiomelanocortin (POMC; Li & Ritter 2004; Bugarith *et al.* 2005). These hindbrain neurons relay information from the periphery to hypothalamic areas which mediate feeding behaviour and metabolic processes involved in the control of energy homeostasis (Tang-Christensen *et al.* 2000; Ritter *et al.* 2001; Fraley *et al.* 2002; Watts *et al.* 2002; Fraley & Ritter 2003; Bugarith *et al.* 2005), as well as to limbic and forebrain structures involved in the affective and rewarding properties of food (Ricardo & Koh 1978; Gallagher *et al.* 1990). Metabolic-sensing NPY and POMC neurons in the hypothalamic arcuate nucleus (ARC) receive some of these hindbrain inputs as do several neuropeptide and neurotransmitter expressing neurons within the paraventricular nucleus (PVN) and lateral hypothalamus (LH). The PVN and LH are major effector areas involved in neuroendocrine function, food intake, energy assimilation and expenditure (Muroya *et al.* 1999; Ritter *et al.* 2001; Dunn-Meynell *et al.* 2002; Fraley *et al.* 2002; Watts *et al.* 2002; Fraley & Ritter 2003; Ibrahim *et al.* 2003; Ritter *et al.* 2003).

In rodents, much more of brain development occurs postnatally than it does in primates (Rinaman 2001; Grove *et al.* 2003; Grove & Smith 2003; Rinaman 2003; Bouret *et al.* 2004a,b). Nevertheless, there are enough similarities between human and rodent brains so that we can learn a great deal from developmental studies in rodents. Neuropeptides and neurotransmitters affecting various aspects of energy homeostasis can be grouped according to their predominantly catabolic, anabolic or reward-related properties. Many neuropeptide and transmitter systems also serve other functions besides the regulation of energy homeostasis. However, regulation of energy homeostasis seems to be the primary role of ARC and hindbrain NPY and POMC neurons (Levine & Morley 1984; Stanley & Leibowitz 1985; Stanley *et al.* 1986; Yoshida & Taniguchi 1988; Shimizu *et al.* 1989; Brady *et al.* 1990; Bergendahl *et al.* 1992; Grill *et al.* 1998; Bouret *et al.* 2004a,b). NPY is a prototypic anabolic neuropeptide. Injections of NPY into the brain increase food intake and decrease energy expenditure (Levine & Morley 1984; Stanley & Leibowitz 1985; Stanley *et al.* 1986; Billington *et al.* 1991). POMC is the precursor of α -melanocyte stimulating hormone (α -MSH), a prototypic catabolic peptide which interacts with brain melanocortin 3 and 4 receptors (MC3/4-R) to inhibit food intake and increase energy expenditure (Shimizu *et al.* 1989; Kask *et al.* 1998; Chen *et al.* 2000; Butler *et al.* 2001; Williams *et al.* 2003). The ARC NPY neurons also produce agouti-related peptide (AgRP) which is an endogenous inverse agonist (functional antagonist) of the MC3/4-Rs (Ollmann *et al.* 1997; Marsh *et al.* 1999; Wilson *et al.* 1999). Thus, activation of ARC NPY neurons leads to the release of both a potent anabolic peptide and a potent inhibitor of the catabolic melanocortin system. The anabolic NPY and catabolic POMC neuron projections from the ARC to the neurohumoral output neurons in the PVN and LH

overlap almost completely. In rats, these projections from the ARC do not reach their targets until the eighth to tenth day of life (Grove & Smith 2003; Grove *et al.* 2003; Bouret *et al.* 2004a,b). Hindbrain NA and Adr neurons also project to hypothalamic targets where they modulate the expression and release of NPY, AgRP and α -MSH (Baker *et al.* 1996; Fraley *et al.* 2002; Fraley & Ritter 2003). But these catecholamine neurons do not fully innervate their hypothalamic targets until the end of the third post-natal week in rats (Rinaman 2001).

Thus, since the development of critical pathways involved in energy homeostasis in rodents continues well into the post-natal period, it can be influenced by both pre- and post-natal environmental conditions. This may account for the fact that several manipulations of the pre-natal environment have on the development of obesity in offspring can be either reversed or accentuated by other manipulations carried out postnatally. It is likely that similar principles hold for human beings although the timing of pathway development occurs earlier than in rodents. In rats, maternal obesity throughout gestation and weaning has a major impact on the development of monoamine pathways from the hindbrain to the hypothalamus. Offspring of obese dams with a genetic predisposition to develop DIO have abnormal development of both NA and 5HT projections to the hypothalamus (Levin & Dunn-Meynell 2002a-c). These offspring become more obese as adults in association with a reduced complement of NA reuptake transporters in the PVN as compared to that seen in offspring of either lean or obese obesity-resistant dams or lean DIO dams (Levin & Govek 1998; Levin & Dunn-Meynell 2002a-c). Since NA is removed from the synapse after release primarily by reuptake into noradrenergic terminals, reduction of reuptake transporters would increase NA availability at receptors. This should predispose such animals to become obese since acute injections of NA into the PVN increase food intake and chronic administration causes hyperphagia and obesity (Leibowitz 1978; Leibowitz *et al.* 1984). Thus, the reduced complement of NA transporters in the PVN of offspring of obese DIO dams may explain why they become obese and hyperinsulinemic as adults, even when fed low-fat diets from weaning (Levin & Govek 1998).

Obese DIO dams are hyperinsulinemic during gestation and lactation (Levin & Govek 1998) and this may promote the development of obesity in their offspring. For example, injection of insulin into non-obese dams during the last trimester produces obese offspring, which have increased PVN NA innervation and release (Jones *et al.* 1995, 1996). This similarity to the offspring of obese DIO dams suggests that gestational hyperinsulinaemia leading to increased PVN synaptic NA levels may be one common denominator, which promotes offspring hyperphagia and obesity. Since leptin also has trophic effects on neural pathways, hyperleptinaemia associated with maternal obesity might also play a role in promoting offspring obesity. Leptin is secreted into the milk and can elevate plasma leptin levels in pups, which ingest it (Casabiell *et al.* 1997). Thus,

maternal hyperleptinaemia might alter development of pathways in their pups by direct transfer from their milk to the pups' blood stream (Proulx *et al.* 2002).

Once obesity develops, it effectively becomes a permanent condition, particularly in genetically pre-disposed individuals (Leibel & Hirsch 1984; Levin & Keesey 1998; Levin & Dunn-Meynell 2000; MacLean *et al.* 2004a-c). Even in lean individuals, the brain and periphery conspire to conserve adipose stores when food supply is limited. Thus, during prolonged periods of caloric restriction, rats maintain a reduced level of energy expenditure. When allowed *ad libitum* access to food, they increase their intake and maintain a reduced level of energy expenditure until they regain their previous level of obesity (Levin & Keesey 1998; Levin & Dunn-Meynell 2000; MacLean *et al.* 2004a-c). However, certain individuals appear to have their neural circuitry wired in such a way as to promote the development of obesity when they are presented with a diet relatively high in calories and fat content. Rats which express the DIO phenotype have a number of inborn abnormalities of oxidative metabolism (Chang *et al.* 1990), leptin (Levin & Dunn-Meynell 2002a-c; Levin *et al.* 2003a,b) and insulin sensitivity (Clegg *et al.* 2005), glucose sensing (Levin & Sullivan 1989; Levin *et al.* 1996; Dunn-Meynell *et al.* 2002; Tkacs & Levin 2004) and neuropeptide (Levin & Dunn-Meynell 1997; Levin 1999) and neurotransmitter function (Wilmot *et al.* 1988; Levin 1990a,b, 1995, 1996; Hassanain & Levin 2002) which predispose them to become obese when fed a high-fat diet. In many cases, the development of obesity on such diets in adult rats is not associated with abnormal neural functions suggesting that obesity might be the 'normal' physiologic state of these animals (Wilmot *et al.* 1988; Levin 1990a,b, 1994; Levin & Hamm 1994; Levin *et al.* 1996; Hassanain & Levin 2002; Levin & Dunn-Meynell 2002a-c). Whereas these pathways can be altered in adults, the developmental period is even more prone to diet-induced alterations in neural function. Thus, aside from dietary manipulations in DIO dams and the injection of dams (Jones *et al.* 1995, 1996) and neonates with insulin (Plagemann *et al.* 1992a,b), several other manipulations of the perinatal environment can alter the function of neural systems involved in the regulation of energy homeostasis. These include raising rats in large or small litters (Plagemann *et al.* 1999a-d; Davidowa & Plagemann 2000, 2001), feeding dams either a high-fat or high carbohydrate diet (Kozak *et al.* 1998, 2000; Gao *et al.* 2002; Velkoska *et al.* 2005), gestational diabetes (Plagemann *et al.* 1998) and maternal undernutrition (Plagemann *et al.* 2001). The majority of changes in neural function induced by these manipulations promote the development of obesity and/or insulin-resistance, especially when the individual is exposed to high-fat diets later in life.

6. SUMMARY AND CONCLUSIONS

A variety of perturbations of both the pre- and post-natal environment interact with the genetic background, and gender, of the individual to alter the

ingestive behaviour, energy expenditure and storage in the offspring. The fact that opposing conditions such as under- and overnutrition or hypo- and hyperinsulinaemia during gestation can lead to offspring obesity and insulin-resistance suggests that the systems regulating energy homeostasis have evolved to assure survival of the individual and species by producing an individual who can maximize the storage of calories during times of plenty and minimize loss of energy stores during times of famine. While such developmental adaptations probably affect all organs, those which affect the neural pathways involved in the regulation of energy homeostasis are undoubtedly among the most important for ensuring survival. In the past, such evolutionary changes were beneficial. However, in the present world where there is a surfeit of highly palatable food, which can be obtained with a minimal expenditure of energy, such individuals are at high risk of becoming obese and developing the co-morbidities associated with obesity. Given present evidence, it is unlikely that we will be able to permanently reverse the obese state once it is fully developed in the majority of individuals. This suggests that primary prevention will be the most effective way to stem the tide of the world wide obesity epidemic.

Thus, it is imperative for us to gain better insights into the conditions, which promote or ameliorate the development of obesity during the perinatal period. Animal studies demonstrate that a variety of manipulations of the perinatal environment can permanently set the defended body weight at a higher level. Maternal obesity and diabetes and/or ingestion of high-fat diets appear to predispose offspring to obesity and insulin-resistance, although gestational undernutrition can lead to the same outcome. A common thread is that either an excess or deficiency of leptin, or insulin, during the perinatal period can alter the development of neural pathways involved in the regulation of energy homeostasis. Such changes may be mediated by the metabolic or neurotrophic properties of these hormones. However, these conclusions are only inferential since we lack definitive studies that clearly establish the critical periods and underlying factors in the perinatal environment, which promote this upward resetting. A review of the current data points to a number of fertile areas for further investigation: (i) development of standardized experimental paradigms which allow clear separation of the independent effects of manipulating the pre- from post-natal environments; (ii) identification of the hormonal, nutritional and metabolic factors which alter organ and brain development and function during each of the developmental periods; (iii) provision of additional insights into the differences between the development of the rodent and primate brain for better extrapolation of results from rodent studies to humans; (iv) identification of the specific central and peripheral neural pathways which are altered by the various factors and (v) identification of those individuals most at risk for the development of obesity and diabetes following manipulations of the perinatal environment.

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