Chapter 14
The Influence of Maternal Obesity on Offspring Cardiovascular Control and Insights from Rodent Models

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Abstract Human cohort studies of mother–child associations around pregnancy suggest that pre-pregnancy body mass index (BMI) is causally associated with cardiometabolic risk factors in young adult offspring. Corroborative evidence in mammals for the influence of maternal obesity on offspring cardiovascular function is provided by obese pregnancy models in sheep and non-human primates, whilst more mechanistic studies in rodents suggest that perinatal exposure to the metabolic and hormonal milieu of maternal obesity may permanently change the central regulatory pathways involved in cardiovascular development and control. Shared central pathways of leptin and insulin signalling play an important role in the hypothalamic control of appetite and energy expenditure via sympathetic innervation of metabolically and thermogenically active tissues such as brown adipose tissue (BAT), but are also involved in sympathetic activation of non-thermogenic tissues, including the kidney, and central selective leptin sensitivity is implicated in obesity-related hypertension. In rodent studies, maternal obesity confers persistent sympathoexcitatory hyper-responsiveness and hypertension to the exposed offspring which appears to be mediated by neonatal hyperleptinaemia associated with permanently altered hypothalamic structure and function. Indeed, the neurotrophic role of leptin in hypothalamic development and aberrant cardiovascular control is evidenced by a rat model of experimental neonatal hyperleptinaemia in which leptin administration in naive pups during the critical period of postnatal hypothalamic plasticity leads directly to permanent cardiovascular dysregulation and hypertension. This chapter will discuss the epidemiological evidence and mechanistic insight from rodent studies on the influence of maternal obesity on offspring cardiovascular control.

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L.R. Green, R.L. Hester (eds.), *Parental Obesity: Intergenerational Programming and Consequences*, Physiology in Health and Disease,
DOI 10.1007/978-1-4939-6386-7_14

Keywords Obesity • Pregnancy • Developmental programming • Hypertension • Leptin • Insulin • Hypothalamus • Sympathetic nervous system • Autonomic nervous system • Microbiome

14.1 Introduction: Prevalence and Relevance of Maternal Obesity in Pregnancy

The Health Survey for England (2013) currently estimates the rate for obesity is 26 % for men and 24 % for women. More recent projections suggest that by 2030, 41–48 % of men and 35–43 % of women could be obese if current trends continue (*Statistics on Obesity*, *Physical Activity and Diet*: *England 2015*) [1]. The prevalence of maternal obesity is rising in line with the general population trends, and has more than doubled in the past 20 years, with an estimated 20 % of pregnant women classified as obese in the UK [2, 3]. Recent evidence addressing longevity and morbidity associated with maternal obesity indicates an increase in all-cause mortality in adult offspring and increased mortality from cardiovascular events in particular [4]. It is, therefore, critical that we understand the consequences of the obesity epidemic not least in terms of the impact on the cardiovascular and metabolic health of the future generations. Whilst human mother and child cohort studies indicate associations between maternal factors in obese pregnancy with childhood cardiovascular outcomes, they are by their nature limited in their potential to assign cause and effect due to residual confounding factors around shared genetic, environmental and social influences in childhood. Animal models have proved invaluable in dissecting out the various developmental influences and mechanistic pathways that conspire to affect changes in offspring phenotype and predispose to cardiovascular morbidity and mortality. This chapter will discuss the evidence from animal studies that maternal obesity predisposes offspring to cardiovascular dysfunction in later life. It will illustrate the potential mechanisms involved in the developmental programming of hypertension in particular, which is arguably the single best predictor of premature death from cardiovascular disease.

14.2 Clinical and Epidemiological Evidence for the Influence of Maternal Obesity on Offspring Cardiovascular Function

Maternal obesity in pregnancy, whether characterised by pre-pregnancy BMI $>30\ kg^2$ or excessive gestational weight gain (GWG), is now considered the single biggest obstetric risk factors and is associated with an increased incidence of all common complications of pregnancy affecting maternal morbidity and mortality outcomes [3, 5, 6]. Increased rates of Caesarean section (CS) in obese pregnancy,

now the most common surgical procedure performed in women of reproductive age [7] and longer stays in neonatal intensive care units, also have healthcare and health economics implications [3, 8]. Caesarean section may carry its own inherent risk of long-term cardiometabolic risk centred around mode of delivery and suboptimal microbial colonisation of the neonatal intestinal tract by the maternal microbiome [9]. However, there is increasing evidence that maternal obesity per se is a risk factor for obesity and related disorders in the next generation [10–12]. Some commentators have referred to the 'transgenerational acceleration' of obesity, an independent relationship between maternal body mass index (BMI) and adiposity in children. There is now widespread concern that exposure to the metabolic milieu of maternal obesity and associated gestational diabetes mellitus (GDM) may initiate developmental changes which set metabolic and cardiovascular development on a trajectory for both childhood obesity and hypertension [13–15].

14.2.1 Maternal BMI GWG and Blood Pressure in Offspring

Whilst the underlying mechanisms are not yet understood, numerous studies have demonstrated the association between maternal BMI and offspring adiposity or BMI, supporting the observation that 'maternal obesity begets offspring obesity' [16–18]. Recent meta-analyses estimated that maternal pre-pregnancy obesity confers a threefold increased risk of obesity in the child [19], whereas GWG (above Institute of Medicine Guidelines, in the USA) is associated with a more modest 33 % increased risk. Moreover, both maternal pre-pregnancy obesity and GWG (especially in first trimester) are also associated with other cardiovascular risk factors in children including adverse lipid profiles, insulin resistance and inflammatory markers [20–23]. Together with increased risk of obesity in children born to obese pregnant women, these cardiovascular risk factors will contribute to the elevation of blood pressure in childhood, and for the most part, the reported association between maternal pre-pregnancy BMI and GWG with offspring blood pressure appears to be largely mediated by these cardiovascular risk factors especially child's current BMI [24], suggesting perhaps not surprisingly that maternal obesity begets obesity-related hypertension in the child. However, there is emerging evidence from both human and animal data for an independent relationship between maternal BMI and offspring blood pressure.

Wen et al. (2011) studied over 30,000 mother–child pairs in the Collaborative Perinatal Project and investigated the influence of childhood BMI status in the association between childhood systolic blood pressure (SBP) and pre-pregnancy BMI [25]. Higher offspring SBP was significantly associated with pre-pregnancy overweight and obesity (vs. normal weight); however, the relationship attenuated to null after adjustment for childhood BMI. Hence, a child's current BMI may largely mediate the associations of maternal pre-pregnancy BMI with offspring blood pressure. Similarly, the Jerusalem Perinatal Family Follow-up Study, a birth cohort of 1400 young adults born in Jerusalem who had extensive archival data and

clinical information, reported that both pre-pregnancy BMI and GWG were independently associated with cardiometabolic risk factors in adulthood, including systolic and diastolic blood pressure [26]. Again, after adjustment for offspring adiposity the observed association was lost, indicating that the relationship between maternal obesity and offspring blood pressure appears to be driven mainly by current offspring adiposity. Of course that is not to say that both obesity and hypertension could not be programmed concurrently through shared causal pathways, e.g. in the hypothalamus, which regulates both blood pressure regulation and body weight through energy balance.

In support of an independent association, between maternal obesity and offspring blood pressure, the Amsterdam Born Children and their Development (ABCD) Study recently reported that pre-pregnancy BMI, in over 3000 women, was positively linearly associated with offspring diastolic (DBP) and SBP age 5–6 years [24]. After adding birth weight and child BMI to the model, the independent effect size of pre-pregnancy BMI on SBP and diastolic blood pressure decreased by approximately 50 %, indicating that child's current BMI partly mediated the association. However, the relationship still held, indicating for the first time an independent relationship between maternal BMI and childhood blood pressure. Respiratory sinus arrhythmia (RSA, a derivate of parasympathetic activity) was positively associated with pre-pregnancy BMI but disappeared after adjusting for possible confounders.

So what are the potential mechanisms? Clearly, there is something about the obese and diabetic milieu in pregnancy which is influencing the development of the fetal/neonatal heart and cardiovascular system to increase blood pressure and cardiovascular disease risk. Candidate 'vectors' in the transmission of obesogenic and cardiovascular risk to the developing fetus or neonate include those hormonal and metabolic elements that can cross or signal via the placenta or be mediated as milk-borne factors. Such factors may include, but are not limited to, macronutrients such as glucose and lipids (fetal overnutrition hypothesis), which via increased placental transfer can trigger a reactive hormonal response in the developing fetus to activate insulin, leptin and glucocorticoid signalling pathways. Similarly, immune and inflammatory mediators may also interfere with developmental processes during periods of developmental plasticity. In humans, the first trimester seems particularly susceptible to the effects of excessive GWG on childhood cardiometabolic outcomes. The Generation R study, from Rotterdam, The Netherlands, recently reported that increased weight gain in the first trimester of pregnancy was associated with increased risks of childhood overweight and clustering of cardiometabolic risk factors, largely mediated by childhood adiposity [21]. Childhood diastolic blood pressure at 4 years of age, and increased adiposity from 2 years of age, has also been associated with rapid weight gain in the first trimester [27]. Interestingly, the first trimester is associated with accumulation of maternal fat depots and may provide insight into the kind of developmental signals that might arise for excessive weight gain during this critical period for placental development. Indeed, leptin may play an important role in early placentation by stimulating several genes involved in angiogenic signalling pathways and fatty acid

metabolism [28]. Moreover, elevated serum leptin levels in the first trimester have been associated with placental disease and pre-eclampsia in lean women [29]. In the rodent, trans-placental passage of I^{125} leptin from the maternal to the fetal circulation increases tenfold in late gestation, consistent with leptin's putative role as a fetal growth factor [30]. A similar elevation in fetal cord blood leptin concentration occurs in human pregnancies towards term [31].

14.2.2 Insight from Intervention Studies Designed to Improve Maternal Metabolic Profiles in Obese Pregnancy

Most studies examining the consequences of maternal obesity for offspring cardiometabolic outcomes have been observational in nature and therefore are subject to the influence of confounding variables which can affect the outcome e.g. maternal education, socioeconomic factors, lifestyle factors, ethnicity and genetics. Intervention studies, especially randomised control trials (RCTs), have greater validity to establish cause and effect, in that putative mediators can be modulated to influence a given outcome. Interventions, therefore, designed to improve GWG, glucose homeostasis and/or metabolic profiles in obese pregnancy would be hypothesised to improve fetal and childhood cardiometabolic outcomes. However, to date, very few relevant studies in obese pregnancy have been reported which might provide mechanistic insight and potentially inform policy for effective intervention strategies [32, 33]. RCTs that have attempted to address the consequences of maternal obesity and weight gain in pregnancy are logistically quite difficult and have tended to focus on determinants of energy balance such as diet and exercise as lifestyle interventions. Studies have been of varying quality with little consensus on the core outcomes affecting maternal and fetal health. A recent systematic review and meta-analysis identified 44 relevant randomised controlled trials, involving 7278 women, that had diet or lifestyle interventions in pregnancy and reported obstetric outcomes [34, 35]. Overall, there was 1.42 kg reduction (95 % confidence interval 0.95–1.89 kg) in GWG with any intervention compared with control. Combining interventions, there were no apparent effects on birth weight or the incidence of large for gestational age (LGA) or small for gestational age (SGA) babies between the groups, although physical activity intervention alone was associated with reduced birth weight (mean difference −60 g, −120 to −10 g). Dietary intervention resulted in the largest reduction in maternal GWG (3.84 kg, 2.45–5.22 kg), with improved pregnancy outcomes compared with other interventions, although the overall evidence rating was low to very low.

Certainly, diet and lifestyle interventions in pregnancy can reduce GWG and influence fetal outcomes; however, there is some controversy around intervention targeting weight gain in pregnancy due to potential adverse fetal outcomes. Current UK guidelines, contrary to IOM (USA) guidelines which provide ranges of

recommended weight gain based on pre-pregnancy BMI, do not advocate targeted weight management during pregnancy. A consensus statement from the ILSI Europe Workshop Obesity in pregnancy concluded that the evidence available on short- and long-term health impact for mother and child currently favours actions directed at controlling pre-pregnancy BMI women of reproductive ages. The consensus called for more randomised controlled trials to evaluate the effects of nutritional and behavioural interventions on pregnancy outcomes [6]. Those RCTs which have reported to date suggest that diet and exercise interventions in obese and overweight pregnancy can be effective in changing maternal behaviour, but that diet and exercise alone may not be sufficient to prevent pregnancy outcomes such as gestational diabetes and pre-eclampsia; improvement in metabolic profiles may still be beneficial to longer-term offspring cardiovascular health [36–38].

A recent 'diet and exercise' lifestyle intervention in 157 obese and 97 lean pregnant women, conducted in Odense and Aarhus University Hospitals in Denmark, reported on offspring metabolic risk factors at 2.8 years of age [39, 40]. The outcome measures were BMI Z-score, abdominal circumference, blood pressure and fasting plasma glucose, insulin, high-density lipoprotein and triglycerides. No differences were observed between the intervention and control obese groups, or between the obese and lean groups. The authors concluded that early childhood metabolic risk factors were largely unaffected by lifestyle interventions in obese pregnant women. This relatively small negative study is the first of its kind and the results of larger ongoing RCTs are eagerly awaited. It should also be noted, despite strong evidence from meta-analyses [19, 41], that not all mother–child observational cohort studies have supported an association between maternal obesity or GWG and increased cardiovascular risk [14, 42]. However, many of the mother–child cohort studies were cross-sectional and reported a relatively low prevalence of obesity in their pregnant populations, which may have masked associations with childhood outcomes.

There are two large RCTs currently evaluating the efficacy of dietary and lifestyle interventions in obese pregnancy: the UK Pregnancies: Better Eating and Activity Trial (UPBEAT, NIHR programme; ISRCTN89971375) and the LIMIT trial in Adelaide, Australia (ACTRN12607000161426). As well as reporting on pregnancy outcomes [36–38], both studies now have the invaluable opportunity to follow up the children to investigate long-term cardiovascular and metabolic development. The wealth of data from these highly characterised pregnancies will allow detailed investigation of the potential benefits of intervention and the relationship between maternal metabolic profile and offspring cardiometabolic health. A subsidiarity study, UPBEAT Tempo Heart, funded by the British Heart Foundation is currently ongoing and is specifically investigating cardiovascular structure and function in neonates and 3-year-old children born to the UPBEAT participants. Various state of the art neonatal magnetic resonance imaging modalities and cardiac and vascular ultrasound techniques will, for the first time, investigate the consequences of maternal obesity for infant cardiovascular development related to targeted modulation of the maternal metabolic profile.

In addition to the very valuable RCTs conducted, some rather elegant 'sibling pair' studies, performed in children born to mothers before and after bariatric surgery for extreme obesity, have provided strong evidence for an association between maternal and offspring cardiometabolic risk factors [43, 44]. The prevalence of overweight and obesity was higher in the children born before, compared to those born after maternal biliopancreatic diversion bariatric surgery. At the time of follow-up, children born after maternal surgery (AMS) exhibited threefold lower prevalence of severe obesity, greater insulin sensitivity (homeostasis model assessment of insulin resistance index), improved lipid profile (cholesterol/high-density lipoprotein cholesterol and high-density lipoprotein cholesterol) and lower C-reactive protein and leptin, than children born before maternal surgery. These studies, therefore, powerfully demonstrate the benefits of weight reduction in obese pregnancy for offspring cardiometabolic risk sustained into adolescence and most likely attributable to an improved intrauterine environment. More recent mechanistic studies from the Canadian Institutes of Health Research suggest that improved maternal gestational metabolic profile (lipid and carbohydrate metabolism) interacts with offspring gene variations to modulate gene expression levels and ameliorate cardiometabolic risk profiles in those siblings born AMS [45–47]. Specifically, improvements in cardiometabolic risk markers in siblings born after as compared to those born before maternal weight loss surgery may be mediated through differential methylation of genes involved in immune and inflammatory pathways. Although sibling studies such as these help to minimise residual confounding through shared genetic background and social environment, one caveat is the potential influence of an altered postnatal 'maternal' nutritional environment pre- versus post-maternal surgery. Although impressive, these intervention studies are still essentially observational and do not carry the same weight of evidence as randomised controlled trials in establishing causality.

Animal models can, to a large degree, avoid confounding variables associated with human epidemiological studies. Rodent studies in particular provide mechanistic insight into the effects of obesity in pregnancy and have generated testable hypotheses that can be back-translated to human studies.

14.3 Insight from Animal Models into the Effects of Maternal Obesity on Offspring Cardiovascular Development and Control

Numerous animal models have been developed to recreate the conditions described in the early epidemiological association studies that generated the DOHaD hypothesis and allow investigation nutritional and hormonal factors that can shape offspring phenotype [48, 49]. Animal studies have certain advantages over the human mother–child cohort studies, which as we have seen are limited in terms of establishing cause and effect. Rodents are mammals and share all but 1 % of our

genes and have highly conserved physiological systems and similar placentation which, despite altricial versus precocial species differences in the developmental stage at birth, make them an excellent model for human pregnancy. Rodent models are particularly amenable to developmental programming and life-course studies due to the relatively short life cycles. Rats and mice reach sexual maturity in a little over 1 month of age, which means that the consequences of environmental influences in development on the adult phenotype can be studied within a reasonable timeframe. Rodent models can avoid many of the residual confounding observed in human population studies by reducing genetic variability in subjects (through the use of inbred strains and genetically identical animals) and tightly controlling environmental conditions, e.g. standardising animal husbandry. Experimental diets can be tested that could not ethically be tested in human cohorts. Moreover, rodent models facilitate the investigation of underlying physiological, cellular and molecular mechanisms during critical periods of development not easily available to clinical researchers.

14.3.1 Animal Models of Maternal Overnutrition and Obesity in Pregnancy

As with the early epidemiological studies which focused on the developmental programming effects of famine and low birthweight, much of the basic science research in developmental programming of cardiovascular function has focused on maternal undernutrition (for reviews, see [50, 51]). Relatively few studies have examined the effects of maternal obesity or overnutrition on blood pressure and by far the majority have been in rats and mice. Maternal overnutrition in rodents has been found to result in increased SBP in the offspring with some gender differences depending on the model employed (for reviews, see [52–54]. There are many routes to obesity; however, diet-induced obesity is normally preconditioned in female rats and mice by the ad libitum introduction of a highly palatable semi-synthetic high-fat diet or ‘chow’ in which carbohydrates are replaced with dietary fats and simple sugars to promote weight gain. Alternatively a highly palatable ‘cafeteria’ diet or ‘junk food’ diet has been employed, high in saturated fat, simple starches and sugars often reported to mimic the Western diet [55, 56]. The addition of simple sugars in particular appears to stimulate appetite and increase calorific intake, which is normally under tight homeostatic control in rodents. Sugar, either in the chow or presented as sugar water [57], appears to affect a more rapid shift towards a positive energy balance and development of obesity. Obesity in pregnancy is a risk factor for gestational diabetes in human pregnancy and in obese rodent dams also there is a degree of gestational diabetes apparent with maternal hyperinsulinaemia and glucose intolerance in pregnancy and/or lactation [58–63].

14.3.2 Cardiovascular Dysfunction in Animal Models of Maternal Overnutrition and Obesity

The early rodent models of overnutrition involving a high-fat diet in pregnancy [60, 61, 64–70] showed deleterious consequences for cardiometabolic function in the progeny of fat-fed animals, exhibiting many facets of the metabolic syndrome including hypertension. Similar corroborative findings were subsequently reported by different groups all over the World employing subtly different rodent models [53, 54, 71, 72]. Offspring of diet-induced obese mice (OffOb) develop systolic and mean arterial hypertension which deteriorates with age as measured by 24 h ambulatory blood pressure radio-telemetry. Hypertension at 3 months of age was associated with resistance artery endothelial dysfunction, a criteria for metabolic syndrome and another risk factor for cardiovascular disease [60]. The attendant complications of metabolic syndrome may play a significant part in the aetiology of the hypertension in this model. Visceral adiposity and insulin resistance develop with age; hence, there is a likely component of obesity-related hypertension in mature adult mice (for review, see [73]). However, it is technically possible to measure ambulatory blood pressure in very young offspring of obese rat dams employing mouse radio-telemetry technology in neonatal rats, and blood pressure is already elevated in juvenile offspring of obese dams prior to the development of offspring obesity [74]. Basal night-time (active phase) mean arterial pressure (MAP) was elevated in the offspring of obese dams (OffOb) relative to offspring of controls (OffCon; MAP, males: OffOb, 121.8 ± 0.6 mmHg vs. OffCon, 115.0 ± 0.5 mmHg, $n = 6$, $p < 0.01$; females: OffOb, 125.4 ± 0.4 mmHg vs. OffCon, 114.4 ± 0.5 mmHg, $n = 6$, $p < 0.001$). Blood pressure response to a brief restraint stress is also exaggerated in OffOb mice which implicates hypersensitivity of the cardiovascular stress response and the sympathetic nervous system (SNS).

14.3.3 Autonomic Nervous System Dysfunction in Offspring of Obese Rodents

Early-onset juvenile hypertension in offspring of the obese dams is associated with marked perturbations in the autonomic control of blood pressure. Power spectral analysis of the heart rate variability (HRV) derived from continuous waveform analysis of the blood pressure telemetry record revealed a significant increase in the sympathetic component of the autonomic control of blood pressure, as indicated by the ratio of low-frequency (LF) to high-frequency (HF) oscillations at 30 and 90 days of age. The parasympathetic component of ANS control of blood pressure was also significantly reduced at 90 days whereby high-frequency heart rate oscillators were strongly attenuated in offspring of obese rats versus offspring of control. This could contribute to a further increase in blood pressure. In the time-

domain parasympathetic indexes, the standard deviation of normal to normal intervals and root mean square of successive differences were also reduced, confirming the parasympathetic dysfunction shown by power spectral analysis. Consistent with the observed increase in basal sympathetic tone and the increased cardiovascular reactivity to stress, renal tissue norepinephrine content and renin expression were markedly raised in OffOb compared with OffCon. Similarly, the pressor response to a leptin challenge was enhanced in OffOb rats (Delta MAP: OffOb, 9.7 ± 0.8 mmHg vs. OffCon, 5.3 ± 1.3 mmHg; $n = 8$; $p < 0.05$). Leptin increases blood pressure through an increase in hypothalamic and nucleus of the solitary tract (NTS) efferent sympathetic tone via the brainstem and renal nerve [75], and both systemic and central administrations of leptin increase renal nerve activity and MAP in the rat [76] (Fig. 14.1).

The observed hypertension, which persisted into adulthood, was abolished by alpha- and beta-adrenergic blockade indicating sympathetic involvement. Moreover, OffOb rats demonstrate reduced baroreflex sensitivity, with attenuation of the tachycardia and bradycardia responses to sodium nitroprusside and phenylephrine, respectively, resulting in a decreased slope of the curve of HR against MAP.

Taken together these observations suggest the developmental programming of a primary hypertension of sympathetic origin in the offspring of obese dams arising from persistent sympathoexcitatory hyper-responsiveness acquired in the perinatal period. Leptin also triggers sympathetic hyperactivity, but intriguingly, the juvenile offspring of obese rats display very specific and highly divergent responses to a leptin challenge in terms of appetitive behaviour, suggestive of selective leptin responsiveness in pathways originating at the level of the hypothalamic nuclei.

14.3.4 Selective Leptin Responsiveness in Offspring of Obese Rodents

Leptin is an adipokine peptide hormone released from fat cells in proportion to their size, as they become enlarged with stored triglyceride. Leptin is critical to the regulation of energy balance and feeds back to the appetite regulatory centres in the brain to report a positive energy balance. Activation of leptin receptors (LepR) at the arcuate nucleus (ARC) of the hypothalamus activates satiety pathways to inhibit further food intake, but also promotes energy expenditure via sympathetic stimulation of the metabolically active tissues such as brown adipose tissue (BAT) involved in thermoregulation [77]. SNS stimulation by leptin also appears to have an important role in cardiovascular control [77]. Leptin infusion or leptin overexpression in genetically modified mice increases renal sympathetic nerve activity (RSNA) and elevates blood pressure and heart rate [73, 78–80]. In the ARC, leptin stimulates the expression of pro-opiomelanocortin (POMC) and activates POMC neurons to release melanocyte-stimulating hormones (MSH) that act on secondary neurons expressing melanocortin receptors (MC4R) in the

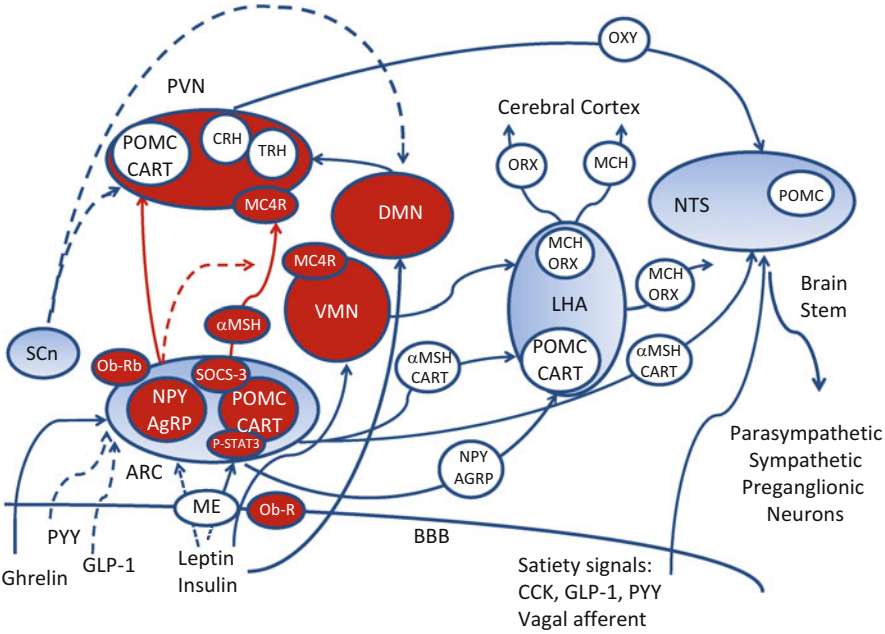

Fig. 14.1 The hypothalamic nuclei and related brain regions. The arcuate nucleus (ARC) is located in the hypothalamus, close to the median eminence (ME) where the blood–brain barrier (BBB) is incomplete allowing blood-borne signals to reach ARC neurons. Leptin, insulin and ghrelin are the most important hormonal satiety signals and are also actively transported across the BBB where they activate anorexigenic neurons coexpressing alpha melanocyte-stimulating hormone (αMSH) and cocaine- and amphetamine-regulated transcript (CART) and inhibit orexigenic neurons coexpressing agouti-related protein and neuropeptide Y (AgRP and NPY). Both populations of neurones project widely throughout the brain. CART is also expressed in the paraventricular hypothalamic nucleus (PVN) and LHA. αMSH is cleaved from the precusor polypeptide proopiomelanocortin (POMC) along with other peptides such as β-endorphin and ACTH. The ARC integrates this information together with inputs from brainstem areas and signals other hypothalamic nuclei such as the ventromedial hypothalamic nucleus (VMN), dorsomedial hypothalamic nucleus (DMH) and PVN, to reduce food intake. Signals from the ARC to the PVN and the lateral hypothalamic area (LHA) also increase feeding. Divergent projections from the orexin containing neurons (ORX) and melanin-concentrating hormone (MCH) neurons in the LHA ascend to the cerebral cortex and descend to the brainstem and spinal cord. Oxytocin containing neurons (OXY) of the PVN innervate vagal preganglionic parasympathetic neurons involved in gastrointestinal control (OXY). Hormones from the gastrointestinal tract including cholecystokinin (CCK) and glucagon-like peptide (GLP-1) modulate these processes through shorter-term changes in satiety and hunger. Inputs from the suprachiasmatic nucleus (SCn) to the PVN and DMN also regulate diurnal feeding patterns. The three possible outputs from the hypothalamus that regulate food intake and energy expenditure are activation of motor neurons via the brain stem; activation of neuroendocrine neurons in the PVN that secrete corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) to activate the pituitary axes (e.g. hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid axis activation result in secretion of glucocorticoids and thyroid hormone); autonomic nervous system both sympathetic and parasympathetic e.g. influencing heart rate and blood pressure and thermogenesis in metabolically active tissues

paraventricular nucleus of the hypothalamus and related brain regions (NTS) to increase sympathetic activity.

Leptin deficiency, on the other hand, in both humans and animals, causes obesity in the absence of hypertension [81, 82]. In established obesity, chronic hyperleptinaemia can lead POMC neurons to become unresponsive to leptin with the loss of the anorectic actions of leptin, yet with preservation of the pressor effects on blood pressure, effectively a state of acquired *selective leptin resistance*, which has been hypothesised to underlie obesity-related hypertension [43, 73, 83]. Offspring of obese rats also appear to exhibit a developmentally programmed early leptin resistance as juvenile animals which precedes the onset of obesity and hyperleptinaemia. Administration of exogenous leptin at a dose (10 mg/kg i.p.) which inhibits 24 h food intake and promotes weight loss in control animals had no apparent effect in 30-day-old offspring of obese rat dams [70, 84, 85]. Following similar administration of leptin in young OffOb rats, phosphorylated-STAT3, a marker of leptin signalling, was selectively reduced in the ARC, but not in other hypothalamic nuclei [70]. The dorsomedial hypothalamus (DMH) and ventromedial hypothalamus (VNH) in addition to the PVN also express LepR and have been implicated in leptin's ability to stimulate BAT and cardiovascular control independently of MC4R signalling (Fig. 14.1). This provides a possible explanation for selective leptin resistance in chronic obesity and also potentially the selective leptin responsiveness observed in young offspring of obese rats which was not obesity related, but a direct consequence of early-life 'exposure' to maternal obesity.

14.3.5 Neuronal Development of the Neonatal Brain: A Role for Leptin

This then begs the question, what is it about the immediate maternal environment that gives rise to the primary programming of sympathetic hypertension in offspring of obese rodents? Hypertension appears to arise as a direct consequence of in utero or postnatal exposure to maternal obesity and is not the result of increased adiposity in the offspring, which only becomes evident in older animals. Intriguingly, the observed alteration in central leptin sensitivity in offspring of obese rodents may provide a clue, especially when we consider the critical role that leptin plays in development of the CNS and the neonatal hyperleptinaemia associated with maternal obesity in rodents.

The apparent primary programming of a sympathetically mediated hypertension secondary to maternal obesity in young offspring of obese rodents may arise not only from perturbation of central leptin sensitivity, but also through dysregulation of the normal neurotrophic action of leptin resulting in both structural and functional deficits in leptin signalling during neuronal development [70].

Maternal obesity in rodents is associated with marked hyperleptinaemia in the neonate during a critical period in brain development when leptin is thought to play

a permissive neurotrophic role in establishing the neural circuitry of the hypothalamic nuclei [86]. Leptin, possibly in concert with other neurotrophic factors including insulin and corticosterone, appears to be critical during this period of developmental plasticity for promoting neural growth of the hypothalamic nuclei involved in both appetite and blood pressure regulation.

A physiological postnatal surge in the plasma leptin concentration was first described in neonatal rats by Ahima and colleagues in 1998 and has since been described by others in both rats and mice [87–92]. The leptin surge peaks during the second postnatal week in rodents (postnatal day 10) before returning to normal levels at weaning. Leptin signalling pathways are incomplete at this stage of development and pups are able to maintain a high level of food intake despite higher plasma leptin levels. The physiological role of the leptin surge appears to be in orchestrating hypothalamic neuronal outgrowth and connectivity between hypothalamic nuclei [92, 93].

In a landmark paper, Sebastian Bouret *and colleagues* (2004) first described the neurotrophic action of leptin in leptin-deficient (ob/ob) mice. Bouret initially observed incomplete formation of the neural projections between the arcuate nucleus (ARC) to the paraventricular hypothalamic nucleus (PVH) of the hypothalamus in the hyperphagic and obese ob/ob mice [86]. Bouret *and colleagues* were able to restore normal hypothalamic development by giving neonatal mice replacement leptin treatment critically during the second postnatal week. Leptin treatment in adult (ob/ob) mice had no apparent effect again highlighting the early postnatal period as being critical to hypothalamic development in rodents. Similar attenuation of hypothalamic neural projections from the ARC is also observed in DIO rats genetically predisposed to develop diet-induced obesity [94]. These two genetic models of hyperphagia and obesity [94, 95] also show reduced immunoreactivity for agouti-related peptide (AgRP) containing neurons in the PVH which originate in the ARC [94, 95]. Reduced density of arcuate projections and AgRP-containing neurons in the hypothalamus may permanently influence the structure and function of neural circuits involved in both energy balance and autonomic regulation of cardiovascular control (Fig. 14.1). Moreover, AgRP is the endogenous antagonist of MC4R, and reduced antagonism would increase melanocortin signalling at sites relevant to blood pressure regulation to promote hypertension [96].

It seems likely that the exaggerated and prolonged neonatal leptin surge reported in offspring of obese rat dams may have precipitated the attenuated AgRP immunoreactivity reported in the PVH at postnatal day 30. It is tempting to speculate that similarity in neonatal AgRP neural development between this model and Bouret's study in ob/ob mice which lack leptin [86] is a consequence of leptin resistance in the former and leptin deficiency in the latter. These studies, and others since Bouret's pivotal study, which have focused on the neurotrophic action of leptin and the influence of early nutrition, seem to indicate a permissive role for leptin and leptin signalling in the normal development of the neonatal hypothalamus and may provide the strongest mechanistic link between maternal obesity and permanent programming of cardiovascular control [63, 72, 94, 97–106].

14.3.6 Nutritional Impact on Leptin Signalling in Development

Little has been reported on the origins or determinants of the leptin surge in rodents. In neonatal OffOb rats, the plasma leptin surge is matched by a similar profile of adipocyte leptin mRNA expression, suggesting that neonatal adipose tissue is the source of the plasma leptin surge, as has been suggested by others [87, 89, 91]. Maternal nutritional status has been shown to affect the timing of the neonatal plasma leptin profile [91, 107], which is thought to reflect the differentiation of pre-adipocytes into mature adipocytes which can then produce leptin [108]. Factors such as insulin which affect maturation of the pre-adipocytes may therefore influence the timing of the leptin surge [109]. Indeed, in offspring of obese rats there is a peak in the neonatal plasma insulin profiles in response to elevated glucose concentrations in the milk, which appears to precede the neonatal plasma leptin surge [110].

Whilst several models of developmental programming report maternal nutritional modulation of neonatal leptin profiles associated with changes in offspring cardiometabolic phenotype [91, 105] pharmacological manipulation of the leptin surge in rodents provides further support for the role of leptin in shaping cardiometabolic outcomes [91, 107, 111, 112]. A greater understanding of the determinants of the neonatal leptin surge and the comparative physiology in humans, which is poorly understood, might inform interventions to reduce the risk of obesity and hypertension.

14.3.7 Experimental Neonatal Hyperleptinaemia in Rodents

To investigate the cardiovascular consequences of the exaggerated and prolonged leptin surge observed in offspring of obese rat dams, we treated naive rat pups with exogenous leptin to mimic leptin concentrations over the same time course [113]. Neonatal rats born to control dams were treated twice daily either with recombinant rat leptin (10 mg/kg i.p.) or saline vehicle control from postnatal day (PD) 9–15. Cardiovascular function was assessed remotely by radio-telemetry. In juvenile leptin-treated animals SBP was raised by 13 mmHg compared to controls. The cardiovascular response to a brief restraint stress and a pharmacological challenge to a bolus dose of leptin was enhanced in the leptin-treated animals. Power spectral analysis of HRV derived from the blood pressure waveform of the telemetry record confirmed heightened sympathetic drive contributing to hypertension in the leptin-treated animals. Analysis of tissue catecholamine levels at 30 days of age showed a twofold elevation in renal noradrenaline concentrations in the leptin-treated animals. Hypertension in the leptin-treated animals was normalised following mixed alpha and beta blockade (terazosin and propranolol). Hypertension and heightened sympathetic tone were observed independent of changes in adiposity and/or hyperleptinaemia suggesting a direct influence of neonatal leptin exposure on the developing pathways of blood pressure control [113].

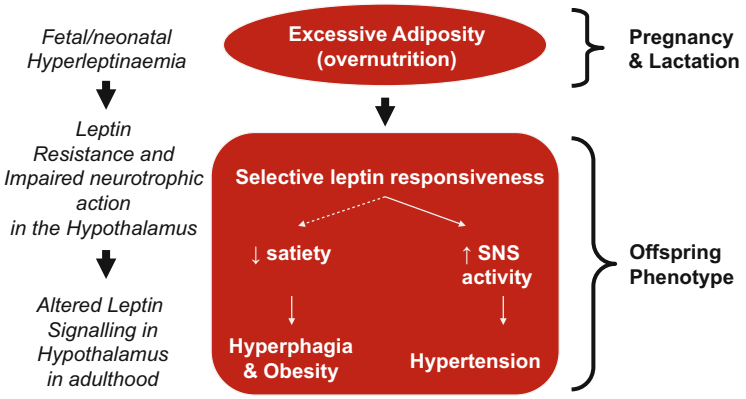

Fig. 14.2 Developmental programming of obesity and hypertension secondary to maternal obesity and/or neonatal hyperleptineamia. The schematic shows the proposed developmental origins of 'selective leptin responsiveness' in which the anorexic actions of leptin are lost whilst the pressor effect of leptin is enhanced

Leptin-treated animals were 'leptin resistant' at 30 and 90 days of age, with no response in feeding behaviour or weight loss following a leptin challenge. Similar studies have reported hypothalamic leptin resistance following leptin administration in neonatal rats [107, 114] and mice [91]. However, the studies by Samuelsson et al. provide the first direct evidence that exposure to hyperleptinaemia in early development causes adulthood hypertension of sympathetic origin and supports a role for leptin in the cardiovascular phenotype of acquired 'selective leptin responsiveness' secondary to maternal obesity in the OffOb model (Fig. 14.2). Comparing the two phenotypes, however, the offspring of the obese rat dams appear to have a more pronounced hypertension and more robust cardiovascular phenotype than the leptin-treated rats [84]. This suggests that other factors relating to maternal obesity contribute the OffOb phenotype in addition to neonatal leptin exposure [113]. Neonatal hyperinsulinaemia may also have a part in aberrant hypothalamic development [115] and may influence offspring cardiovascular control secondary to maternal obesity and glucose intolerance [60, 61]. Indeed, maternal high-fat feeding during lactation in mice causes offspring obesity associated with severely impaired POMC and AgRP projections to PVH, which is prevented by specifically knocking out insulin signalling in POMC-specific insulin receptor-deficient mice [116].

14.4 Identifying the Site of the Hypothalamic Lesion in Offspring of Obese Rodents

14.4.1 A Role for Hypothalamic Melanocortin Signalling

Rodent studies of maternal obesity and experimental hyperleptinaemia indicate that increased sympathetic nerve activity (SNA) is an important mediator of

hypertension since alpha- and beta-adrenergic receptor blockade and renal denervation ameliorate the elevation of blood pressure in these models [60, 74, 84]. However, the molecular mechanisms and neuronal pathways are yet to be fully elucidated. We can hypothesise that the 'selective leptin responsiveness' observed and the exaggerated pressor response to leptin identifies the hypertensive lesion in the hypothalamic leptin signalling pathways that regulate sympathetic efferent activity. Leptin activates POMC neurons in the arcuate nucleus, which release peptide melanocyte-stimulating hormones (MSH) that act on MC4R expressing neurons in the PVH and other brain regions to increase SNA [117, 118]. Humans with loss-of-function mutations of MC4R are obese but have normal blood pressure [119]. Moreover, the SNA responses to acute leptin are abolished in MC4R-deficient mice [120] and by central administration of the MC4R antagonist SHU9119 [119]. We have reported that hypothalamic MC4 mRNA expression is increased in adult offspring of obese rats compared to controls and that central administration of the MC3/4R antagonist SHU9119 decreases MAP to a greater degree in offspring of obese rats compared to controls [121]. Maternal obesity appears to result in increased MC4R signalling which contributes to hypertension in this rodent model. It is tempting to speculate, therefore, that increased signalling via MC4R in the PVN or possibly in the brainstem mediates the primary sympathetic hypertension in offspring of obese pregnant rats. Indeed, recent unpublished observations by Samuelsson and colleagues on the effects of maternal obesity imposed on the genetic background of MC4R null mice mouse model indicate that hypertension in offspring of diet-induced obese is dependent on the presence of functional MC4R in the PVH [122]. Heterozygote loxTB Mc4r mice were mated with Sim1-Cre genetically modified heterozygote loxTB Mc4r littermates [123] to generate WT, homozygous loxTB MC4R (MC4R null mice) and Sim1-Cre, loxTB MC4R (MC4R–PVH) offspring in which MC4R is re-expressed specifically in the PVN. These studies identify MC4R signalling in the paraventricular hypothalamus as the primary lesion in the development of sympathetic hypertension secondary to both maternal obesity and experimental neonatal hyperleptinaemia (Fig. 14.3).

14.4.2 Leptin Receptor Signalling Beyond the Arcuate Nucleus

As evidenced in chronic obesity and potentially in offspring of obese rodents, POMC neurons in the arcuate nucleus may become leptin resistant; however, leptin can act independently of MC4R signalling to affect changes in cardiovascular control. The DMH is intimately involved in the activation of BAT and regulation of the cardiovascular system and both humans and animals with loss-of-function mutations in leptin and LepR are obese but not hypertensive. Selectively blocking the action of leptin in diet-induced obese mice using specific antibodies, antagonists

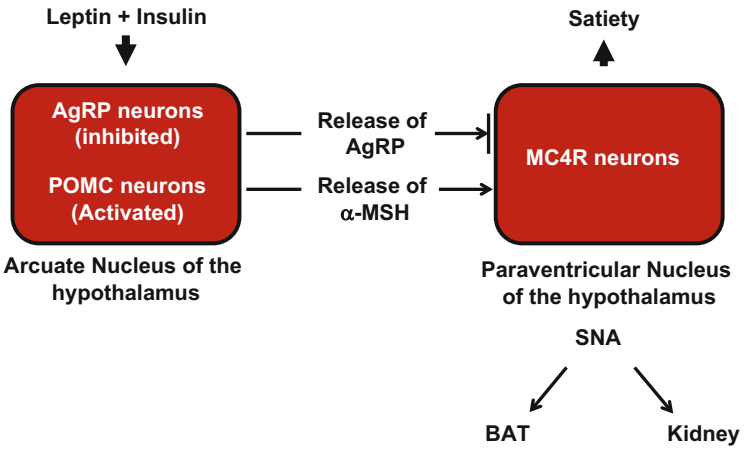

Fig. 14.3 Leptin signalling, blood pressure and MC4-R pathway. Leptin and insulin act synergistically to activate shared central sympathoexcitatory pathways which are mediated by the melanocortin 4 receptor (MC4R) and the PI3 kinase pathway. AgRP is the endogenous antagonist of MC4R, and reduced antagonism would increase melanocortin signalling at sites relevant to blood pressure regulation to promote hypertension

or inhibiting activity of LepR expressing neurons originating in the DMH prevents the elevation in HR and BP in diet-induced obese mice [124, 125] although the effects on RSNA were not reported. Re-instating LepR in the DMH of obese LepR-deficient mice elevates BP. Hence, the DMH, independent of MC4R signalling, represents another potential candidate site for the hypertensive lesion and leptin hyper-responsiveness in offspring of obese mice.

14.4.3 The Gut Microbiome and Epigenetic Modifications Arising from Obesity in Pregnancy

Whilst the aforementioned alterations in hypothalamic structure and function secondary to maternal obesity may be mediated through classical processes of developmental neuroendocrinology, they do not exclude a potential role for novel molecular mechanisms which may shape gene expression during critical periods of developmental plasticity. The gut microbiome is emerging as a key player in obesity research and presents yet another very immediate environmental stimulus to developmental programming through epigenetic modification of gene environment and expression and shaping offspring phenotype in development and beyond. Moreover, the transfer of gut microbiota from mother to baby that occurs during normal vaginal delivery presents another vector for inheritance of epigenetic traits that may influence obesity and cardiometabolic risk. From the obstetric perspective, there has been much recent interest around mode of delivery establishing

phenotypic traits in the offspring. Obesity is a major risk factor for Caesarean section, and babies born particularly by pre-labour caesarean section (CS) can develop acute and chronic physiological changes which are hypothesised to reflect aberrant microbial colonisation of the infant intestinal tract [126, 127]. Associated phenotypic changes range from altered feeding behaviour, metabolism and blood pressure to type II diabetes, immune-related conditions and neurological and stress-related problems [128]. Mode of delivery and antibiotic use in late pregnancy are potential confounders in studying the effect of obesity in mother/child cohorts, associated with as much as 46 % increased risk of childhood obesity [129].

The gut microbiota with an estimated biomass of 2–3 kg in humans contains a unique group of symbiotic micro-organisms both bacteria and viruses with a combined gene pool or 'microbiome' far in excess of the human genome. Besides the more mundane yet essential biological functions such as the digestion of complex carbohydrates, these microbial genes influence innate and adaptive immunity and may have key regulatory functions in metabolic pathways in health and in disease [130–132].

Some elegant inoculation studies in animals demonstrate the power of the gut microbiota to affect metabolic and cardiovascular phenotype. Toll-like receptors of the innate immune system are critical for both colonisation and homeostasis of the human microbiota. Genetically altered mice specifically lacking TLR 5 exhibit hyperphagia, obesity and hypertension associated with a dysbiotic gut microbiota. Remarkably, transfer of faecal material from affected mice to germ-free wild-type mice (treated with antibiotics) confers similar features of the metabolic syndrome in recipient mice [133]. Diet also has an important role in shaping the composition of the gut microbiome, with high-fat Western diets favouring a more 'Bacteroides' enterotype associated with obesity [134–136]. These studies therefore highlight the importance of the healthy colonisation and maintenance of the microbiota and imply that diet and/or obesity in pregnancy could set up a dysbiosis in the offspring through the inherited microbiome.

14.4.4 The Gut Microbiota and Cardiovascular Control

Emerging evidence suggests that gut microbiota influence blood pressure regulation and salt sensitivity through interactions with genetics, epigenetics diet and lifestyle factors and the widespread use of antibiotics [137]. Human essential hypertension along with several models of hypertension in rodents [the spontaneously hypertensive (SHR) and Dahl salt-sensitive rat] is associated with altered microbiota and the relative ratio of gut species *Firmicutes* and *Bacteroidetes* [138, 139]. Fermentation products derived from gut bacteria can influence blood pressure control via modulation of sympathetic pathways of energy expenditure and catecholamine metabolism in the gut, together with intestinal and renal ion transport which can influence salt sensitivity.

Short-chain fatty acids (SCFA) derived from gut bacteria can also modulate renal sensory nerves to affect renin release and blood pressure via the gastro-renal axis [140]. SCFA can increase energy expenditure via the gut–brain axis stimulating the SNA via G protein-coupled receptor—GPR41 and elevating blood pressure [141].

Hypertension is affected by low-grade inflammation which can arise from compromised microbiome diversity. Pre-eclampsia is characterised by hypertension and inflammation in pregnancy and is improved by long-term probiotic use [142]. Probiotics may therefore find prophylactic use in blood pressure control via epigenetic modification of the complex regulatory pathways involved in hypertension.

Animal studies addressing the probiotic modulation of the microbiome in obese pregnancy and epigenetic effects on the offspring are ongoing in our laboratory, and it remains to be seen whether the colonisation and the diversity of intestinal microbes is a modifiable risk factor for offspring cardiovascular outcomes secondary to obese pregnancy.

14.5 Translation from Animal Models Back to Human Obesity in Pregnancy

The rodent models of obesity in pregnancy share many similarities with the metabolic profiles in obese pregnant women including insulin resistance and maternal hyperglycaemia leading to a reactive fetal hyperinsulinaemia [143]. Obese pregnant women, like their obese rodent counterparts, also demonstrate hyperleptinaemia, and cord blood leptin is raised in babies born to obese women [143]. Thus, in common with the neonatal rodent, the fetus of an obese woman is exposed to both hyperinsulinaemia and hyperleptinaemia [144]. It is important, however, in extrapolating to humans from rodents, to acknowledge that as an altricial species, rodents give birth to young at a less advanced stage of development compared to human infants (precocial) and that the period of hypothalamic plasticity that occurs in rat pups postnatally probably equates to the third trimester in human pregnancy. However, there is evidence from non-human primates that this developmental window may extend into the suckling period [99, 145]. Studies of human fetal brain development are understandably limited, but there is evidence that neural projections begin to develop between hypothalamic nuclei from 21 weeks of gestation [146]. It seem likely, therefore, that the critical window for hypothalamic developmental in humans is quite broad and that there is potential for exposure to the adverse neurotrophic effects of pathological levels of leptin in obese pregnancy both antenatally and potentially post-partum via mother's milk.

In comparison with rodents, a leptin surge has not been described in human development as such; a developmental role for leptin might be suggested by the

unexplained high concentration of leptin in fetal cord blood, which falls rapidly post-partum [31], and is related to birth weight [147, 148]. Recent studies provide strong evidence for a positive correlation between maternal and fetal plasma leptin concentrations (and a negative correlation between fetal leptin and insulin sensitivity), evidence of the maternal–fetal transmission of this potentially critical neurotrophic factor [149].

The hyper-reactivity of the SNS in offspring of obese rodents has not been established in human studies. Whilst the ANS has not been extensively studied in the children of obese women, a correlation has been observed between fetal cardiac sympatho-vagal activation during labour and maternal BMI [150]. The ABCD study of 3074 women reported that pre-pregnancy BMI was positively linearly associated with offspring blood pressure, but not with sympathetic or parasympathetic drive in 5–6 year olds. However, only a small proportion (5 %) of the women studied were clinically obese [24]. Ongoing studies will characterise ANS as part of a follow-up study of neonates and 3-year-old children born to obese pregnant women participating in the UPBEAT RCT (UK pregnancy and better eating trial) compared with offspring born to lean control mothers.

14.6 Conclusions

The prevalence of maternal obesity in the UK has more than doubled in the past 20 years and is predicted to rise with in line current secular trends. Not only is maternal obesity the single biggest obstetric risk factor for adverse pregnancy outcome, but it carries with it reduced life expectancy in adult offspring through increased cardiovascular mortality. Maternal obesity, in particular pre-pregnancy BMI, is associated with childhood and adult hypertension; however, the extent to which elevated blood pressure and other cardiovascular risk factors are dependent on the offspring BMI requires further studies in younger children. Ongoing RCTs of diet and lifestyle interventions aimed at modulating the determinants of obesity in pregnancy have the greatest potential to establish cause and effect and inform intervention strategies to improve offspring cardiovascular outcomes. Animal studies, which to a large extent avoid confounding variables, support a strong association between maternal obesity and offspring blood pressure. This involves early activation of the SNS and suppression of parasympathetic drive, which is independent of offspring adiposity and, therefore, secondary effects of obesity-related hypertension. Evidence suggests the developmental programming of a primary hypertension secondary to maternal obesity and neonatal hyperleptinaemia which is of autonomic nervous system origin and associated with selective leptin responsiveness at the level of the hypothalamic nuclei. Altered leptin signalling in the hypothalamus may arise through neonatal hyperleptinaemia during the critical developmental window of neuronal development and hypothalamic plasticity when leptin appears to have a permissive neurotrophic role in normal physiological development. Leptin resistance arising from downregulation of LepR during this

period may produce suboptimal neural outgrowth and connectivity between the hypothalamic nuclei resulting in altered structure and function of pathways involved in energy expenditure and blood pressure control. In situ hybridisation experiments that can map LepR expression within the highly heterogeneous neuronal populations and cell types with the ARC will identify the aetiology involved. Meanwhile, preliminary studies not yet published from our laboratory, employing Cre-lox technology, identify a role for the hypothalamic melanocortin system in the origins of the hypertension secondary to maternal obesity and experimental neonatal hyperleptinaemia. These studies pinpoint MC4R in the PVH as the primary lesion in the autonomic hypertension in these models. The intestinal microbiota sometimes referred to as the 'second brain' presents some exciting new pathways in the gut–brain axis which can influence physiology through innate immune and metabolic systems to potentially influence developmental programming of the central nervous system. The colonising gut flora present a plausible vector in the transmission of maternal epigenetic traits to offspring and it remains to be seen whether the microbiota colonisation and the diversity of intestinal microbes might be a target for intervention in maternal obesity.

Finally, whether increased fetal exposure to leptin secondary to maternal obesity influences human hypothalamic development to a similar degree remains to be seen, but evidence from non-human primates supports translation of similar underlying cellular and molecular mechanisms. In fact, it would be surprising if the neurotrophic effects of leptin and the consequences of leptin overexposure on hypothalamic development were not conserved across mammalian species. However, at present, the prospect of pharmacological interventions in leptin signalling during pregnancy seems unlikely. Therefore, diet and lifestyle interventions that modulate adiposity levels and reduce possible fetal leptin overexposure remain the best option for intervention.

Acknowledgments

Funding PT is supported by the British Heart Foundation (http://www.bhf.org.uk), the BBSRC (http://www.bbsrc.ac.uk) and EarlyNutrition (EU, Framework 7; www.metabolic-programming.org). Support was also received from the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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