

The developmental origins of obesity-related hypertension

Sarah L. Henry,¹ Benjamin Barzel,^{1,2} Ryan J. Wood-Bradley,¹ Sandra L. Burke,²
Geoffrey A. Head² & James A. Armitage^{1,2}

¹Department of Anatomy and Developmental Biology, Monash University, VIC 3800, Australia and

²Neuropharmacology Laboratory, Baker IDI Heart and Diabetes Institute,
PO Box 6492, St Kilda Road Central, VIC 8008, Australia.

Summary

1. In the past 30 years the prevalence of obesity and overweight have doubled and it is now estimated that globally, over 500 million adults are obese and a further billion adults are overweight. Obesity is a cardiovascular risk factor and some studies suggest that up to 70% of cases of essential hypertension may be attributable, in part, to obesity. Increasingly, evidence supports a view that obesity-related hypertension may be driven by altered hypothalamic signaling which results in inappropriately high appetite and sympathetic nerve activity to the kidney.

2. In addition to the adult risk factors for obesity and hypertension, the environment encountered in early life may “programme” the development of obesity, hypertension and cardiovascular disease. In particular, maternal obesity or high dietary fat intake in pregnancy may induce changes in fetal growth trajectories and predispose individuals to develop obesity and related sequelae.

3. The mechanisms underlying the programming of obesity-related hypertension are becoming better understood. However several issues require clarification, particularly in regard to the role of the placenta in transferring fatty acid to the fetal compartment, the impact of placental inflammation and cytokine production in obesity.

4. By understanding which factors are most associated with the development of obesity and hypertension in the offspring, we can focus therapeutic and behavioural interventions to most efficiently reduce the intergenerational propagation of the obesity cycle.

The obesity epidemic

The past 30 years has seen a secular trend of increased overweight and obese humans worldwide. In 2009 it was estimated that ~60% of Australian adults were obese or overweight.¹ The prevalence of childhood obesity has also risen alarmingly; in Australia there was a 230% increase in obesity in young boys and 170% increase in young girls between the years 1985 and 2004.² These trends are not limited to Australia; The World Health Organization predicts that in the 21st Century, the burden of obesity-related disease will exceed that of infectious disease and malnutrition. Once considered to be exclusively within the purview of Western societies, the incidence and prevalence of obesity is rising sharply in developing nations. For

example, a recent study of slum dwellers in New Delhi found obesity in approximately 10% of males and 40% of females.³

One of the major sequelae of obesity is hypertension. Data from the Framingham Heart Study implicate obesity as a contributory factor in 60% -70% of essential hypertension. Although some early studies postulated that the hypertension associated with obesity was less of a cardiovascular risk⁴ subsequent analyses of large cohorts indicated that obesity-related hypertension poses a significant risk to morbidity and mortality.⁵ In Australia, it is estimated that over 50% of the burden of diabetic and cardiovascular disease¹ are obesity related and the financial cost of obesity in Australia is an estimated \$3.5 billion per year.⁶ The steep increase in the prevalence of obesity worldwide is due to a range of factors; increased intake of total calories, fatty acids and simple sugars, and a reduction in physical activity.⁷ Data from the UK⁸ suggest that the average person receives 36% of their daily total energy from all fats, with saturated fats a major component of this daily caloric intake. Individuals in many developed nations, including Australia, USA and Europe derive more than 900 calories per day from fats, oil and sugar.⁹

In addition to the importance of the above risk factors, the aetiology of obesity is complex and additional factors must be contributing to overall prevalence rates.

There is accumulating evidence that the environment encountered in early life can contribute to the development of disease later in life. The study of this process is termed the “developmental programming of adult health and disease”. A range of factors, including maternal dietary imbalance in pregnancy, result in fetal and neonatal adaptations and altered organogenesis that predisposes individuals to later obesity and hypertension.¹⁰ The original Barker studies focused on the role of low birth weight in programming later disease, and later studies showed maternal nutrition status to be a key determinant of fetal growth and weight at birth. Although millions of women are undernourished during pregnancy, maternal over-nutrition may also be a significant contributor to later disease in offspring.

Approximately 10% of pregnant women in Australia are now obese, and maternal obesity poses an increased obstetric risk to mother and fetus.¹¹ However, even moderate overweight may programme disease in the offspring and the burden of mild overweight and dyslipidaemia due to poor dietary habits in pregnancy

cannot be ignored as >25% of children in Australia are born to overweight women.¹¹ The typical Australian diet contains excessive quantities of saturated fat and sugar⁷ and this excessive fat intake contributes to elevated adiposity in the mother which in turn can programme infant¹² and childhood adiposity.¹³ Maternal obesity in pregnancy is associated with disturbances in maternal blood glucose, lipids, cytokines and hormones and in addition to complicating pregnancy outcomes, obesity has an impact on the next generation and perpetuates the cycle. Offspring of obese women are 36% more likely (Odds ratio 1.07-1.73) to develop type 2 diabetes than controls.¹⁴ Animal models indicate that offspring of obese mothers are more susceptible to chronic conditions including obesity, cardiovascular,¹⁵⁻¹⁷ renal¹⁸ and metabolic disease.¹⁹

This review will discuss the current understanding of factors underlying obesity-related hypertension with a particular focus on how maternal diet in pregnancy may “programme” the development of obesity-related hypertension.

What causes hypertension in obesity?

Despite the ubiquity of hypertension in obesity, the underlying mechanisms are not fully understood. Certainly the condition is multifactorial. Obesity is associated with peripheral vascular disease including endothelial disease and increased vascular stiffness. Moreover the increase in body size requires an increase in blood volume and elevated cardiac output to perfuse this extra tissue. In addition, adipose tissue is an active endocrine tissue that secretes a range of chemokines. One such chemokine is leptin, which may trigger the genesis of obesity-related hypertension. The kidney is also a vital determinant of long-term blood pressure control. There is evidence that increased tubular sodium reabsorption, elevated activity of the renin angiotensin system and a rightward shift in the pressure natriuresis curve all occur in obesity, thereby contributing to hypertension.²⁰

Recently, a number of studies in humans and animal models have established that dysregulation of the sympathetic nervous system may be pivotal in the development of obesity-related hypertension. Early hypotheses, based on measures of plasma catecholamine concentration and spectral analysis of heart rate variability, suggested that weight gain occurred due to low sympathetic activity.²¹ Direct sympathetic nerve recording and noradrenaline spillover from sympathetic nerves, indicate sympathetic outflows to kidneys and blood vessels in skeletal muscle are elevated in obese humans and cardiac tone is reduced.²² The disparity in sympathetic nerve activity to differing beds may explain why the deranged energy homeostasis and haemodynamics of obesity and the suggestion that heart rate variability in obese individuals was the result of decreased sympathetic activity.

Animal models of diet-induced obesity also support the hypothesis that net sympathetic activity is elevated in obesity. Pharmacological blockade of adrenergic activity markedly attenuates the elevated BP in both dogs²⁰ and

rabbits²³ caused by diet-induced obesity. Moreover, we have recently shown that New Zealand White rabbits fed a high fat diet for 3 weeks develop elevated adiposity, hypertension, tachycardia and elevated sympathetic nerve activity, all of which are proportional to the plasma concentration of leptin.²⁴ In addition to elevated sympathetic outflow to the kidneys under basal conditions we have also shown that New Zealand White rabbits fed a high fat diet demonstrate an exaggerated renal response to exogenous stimulation of the sympathetic nerves.²⁵ In mouse models, where nerve activity cannot be directly measured in conscious animals, sympathetic mediated thermogenesis in brown adipose tissue has been found to be elevated in obesity.²⁶ Chronic stimulation of the sympathetic nervous system is normally associated with elevated blood pressure, suggesting that obesity-related hypertension may be due to increased sympathetic activity and the factors that initiate this sympathetic activity are likely to be peripheral energy homeostatic signaling molecules such as leptin and insulin. Figure 1 illustrates this working hypothesis.

Nuclei in the hypothalamus integrate information about energy homeostasis from the peripheral nervous system and circulation and initiate neural signals that modulate appetite and thermogenesis. Among the links between appetite and sympathetic tone is the generation of efferent neural signals regulating both that originate in the hypothalamus in response to stimulation by leptin.²⁷ Leptin, a protein hormone, produced primarily by white adipose tissue, is one of the most potent mediators of long-term energy homeostasis.²⁸ Plasma leptin correlates with adiposity and leptin accesses the brain by active and passive systems at the leaky blood brain barrier at the median eminence to act on neurons expressing the long form of the Ob receptor in the hypothalamic arcuate nucleus.²⁹

Leptin stimulates the pro-opiomelanocortin (POMC) system that comprises α -melanocyte stimulating hormone (α -MSH) containing neurons to reduce food intake and increase sympathetic outflow *via* melanocortin (MC) 3 and 4 receptors. Sympathoexcitatory neural pathways are highly dependent on the MC4 receptor which is also crucial for the development of obesity-related hypertension. MC4 receptor knockout mice develop diet-induced obesity but not hypertension or renal disease.³² Leptin inhibits neurons containing neuropeptide Y (NPY) or agouti related peptide (AgRP) that initiate feeding and suppress sympathetic outflow *via* Y1 and Y5 receptors.³³ Activation of NPY receptors also results in a reduction of cardiovascular response to stress³⁴ but the role of NPY receptors in obesity-related hypertension is in need of further clarification.

Therefore, the expected effects of short-term elevations of body fat include a feedback loop wherein leptin is released from white adipose tissue to the circulation, resulting in hypothalamic mediated satiety and increased sympathetic nerve activity that increases energy expenditure. This results in a net energy deficit and a return to the body weight set point (See Figure 2A). In contrast, in the presence of persistent energy excess, continuously

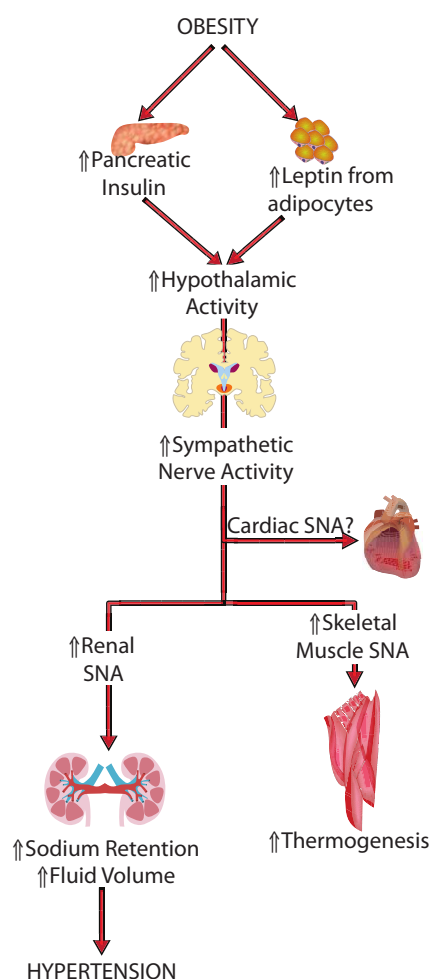


Figure 1. Working hypothesis of the role of the sympathetic nervous system in obesity-related hypertension. In excess energy balance (such as that seen in obesity) there is increased secretion of insulin from the pancreas and leptin from white adipose tissue into the circulation. These act at the hypothalamus to initiate a series of neural pathways which culminate in activation of sympathetic nerve activity (SNA) to the skeletal muscle in order to facilitate thermogenesis and restore energy balance. Heart sympathetic drive may not be increased in obesity but it appears that elevated kidney SNA does occur and this may lead to sodium retention, volume expansion and hypertension.

increased plasma leptin induces a state of selective leptin resistance. Appetite remains inappropriately high, leading to an imbalance in caloric intake and energy expenditure and a loss of energy homeostasis. Interestingly, leptin resistance appears to be selective to appetite-inhibitory aspects of leptin signaling but not sympatho-excitatory elements, leading to persistent sympathetic over-activity and hypertension. Leptin resistance has been observed in humans³⁵ and in animal models of obesity. It is thought to be localised to the hypothalamus and mediated by SOCS³⁷ (See Figure 2B).

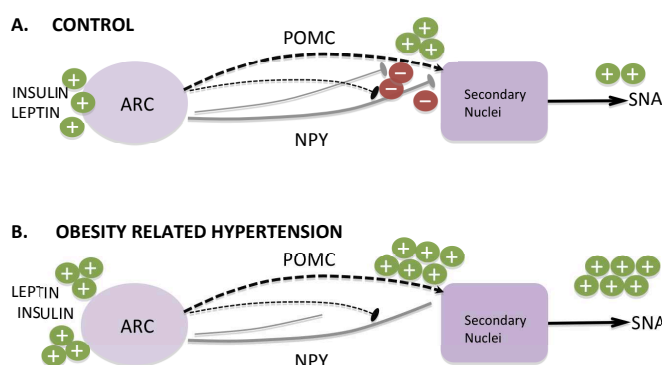


Figure 2. Working hypothesis of the role of insulin and leptin at the hypothalamus. Under normal conditions (A), leptin acts on the arcuate nucleus (ARC) to stimulate pro-opiomelanocortin (POMC) and inhibit neuropeptide Y (NPY) containing neurons. The balance between these excitatory and inhibitory inputs results in a small increase in sympathetic nerve activity (SNA). In obesity (B) there is up-regulation of the POMC and down-regulation of NPY neurons, which results in a loss of balance in these systems and a net increase in SNA.

Insulin also plays an important role in energy homeostasis via modulation of hypothalamic activity. Insulin crosses the blood brain barrier by high affinity transporters and stimulates insulin receptors in the arcuate nucleus. The action of insulin on CNS appetite control is similar to that of leptin.³⁸ Leptin and insulin also share common elements of their respective signal transduction pathways.³⁹ Insulin receptors are present on both NPY and α -MSH-containing neurons in the ARC, suggesting that insulin modulates cardiovascular and sympathetic tone⁴⁰ in leptin-sensitive neural populations. Insulin injected in the arcuate nucleus elevates lumbar sympathetic nerve activity (SNA) in anaesthetised rats⁴¹ via MC 3/4 receptors. Moreover, intracerebroventricular insulin injection produces renal SNA-mediated sodium retention in rats.⁴²

Evidence that obesity-related hypertension is programmed in response to maternal obesity, or excessive calorie/fat intake

Evidence from a number of animal studies support the hypothesis that maternal obesity, overweight or high fat dietary intake are associated with offspring obesity and hypertension. What is yet to be established is whether hypertension is programmed secondary to obesity (*i.e.* it manifests after the establishment of obesity) or if the two can exist separately in programmed offspring. Offspring of Sprague Dawley rats fed a lard-rich diet for 10 days prior to mating, during pregnancy and in the suckling period become obese in adulthood. Interestingly only the female progeny become hypertensive.¹⁵ Offspring of Sprague Dawley rats fed a fed a highly palatable diet rich in sugar and saturated fat-rich for 5 weeks prior to mating in order to induce obesity, develop programmed hypertension, elevated

renal noradrenaline concentration (an index of elevated renal sympathetic nerve activity) and an exaggerated cardiovascular response to leptin.¹⁷ In contrast to offspring of lard fed dams, both male and female offspring of obese rats develop hypertension and reductions in hypothalamic expression of AgRP and STAT3.⁴⁵ Male and female offspring of C57Bl/6J mice made obese by 6 weeks consumption of a highly palatable diet rich in fat and sucrose demonstrate obesity-related hypertension by 3 months of age.⁴⁶

Maternal obesity and diabetes are known to alter the development of appetite circuits in the neonatal rodent brain, which may result in long-term imbalance in appetite and sympathetic control. The majority of studies to consider the programming effects of maternal obesity or diabetes on neonatal hypothalamic circuitry do not assess hypertension, but excellent reviews on the role of insulin and leptin in the formation of appetite circuits have been published.^{47,48} There is some evidence that offspring of fat fed mothers show disparity between obesity and hypertension. Male offspring of fat fed C57 mice develop increased systolic blood pressure and show hypertriglyceridaemia without elevated body fat, but the female littermates show programmed obesity and hypertension.⁴⁹ What is now required is a careful analysis of whether obesity and hypertension are programmed together in offspring of fat-fed or obese mothers and whether the programmed obesity related hypertension phenotype differs from “simple” adult onset obesity related hypertension.

Sheep models are also useful to examine the effects of maternal high calorie intake. Recently, a study by George and colleagues⁵⁰ provides evidence that the degree of fetal adiposity is related to maternal adiposity. Sheep were provided 100%, 125% or 150% of the National Research Council recommended calorie intake for 10 weeks prior to conception until mid gestation. Fetal offspring of overfed ewes demonstrated altered growth trajectory, fatty liver and increased organ weight but only offspring of 150% overfed ewes demonstrated increased adiposity.

Offspring of ewes fed 160% recommended intake demonstrate obesity as well as elevated concentrations of appetite and sympathetic modulatory peptides POMC, and decreased concentrations of NPY and AgRP.⁵¹ Consistent with this report, offspring of fat fed macaques demonstrate elevated hypothalamic POMC concentrations and reduced AgRP concentration.⁵² This neurochemical signature is indicative of elevated sympathetic nerve activity. Unfortunately the adult cardiovascular or sympathetic phenotype of offspring from these maternal dietary manipulation is not known, nor are there reports of obesity-related hypertension being programmed in sheep or primate models as a result of maternal obesity or over nutrition. Notwithstanding this limitation, further studies in ovine models will be useful in determining the origins of programmed obesity-related hypertension. A model of early onset obesity in sheep (an obesogenic diet from 10 weeks of postnatal age) demonstrates that these animals develop obesity, hypertension and renal pathology that appears to be dependent on endoplasmic reticulum stress.⁵³ Interestingly

a mismatch between the in utero and postnatal diet can also programme cardiovascular and renal dysfunction in sheep.⁵⁴

Identifying the “programming vectors” responsible for the developmental origins of obesity-related hypertension in offspring of obese mothers

To date there is very little understanding of exactly which facets of obesity (for example dyslipidaemia, hyperglycaemia, hyperinsulinaemia, hyperleptinaemia or hypertension) are responsible for the programming of obesity-related hypertension in offspring and uncertainty as to whether established obesity or a hypercaloric/ high fat diet is the stimulus for programming. Identification of factors or “programming vectors” that cross from the maternal to fetal/neonatal compartments is of great importance because this offers a target for therapeutic treatment or behavioural modification.

Maternal obesity, overweight or dietary imbalance; which is more important?

Given the continuous relationship between body mass index and cardiovascular risk in adulthood maternal overweight likely produces a programming stimulus proportional to the level of adiposity as seen in an ovine model.⁵⁰ The blood pressure of these offspring is not known. Given the prevalence of maternal overweight it is surprising how few studies have examined programming effects. Moreover, the studies that examined the effect of maternal overweight without frank obesity are contradictory. Studies in Japanese macaques suggest that maternal obesity is not required for programming to occur but maternal fat intake is important; fetal offspring of monkeys that are resistant to diet-induced obesity demonstrate a fatty liver phenotype that is no different to the offspring of obese monkeys.⁵⁵ Similarly, studies in sheep indicate that maternal body condition prior to pregnancy can programme offspring disease irrespective of maternal condition in pregnancy.⁵⁶ Other studies suggest that maternal obesity is a prerequisite for programmed obesity; offspring of Long-Evans rats fed a fat rich diet in pregnancy and suckling only demonstrated programmed obesity or metabolic disease when their mothers were obese.⁵⁷ There is no consensus on whether maternal obesity/ overweight or diet in pregnancy is most likely to contribute to programmed obesity in her offspring but given that a recent study reported obesity and overweight in 34% of the Australian obstetric population¹¹ it is vital that future studies address this knowledge gap. Similarly, an appreciation of the programming effects of high fat feeding in lean women would be useful.

Is the type of fatty acid intake in pregnancy important?

Most diet induced obesity models rely on high saturated/monounsaturated diets based on lard or pork fat. The studies that have considered the differential effects of manipulating maternal saturated, polyunsaturated or

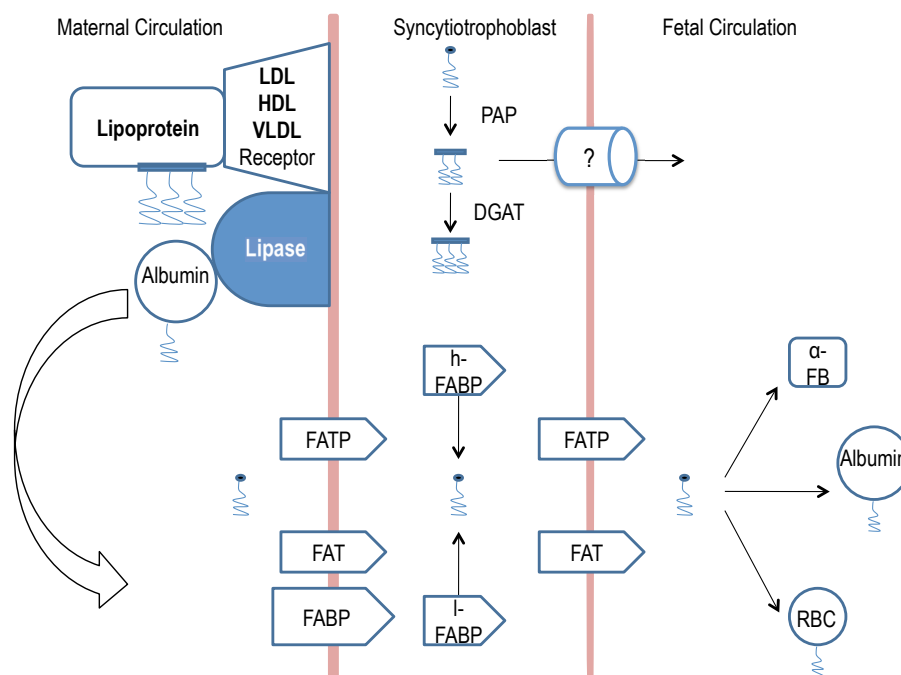


Figure 3. Placental fatty acid transport. Lipases liberate non-esterified fatty acids (NEFA) from triglycerides in the maternal circulation. These are transported across the syncytiotrophoblast to the fetal circulation by fatty acid translocase (FAT) and a range of binding proteins (FABP). Diglyceride and triglyceride production (by phosphatidic acid phosphohydrolase; PAP and diacylglyceroltransferase DGAT) in the placenta may occur but it is limited and the transporters are yet to be described. Fatty acids are carried as NEFA in fetal albumin, red blood cells (RBC) and α -fetoprotein (α -FB) and the fetal liver is responsible for metabolism of these fatty acids.

omega-3 polyunsaturated fatty acid content appear to present a common conclusion; that maternal saturated fatty acid intake is deleterious to offspring health, and that omega-3 polyunsaturated fatty acids may be beneficial to offspring health. Offspring of Sprague Dawley rats fed an omega-3 fatty acid rich diet in pregnancy, suckling and for the first 6 weeks post-weaning demonstrate normal blood pressure even though the absolute fat content of the diet was high (10%).¹⁶ Moreover, a low omega-3 fatty acid maternal diet programmes hypertension and exaggerated sodium appetite.⁵⁹ This is associated with persistent alterations in the fatty acid composition of the hypothalamus.⁶⁰ Other studies indicate that offspring of high fat fed Sprague Dawley rats do not show programmed alterations to blood pressure⁶¹ or Na^+ , K^+ -ATPase activity in the brain if the fat source is rich in omega-3 fatty acids.⁶² From these studies it may be concluded that maternal saturated fatty acid intake rather than polyunsaturated fatty acid intake programmes obesity-related hypertension in the offspring.

Is placental lipid transfer altered in obesity?

Fatty acids provide energy for the developing fetus and lipid transfer from the mother is vital for fetal development. Triglycerides do not cross the barrier but a series of placental lipases (lipoprotein-, endothelial-, lysosomal- and hormone-sensitive lipases) liberate non

esterified fatty acids (NEFA) from triglycerides and these NEFA are transferred to the syncytiotrophoblast by the cytoplasmic, heart and plasma membrane fatty acid binding proteins (hFABP, FABPp), fatty acid binding protein (FABPp), fatty acid translocase (FAT) and the fatty acid binding protein (FABP) (see Figure 3). Elevated maternal plasma triglyceride and diglyceride concentration is associated with excessive fetal growth rates⁶³ and atherosclerosis is accelerated in offspring of hypercholesterolaemic humans and rabbits.⁶⁴ Type 1 diabetes is associated with elevated placental lipase expression⁶⁵ and maternal overfeeding in sheep is associated with increased fetal plasma triglyceride concentration and up-regulation of fatty acid translocase but not lipase expression.⁶⁶ Placental lipid transporter expression in moderate overweight is not established. NEFA that cross the syncytiotrophoblast are carried to the fetal liver in albumin, red blood cells (RBC) and α -fetoprotein (α -FB) where they are re-assembled into diglycerides by phosphatidic acid phosphohydrolase (PAP) and then triglycerides by diacylglyceroltransferase (DGAT) in the fetal liver. Very minimal placental triglyceride formation occurs, so most triglycerides in the fetal compartment are of fetal liver origin. The passage of fatty acids containing stable ^{13}C isotopes to the fetus or neonate⁶⁷⁻⁶⁹ can be quantified, but to date it is not known whether these kinetics are increased in maternal

overweight.

Fetuses of women with gestational diabetes demonstrate higher concentrations of saturated fatty acids and lower concentrations of long chain omega-3 fatty acids independent of maternal fatty acid levels indicating alterations in fetal liver fat metabolism,⁷⁰ but there are no data pertaining to the study of liver lipogenesis in the fetuses of obese and overweight women where the pregnancy is not complicated by gestational diabetes. Maternal consumption of a high fat diet in macaques results in fetal hepatic triglyceride accumulation along with disturbances in the gluconeogenic pathway⁵⁵ irrespective of whether the mother develops diet-induced obesity.

Are inflammation and placental cytokines increased in obesity?

Normal conception, placentation, fetal growth and parturition require cytokine, inflammatory factors and immune cell activity. Obesity in pregnancy is associated with an exaggerated inflammatory response, however the effect of this maternal inflammation upon fetal development requires further clarification. It is known that placentae from obese women with gestational diabetes release greater concentrations of leptin in response to cytokine stimulation but to date it remains unclear how this leptin may act on the fetus. Maternal obesity is associated with macrophage recruitment to the placenta resulting in elevated cytokine production. Indeed, fetal cytokine profiles in obesity are consistent with up-regulation of pro-inflammatory cytokines and adipokines including IL-6, leptin, tumour necrosis factor (TNF)- α ,⁷³ MCP-1 and TLR4.⁷⁴ Late gestation fetuses of overfed sheep demonstrate elevated TLR4 in skeletal muscle⁷⁵ and placenta.⁷⁶ Such cytokine profiles may be associated with insulin resistance and inflammation most likely due to activation of macrophages. Macrophage infiltration of adipose tissue is a hallmark of established obesity.⁷⁷ Macrophage-associated cytokines including monocyte chemoattractant protein 1 (MCP-1), macrophage inhibitory protein 1- α , (MIP1- α), and interleukins (including IL-1, IL-18, IL-6) contribute to the development of insulin resistance in obesity. Toll-like receptors (TLR) 2 and 4 are likely modulators of macrophage-mediated inflammation in obesity.⁷⁸ TLR2⁷⁹ and TLR4⁸⁰ null mice develop diet-induced obesity without inflammation.

Conclusions

Hypertension in obesity is associated with elevated renal sympathetic nerve activity and altered hypothalamic responses to insulin and leptin. Although clear adult risk factors exist, it is also likely that exposure to maternal obesity, overweight or a maternal diet rich in saturated fatty acids can programme changes in the hypothalamus that promotes the development of obesity-related hypertension in later life. The transfer of lipids across the placental barrier to the fetus may be one of the programming "vectors". Moreover, fetal exposure to cytokines of placental or fetal membrane origin may represent another

programming vector. As we gradually identify the mechanisms that may drive the developmental programming of obesity and hypertension we can then look to devise behavioural or therapeutic strategies to mitigate the development of a disease that affects billions of humans worldwide.

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Author for correspondence:

Dr James A Armitage
Department of Anatomy and Developmental Biology
School of Biomedical Sciences, Building 76
Monash University Clayton Campus
Wellington Road
Clayton VIC 3800
Australia

Tel: +61 3 9902 9111

Fax: +61 3 9902 9223

Email: james.armitage@monash.edu