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The conflicting effects of maternal nutrient restriction and early-life obesity on renal health

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Epidemiological and animal studies have demonstrated that early-life nutrition alters the metabolic responses and generates structural changes in complex tissues, such as the kidneys, which may lead to a reduction in the offspring lifespan. Independently, obesity induces a spontaneous low-grade chronic inflammatory response by modulating several of the major metabolic pathways that ultimately compromise long-term renal health. However, the combined effects of maternal nutrition and early-life obesity in the development of renal diseases are far from conclusive. Previous results, using the ovine model, demonstrated that the combination of a reduction in fetal nutrition and juvenile obesity induced a series of adaptations associated with severe metabolic syndrome in the heart and adipose tissue. Surprisingly, exposure to an obesogenic environment in the kidney of those offspring produced an apparent reduction in glomerulosclerosis in relation to age- and weight-matched controls. However, this reduction in cellular apoptosis was accompanied by a rise in glomerular filtration rate and blood pressure of equal intensity when compared with obese controls. The intention of this review is to explain the adaptive responses observed in this model, based on insights into the mechanism of renal fetal programming, and their potential interactions with some of the metabolic changes produced by obesity.

Maternal nutrient restriction: Renal health: Fetal programming

Deterioration in renal health is the result of both heritable and environmental factors which, in turn, influence the rate of functional decline. A clear environmental factor that reduces kidney function is that produced with chronic inflammation and induced by metabolic disorders, such as obesity[1,2]. A good example of the intricate relationship between the nutritional environment and metabolic-renal-associated diseases at the population level is observed in previously underdeveloped countries, such as China, a society that has experienced rapid growth in the prevalence of obesity due to several changes in lifestyle[3]. In less than a generation, medical conditions associated with overweight or obesity, including type 2 diabetes, hypertension and renal diseases, have increased to unprecedented levels, matching those existing in western developed countries. Unfortunately, this rapid change in the nutritional environment has exposed an inherent human vulnerability to the complications of excess weight gain particularly in young children[3].

In an attempt to explain the effects of early-life nutrition observed in previous epidemiological studies and their association with the development of metabolic complications in later life, Barker and Hales proposed the 'thrifty phenotype hypothesis'[4]. The basis of this hypothesis is that the maternal nutritional environment and early postnatal life nutrition play a major role in the pathogenesis of

Abbreviations: GH, growth hormone; IGF, insulin-like growth factor; RAS, renin–angiotensin system.

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renal-CVD by affecting tissue structure and function, in conjunction with other multiple mechanisms, which alter the hormonal milieu of the offspring[4]. Today, there is good evidence supporting the influence of the composition of *in utero* nutrition with a predisposition to develop cardiovascular and renal complications in later life[5–7]. Importantly, extensive animal studies have demonstrated that alterations in maternal diet can permanently alter renal structure and function, which, depending on the nutritional composition, may result in substantial reduction in offspring longevity, thus validating the principles of the thrifty phenotype hypothesis[8].

The relationship between renal programming and the maternal environment

During the early- and mid-20th century, at least in industrialised countries, maternal and early-life undernutrition were important factors affecting long-term health[9]. For that reason, Barker and other epidemiologists based their research on those groups of society that suffered chronic food shortages or imbalances in dietary composition (micro- and macronutrients) during pregnancy or early infancy. Not surprisingly, these early studies attributed radical declines in renal–vascular function to differences in birth weight[5,10,11]. However, more recent analysis of renal autopsies of adults born in the lower range of birth weight showed substantial variation in renal composition, revealing the possibility of an innate ability of the kidney to overcome an adverse fetal environment[12].

The apparent natural capacity of the kidney to alleviate the negative effects of low birth weight were also observed and described in other epidemiological studies, such as those conducted on adults exposed *in utero* to the Dutch winter famine of 1944–45 (at the peak of which daily rations declined to under 8368 kJ/d (2000 kcal/d)).[13] By dividing the period of malnutrition into trimesters, the authors of these investigations were able to determine very different long-term health outcomes for the adult offspring[13]. These studies demonstrated that the only group of individuals to develop a long-term tendency towards renal–vascular deterioration were those exposed to the famine around the second trimester of gestation[13]. In addition, this group of offspring, as mature adults, showed an increased risk of developing insulin resistance and other traits of the metabolic syndrome, including obesity[14]. The important contribution of these cohorts is to show that the time at which nutrient supply to the fetus was reduced produced specific health outcomes in later life, irrespective of birth weight, thus emphasising the importance of the different stages of embryonic and fetal development[14–16].

Potential mechanisms linking the maternal nutritional environment and renal development

Early renal embryonic development involves extensive cell proliferation to form different complex structures on which maternal nutritional and metabolic environment may play an important role[17,18]. Thus, the subsequent cycle of renal cell differentiation, including proliferation as well as extensive cell death to eliminate not only damaged cells but also immature ones, is clearly a process that may have lasting and permanent consequences for the offspring[19]. It is important to mention that the formation of the early embryonic renal structures that subsequently form the nephrons (the basic units of renal filtration) starts around the first week of gestation. In human subjects, the first permanent structures of future nephrons commence their formation at about the fifth week of gestation, and at about week 32, the first fully developed nephrons appear in the fetal kidney[20]. Although these structures continue to mature in the days before birth and after birth, a total inhibition of the formation of new nephrons in large mammals, such as human subjects and sheep, extends throughout their lifetime. At the time of birth, the total number of nephrons per kidney is around 1 million[17,18].

All these processes that regulate the intra-uterine renal development, as expected, involve a large number of fetal genes and hormones; although the maternal hormonal milieu and the nutrient supply to the fetus influence its development[12,19,21].

The following section describes some of the fetal hormonal axes known to interact with the maternal nutritional status during gestation, which may influence renal development.

The role of the insulin-like growth factor axis

In human subjects and rodents, manipulating the supply of nutrients to the fetus produces alterations in cord blood concentration of several anabolic hormones, including the different members of the insulin-like growth factor (IGF) family (IGF-I and -II), their receptors and binding proteins[22]. During gestation, the receptors of this hormone family are detectable in growing kidneys and other tissues, including the adipose tissue[23,24]. Furthermore, the crucial role of the IGF-I receptor in fetal renal development was confirmed in transgenic mouse models[23–25]. The lack of activity of this receptor during renal embryonic differentiation had a number of negative effects on the renal constitution of those rodents including a reduction in the number of nephrons and other irregularities in gomerular morphology that would contribute to the progression of renal disease[25–27].

The role of leptin

Leptin is another hormone associated with maternal diet that may have an impact on the developing offspring[28,29]. Circulating concentrations of leptin in the mother are proportional to her fat mass. Normally, adipocytes are the primary source of leptin, which then interacts with receptors in the hypothalamus, to inhibit food intake by acting through neuropeptide Y[30].

The concentration and function of leptin varies depending on the stage of gestation. For instance, during the last third of pregnancy in human subjects, the production of leptin by adipose tissue declines while there is an increased secretion of this hormone by the placenta and fetus[29,31–33]. Furthermore, a reduction of 40 % of maternal food intake during early to mid-gestation (3·6 MJ/d, on

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days 28 to 80 (145 to full-term)) has been shown to produce a decline in leptin plasma concentrations in comparison with control-fed mothers.

Although the direct effects of leptin in the fetal kidney are unknown, the localisation of its receptors and its gene expression in fetal perirenal adipose tissue, bone and cartilage, suggest that this hormone has a role in the control of early growth, which may influence renal function in later life[33]. In mature kidneys, five isoforms of the leptin receptors are known to be active and these are mainly located in the inner medullar[34]. *In vivo* studies demonstrate that leptin can regulate Na handling and increase renal sympathetic nerve activity, which are early signs of hypertension[35,36]. Importantly, although in obese individuals there is a partial lack of function of leptin in the hypothalamus its renal actions are unaffected[37].

The role of glucocorticoids and other hormones

Thyroxine and cortisol hormone concentrations, which are involved in vascular development of the newborn, are also compromised by changes in maternal nutritional intervention[18,33]. Bispham and colleagues observed, when using an ovine model, that changes in maternal thyroxine and leptin are accompanied by an increase in NEFA in the plasma of nutrient-restricted mothers during mid-gestation (3·5 MJ/d, on days 30 to 80), without a change in glucose concentration. The authors concluded that the increase in lipolysis may act as a physiological response to sustain the glucose supply for the optimal development of the offspring and the placenta during the nutritional challenge. However, this adaptation was insufficient to avoid a reduction in placental growth; although the subsequent weight of the offspring was similar to that of their controls[33]. A reduction in maternal cortisol secretion may have important consequences for the endocrine programming of the offspring, due to its effects in the maturation of the hypothalamic-pituitary adrenal axis, but these are yet to be confirmed. In turn, changes in the activation of the glucocorticoids complex may alter the control of important physiological and other endocrine functions, including adipogenesis and the renin–angiotensin system (RAS), affecting renal function[18].

Changes in maternal diet during mid-gestation in sheep and their consequences on the offspring

In an attempt to understand the biological mechanisms behind the association between maternal diet, particularly around the period of fetal renal development, and long-term physiological changes in the offspring, several animal models have been proposed. Between the different animal models studied, the ovine model, due its relatively long pregnancy (145 d) and its ability to produce an offspring of similar weight to human subjects, with fully developed organs, has proven to be useful for increasing the understanding of the effects of changes in maternal diet at specific stages of pregnancy[38].

In different ovine studies, it was observed that a reduction of 50% in maternal food intake up to mid-gestation (days 30 to 80 (145 d to full-term)) produced an offspring of weight similar to those born to control-fed mothers[39,40]. However, as noted in the human Dutch winter cohorts, kidney physiology, blood pressure and fat mass were affected at different points in the offspring's life[39,41,42]. Near-term nutrient-restricted offspring (days 140 to 145 (145 d to full-term)) exhibited increase in the gene expression of a range of factors associated with the development of adipose tissue, including IGF-I and -II[33]. In the same model, adaptations were also observed in other key regulatory components of fat metabolism, including gene expression of the mitochondrial uncoupling protein 2 and PPARα. All these responses were accompanied by increased adiposity[41]. In the newborn kidney, an increase in renal length was observed, followed by an increase in the gene expression of the receptors for glucocorticoids and angiotensin, particularly the type 1 isoform[39]. Therefore, an important factor affecting the long-term health of the offspring is body composition at birth, which is indirect evidence of an unfavourable maternal metabolic and hormonal environment during earlier pregnancy[43].

Changes in body composition, influenced by maternal nutrition, may have long-term consequences for the offspring. In a similar maternal nutritional intervention (30–80 d of gestation), six-month-old offspring showed a reduction in nephron number, which was linked to cellular apoptosis, followed by a reduction in blood pressure, in relation to those offspring born to control-fed mothers[44]. One of the few long-term studies on the effects of early to mid-gestation maternal nutrient restriction (3·5 MJ/d, from 0 to 95 d of gestation) demonstrated that, at three years of age, offspring born to nutrient-restricted mothers were transiently hypertensive prior to feeding and the heart rate response to noradrenaline infusion blunted, which is a sign of cardiovascular decline. In addition, the hormonal plasma profile indicated an increase in leptin concentration that correlated with greater fat mass[42]. These results indicated that maternal nutrient restriction during early to mid-gestation alters the long-term physiological and endocrine responses in the kidney and other tissues, including adipose tissue and could ultimately increase the risk of CVD in later life[44].

Early life nutrition and its subsequent effects on renal health

In addition to the maternal nutritional environment postnatal diet may also affect later renal health. Human epidemiological and animal studies indicate that early infant nutrition, independently of the *in utero* environment, modulates susceptibility to chronic diseases in adulthood[45]. During the first nine months of postnatal life, there is an accelerated and linear period of growth, influenced by the endocrine actions of growth hormone (GH), the secretion of which is regulated mainly by nutritional intake[2,46,47]. The secretion of GH induces the production of IGF-I which, in turn, binds to its own receptor (IGF-I receptor) and triggers growth. However, the binding of IGF-I to IGF-I receptor inhibits the actions of GH, particularly in young animals. These actions of GH regulated

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by the nutritional environment persist until one year of age in human subjects[48].

In addition to having a role in general physiological development, several observations indicate that the IGF–GH axis has a role in renal function. For instance, the infusion of GH, through the action of IGF-I, resulted in an increase in glomerular filtration rate and renal plasma flow[25]. Possibly for that reason, it was observed that individuals, who, as adults, were overweight and also suffered from rapid vascular deterioration, experienced as young infants rapid increase in height and weight[2].

Adult obesity and renal health

Independent of diet in early life, exposure to a juvenile or adult obesogenic environment also produces a significant deterioration in renal health through similar endocrine mechanisms. In human subjects and animal models, it was observed that obesity produced an increase in a series of haemodynamic changes, indicated by an elevation in blood pressure followed by initial elevation of renal plasma flow as well as glomerular filtration rate, which then with time is accompanied by variable degrees of proteinuria[36,49,50]. Some observations indicate that inflammation, in particular of the renal proximal tubules, may be one of the first morphological changes linked to kidney disease in obese non-diabetic individuals[51,52]. Inflammation is an important feature in obesity-associated diseases; several cohorts demonstrated a correlation between increased serum concentrations of pro-inflammatory molecules of obese individuals and markers of renal disease, such as microalbuminuria[53,54]. In severely obese human subjects with a BMI >30 kg/m^2, signs of advanced renal dysfunction, such as the appearance of ectopic lipid deposition, are accompanied by the secretion of pro-inflammatory molecules and other hormones, including angiotensin II, by the adipose tissue[55–57].

The production of angiotensin II by the adipose tissue and its effects on the kidney

Angiotensin II (the active component of the RAS), in addition to acting as a key regulator of arterial blood pressure, can activate multiple cellular responses in renal and adipose tissue, which are associated with cellular proliferation and stress[58,59]. RAS is a complex enzymatic cascade, involving several tissues and hormones activated by alterations in blood pressure, volume or simple reductions in blood electrolytes (mainly NaCl concentration) causing a range of physiological responses including contraction of vascular vessels and Na retention. In lean individuals, the majority of angiotensinogen (one hormone in this cascade) is secreted into the circulation by the liver. Later, it is transformed to angiotensin I through the catalytic action of renin, an enzyme produced by granular cells residing in the renal juxtaglomerular apparatus, and converted by an angiotensin-converting enzyme to angiotensin II[20]. However, adipocytes can also secrete angiotensinogen and, with obesity, this increases in parallel with raised lipid accumulation by mature adipocytes[60].

The increase in angiotensin II concentrations has been associated with renal injury, in part mediated by its own vasoconstrictive actions, which trigger a rise in the production of reactive oxidative species[61]. In the first instance, increased exposure to angiotensin II induces a rise in cell proliferation, particularly of mesangial cells[62]. As observed with other hormones, plasma concentrations of angiotensin II increase with obesity and, as noted for IGF-I and insulin, angiotensin II is also associated with lipid and collagen accumulation in renal tissue[63–65]. Long-term exposure to angiotensin II, due to its contractile actions as well as the subsequent increase in metabolic activity in proximal tubules, leads to an increase in oxygen consumption producing renal ischaemia[66]. The resultant reduction in oxygen supply and the rise of oxidative stress in the glomerulus and proximal tubules may be the first stages leading to cell cycle arrest or apoptosis; cellular processes that characterise several renal diseases associated with obesity[67,68]. However, epidemiological evidence has demonstrated that in obese patients this process of renal health decline may be prolonged for years[69]. This may be due to the innate ability of the kidneys to adapt to low-oxygen tensions by an efficient tissue neovascularisation, which is a major difference from adipose tissue, allowing it to overcome some of the metabolic changes induced by obesity[50,66,70].

The combined effects of maternal nutrient restriction and obesity in juvenile sheep

In sheep, as observed in other animal models, including human subjects, an expansion of adipose tissue produces a rise in plasma leptin, NEFA, catecholamines and insulin, which was the only systemic hormone when secretion was amplified in offspring previously exposed to maternal nutrient restriction (3·5 MJ/d, from days 28 to 145 (term = 147 d of gestation))[40,71]. Surprisingly, other plasma metabolites also associated with metabolic dysfunction, such as glucose, cortisol and TAG, were unaffected by the increase in adult body weight[71].

Despite the similarities in plasma profiles between both obese groups (i.e. obese with maternal nutritional restriction and obese with normal maternal diet), only the adipose tissue of obese sheep born to nutrient-restricted mothers showed similarities to tissue from animal models exposed to severe obesity, such as an increase in the number of necrotic adipocytes and the secretion of pro-inflammatory factors linked with macrophage infiltration[56,72]. These responses were accompanied by endoplasmic reticulum stress, a possible response to a reduction in oxygen supply to the adipose tissue[72]. In other tissues associated with the reno–cardiovascular system, these adaptations in the adipose tissue are followed by a subsequent increase in ectopic lipid deposition in the heart[73].

From the point of view of the cardiovascular system, the increase in fat mass generated considerable structural changes in the heart, particularly in the left ventricular region, irrespective of the early-life environment[73]. In comparison with obese controls, offspring exposed to maternal nutrient restriction showed important alterations

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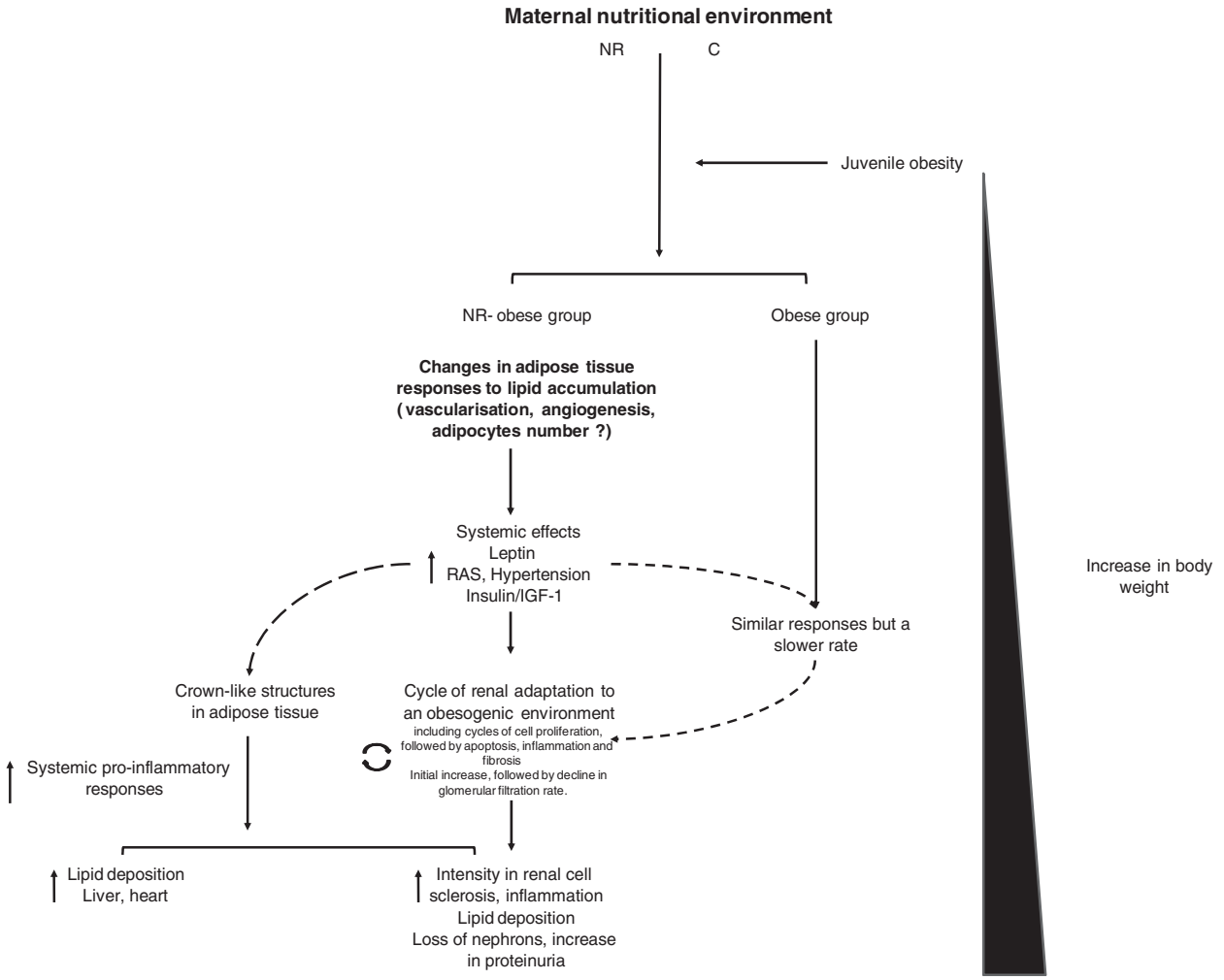

Fig. 1. Diagrammatic representation of renal responses in offspring born to mid-gestation nutrient-restricted (NR) mothers compared to their control (C) group, as observed previously in sheep. Exposure to an obesogenic environment induced a series of hormonal responses triggered by changes in adipocyte responses to excess lipid accumulation leading to tissue remodelling and alterations in renal and related peripheral tissues. RAS, renin–angiotensin system; IGF, insulin-like growth factor.

in myocardial energy metabolism, as indicated by an increase in ectopic lipid deposition and by a subsequent reduction in the expression of genes associated with lipid cellular transport and with severe metabolic dysfunction[73,74]. However, the nutrient-restricted obese group showed a blunted cardiac parasympathetic response to atropine infusion[73].

Changes in kidney function and structure in sheep

Obesity in sheep, as reported in human subjects, causes increases in blood pressure and glomerular filtration rate, which are important signs of renal dysfunction[50]. In the heart and in the kidney, significant changes occurred in gene expression between the maternal nutrient-restricted group and their obese controls, principally of factors associated with exposure to cytokines and angiotensin II, possibly suggesting an enhanced adaptation to obesity[40]. However, similar increases in haemodynamic parameters may suggest similar vasomotor afferent responses in both obese groups to the RAS, which also include extensive cell proliferation, particularly of mesangial and proximal tubular endothelial cells[36]. This suggests that the substantial changes in the composition in the kidney of those offspring exposed to maternal nutrient restriction, potentially may include an increase in lipid deposition[73]. We have also demonstrated that the cellular apoptosis observed in the obesity group was associated with endoplasmic reticulum stress that, in the kidney, is a temporary adaptation to a reduction in oxygen supply[72]. However, the activation of this response may lead, in extreme circumstances, to significant renal injury[72] as summarised in Fig. 1. Therefore, we conclude that the ovine model mimics many of the characteristics observed in obese human subjects and in other animal models[52,75].

Conclusions

Human and animal studies have demonstrated the notable influence of maternal nutritional environment on the offspring growth trajectory, and its impact in the development

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of non-transmissible diseases in later life. The prevalence of obesity worldwide, particularly in children, makes us re-evaluate policies involving maternal and infant nutrition. As noted in this review, obesity *per se*, even accounting for different types of maternal diet, undoubtedly produces an extensive decline in renal function, and has a deleterious effect on various other tissues, including adipose tissue. However, by altering the *in utero* nutritional environment, it is possible to observe different phenotypes, which are more distinct when those individuals are exposed to an obesogenic environment.

Obesity, through metabolic disarrangement, produces many structural and functional alterations in the kidney that can differ according to the *in utero* experience. In order to understand the alterations induced by both maternal and early nutritional environment, it is necessary to follow up offspring over an extensive period of time, analysing development through a range of physiological and metabolic measurements. One potential link between the changes triggered by alterations on the maternal–fetal nutrition and the following metabolic derangements during obesity may include functional alterations of adipose tissue and the subsequent resetting of the RAS, which has an adverse impact on renal health.

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