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OVERVIEW

Development, brain plasticity and reward: early high-fat diet exposure confers vulnerability to obesity—view from the chair

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The significant increase in childhood obesity has become a particular concern, and it is recognized that the programming of obesity can arise from events occurring in the peri-conception period, prenatally and/or during the early postnatal period. In particular, high intake of dietary fat by the mother has long-term effects that are worse than once thought. This symposium was designed to outline some of the important consequences of maternal high-fat feeding during gestation and lactation, as well as exposure to a high-fat diet (HFD) after weaning, on the programming of homeostatic and hedonic regulation of food intake in both rodents and nonhuman primates (NHPs). Although a consensus emerges that high-fat feeding in early development increases the risk of developing obesity and the metabolic syndrome in adulthood, there is less agreement on the mechanisms through which this risk is conferred. Epigenetic modifications in specific gene promoters within the dopaminergic reward pathways and on the histone code will be discussed. We will also examine the effects of metabolic hormones such as leptin and ghrelin to shape the early development of hypothalamic projections that are critical to control food intake; finally, the importance of placental function in increasing obesity risk in NHP fetus from HFD mothers will be debated.

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The explosion of research on obesity in the past 15–20 years has paralleled a similar rapid rate of increase in the incidence of obesity, which is now a major world-wide concern and reaches every type of population. The significant growth in childhood obesity has become a particular concern.[1,2] It is now recognized that the programming of obesity can arise from events occurring prenatally and/or during the early postnatal period. The initial studies in humans showed that a low birth weight was associated with increased risk for cardiovascular and metabolic syndrome,[3,4] because the undernourished fetus was shown to make predictive adaptive responses to an environment that appeared to be suboptimal. Although the initial phenotype is opposite, a similar risk is associated with neonates born from obese mothers or mothers suffering from gestational diabetes, which results in large-for-gestational-age babies.[5] More recent studies within the field of the developmental origin of health and adult disease have demonstrated that a rapid weight gain in early childhood is associated with an increased risk of adult obesity and that this relationship is independent of birth weight or weight at 1 year of age.[6,7] This suggests that increases in weight in the first year of life might produce additional programming effects that increased the risk for obesity in early childhood and thus may have a greater influence on the risk for later obesity than fetal programming, which is assumed to be reflected in birth weight.

Maternal and childhood nutrition, in particular the intake of high-fat and carbohydrate-rich foods, are among the critical high-risk factors for adult obesity. The theme of the present symposium highlights some of the current research on the long-term consequences of maternal ingestion of high-fat diet (HFD) on the offspring using both nonhuman primate (NHP) and rodent models. This research focuses on the two main systems mediating energy balance: the homeostatic system responsive to nutrient sensing and energy stores, including brain stem and hypothalamic nuclei,[8] and the 'hedonic' system, which refers to the involvement of cognitive, reward and emotional factors and their respective modulating pathways, in particular the mesocorticolimbic dopaminergic system.[9,10] Hypothalamic and mesocorticolimbic dopamine (DA) system plasticity during the early period of development has a major role in the programming of metabolism and appetite in the offspring.[11,12] For instance, exposure to a HFD during gestation in the rat has been shown to increase proliferation and migration of neuronal precursor cells of the embryonic third ventricle toward hypothalamic areas, ultimately leading to increased neuronal production of orexigenic peptides in the paraventricular nucleus (PVN) of the hypothalamus and the perifornical lateral hypothalamic area.[13] These two hypothalamic brain areas receive important inputs from the arcuate nucleus (ARC) and are central to the interactions between the hypothalamic food- and energy-regulating pathways and those implicated in the hedonic attributes of feeding. Earlier studies by Bouret *et al*.[14,15] have demonstrated that neurite outgrowth from the ARC that ultimately forms the projections from this nucleus to the PVN, lateral hypothalamic and other hypothalamic areas is modulated by neonatal leptin, a circulating hormone sensitive to maternal dietary fat intake.[16] In leptin-deficient neonatal mice (Lep^{ob}/Lep^{ob}), treatment with exogenous leptin restored a normal pattern of ARC connectivity to other hypothalamic areas, whereas a similar treatment in adulthood did not reverse the abnormalities found in these mutant mice, emphasizing the unique plasticity of early neonatal life. Disruption of ARC neuronal projections in offspring from diabetic mothers or mothers exposed to other metabolic manipulations such as maintenance on a low-protein diet[17] also

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appear to be ameliorated by leptin treatment during the neonatal period. However, in the case of gestational diabetes, offspring sensitivity to leptin was greatly reduced, which contributed to impair ARC projections to PVN.[18]

Recent elegant work from Bouret and colleagues has identified some of the intracellular pathways mediating the neurotrophic effects of neonatal leptin on ARC projections to the PVN. Although activation of MAPK signaling (and the production of pERK) is required for the appropriate development of these projections, the role of leptin signaling through STAT3 is more tightly linked to the specific POMC neurons and to the development of their projections to PVN.[19] Activation of STAT3 does not appear to mediate the development of NPY/AgRP projections from ARC neurons, suggesting that other signaling pathways downstream of the leptin receptor and/or other metabolically related developmental signals might be involved. In the present symposium, Dr Bouret presented some evidence for the reciprocal relationships between leptin and ghrelin on hypothalamic development in rodents. Similar to leptin, ghrelin, a short peptide (28 amino acids) that is primarily secreted by the stomach, but also by many peripheral tissues in fetal and perinatal life, is known to exhibit neurogenic properties, especially during fetal development.[20] Interestingly, ghrelin is expressed both by the embryo and the maternal uterus, and secretion in the uterine fluid is influenced by maternal diet. Thus, very early maternal dietary manipulations at the time of blastocyst development, for instance, might influence ghrelin production and the evolution of the embryo through programmed stages of proliferative/apoptotic development. During neonatal life, ghrelin secretion increases after the leptin surge that is normally observed around PND10 in rodents, and this increase is hypothesized to reflect an inhibitory signal to hypothalamic axonal growth. Neutralization of ghrelin's action during the first 3 weeks of life, but not in adulthood, increases the density of ARC axonal projections to the PVN and results in large increases in body weight, visceral fat mass and food intake in adult offspring.[21] A precise time-dependent balance between both hormones influenced by maternal diet might constitute an optimal signal for the development of ARC projections to other hypothalamic areas regulating later food intake, energy balance and the propensity to develop metabolic disorders.

In addition to their hypothalamic targets, both leptin and ghrelin have been shown to directly and indirectly modulate activity in the 'hedonic' pathways to food intake, notably the activity of dopaminergic neurons in the midbrain/ventral tegmental area (VTA). Although leptin administration is known to reduce DA neuron firing rate,[22] the opposite is documented after ghrelin treatment either *in vivo* or *in vitro*.[23] Similarly, high-fat feeding is known to have opposite effects on the production of leptin and ghrelin, with reductions in ghrelin observed after long-term HFD in adult rats.[24] However, the precise effect of these hormones on the mesolimbic system during the prenatal/period, as well as their contribution to the development of obesity, is currently unclear. Maternal exposure to HFD, varying in proportion (30–60%) and quality of fat (saturated vs unsaturated), as well as in carbohydrate content (21–60% approximately), has produced evidence for a general 'hypofunction' in the mesolimbic DA system.[9] A number of observations support this hypothesis, such as a reduction in locomotor responses and nucleus accumbens DA release after amphetamine administration in adult offspring of HFD mothers[25,26] and reduced D2 receptor expression (mRNA) in the VTA,[26] although others have shown an increase in locomotor responses to AMP in rat offspring of mothers fed a high-fat/high-carbohydrate diet.[27] Nutritional modifications also increased the expression and activity of DAT in several areas of the reward circuitry,[25,28,29] potentially reducing synaptic concentrations of DA. It is suggested that decreased DA turnover and reduced function of the reward system following early exposure to a HFD[30] might increase motivation to consume palatable foods in an effort to 'mitigate' a state of reduced reward. Indeed, operant responding for high fat, but not sucrose pellets, was increased in adult offspring from HFD mothers.[26]

Interestingly, the effects of early exposure to HFD are persistent and do not require continuous exposure to the high-caloric food, suggesting that epigenetic modifications might mediate these environmental effects on gene expression in the long term. Indeed, by using a model of diet-induced obesity in the early postweaning period, Reyes *et al*.[31] have documented several epigenetic modifications in critical functional genes of the mesocorticolimbic circuit possibly contributing to the development and maintenance of the obese phenotype. In this symposium, Dr Reyes provided evidence that HFD feeding (60% fat) in mice post weaning modified TH and DAT promoter methylation in a region-specific manner, increasing methylation in the VTA while reducing it in the hypothalamus. Corresponding gene expression and behaviors were consistent with opposite regulation of the DA systems in both structures, suggesting that environmental inputs can regulate gene expression as a function of the specific cellular environment and/or functional pathway to which they belong.[32] Within reward-related regions, μ-opioid receptor expression was also consistently reduced in offspring from mothers fed HFD or junk-food diet.[28,31] This was associated with increased promoter methylation and chromatin remodeling. Beyond the demonstration of the long-term effects of maternal HFD feeding or postnatal exposure to HFD, these studies are the first to start identifying the potential mechanisms linking environmental nutritional changes with modifications in the 'hedonic' circuitry implicated in the control of food intake in the long term. The fact that some of those methylation patterns, especially hypomethylated states, can be reversed in a time-specific manner by diets containing methyl donors provides some fundamental basis to investigate therapeutic avenues.

Rodent, sheep and NHP models have provided an extensive body of evidence linking maternal HFD exposure to increased risk for metabolic disease,[33,34] consistent with the many epidemiological studies in humans. Newborn rodents are, however, much more immature than newborn humans, and NHP models have the advantage of greater similarity both to the pattern of human development during gestation and also to placental morphology and function. Earlier studies in baboons showed that overfeeding during the preweaning period permanently increased adiposity in the offspring,[35] and subsequent studies by Grove and colleagues in macaques have firmly established that prenatal maternal HFD feeding predisposes the offspring to develop an obese phenotype with increased risk for nonalcoholic fatty liver disease.[36] NHP fetuses are particularly vulnerable to HFD because of the late development of their white adipose tissue, which reduces their ability to store circulating fatty acids and causes excess fat deposition and lipotoxicity in other tissues such as the liver, pancreas and muscle. Interestingly, when mothers are reexposed to a normal diet after several reproductive episodes, their subsequent offspring have a non-obesogenic phenotype, although the mother remains slightly overweight. These data suggest a close relationship between acute maternal diet and metabolic outcome in the offspring. In this symposium, Dr Grove emphasized changes in placental function in NHP as potential mediators of the maternal HFD exposure. It is known that hyperinsulinemia and hyperglycemia associated with increased body weight can cause several complications in placental morphology and function.[37] Among these, decreased placental blood flow and tonic placental inflammation, which increase circulating cytokines in the fetus, are both considered to contribute significantly to reduced fetal weight. After birth, HFD infants exhibit higher food intake and a marked preference for high-fat/high-sucrose foods before any changes in body weight or proportion of body fat. Thus, according to the original hypothesis on the developmental origins of adult disease developed by

Barker *et al*.,[3,4] fetuses from HFD mothers born with a lower birth weight may undergo a period of rapid catch-up growth postnatally, which has been linked to obesity in humans.[5]

In addition to the well-documented metabolic dysfunctions observed in NHP of HFD mothers, programming of behavioral characteristics that increase vulnerability to mental disorders is maybe the least understood. Recently, maternal HFD consumption has been associated with increased anxiety in rodents[38] and in NHP offspring,[39,40] but only in females. Modifications in serotoninergic neurotransmission are thought to underline changes in aggressivity/anxiety, and the findings that female offspring appear to be more susceptible to maternal HFD-induced changes than males is consistent with evidence in humans that suggests that the association between obesity and anxiety is stronger in women than in men.[39]

As for those epigenetic modifications documented within the reward circuits by Reyes and colleagues, metabolic programming of offspring born from mothers exposed to a HFD might affect expression of several genes important for homeostatic central and peripheral regulation, such as those encoding for the glucocorticoid receptor,[41] hepatic PPAR-alpha, leptin,[42] GLUT4 and UCP-2, both of which are involved in glucose metabolism.[43] As presented by Dr Aagaard during the symposium, epigenetic modifications occurring during fetal life are the most likely to persist as opposed to those occurring during postnatal life, thus conferring specific vulnerability of the fetus to environmentally induced epigenetic changes.[44] Histone modifications, in addition to DNA methylation, partly determine DNA transcription, and there is now good evidence that the activity of specific enzymes such as histone deacetylases (HDACs), histone acetyl transferases (HAT) and histone demethylases is sensitive to dietary factors, albeit differently according to each class of enzymes.[45] Research is progressing to determine the most influential histone modifications induced by early exposure to HFD, although it appears that the regulation of HDAC, but not HAT activity, might confer higher risk of metabolic disorder in NHP. For instance, overexpression of sirt1, a protein and HDAC, was reported to protect from nonalcoholic fatty liver disease, and administration of resveratrol, a sirt1 activator, protects from the cardiovascular and metabolic consequences of diabetes in rodents.[46,47] Taken together, these results emphasize the important role of diet-induced modifications in the histone code and promoter methylation in determining the long-term consequences of HFD exposure.[48]

In conclusion, this symposium has described some of the important consequences of maternal high-fat feeding during gestation and lactation, as well as early exposure to HFD after weaning, on programming of homeostatic and hedonic regulation of food intake in both rodents and NHPs. Although a consensus emerges that HFD in early development increases the risk of developing obesity and the metabolic syndrome in adulthood, there is less agreement on the mechanisms through which this risk is conferred. The diverse underlying mechanisms are probably linked to the initial phenotype of either reduced (as seen in offspring of HFD mothers or obese mothers) or increased (as seen in offspring from diabetic mothers) fetal growth. Species-specific, precise, developmental windows of susceptibility to dietary manipulations are still unclear, although it is likely given that they will span a large portion of the gestational period, as well as the peri-conception[49] and early postnatal periods.

The large variation in experimental diets used in reported studies, as well as the balance between fat and carbohydrate composition, might represent an important, yet still neglected, factor in the HFD effect. Evidence suggests that a simple change in the macronutrient composition during the suckling period, even in the absence of changes in total caloric intake, causes metabolic programming in rats fed a high-carbohydrate diet. When a high-carbohydrate/HFD is fed to rat pups, increased insulin secretion might induce compensatory mechanisms that would not be observed when high-fat/low-carbohydrate diets are imposed.[5] The source of fat also matters in the resulting effects of HFD diet exposure. For instance, pups from mothers maintained on a 30% high-fat fish oil diet do not exhibit the increased body weight and fat pad weight gain that pups from HFD (30%)-saturated fat mothers exhibit.[40,50] Furthermore, as early as PND10, pups nursed by mothers fed the fish oil diet that is high in polyunsaturated fatty acids show higher CORT and lower leptin levels than either controls or pups nursed by mothers fed the high saturated fat diet. The metabolic, epigenetic and behavioral consequences of variations in the source of fat in the maternal diet need to be further explored.

Finally, an important extension of this work will be to determine the transgenerational effects of developmental exposure to HFD. Recent studies have shown that maternal HFD effects can extend as far as the third generation in mice, and that transmission was passed on via the paternal lineage.[51] Interestingly, the most conserved effect of the HFD was on increased weight and length in female offspring only. Changes in leptin signaling and insulin insensitivity were lost within the first and second generation, respectively. These studies are important because they might point out to predominant HFD resulting phenotypes that can be preferentially transmitted across several generations without reinforcement. Studies on transgenerational transmission of epigenetic marks might elucidate some of the resulting phenotypes and allow for a more specific targeting of interventions.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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REFERENCES

1 Karnik S, Kanekar A. Childhood obesity: a global public health crisis. *Int J Prev Med* 2012; **3**: 1–7.
2 Waters E, de Silva-Sanigorski A, Hall BJ, Brown T, Campbell KJ, Gao Y *et al.* Interventions for preventing obesity in children. *Cochrane Database Syst Rev* 2011; **12**: CD001871.
3 Barker DJ. The origins of the developmental origins theory. *J Intern Med* 2007; **261**: 412–417.
4 Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med* 2009; **27**: 358–368.
5 Dyer JS, Rosenfeld CR. Metabolic imprinting by prenatal, perinatal, and postnatal overnutrition: a review. *Semin Reprod Med* 2011; **29**: 266–276.
6 Patel AI, Madsen KA, Maselli JH, Cabana MD, Stafford RS, Hersh AL. Underdiagnosis of pediatric obesity during outpatient preventive care visits. *Acad Pediatr* 2010; **10**: 405–409.
7 Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol* 2007; **196**: 322. e1–8.
8 Woods SC, D'Alessio DA. Central control of body weight and appetite. *J Clin Endocrinol Metab* 2008; **93** (Suppl 1): S37–S50.
9 Berthoud HR. Metabolic and hedonic drives in the neural control of appetite: who is the boss? *Curr Opin Neurobiol* 2011; **21**: 888–896.
10 Kenny PJ. Reward mechanisms in obesity: new insights and future directions. *Neuron* 2011; **69**: 664–679.
11 McNay DE, Briançon N, Kokoeva MV, Maratos-Flier E, Flier JS. Remodeling of the arcuate nucleus energy-balance circuit is inhibited in obese mice. *J Clin Invest* 2012; **122**: 142–152.
12 Orozco-Solís R, Matos RJ, Guzmán-Quevedo O, Lopes de Souza S, Bihouée A, Houlgatte R *et al.* Nutritional programming in the rat is linked to long-lasting changes in nutrient sensing and energy homeostasis in the hypothalamus. *PLoS One* 2010; **5**: e13537.

13 Chang GQ, Gaysinskaya V, Karatayev O, Leibowitz SF. Maternal high-fat diet and fetal programming: increased proliferation of hypothalamic peptide-producing neurons that increase risk for overeating and obesity. *J Neurosci* 2008; **28**: 12107–12119.
14 Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 2004; **304**: 108–110.
15 Bouret SG, Draper SJ, Simerly RB. Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. *J Neurosci* 2004; **24**: 2797–2805.
16 Walker CD, Naef L, d'Asti E, Long H, Xu Z. Maternal fat intake and offspring brain development: focus on the mesocorticolimbic dopaminergic system'. In: Bridges R (ed). *Neurobiology of the Parental Brain*. Academic Press, 2008, pp 293–300.
17 Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A *et al.* Neonatal leptin treatment reverses developmental programming. *Endocrinology* 2005; **146**: 4211–4216.
18 Steculorum SM, Bouret SG. Maternal diabetes compromises the organization of hypothalamic feeding circuits and impairs leptin sensitivity in offspring. *Endocrinology* 2011; **152**: 4171–4179.
19 Bouret SG, Bates SH, Chen S, Myers Jr MG, Simerly RB. Distinct roles for specific leptin receptor signals in the development of hypothalamic feeding circuits. *J Neurosci* 2012; **32**: 1244–1252.
20 Zhang W, Hu Y, Lin TR, Fan Y, Mulholland MW. Stimulation of neurogenesis in rat nucleus of the solitary tract by ghrelin. *Peptides* 2005; **26**: 2280–2288.
21 Steculorum SM, Bouret SG. Developmental effects of ghrelin. *Peptides* 2011; **32**: 2362–2366.
22 Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN *et al.* Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* 2006; **51**: 811–822.
23 Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD *et al.* Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *J Clin Invest* 2006; **116**: 3229–3239.
24 Gomez G, Han S, Englander EW, Greeley Jr GH. Influence of a long-term high-fat diet on ghrelin secretion and ghrelin-induced food intake in rats. *Regul Pept* 2012; **173**: 60–63.
25 Naef L, Srivastava L, Gratton A, Hendrickson H, Owens SM, Walker CD. Maternal high fat diet during the perinatal period alters mesocorticolimbic dopamine in the adult rat offspring: reduction in the behavioral responses to repeated amphetamine administration. *Psychopharmacology (Berl)* 2008; **197**: 83–94.
26 Naef L, Moquin L, Dal Bo G, Giros B, Gratton A, Walker CD. Maternal high-fat intake alters presynaptic regulation of dopamine in the nucleus accumbens and increases motivation for fat rewards in the offspring. *Neuroscience* 2011; **176**: 225–236.
27 Shalev U, Tylor A, Schuster K, Frate C, Tobin S, Woodside B. Long-term physiological and behavioral effects of exposure to a highly palatable diet during the perinatal and post-weaning periods. *Physiol Behav* 2010; **101**: 494–502.
28 Ong ZY, Muhlhausler BS. Maternal ″junk-food″ feeding of rat dams alters food choices and development of the mesolimbic reward pathway in the offspring. *FASEB J* 2011; **25**: 2167–2179.
29 Vucetic Z, Kimmel J, Totoki K, Hollenbeck E, Reyes TM. Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. *Endocrinology* 2010; **151**: 4756–4764.
30 Teegarden SL, Scott AN, Bale TL. Early life exposure to a high fat diet promotes long-term changes in dietary preferences and central reward signaling. *Neuroscience* 2009; **162**: 924–932.
31 Vucetic Z, Kimmel J, Reyes TM. Chronic high-fat diet drives postnatal epigenetic regulation of ì-opioid receptor in the brain. *Neuropsychopharmacology* 2011; **36**: 1199–1206.
32 Vucetic Z, Carlin JL, Totoki K, Reyes TM. Epigenetic dysregulation of the dopamine system in diet-induced obesity. *J Neurochem* 2012; **120**: 891–898.
33 Levin BE. Metabolic imprinting: critical impact of the perinatal environment on the regulation of energy homeostasis. *Philos Trans R Soc Lond B Biol Sci* 2006; **361**: 1107–1121.
34 Alfaradhi MZ, Ozanne SE. Developmental programming in response to maternal overnutrition. *Front Genet* 2011; **2**: 27.
35 Lewis DS, Bertrand HA, McMahan CA, McGill Jr HC, Carey KD, Masoro EJ. Preweaning food intake influences the adiposity of young adult baboons. *J Clin Invest* 1986; **78**: 899–905.
36 McCurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE *et al.* Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. *J Clin Invest* 2009; **119**: 323–335.
37 Frias AE, Morgan TK, Evans AE, Rasanen J, Oh KY, Thornburg KL *et al.* Maternal high-fat diet disturbs uteroplacental hemodynamics and increases the frequency of stillbirth in a nonhuman primate model of excess nutrition. *Endocrinology* 2011; **152**: 2456–2464.
38 Bilbo SD, Tsang V. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. *FASEB J* 2010; **24**: 2104–2115.
39 Sullivan EL, Grayson B, Takahashi D, Robertson N, Maier A, Bethea CL *et al.* Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring. *J Neurosci* 2010; **30**: 3826–3830.
40 Sullivan EL, Smith MS, Grove KL. Perinatal exposure to high-fat diet programs energy balance, metabolism and behavior in adulthood. *Neuroendocrinology* 2011; **93**: 1–8.
41 Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. *Br J Nutr* 2007; **97**: 1064–1073.
42 Stöger R. *In vivo* methylation patterns of the leptin promoter in human and mouse. *Epigenetics* 2006; **1**: 155–162.
43 Li M, Sloboda DM, Vickers MH. Maternal obesity and developmental programming of metabolic disorders in offspring: evidence from animal models. *Exp Diabetes Res* 2011; **2011**: 592408.
44 Suter M, Bocock P, Showalter L, Hu M, Shope C, McKnight R *et al.* Epigenomics: maternal high-fat diet exposure in utero disrupts peripheral circadian gene expression in nonhuman primates. *FASEB J* 2011; **25**: 714–726.
45 Gabory A, Attig L, Junien C. Epigenetic mechanisms involved in developmental nutritional programming. *World J Diabetes* 2011; **2**: 164–175.
46 Dolinsky VW, Rueda-Clausen CF, Morton JS, Davidge ST, Dyck JR. Continued postnatal administration of resveratrol prevents diet-induced metabolic syndrome in rat offspring born growth restricted. *Diabetes* 2011; **60**: 2274–2284.
47 Chen KH, Cheng ML, Jing YH, Chiu DT, Shiao MS, Chen JK. Resveratrol ameliorates metabolic disorders and muscle wasting in streptozotocin-induced diabetic rats. *Am J Physiol Endocrinol Metab* 2011; **301**: E853–E863.
48 Hanley B, Dijane J, Fewtrell M, Grynberg A, Hummel S, Junien C *et al.* Metabolic imprinting, programming and epigenetics–a review of present priorities and future opportunities. *Br J Nutr* 2010; **104** (Suppl 1): S1–S25.
49 Melzer K, Schutz Y. Pre-pregnancy and pregnancy predictors of obesity. *Int J Obes (Lond)* 2010; **34** (Suppl 2): S44–S52.
50 d'Asti E, Long H, Tremblay-Mercier J, Grazier M, Cunnane S, Di Marzo V *et al.* Maternal dietary fat determines metabolic profile and the magnitude of endocannabinoid inhibition of the stress response in neonatal rat offspring. *Endocrinology* 2010; **151**: 1685–1694.
51 Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. *Endocrinology* 2011; **152**: 2228–2236.