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Review article

Pre-birth origins of allergy and asthma

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ABSTRACT

Allergy is a chronic disease that can develop as early as infancy, suggesting that early life factors are important in its aetiology. Variable associations between size at birth, a crude marker of the fetal environment, and allergy have been reported in humans and require comprehensive review. Associations between birth weight and allergy are however confounded in humans, and we and others have therefore begun exploring the effects of early life events on allergy in experimental models. In particular, we are using ovine models to investigate whether and how a restricted environment before birth protects against allergy, whether methyl donor availability contributes to allergic protection in IUGR, and why maternal asthma during pregnancy is associated with increased risks of allergic disease in children. We found that experimental intrauterine growth restriction (IUGR) in sheep reduced cutaneous responses to antigens in progeny, despite normal or elevated IgE responses. Furthermore, maternal methyl donor supplementation in late pregnancy partially reversed effects of experimental IUGR, consistent with the proposal that epigenetic pathways underlie some but not all effects of IUGR on allergic susceptibility. Ovine experimental allergic asthma with exacerbations reduces relative fetal size in late gestation, with some changes in immune populations in fetal thymus suggestive of increased activation. Maternal allergic asthma in mice also predisposes progeny to allergy development. In conclusion, these findings in experimental models provide direct evidence that a perturbed environment before birth alters immune system development and postnatal function, and provide opportunities to investigate underlying mechanisms and develop and evaluate interventions.

1. Introduction

Several of the authors within this special issue have discussed the evidence that inflammation during pregnancy induces pregnancy complications, and the underlying mechanisms act *via* activation of toll-like receptor pathways. For example, maternal inflammatory signals induced by infectious and non-infectious stimuli are critical for normal labour and delivery and are implicated as causes of preterm labour. Intriguingly, the converse is also true, that exposures during gestation can predispose the progeny to later development of the inflammatory state of allergy. Rates of allergy are increasing rapidly, particularly in young children; the rate of hospitalisations for food-related anaphylaxis increased more than 5-fold in the 10 years from 1994–5 to 2004–5 in Australian children up to 4 years of age (Poulos et al., 2007). Understanding the aetiology of allergy and identifying preventative strategies is therefore increasingly important. The objectives of this review are to discuss key evidence for pre-birth origins of allergy and asthma from human cohorts and experimental models, in particular focussing on programming of allergy by three gestational exposures; intra-uterine growth restriction (IUGR), *in utero* methyl donor supply, and maternal allergy and inflammation. We conclude with suggestions for future research directions.

2. *In utero* exposures and later health

Associations between exposure to an adverse environment during pregnancy and infancy and later poor health were initially described at the regional level in seminal studies led by David Barker. Their subsequent work first linked individual birth and death records, and then progressed to studies of cardiometabolic outcomes in adults, and

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consistently demonstrated that individuals with low birth weights were at greater risk of poor cardiometabolic outcomes, including ischaemic heart disease and impaired glucose control (reviewed by Barker, 1998). Subsequent studies of populations exposed to defined periods of famine revealed critical developmental periods *in utero* when different systems and their associated risks of later diseases were most susceptible to effects of maternal nutrient restriction, and showed that *in utero* exposures could change postnatal outcomes even in the absence of reduced birth weight (Roseboom et al., 2001). Adding to this evidence from opportunistic cohorts, studies in the Pima Indian population who have extremely high rates of diabetes in adulthood also provide strong evidence that the associations between gestational exposures and progeny health outcomes are not explained by genetics alone. In this population, siblings of mothers with diabetes are at > 3-fold higher risk of diabetes themselves compared to siblings born before their mother was diagnosed with diabetes (Dabalea et al., 2000). Thus, exposures during critical windows of development have a lasting impact and impact adult health, a concept now referred to as 'developmental programming'. Since events early in life generally have the greatest impact on developmental trajectories, interventions early in life also have the greatest potential to improve adult health (Hanson and Gluckman, 2014). To date, developmental programming of allergy has been far less studied than that of outcomes such as metabolic diseases.

We have recently reviewed evidence, largely in humans, for effects of perinatal exposures on the risks of allergy in progeny (Grieger et al., 2016). Parental and *peri*-conceptual factors such as low socioeconomic status, having a younger mother, and having older siblings, are each associated with reduced risk of developing allergy (Grieger et al., 2016). Having an older or obese mother, excessive maternal weight gain during pregnancy, being the first-born child and maternal smoking are associated with greater risk of developing allergy (Grieger et al., 2016). Restricted growth before birth appears to be protective against allergy, but is a risk factor for asthma. Most evidence suggests that maternal folic acid abundance in late pregnancy is positively associated with the risk of allergy in the offspring. Similarly, maternal inflammation due to allergy or asthma during pregnancy is a susceptibility factor for later development of allergy in progeny. The evidence from epidemiological and experimental studies for programming of allergy by these three exposures is discussed below.

3. Protective effects of IUGR against allergy but not asthma

3.1. Evidence for IUGR as a protective factor from human cohorts

Overall, the evidence from human studies suggests that restricted growth *in utero* reduces the risk of allergy in infancy, although findings are variable. Data on allergic outcomes at later ages is limited and even more variable than that available for infants. In the ISAAC Phase III study, the risks of having had eczema by 6–7 years old were decreased overall in children with birth weights of < 2.5 kg (OR 0.88, 95% CI: 0.82–0.96) and 2.5 to < 3.0 kg (OR 0.94, 95% CI: 0.90–0.99) compared to the reference category with birth weights of 3.0 to < 4.0 kg (Mitchell et al., 2014). When stratified for country of origin, the protective effect of low birth weight (LBW) for eczema was only significant for children from affluent countries, and not in those from non-affluent countries, implying interactions between fetal growth and other environmental exposures, and risks of hay fever were not related to birthweight (Mitchell et al., 2014). Strengths of this study include the large numbers of subjects (> 162,000 children) and inclusion of centres from both developed and developing countries, but this data may be limited by use of absolute birth weights (not adjusted for gestational age), and parent recall/non-clinical diagnosis of allergy. In the PARIS cohort of 1860 French infants at 18 months old, high relative birth weight (3rd or 4th quartile of population) was associated with increased risks of sensitisation to food allergens, most commonly cow's milk and egg white, measured as elevated circulating allergen-specific IgE (Gabet et al., 2016). Risks of sensitisation to common aeroallergens were unaffected by birth weight in this cohort, however (Gabet et al., 2016).

Twin cohort studies can reduce confounding and variation due to genetics and environmental factors, and also support a protective effect of LBW on later allergy. Within the Swedish Twin Registry (Lundholm et al., 2010), rates of eczema increased with birth weight (for 500 g increase in birth weight, OR 1.62, 95% CI: 1.27–2.06) although hay fever was not associated with birth weight. This relationship was strengthened (for 500 g increase in birth weight, OR 3.83, 95% CI: 1.55–9.98) in co-twin analyses of twin pairs discordant for eczema, an approach that controls for gestational age and shared genetic and environmental factors (Lundholm et al., 2010).

Relationships between size at birth and asthma are generally in the opposite direction to those between size at birth and the allergic diseases discussed above. Using an absolute birth weight criterion of 2.5 kg to define LBW, the incidence of wheezing disorders (predominantly asthma), in childhood and adolescence was 60% higher in LBW than non-LBW in a recent *meta*-analysis of > 1.7 million participants in 37 studies (Mebrahtu et al., 2015). Consistent with this, a recent *meta*-analysis of data from nearly 25,000 individuals in 24 European birth cohorts identified a 32% greater risk of asthma in LBW (< 2.5 kg) individuals compared to all others (den Dekker et al., 2016). Another *meta*-analysis, again of cohorts in developed countries, found similarly increased OR of asthma in children (↑28%) and adults (↑25%) for LBW (< 2.5 kg) compared to all others (Mu et al., 2014). In the ISAAC Phase III study, asthma incidence was increased in children whose birth weights were < 2.5 kg or 2.5 to < 3 kg compared to the reference category of 3.0 to < 4.0 kg, with a trend to stronger effects of LBW in affluent countries (Mitchell et al., 2014). In twin studies and co-twin analyses, lower birth weight is also associated with increased asthma risk (Örtqvist et al., 2009). The association between LBW and increased asthma risk probably reflect effects of a restricted *in utero* environment on lung development rather than allergy, since these studies do not differentiate allergic and non-allergic asthma, and the association with asthma is at least partly explained by poorer lung function (den Dekker et al., 2016). Although effects of LBW on asthma are likely confounded by gestational age, and preterm birth is also a risk factor for asthma, the increased risk of asthma is also apparent in children born small for gestational age (SGA, birth weight < 10th percentile, OR 1.18) as well as LBW (den Dekker et al., 2016). Unlike allergies, these *meta*-analyses suggest that high birth weight does not affect risk of asthma (Mebrahtu et al., 2015).

In addition to the lack of differentiation of allergic and non-allergic asthma, the mixed reports of associations between markers of growth *in utero* and later allergic outcomes in progeny probably also reflect the use of variable exposure markers; such as absolute birth weight, birth weight categories, LBW and SGA; and variability in the outcomes assessed and the age/s at which this has been done. Given this variation between studies and the lack of consensus in this area, we are conducting a systematic review of the evidence for relationships between birth weight or fetal growth rate and postnatal allergy (as per published protocol, Wooldridge et al., 2016). Although the available epidemiological data suggests that allergy is programmed by *in utero* exposures in humans, it does not enable clear separation of the effects of environmental factors and genetic susceptibility. The epidemiological evidence is also likely to be confounded by environmental factors such as nutrition that persist from prenatal to postnatal life, or by co-morbidities such as IUGR and preterm birth. Experimental models have therefore been used to directly test effects of induced IUGR on progeny allergy, and may in the future allow evaluation of intervention strategies to reduce allergy risk.

3.2. Chronic experimental IUGR reduces allergic sensitisation

Allergic sensitisation has been reported in only a few experimental models of IUGR to date, with variable effects possibly reflecting the