THEMATICAL REVIEW

Risk of hypertension following perinatal adversity: IUGR and prematurity

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Abstract

Consistent with the paradigm shifting observations of David Barker and colleagues that revealed a powerful relationship between decreased weight through 2 years of age and adult disease, intrauterine growth restriction (IUGR) and preterm birth are independent risk factors for the development of subsequent hypertension. Animal models have been indispensable in defining the mechanisms responsible for these associations and the potential targets for therapeutic intervention. Among the modifiable risk factors, micronutrient deficiency, physical immobility, exaggerated stress hormone exposure and deficient trophic hormone production are leading candidates for targeted therapies. With the strong inverse relationship seen between gestational age at delivery and the risk of hypertension in adulthood trumping all other major cardiovascular risk factors, improvements in neonatal care are required. Unfortunately, therapeutic breakthroughs have not kept pace with rapidly improving perinatal survival, and groundbreaking bench-to-bedside studies are urgently needed to mitigate and ultimately prevent the tsunami of prematurity-related adult cardiovascular disease that may be on the horizon. This review highlights our current understanding of the developmental origins of hypertension and draws attention to the importance of increasing the availability of lactation consultants, nutritionists, pharmacists and physical therapists as critical allies in the battle that IUGR or premature infants are waging not just for survival but also for their future cardiometabolic health.

Introduction

The developmental origins of adult disease construct gained traction following a series of epidemiological studies by Barker and colleagues that suggested early influences during intrauterine and early postnatal development could lead to potentially irreversible modifications in physiology and metabolism that influence disease risk in adulthood. Barker’s seminal observation that the geographic areas in England with the highest infant mortality rate in the early twentieth century went on to report higher rates of coronary heart disease sparked follow-up investigations that demonstrated low birth weight was a strong predictor of subsequent cardiovascular disease risk (Barker et al. 1989a, De Boo & Harding 2006).

Shortly after the initial publication of the association between low birth weight and adult disease, the ‘fetal origins’ hypothesis was expanded by realization that the
vulnerable phase of human development extends beyond the time of parturition. This is especially important when considering preterm infants that emerge from the intrauterine environment more developmentally immature than term infants, who themselves lack the maturation typical of more precocious animal species. Furthermore, low birth weight itself must always be considered a marker, rather than a cause of subsequent disease, with the varying etiologies of low birth weight encompassing relatively benign normal genetic variation and more life-threatening events including intrauterine growth restriction and preterm delivery. Herein, after reviewing the mechanistic insight obtained from model species, we turn our attention to recent insight into the perinatal origins of subsequent disease susceptibility with focus on the cardiovascular implications of intrauterine growth restriction and prematurity (Fig. 1).

**Developmental origins in model organisms**

**Developmental origins**

Programming is a phenomenon co-opted by the developmental origins hypothesis to explain a process whereby an insult during a critical period of development evokes potentially irreversible long-term effects. Gluckman & Hanson (2004) have proposed a more active process where the fetus detects its environment and uses that information to adapt to the predicted future. Unfortunately, as the environment changes, those predictions can be maladaptive. Even if the adaptations improve immediate survival, they typically come at the cost of long-term health and longevity. This phenomenon, labeled a ‘predictive adaptive response’, is seen across species. A quintessential example of the trade-off that
occurs between short-term survival and future health is the wood frog (*Rana sylvatica*). At times of early life adversity, stress hormone exposure causes the tadpole to develop a long strong tail to escape predation and accumulate scarce resources, but after metamorphosis, health and longevity are sacrificed with the early drive for survival leaving the animal with foreshortened size and a loss of competitive advantage (Middlemis Mahet et al. 2013).

Regarding the developmental origins of hypertension, multiple downstream mechanisms have been described including vascular alterations, decreased nephron endowment and hyperactivity of the hypothalamic–pituitary–adrenal axis, especially central leptin–melanocortin signaling pathways (Samuelsson 2014, Taylor et al. 2014). Potential triggers of the pathologic cascade include reduced caloric intake, nutritional imbalance and hypoxia, all of which affect the growth and maturation of organ systems and influence homeostatic regulation. The programming field has benefited from novel investigations in a variety of species, with each species offering distinct advantages. These basic science studies, including prominent investigations in fish, chicken, rodents and larger mammals have been indispensable in the pursuit of mechanistic and therapeutic advancement.

**Model organisms**

Given their transparency and *ex utero* development, zebrafish (*Danio rerio*) have been an important model species in the elucidation of the genetic requirements for normal cardiovascular development. Studies on the vascular anatomy have defined the ontogeny of vascular networks and the onset of nitric oxide (NO) responsiveness. These data have clearly demonstrated an important reciprocal role of NO as a mediator of vasculogenesis and mediator of nutrient distribution during early development (Pelster et al. 2005, Clough 2015). While developmental insight expands, the zebrafish model has already shown its utility in the exploration of gene–environment interactions seen with a number of programming stimuli, including dysglycemia, dyslipidemia, early nutritional conditioning, oxidative stress and pharmaceutical exposures (Wang et al. 2013, Williams et al. 2013, Wilkinson & van Eeden 2014, Kalichak et al. 2016).

Chickens retain advantages of fish models, including *ex utero* development, and they have specific advantages including a cardiac structure more reminiscent of humans. Professor Giussani capitalized on those advantages in a series of fascinating studies that isolated the effects of fetal hypoxia on development by incubating embryos under normoxic (sea level) or hypoxic (high altitude) conditions with prominent cardiovascular changes seen even prior to hatching (Salinas et al. 2010, Herrera et al. 2013). Developmental changes in arterial reactivity have also been described in embryonic and newly hatched chicks in a hypoxic-induced growth restriction model with the data suggesting that the vasodilatation mechanism matures prior to the vasoconstriction mechanism and that alterations in this maturational timeline, as a result of hypoxic events, can later contribute to a reduced microvascular perfusion capacity (Moonen et al. 2012).

To further explore maternal influences on development, rodent models have been extensively characterized following the introduction of triggers including both genetic mutation and environmental manipulation. Many of these studies initially focused on the influence of maternal nutrition on development of vascular function and blood pressure, and most have shown a strong association between vascular endothelial dysfunction and hypertension in the offspring of both underfed and overfed mothers (Armitage et al. 2005, Khan et al. 2005, Samuelsson et al. 2008, Elahi et al. 2009). Furthermore, offspring of isocaloric but low protein-fed mice also develop high blood pressure and postnatal endothelial dysfunction (Clough 2015). Likewise, rat models of IUGR display endothelial dysfunction as a consequence of impaired NO availability with adult phenotypes including exercise-induced sympathetic overactivation and hypertension (Mizuno et al. 2013, Grandvuillemin et al. 2018).

Experimental rodent models have also interrogated early and late windows of developmental susceptibility by assessing the impact of alterations in antenatal and early postnatal growth and nutrition. Khan et al. (2005) cross-fostered offspring to compare the effects of high-fat diet exposure during the prenatal and early postnatal periods, and their data suggest isolated prenatal exposure to high-fat diet is sufficient to induce hypertension (Matthews et al. 2011). We have performed a series of complementary investigations by leveraging the natural variation that occurs in rodent growth as a consequence of variance in the intrauterine or postnatal litter size (Hermann et al. 2009). In our investigations, postnatal growth restriction interferes with neurodevelopment and increases the hypertensive response to stress in a pathway dependent on central leptin and angiotensin II signaling (Meyer et al. 2014, Peotta et al. 2016). These alterations can be prevented by neonatal supplementation of the neurotrophic hormone leptin (Vickers et al. 2005, Erkonen et al. 2011).
In sheep, prenatal maternal nutrition and birth size have also been shown to affect fetal cardiovascular development, and the larger animal size has allowed for reproducible assessment of cardiomyocyte kinetics and microvasculature modifications such as decreased capillary density and deviation of normal distribution pattern of metabolic substrates in body tissues (Costello et al. 2008, Ma et al. 2010). Along with others, we have capitalized on the similarities between ovine and human cardiovascular structure and the ability to instrument the developing fetus to demonstrate primary alterations in baroreceptor reflex regulation and coronary artery reactivity that preceded the development of hypertension (Roghair et al. 2005, Segar et al. 2006). Harkening back to Dr. Barker’s initial focus on cardiovascular mortality, it is important to note than both placental insufficiency and fetal anemia have been shown to modulate cardiomyocyte fate, increasing wall stress and the susceptibility to myocardial ischemia (Louey et al. 2007, Jonker et al. 2010). Furthermore, as a species often examined prior to clinical introduction of novel perinatal therapeutics, there is an extensive database regarding the effect of antenatal glucocorticoid exposure on both short-term and long-term outcomes of sheep, with late gestation glucocorticoids shown to have short-term benefit and early gestation glucocorticoid exposure, as seen with maternal–fetal metabolic or psychological stress, shown to exert detrimental effects on cardiovascular and neuronal development predisposing to hypertension later in life (Padbury et al. 1995, Dodic et al. 1998).

Developmental origins and IUGR

Intrauterine growth restriction (IUGR), a reduction in expected fetal growth, affects approximately 5–15% of all pregnancies in developed countries with at least six-fold higher rates in developing countries (Sharma et al. 2016, Zyzdorczyk et al. 2017). For more than two decades, evidence has accumulated supporting an inverse relationship between birth weight, systolic blood pressure and the prevalence of hypertension. Professor David J P Baker was one of the first to describe the relationship and later refine it by noting that, as a stronger surrogate for suboptimal growth, babies that are born small in relation to placental weight were at even greater risk of developing hypertension (Barker et al. 1990). The cause of hypertension is likely multifactorial and affected by both prenatal and postnatal events.

Renal origins

Protein malnutrition, pharmacologic exposures and hypoxia are important causes of a reduction in glomeruli and reduced nephron number has been considered an important factor associated with elevated blood pressure. Brenner & Chertow (1994) were among the first proposing the association of low birth weight with reduced nephron number and an increased risk of hypertension later in life. While most studies have not reported sex- or race-specific results, there appear to be important racial disparities with black infants showing the strongest associations between birthweight and renal function or blood pressure (Hemachandra et al. 2006, Cassidy-Bushrow et al. 2012).

Although birth weight is considered a barometer for the fetal environment, asymmetrical IUGR, which reflects a redistribution of blood flow away from most intra-abdominal organs including the kidneys and pancreas, may be a more specific indicator of significant fetal nutrient deficiency (Bagby 2007). Human IUGR and experimental undernutrition in animal models has shown a reduced nephron number in association with asymmetric intrauterine growth restriction (Hinchliffe et al. 1991, 1992, Merlet-Benichou et al. 1994, Vehaskari et al. 2001, Woods et al. 2001). Additional studies support a link between reduced nephron number and essential hypertension, and fetal kidney weight during nephrogenesis is linearly related to nephron number (Hughson et al. 2003, Keller et al. 2003, Hoy et al. 2005). Moreover, hyperfiltration with intrarenal renin-angiotensin system activation has been theorized to contribute to the prenatal programming of hypertension (Habib et al. 2011). A disorder of prenatal intrarenal renin-angiotensin system programing with altered renal sodium handling has also been proposed to contribute to cardiovascular disease in animals that sustain prenatal insults and develop salt-dependent hypertension as a consequence of the early anomalies in sodium absorption (Bertram et al. 2001, Manning et al. 2002, Dagan et al. 2008).

Vascular origins

Infants born IUGR have increased vascular stiffness and increased intima media thickness resulting in decreased vascular compliance and impaired endothelial-dependent vasodilation; a role for in utero extracellular protein deposition in the cascade that leads to programmed arterial
stiffness has been demonstrated in both sheep and guinea pig models of late gestation IUGR by Thompson et al. (2011a,b, 2014). These vascular alterations may increase myocardial workload and contribute to the development of hypertension in adulthood (Leeson et al. 1997, Martyn & Greenwald 1997, Martin et al. 2000). While impaired NO-dependent signaling appears to contribute to the vascular phenotype (Roghair et al. 2009), clinical studies have also demonstrated heightened sympathetic tone as an etiology for IUGR-related arterial remodeling, baroreceptor reflex dysfunction and hypertension (Boguszewski et al. 2004, Johansson et al. 2007, Jones et al. 2008). Although prenatal programing limits the postnatal ability to adapt, thus increasing the vulnerability to disease, the postnatal environment plays an important role in reducing or enhancing the likelihood of disease expression. Known exacerbating postnatal factors include nutrient availability and physiologic stress (Bagby 2007).

Exacerbation by growth acceleration

Eriksson et al. (2000, 2001, 2003) further described a relationship between children that were born small with poor growth in the first year of life followed by rapid weight gain in childhood and hypertension in adulthood (Forsen et al. 2004). In their longitudinal study, Barker et al. (2002) reported that children who developed hypertension later in life were born asymmetrically small for gestation then went on to develop accelerated BMI increment between 3 and 11 years of age. Evaluating an earlier phase of catch-up growth, Taine et al. (2016) showed that children born small for gestational age with rapid growth velocity in the first few months of life have the highest blood pressures. Prenatal and postnatal weight gain patterns have also been speculated to influence future adiposity and metabolic risk. Rapid postnatal weight gain during the first 2 years of life has been linked to hypertension by Perng et al. (2016). Unfortunately, neonatal growth acceleration increases the risk of obesity-related hypertension (Ben-Shlomo et al. 2008), while continued growth failure increases the risk of hypertension beyond the effect of IUGR alone (Barker et al. 1989b, Eriksson et al. 2007). This dichotomy emphasizes the effect of dysregulated genetic growth potential on actualization of the disease vulnerability.

Mitigation through nutrition

While they have known impacts on neurodevelopment, very little is also known regarding the role of perinatal micronutrient and iron deficiencies in relation to blood pressure level in adulthood. Lindberg et al. (2017) generated a hypothesis based on their findings from their randomized double-blind controlled trial that the association between low birth weight and increased risk of hypertension in adulthood might be modifiable with micronutrient intervention in infancy such as iron supplements, highlighting the need for ongoing nutritional assessment.

While increased breast milk intake has been shown to improve the metabolic and cardiovascular outcomes of growth-restricted experimental animals (Briffa et al. 2017), this has not been definitively evaluated in IUGR infants. In a meta-analysis by Horta et al. (2015), breastfeeding, regardless of IUGR status, decreased the likelihood of developing major cardiovascular risk factors, including type 2 diabetes and obesity, but no association was observed with blood pressure. Similarly, a randomized study of breast feeding duration, in women already intending to breast feed, did not identify an effect on blood pressure in childhood (Martin et al. 2014).

Developmental origins and prematurity

Prematurity is a major risk factor for hypertension and obesity with the risks increasing with decreasing gestational age (Siewert-Delle & Ljungman 1998, Irving et al. 2000, Leon et al. 2000, Keijzer-Veen et al. 2005, de Jong et al. 2012). Johansson et al. (2005) assessed blood pressure in 329,495 military conscripts and observed the odds of hypertension, adjusted for birth weight and current BMI, increased 93% in subjects born at 24- to 28-week gestation and 48% in those born at 29- to 32-week gestation. This hypertensive phenotype is present in both males and females, including infants born as late as 35-week gestation (Bonamy et al. 2012, Gunay et al. 2014, Sipola-Leppänen et al. 2015). Hypertension has both an early onset, with up to 70% of preterm infants demonstrating elevated systolic blood pressure in infancy (Dagle et al. 2011), and a prolonged duration, with hypertension remaining a significant concern into adulthood, especially in the presence of adult obesity (Pyhälä et al. 2009, Duncan et al. 2011).

Altered body composition and heightened sympathetic activation

Abdominal obesity and the odds of metabolic syndrome are increased by early preterm birth (Sipola-Leppänen et al. 2015), and rebound adiposity with ectopic fat accretion
significantly increases the risk of insulin resistance and hypertension (Barker et al. 1989a, Eriksson et al. 2007, Ben-Shlomo et al. 2008, Crane et al. 2016). By the time they reach 36-week postmenstrual age, nearly 90% of extremely low-birth-weight infants are growth restricted (Dusick et al. 2003), and they typically remain growth restricted as adults (Hack et al. 2014), but the reduction in body weight often masks an underlying increase in central adiposity (Hack et al. 2003, Uthaya et al. 2005, Johnson et al. 2012, Crume et al. 2014).

Basic science investigation in developmentally immature mice have revealed important comorbid hypertension, behavioral and learning disabilities following growth restriction and steroid exposure. The presence of analogous neurodevelopmental consequences following preterm delivery (Kaur et al. 2014, Travis et al. 2015) raise the potential that abnormal neuronal regulation of blood pressure contributes to the origins of hypertension (Miller et al. 2016). Similar to IUGR term infants, preterm infants display features consistent with sympathetic overactivation, including increased catecholamine excretion, increased resting heart rate and exaggerated pressor response to psychological stress (Ward et al. 2004, Johansson et al. 2007, Jones et al. 2007, Pyhälä et al. 2009). The risk of hypertension is also increased in the presence of diabetes and obesity, triggers of sympathetic activation through pathways including the presence of insulin resistance and the elaboration of adipose-derived proteins such as leptin (Bell & Rahmouni 2016).

**Leptin deficiency and insulin resistance**

Leptin and insulin both target hypothalamic neurons and muscle fibers such that a normalization of leptin levels could improve insulin signaling and a reduction in insulin levels could attenuate leptin-evoked sympathetic activation. Within the hypothalamus, leptin triggers central sympathetic tone through a JAK-STAT3 pathway (Dubinion et al. 2013), and insulin enhances leptin-induced STAT3 signaling by inducing the molecular chaperone GRP78 (Thon et al. 2016). Ultimately, hyperinsulinemia induces sympathetic activation in healthy humans (Vaz et al. 2010), and recent investigations have shown the complexity of interactions, with hyperinsulinemia contributing to obesity-linked hypertension and insulin receptors playing an important role in leptin-evoked hypertension (do Carmo et al. 2016, Zhang et al. 2016).

In the presence of sufficient amino acid availability, insulin stimulates muscle hypertrophy through induction of a PI3K–Akt-mTOR pathway (Barazzoni et al. 2012). In elegant preclinical investigations, German et al. (2010) showed physiologic leptin replacement improves insulin-stimulated PI3K activation in rats, leading to reductions in body fat and preservation of lean mass, independent of changes in body weight. Yau et al. (2014) subsequently demonstrated that leptin can improve skeletal muscle insulin sensitivity in sheep via induction of IGF-binding protein-2. Unfortunately, preterm infants are known to be profoundly leptin deficient, with lower levels in males mirroring the male disadvantage in long-term outcomes of prematurity (Erli et al. 1999, Ng et al. 2001, Steinbrekera & Roghair 2016).

Like leptin deficiency, insulin resistance may be a critical early factor in the cascade leading to cardiometabolic disease (Thompson & Regnault 2011). Placental insufficiency and other adverse in utero events can alter insulin sensitivity and skeletal muscle mass, increasing the likelihood of type 2 diabetes (De Blasio et al. 2012, Brown et al. 2016, Limesand & Rozance 2017). Likewise, endothelial dysfunction and vascular remodeling are exacerbated by insulin resistance, increasing the likelihood of hypertension (Abe et al. 1998, Federici et al. 2014). The establishment of novel therapeutic interventions aimed at the preservation of insulin sensitivity in the face of environmental adversity may substantially improve the cardiometabolic health of premature infants. In a recent cross-sectional study, Ahmad et al. (2016a,b) demonstrated high insulin levels in the cord blood of infants <32 vs 32-to 40-week gestation. The inverse correlation between insulin levels and gestational age could suggest unique regulation to stimulate growth and maturation while placental transfer maintains euglycemia or could simply mark a state of relative insulin resistance. Investigations in non-human primates suggest the latter with reduced muscle content of key glucose transport-regulating proteins, including GLUT1 and GLUT4 in preterm baboons (Blanco et al. 2010). When challenged by euglycemic-hyperinsulinemic clamp, preterm baboons have reduced insulin sensitivity in association with impaired insulin-stimulated Akt phosphorylation (Blanco et al. 2015). In a complementary late gestation fetal sheep model, Brown et al. (2016) showed chronic euglycemic hyperinsulinemia fails to increase muscle fiber growth in conjunction with tissue hypoxia and increased noradrenaline levels, suggesting an inhibitory effect by environmental stress and counter-regulatory hormones.
Immobility and physical rehabilitation

Even with adequate nutrient intake, skeletal muscle growth suffers from a lack of physical exercise. Skeletal muscle activity plays a major role in bone health, as evidenced by a reduction in bone density among those with neuromuscular disorders (Khatri et al. 2008). Murine studies have further demonstrated that maternal exercise during pregnancy increases the physical activity and insulin sensitivity of the offspring, with similar effects seen when the offspring themselves are exposed to exercise (Carter et al. 2012, 2013, Acosta et al. 2015, Blaize et al. 2015, Eclarinal et al. 2016). Within the neonatal intensive care nurseries, infant activity may be discouraged over concern the active infant will consume excessive calories, require higher amounts of oxygen or dislodge critical lines and tubes. Even when unbundled, infants may not have the energy to be active and unit staffing may not support the provision of consistent physical therapy, prompting concerns for infant health that led to the investigation of parent-administered therapy (McQueen et al. 2013, Ustad et al. 2016). There is evidence that specific doses of exercise, administered by physical therapists, can at least transiently improve the growth and bone density of premature infants (Schulzke et al. 2014). Encouragingly, in rodents, the early introduction of physical activity has been shown to improve the metabolic health of individuals exposed to an antenatal high-fat diet (Falcão-Tebas et al. 2019).

Glucocorticoid excess and nutritional rehabilitation

Beyond the effects of undernutrition and immobility, exposure to excess glucocorticoids can reduce growth, alter body composition and development and increase blood pressure into adulthood. Again, timing and dosage of exposure are critically important. A single course of late gestation betamethasone administered to women with threatened preterm delivery has not been shown to affect size at birth or offspring blood pressure within 30 years of delivery (De Boo & Harding 2006). However, it is well known that repetitive courses of antenatal steroids in the context of a prolonged threat of preterm delivery can stimulate maturation at the expense of somatic growth, and low birth weight is associated with increased blood pressure (Gennser et al. 1988, Barker et al. 1989a, Bonamy et al. 2012). Fortunately, exposure to repeated course of antenatal betamethasone has not been associated with cardiometabolic disease in childhood (Cartwright et al. 2018). Postnatal synthetic glucocorticoid administration, including dexamethasone but not hydrocortisone, can evoke a catabolic state with impaired lean tissue growth and cerebral hypoplasia (Murphy et al. 2001, Lodyginsky et al. 2005). Iatrogenic growth failure is a source of concern given the associations between brain growth and neurodevelopmental outcomes, and the increasing reports that convalescing preterm infants are already predisposed to altered body composition, including reduced muscle mass and excessive central adiposity (Hack et al. 2003, Uthaya et al. 2005, Johnson et al. 2012, Crume et al. 2014).

Notably, preterm infants are deficient in neurotrophic factors, including leptin, a hormone that is present in breast milk but not infant formulas (Casabiell et al. 1997, Resto et al. 2001, O’Connor et al. 2003). Unlike initial findings in term infants, premature infants randomized to breast milk rather than preterm formula had significantly lower blood pressure in childhood, with a dose–response relationship between the proportion of human milk and later outcomes (Singhal et al. 2001). It is possible the different results in term and preterm infants are reflective of a greater degree of vulnerability among developmentally less mature infants. With a worldwide incidence of prematurity approaching 10% (Beck et al. 2010), long-term follow-up studies focusing on the cardiovascular effects of breast milk and breastfeeding are needed.

Conclusion

The presence of a detrimental intrauterine and neonatal environment significantly increases the risk of asymmetric growth failure followed by the emergence of central obesity, insulin resistance and leptin deficiency with major implications for cardiovascular and metabolic regulation. IUGR and prematurity also trigger the development of adaptive responses, including increased vascular tone and hyperinsulinism that further increase the vulnerability to development of hypertension. With the assistance of lactation support, an increased reliance on breast milk and breast feeding as a source of nutrition and trophic hormones appears to be beneficial for preterm infants. Consultation with nutritionists and pharmacists can further remedy micronutrient deficiency and therapeutic misadventure. Finally, as an aid to the convalescing IUGR or preterm infant, the early introduction of rehabilitative physical therapy holds the promise to improve lean-fat ratios, enhance musculoskeletal health and attenuate the development of metabolic disease and hypertension.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Trassanne Chatmethakul and Robert Roghair drafted and revised the article. Robert Roghair was involved in the design, analysis and interpretation of the primary experiments.

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