Review

MOLECULAR METABOLISM

Sex and gender differences in developmental programming of metabolism

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ABSTRACT

Background: The early life environment experienced by an individual *in utero* and during the neonatal period is a major factor in shaping later life disease risk-including susceptibility to develop obesity, diabetes, and cardiovascular disease. The incidence of metabolic disease is different between males and females. How the early life environment may underlie these sex differences is an area of active investigation.

Scope of review: The purpose of this review is to summarize our current understanding of how the early life environment influences metabolic disease risk in a sex specific manner. We also discuss the possible mechanisms responsible for mediating these sexually dimorphic effects and highlight the results of recent intervention studies in animal models.

Major conclusions: Exposure to states of both under- and over-nutrition during early life predisposes both sexes to develop metabolic disease. Females seem particularly susceptible to develop increased adiposity and disrupted glucose homeostasis as a result of exposure to *in utero* undernutrition or high sugar environments, respectively. The male placenta is particularly vulnerable to damage by adverse nutritional states and this may underlie some of the metabolic phenotypes observed in adulthood. More studies investigating both sexes are needed to understand how changes to the early life environment impact differently on the long-term health of male and female individuals.

1. INTRODUCTION

1.1. Developmental programming of metabolic disease

Obesity and diabetes rates are increasing at an unprecedented rate around the world. While several genetic polymorphisms linked to obesity have been discovered [1,2], these are few, only account for small increases in body weight, and explain less than 5% of the heritability of the condition. This suggests that environmental factors play a key role in determining risk of these conditions. The early life environment experienced by an individual *in utero* and during the neonatal period is now recognized as a major factor in shaping later life disease risk-including susceptibility to develop obesity, diabetes, and cardiovascular disease (see Table 1).

An association between the early life environment and later life metabolic disease incidence was first reported by Hales and Barker, who proposed the "Thrifty Phenotype Hypothesis" based on their observations of an association between low birth weight (as a proxy for reduced fetal growth) and cardio-metabolic disease in adulthood [3,4]. Further studies examining individuals who were *in utero* during the Dutch Hunger Winter (a famine in the Netherlands discussed in more detail later in this review) confirmed the association between *in utero* under-nutrition and the development of metabolic disease and suggested it was a causative relationship [5]. As well as the detrimental effects of exposure to under-nutrition *in utero*, there is now a wealth of evidence that demonstrates early life exposure to over nutrition - for example in cases of maternal obesity, diabetes or neonatal over nutrition - is also associated with increased metabolic disease incidence in individuals later in life. Comparative studies of siblings born before and after the mother underwent weight loss surgery have revealed that the children born after the mother had lost weight had greater insulin sensitivity, reduced adiposity, and reduced blood pressure compared to their siblings born when the mother was obese [6].

1.2. Sex differences in the incidence of obesity and diabetes

Globally, obesity is more prevalent in women than in men [7], although this varies by country, and, in the UK and USA, obesity is more prevalent in men [8,9]. A recent study that tested 100 of the most common variants associated with differences in body size and shape found that 44 of the loci associated with waist to hip ratio - commonly associated with increased adiposity phenotypes - are differentially expressed in males and females [10], which may explain some of the variance in obesity rates. Sex differences in growth are apparent from the very early stages of development; male fetuses grow faster as early as the pre-implantation stage [11], demonstrating fundamental differences in growth and metabolism between the sexes. Some of this difference may be due to the genotype of an individual as the number of X chromosomes affects adiposity, suggesting that genes expressed on the X chromosome can regulate body weight [12–14]. Also, the female sex hormone estrogen has been widely suggested to be

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Table 1 — Summary of reported sexually dimorphic phenotypes in humans (H), non-human primates (NHP), rodents (R), and sheep (S). The color of the box indicates whether the studies reported male (blue shading) or female (pink shading) to be more affected by the maternal environment.

	Maternal undernutrition and/or IUGR	Maternal obesity and/or over nutrition	Maternal diabetes and/or high sugar diet
Body weight/adiposity	⇑ BMI and adiposity females (H) [56,57] ⇑ sub-cutaneous adiposity females (NHP) [71]	⇑ adiposity males (H) [82] ⇑ body weight males (R) [87,88] ⇑ adiposity females (H) [83]	⇑ adiposity and skin fold thickness females (H) [84,86] ⇑ body weight females (H) [85] ⇑ adiposity females (R) [152]
Glucose tolerance		⇓ glucose tolerance females (R) [89]	⇓ glucose tolerance females (R) [89,152] Hyperglycemia females (H) [84]
Insulin/leptin/metabolic profile	⇑ cholesterol, triglycerides females (H) [58]	*In utero or postnatal exposure*: hypothalamic leptin resistance males (R) [95]	⇑ HOMA- IR and hyperinsulinemia females (H) [84]
		In utero exposure: hypothalamic leptin resistance females (R) [95]	Hyperinsulinemia and hyperleptinemia females (R) [152,153]
CNS	⇑ CNS disorders males (H) [59,60] Learning deficits males (NHP) [73]	Gene expression changes hypothalamus and forebrain males (R) [89,91] Hypothalamic inflammation males (R) [92] Anxiety behavior females (NHP) [93]	Gene expression changes hypothalamus males (R) [89]
Liver	⇑ 11βHSD1 males (R,S) [68,69]		
Placenta	⇓ placental size males (H) [122,123]	⇓ placental oxidative capacity males (H) [121] ⇓ placental size, ⇑ inflammation males (R) [120] ⇑ placental size, ⇓ fetal/placental ratio females (H) [126]	⇓ placental weight females (R) [153]

protective against obesity (discussed later). Furthermore, different sensitivities to metabolic hormones and adipokines such as leptin and insulin, which interestingly are often altered as a result of the nutritional environment in early life, may underlie some of the sex differences in prevalence of type 2 diabetes and obesity.

The purpose of this review is to summarize our current understanding of how the early life environment influences metabolic disease risk in a sex specific manner. We also discuss the possible mechanisms responsible for mediating these sexually dimorphic effects and highlight the results of recent intervention studies in animal models and how these can be translated to a human scenario.

2. SEXUAL DIMORPHISMS IN SYSTEMS REGULATING ENERGY HOMEOSTASIS

2.1. The central nervous system

Perhaps unsurprisingly, differences in brain structure are inherent and present from before birth. Among the most basic difference is the observation that male neonates have a larger total brain volume than females [15]. The female sex hormone estradiol has been suggested to regulate neurogenesis and cell migration, as well as cell death during early development of many brain regions, including the hypothalamus. Absence or increased expression of the sex hormones during the perinatal period therefore causes permanent changes to neuronal architecture [16–18]. Estrogen is produced initially by the corpus luteum and later by the placenta and is maintained at a high level throughout pregnancy such that both sexes are exposed equally. The primary source of the male sex hormone testosterone is the fetal Leydig cells, which develop in males just after sex determination; in humans, by 9 weeks post conception, genitalia have begun to develop and testosterone is produced [19]. A perinatal testosterone surge occurs in humans in the second trimester [20] and in rodents in the first week of neonatal life (which interestingly in both species coincides with the timing of development of hypothalamus [21,22]). In males, during gestation, testosterone enters the brain and is converted to estradiol via aromatase. This process is responsible for masculinization of the brain [23]. Diet and sex specific factors continue to interact to regulate neurogenesis in the adult hypothalamus, when estradiol appears to have an inhibitory effect on neurogenesis [24–26].

The sex hormones potently control food intake and body weight [27]. In general, male animals are larger and consume more food than females, and even when expressed as kilocalories per gram body weight, daily food intake is greater in male than female rodents [28]. This is partly explained by the fact that estrogen exerts an inhibitory effect on meal size and daily food intake, as well as regulating diurnal feeding patterns [29,30]. The hypothalamus, a brain region essential for the regulation of energy homeostasis, is highly sexually dimorphic. This dimorphism is not just restricted to the areas of the hypothalamus that are responsible for regulating fertility and reproduction. For instance, pro-opiomelanocortin (POMC) neurons within the arcuate nucleus of the hypothalamus (ARC) show differences in number and function between sexes, which may be in part due to the action of sex steroids on this neuronal population. Male mice have less anorexigenic POMC neurons within the ARC, which may explain their increased food intake compared to female animals. This seems to be an organizational effect of testosterone during development as neonatal testosterone administration to female mice results in a 'masculinization' and lowering of POMC neuron number within the ARC [31].

Gao and colleagues have shown that the number of excitatory glutamatergic synapses onto POMC neurons varies throughout the estrous cycle in mice, and this is likely due to changes in estrogen levels as injection of estradiol directly into the hypothalamus causes an increase in excitatory synapses onto POMC neurons [32]. Furthermore, Mackay et al. have shown that perinatal exposure to the estrogen-like compound BPA also causes rewiring within the ARC [33], similar to the well reported effects of leptin administration on the neonatal hypothalamus [34]. Glucose sensing in the hypothalamus is also different between the sexes, which is reported to be due to the effects that estrogen has on modulating glucose sensing at a cellular level [35,36]. Differences in nutrient sensing and neuronal plasticity during development could result in different vulnerability to programming by the nutritional environment.

Recently, studies using genetically modified mice to investigate the role of different sub-populations of POMC neurons within the ARC in feeding control have revealed interesting sex differences in function.

