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The prenatal environment and later cardiovascular disease

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Abstract Exposure of an embryo or fetus to a sub-optimal environment increases its risk of acquiring coronary disease and heart failure in adult life through a process known as programming. For example, stress experienced in utero and during early postnatal life imparts an increased vulnerability for adult onset cardiovascular disease. Programming is a change in gene expression pattern that occurs in response to a stressor and leads to altered growth of specific organs during their most critical times of development. Known stressors include improper nourishment, hypoxia and excess glucocorticoids. Programming becomes evident through a number of risk factors that are only now becoming understood, including growth patterns in childhood, structural and cellular changes to the heart and coronary vessels, impaired endothelial function, and altered lipid metabolism. Thus, adults most vulnerable for coronary artery disease may have experienced rapid weight gain in childhood and now have dyslipidemias and depressed endothelial function.

1. Introduction

Cardiovascular disease is the most common killer of men and women in developed countries and is predicted to become so world-wide within the next decade. Hypertension is widespread among Western populations and leads to deterioration of the heart muscle and greatly increases the risk of coronary artery disease. Smoking, sedentary lifestyle and diets high in saturated fats are well known behavioural risk factors for coronary artery disease. However, what is often unappreciated is that established risk factors do not fully explain the incidence of cardiac disease. At present, there is no explanation for why some people are highly vulnerable while others are not. There is no doubt that some people have a genetically based propensity for acquiring cardiovascular disease, but genetic background alone does not appear to account for risk differences within specific populations. In 1989 it was shown that a sub-optimal intrauterine envi-

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ronment, as indicated by proxy measures such as low term birth weight or reduced ponderal index, correlates strongly with the risk for chronic disease in adult life including coronary disease and type 2 diabetes [1]. Subsequent studies have shown that nutritional factors during infancy also play an important role in the development of adult cardiovascular disease. It appears that poor nutrition during fetal and infant life combined with rapid childhood weight gain impart the greatest risk for later disease.

The concept that the prenatal environment modifies postnatal physiology is known as "programming". Programming results from adaptive changes in gene expression patterns that occur in response to a stressor(s) and leads to altered growth of specific organs during their most critical times of development. Programming is caused by malnourishment, hypoxia or increased glucocorticoid exposure during early life. Other stressors may yet be discovered and chemical agents in the environment may also be important programming agents. Across the entire normal birthweight range, the smaller the baby, the greater the risk for hypertension, coronary disease, type 2 diabetes, central obesity, osteoporosis or all of these conditions [1]. While early studies of the relationship between birthweight and later disease focussed on outcomes such as incidence of cardiovascular disease, more recent studies have investigated the influence of the prenatal environment on programming mechanisms such as endothelial dysfunction and abnormal lipid metabolism. There is growing evidence that a poor prenatal environment can lead to disease vulnerability without affecting birthweight.

2. Mechanisms of programming

2.1. Intrauterine stressors

The biological bases of programming are largely unknown. Three main categories of prenatal insult have been used in animals to study the aforementioned stressors: 1) dietary manipulations (maternal over- or under-nutrition, maternal protein restriction), 2) fetal hypoxemia (low maternal oxygen) and 3) hormonal manipulations (glucocorticoid administration). None of these models is a "pure" insult because the hypothalamic pituitary axis is activated in response to virtually all stresses. In addition, some models intentionally incorporate a combination of stressors like placental embolization and fetal anemia. The outcome of prenatal stress in the offspring is dependent not only on the type of stressor but also on the gestational timing of the stress [2,3]. A developing organ becomes especially sensitive to stress during the period of time when it is undergoing rapid growth or maturation. For example, the pancreas is vulnerable during waves of endocrine beta cell proliferation and the kidney is vulnerable during nephrogenesis. If a fetus is malnourished during the nephrogenic period, the kidney will develop fewer nephrons and adult hypertension will result. The heart is particularly vulnerable to stressors during two phases of prenatal growth: 1) in the embryo, hemodynamic forces alter gene expression patterns in the wall of the heart; 2) in fetal life (and early postnatal life in rats and mice), cardiomyocytes undergo a maturational phase that includes endoreduplication of DNA or binucleation and escape from the cell cycle.

Different species may respond differently to the same insult; for example, angiotensin II causes hypertrophy in immature rat cardiomyocytes [4] but is hyperplastic rather than hypertrophic in immature ovine cardiomyocytes at an equivalent stage [5]. While, there may be many mechanisms that act in common between species to guide adaptation to developmental stresses, there may also be species-specific effects that do not apply across the phylogenetic scale.

In order to understand the mechanisms underlying fetal programming, the primary and secondary effects of the insult also need to be considered. For example, a high-dose infusion of cortisol in fetal sheep can cause hypertrophy of cardiomyocytes [6]. However, high levels of plasma cortisol also raise fetal arterial pressure which augments the systolic pressure load to the heart and stimulates increases myocyte size and number [7]. Thus the combination of a direct effect on the cardiomyocyte and the indirect effect of systolic load makes conclusions about the direct effects of cortisol on the cardiomyocyte virtually impossible.

2.2. Birth size

It is clear from both human and animal studies that reduced size at birth is a general proxy indicator for a sub-optimal prenatal environment; likewise, ponderal index. However, the patterns of gender specific growth reduction may be more important than birthweight alone. In boys, low body weight and thinness at birth and at one year, followed by rapid growth (increased body weight and body mass index, BMI) in childhood increase the risk for coronary heart disease [8]. Girls who are born short, followed by a rapid increase in body weight