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Review article

Developmental programming by maternal obesity in 2015: Outcomes, mechanisms, and potential interventions

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ABSTRACT

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Obesity in women of child-bearing age is a growing problem in developed and developing countries. Evidence from human studies indicates that maternal BMI correlates with offspring adiposity from an early age and predisposes to metabolic disease in later life. Thus the early life environment is an attractive target for intervention to improve public health. Animal models have been used to investigate the specific physiological outcomes and mechanisms of developmental programming that result from exposure to maternal obesity in utero. From this research, targeted intervention strategies can be designed. In this review we summarise recent progress in this field, with a focus on cardiometabolic disease and central control of appetite and behaviour. We highlight key factors that may mediate programming by maternal obesity, including leptin, insulin, and ghrelin. Finally, we explore potential lifestyle and pharmacological interventions in humans and the current state of evidence from animal models.

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Introduction

The importance of normal foetal growth was first highlighted by associations between low birth weight and the increased risk of heart disease and type 2 diabetes in adulthood (Barker et al., 1989; Hales et al., 1991). Subsequent studies of maternal under-nutrition and, more recently, maternal over-nutrition have demonstrated that the maternal nutritional environment and foetal and neonatal growth, collectively known as the first 1000 days of life, are key determinants of health in the next generation (de Rooij et al., 2006; Lumey and Stein, 1997; Ravelli et al., 1976, 1999). In humans, maternal obesity is associated with low and high birth weight (Cedergren, 2004; Gaudet et al., 2014) and increased risk of obesity and metabolic dysfunction in the offspring both in childhood (Boney et al., 2005; Whitaker, 2004) as well as in adulthood (Brisbois et al., 2012; Cooper et al., 2010). Maternal

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obesity is also associated with increased risk of offspring cardiovascular disease (Drake and Reynolds, 2010), type 2 diabetes (Berends and Ozanne, 2012), and neurodevelopmental and psychiatric disorders, including ADHD, autism, schizophrenia, and mood disorders (Mehta et al., 2014; Rodriguez, 2010).

The prevalence of overweight and obesity has soared in the last 30 years globally (Ng et al., 2014). Worryingly, the number of children classified as overweight or obese has increased 150% worldwide in this timeframe (Ng et al., 2014) and the rate of obesity in women of child-bearing age is still rising (Fisher et al., 2013). Whilst genetic factors that predispose to obesity in an obesogenic environment, have likely contributed to the current global obesity epidemic, the short timescale of this increase implicates non-genetic factors including the impact of the intrauterine and neonatal environment on adult health and disease (McAllister et al., 2009). It is vital that we understand the mechanisms underlying such developmental programming of disease by maternal obesity in order to develop effective interventions to help mitigate the current rise in obesity, cardiovascular and metabolic diseases as well as mental health disorders. Bariatric surgery to induce weight loss lowers the risk of gestational diabetes mellitus (GDM), foetal macrosomia and the rate of obesity in the offspring as well as improving offspring insulin sensitivity, demonstrating that improving the maternal metabolic state prior to pregnancy is an effective intervention that improves the health of both mother and child (Kral et al., 2006; Shai et al., 2014; Smith et al., 2009). However, bariatric surgery is intrusive, high-risk, costly and can cause nutrient deficiency, the latter of which led to severe neural defects in some children conceived very soon after surgery (Pelizzo et al., 2014). A clearer understanding of the mechanisms mediating the increased risk of metabolic disease in offspring of obese women is required in order to develop less intrusive, better targeted interventions. This review will explore recent progress made in the understanding of the developmental programming by maternal obesity and potential avenues for intervention.

Animal models have revealed mechanisms underlying programming by maternal obesity

Animal studies have confirmed that maternal obesity programs metabolic syndrome—like outcomes in the offspring including impaired insulin action and glucose homeostasis (Martin-Gronert et al., 2010; Samuelsson et al., 2008; Shankar et al., 2010; Shelley et al., 2009), hypertension, and cardiovascular dysfunction (Blackmore et al., 2014; Fernandez-Twinn et al., 2012; Samuelsson et al., 2008), as well as increased adiposity (Bayol et al., 2008; Samuelsson et al., 2008; Song et al., 2015), and an increased susceptibility to diet-induced obesity (DIO) (Bayol et al., 2007; Howie et al., 2009; Kirk et al., 2009; Nivoit et al., 2009; Samuelsson et al., 2008; Shankar et al., 2008; Torrens et al., 2012). The choice of animal model is often a compromise between practicality of the research and translatability to humans. Whilst non-human primates (NHPs) share the closest resemblance to human developmental trajectories and pregnancies, they have a long gestation length and time to maturity of the offspring, leading to high research costs. Sheep and pigs are used due to their similarities in placental structure and function to humans, whilst rabbits are a medium-sized mammal with intermediary similarities and differences to humans. These larger mammals are conducive to repeated sampling of blood and tissue, allowing for longitudinal studies and within-subject analysis. Models with larger litter sizes, such as pigs and rodents, allow for the easier investigation of sex differences in programming. Rodent models have been used extensively due to their short gestation (three weeks) and maturity intervals (five weeks to puberty) and the ease with which to generate a well-powered experiment of animals of ages across the lifecourse. Furthermore, they enable genetic engineering to elucidate mechanisms. A disadvantage is that these smaller mammals are limited to one sampling point, precluding true longitudinal analysis. In addition, there are several differences in developmental timings of key tissues between rodents and humans. An overarching observation is that the third trimester in humans is roughly equivalent to the first postnatal weeks in the rodent. Notably adipose tissue develops from early in gestation in humans whereas subcutaneous and visceral depots develop from late gestation and early postnatal life, respectively, in rodents (Rosen and Spiegelman, 2014). Cardiomyocyte proliferation and growth is mostly complete by birth in the human and sheep (Morrison et al., 2007), whereas cardiomyocyte division ends at postnatal day 3 to 4 in the rat, with growth occurring over the first two weeks of life (Li et al., 1996). In addition, the development of key intra-hypothalamic connections occurs during the second postnatal week in rodents but these connections are established by birth in humans and NHPs (Bouret, 2012; Coupe and Bouret, 2013; Liu et al., 2013). The choice of animal model will affect the translatability of the results, however the outcomes seen in these models often recapitulate phenotypes reported in humans, signifying the validity of the use of a range of animals to investigate the mechanisms underlying developmental programming.

Insulin and glucose homeostasis

Maternal obesity programs offspring adiposity, decreased glucose tolerance, and impaired insulin sensitivity (Fernandez-Twinn et al., 2012; Samuelsson et al., 2008; Yan et al., 2011). The mechanisms underlying programming of insulin resistance and glucose homeostasis by maternal obesity include alterations in peripheral insulin signalling and insulin secretion [reviewed in (Berends and Ozanne, 2012) and (Duque-Guimaraes and Ozanne, 2013)]. Adult offspring exposed to maternal obesity are hyperinsulinaemic and have alterations in the expression of key insulin signalling and glucose handling molecules in skeletal muscle, the liver and adipose tissue that indicate a predisposition for insulin resistance and impaired glucose tolerance (Martin-Gronert et al., 2010; Nicholas et al., 2013a; Rattanatray et al., 2010; Shelley et al., 2009; Yan et al., 2011). At least some of the programming of insulin signalling protein expression appears to occur through post-transcriptional mechanisms via changes in microRNA (miR-) levels. Maternal obesity at conception in sheep increases hepatic miR-29b, miR-130, and miR-107 levels (Nicholas et al., 2013b). Increased miR-126 expression in adipose tissue of mice exposed to maternal obesity is associated with down-regulated expression of target genes involved in insulin signalling including insulin receptor substrate 1 (IRS-1) (Fernandez-Twinn et al., 2014). These programmed changes in IRS-1 and miR-126 were maintained following differentiation of pre-adipocytes in vitro, indicating that maternal obesity programs altered insulin signalling in the offspring adipose tissue in a cell-autonomous fashion.

In addition to peripheral insulin signalling, recent evidence suggests that the central control of glucose homeostasis is vulnerable to the hyperinsulinaemic obese maternal environment. Genetically-induced maternal hyperinsulinaemia and insulin resistance is associated with disrupted glucose homeostasis and hyperinsulinaemia in male wild-type offspring despite normal body weight and glycaemia in the mother (Isganaitis et al., 2014). Furthermore, a recent study demonstrated that genetic abrogation of insulin signalling specifically in pro-opiomelanocortin (POMC) neurons of offspring exposed to a maternal high-fat diet (HFD) restores POMC innervation of pre-autonomic paraventricular nucleus (PVH) neurons and normalises the impaired glucose tolerance otherwise seen (Vogt et al., 2014). This is associated with an improvement in pancreatic beta cell glucose-stimulated insulin secretion and parasympathetic innervation of beta cells.

Maternal hyperinsulinaemia with insulin resistance might program altered offspring development via the concomitant maternal hyperglycaemia, since insulin does not cross the placenta whereas glucose does (Dabelea, 2007). In humans, impaired glucose tolerance during pregnancy is often associated with increased birth weight and increased risk of childhood obesity (Catalano et al., 2003; Cottrell and Ozanne, 2007; Hillier et al., 2007; Liu et al., 2014; Plagemann et al.,