Introduction

Suboptimal birthweight (<10th percentile, >90th percentile) has a well-established relationship with several adult cardiometabolic risk factors, including obesity, dyslipidaemia and elevated blood pressure (BP) [1]. Over the past three decades, several animal studies have investigated this relationship. Together, these studies have shown that in sub-optimally grown offspring, adaptive changes occur in key organ systems to maximize chances of ex-utero survival [2]. Unfortunately however, these early life adaptations to organ structure and function render sub-optimally grown offspring vulnerable to chronic disease later in life [3]. This concept is known as the Developmental Origins of Health and Disease (DoHAD) hypothesis, and provides the broad mechanistic framework underpinning the relationship between adverse early life exposures and chronic disease in adulthood [2].

The hypothalamic pituitary adrenal axis (HPA-A) plays a key role in cardiometabolic homeostasis by regulating tissue exposure to endogenous glucocorticoids [4]. Several animal studies have shown that glucocorticoids induce gluconeogenesis, inhibit insulin secretion, enhance vascular responsiveness and promote lipid storage, growth driven HPA-A dysregulation may be an important mechanism through which suboptimal fetal growth is linked to increased cardiometabolic risk in adulthood. While independent relationships between these three components have been established [1,6,7], the precise role of the HPA-A within this relationship remains unclear: As the global cardiometabolic phenotype continues to change [8], clarifying our understanding of the axis’ role in facilitating cardiometabolic disease will become increasingly important.

Hpa-Axis As A Mediator

Several animal studies have suggested that suboptimal fetal growth may increase cardiometabolic risk by acting through changes to the HPA-A. For instance, nutritional deprivation (caloric restriction or low protein) among rat dams produces offspring with blunted HPA-A reactivity via alterations in hypothalamic glucocorticoid and mineralocorticoid receptor expression [9]. Similar outcomes have been observed in humans; in a meta-analysis of 2301 subjects from 11 separate studies, serum cortisol fell by 25.3 nmol/L for every kilogram increase in birthweight [6]. Although there is evidence that suboptimal fetal growth alters HPA-A function, whether this causally increases cardiometabolic risk remains unclear: There is some suggestion this might be the case: in pregnant guinea pigs, caloric restriction generates sub-optimally grown offspring with increased basal and dynamic HPA-A activity, which is accompanied by elevated blood pressure and left ventricular hypertrophy [10].

Similarly, in a study of 370 men from the Hertfordshire cohort, birthweight was inversely related to serum cortisol levels (cortisol declined by 26.2 nmol/L for every kg increase in birthweight); intriguingly, higher cortisol levels were simultaneously associated with elevated blood pressure, fasting glucose, insulin resistance and serum triglycerides [11].

Hpa-Axis As A Moderator

Genetics play an important role in HPA-A function, influencing glucocorticoid synthesis, metabolism and HPA-A responsiveness [12]. It is possible, therefore, that the relationship between suboptimal growth and elevated cardiometabolic risk is simply amplified among offspring who have inherited certain HPA-A
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