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Review article

Programming of cardiovascular disease across the life-course

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality, affecting both developed and developing countries. Whilst it is well recognized that our risk of CVD can be determined by the interaction between our genetics and lifestyle, this only partly explains the variability at the population level. Based on these well-known risk factors, for many years, intervention and primary prevention strategies have focused on modifying lifestyle factors in adulthood. However, research shows that our risk of CVD can be pre-determined by our early life environment and this area of research is known as the Developmental Origins of Health and Disease. The aim of this review is to evaluate our current understanding of mechanisms underlying the programming of CVD. This article is part of a special issue entitled CV Aging.

Contents

1. Introduction

1.1. Aging and cardiovascular disease

Life expectancy is increasing worldwide. World Health Organization statistics state that by 2050, 2 billion people will be more than 60 years

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of age [1]. This increase in lifespan brings about a rise in age-associated conditions such as type 2 diabetes, cancer and cardiovascular disease (CVD). As CVD has a long pre-clinical phase resulting in diagnosis in old age, the identification of biomarkers that precede the clinical state is critical in defining an individual's risk in later life. Left unresolved sub-clinical conditions manifest into diseases such as atherosclerosis, myocardial infarction, stroke and heart failure. Although adverse lifestyle choices in adulthood (poor diet and lack of exercise) are known to prematurely cluster these risk factors in individuals, evidence from the field of Developmental Origins of Health and Disease (DOHaD) shows that a suboptimal early life environment leads to the premature presentation of these pre-clinical conditions. Consequently, such programming effects are associated with higher incidence of cardiovascular conditions and premature mortality in these individuals.

1.1.1. The importance of the early life environment in shaping our vulnerability to disease

The DOHaD hypothesis emphasizes the concept that during early life, insults that occur during critical periods of development can alter offspring structure, function and/or molecular phenotypes that persist into adulthood. Specifically, exposure to adverse conditions *in utero* leads to the sparing of vital organs (such as the brain) at the expense of considered less-essential organs such as the pancreas, resulting in asymmetric growth and altered function [2]. Whilst these adaptations may initially prove beneficial for survival in the short term, they ultimately lead to increased disease susceptibility. According to the theory of the predictive adaptive response proposed by Mark Hanson and Peter Gluckman [3], the propensity for disease in adult life is reduced if the postnatal environment matches the intrauterine "prediction". In contrast, if the pre- and postnatal environments differ, adaptations made *in utero* no longer prove advantageous and therefore manifest in increased adulthood diseases.

Much research has highlighted the importance of the early life environment beginning before conception, spanning across pregnancy, lactation and into the postnatal period. Epidemiological studies have shown that individuals born with low birth weight have aortic wall thickening at birth and elevated blood pressure and impaired endothelial function in adulthood [4–6]. Notably, these individuals also showed the greatest risk of atherosclerosis, coronary heart disease, myocardial infarction, stroke and premature mortality from ischemic heart disease [7–11]. In addition to low birth weight, other proxy markers of an adverse intrauterine environment, including ponderal index and placental weight, have also been associated with adverse cardiovascular outcomes in adulthood [12,13]. Whilst such proxy markers are useful tools in assessing the quality of the intrauterine environment, they are indirect measures and therefore have limited predictive ability. For instance, there is evidence to suggest that fetal growth does not need to be impaired to have a long-term influence on offspring disease susceptibility [14]. Furthermore, in addition to low birth weight, there is evidence to suggest that offspring born with high birth weights (greater than 4 kg) also have an increased propensity for metabolic diseases in adult life [15]. Therefore, assessing the quality of the intrauterine environment requires elaborate study designs. However, through unusual circumstances such as famine (macronutrient deficiency), researchers have been able to assess the direct impact of nutritional deprivation in early life on risk of CVD.

1.2. Maternal macronutrient deficiency

1.2.1. Epidemiological evidence

The Dutch Hunger Winter was a famine that occurred in 1944-1945 due to a German blockade that prevented the delivery of food and fuel to the western region of the Netherlands. The famine affected individuals of all social classes and led to nutritional deprivation of between 400 and 800 calories per day. Offspring exposed to the famine in early gestation were at greater risk for the development of obesity, increased systolic (SBP) and diastolic blood pressure (DBP) in response to stress and premature presentation of coronary artery and heart disease [16–19]. Whilst a difference was observed in blood pressure following a stressor response, no differences were observed in relation to basal blood pressure between individuals exposed or un-exposed to the famine *in utero*. However, an inverse relationship between birth weight and blood pressure was identified, with those born low birth weight having a higher blood pressure [20]. Interestingly, offspring exposed in late gestation were more likely to develop metabolic abnormalities such as impaired glucose tolerance [21]. These studies highlighted that the organs and/or systems affected in adulthood often reflected the period at which the insult occurred during development [22].

The Leningrad famine (1941–1944) was a more severe famine in an area now known as Saint Petersburg, with an average ration during the 'Hunger Winter' period (November 1941–February 1942) of 300 calories per day, mostly consisting of carbohydrates [23]. Unlike the Dutch Hunger Winter, nutritional deprivation was lower both prior to and following the famine. Offspring exposed to the Leningrad famine during gestation showed no increase in blood pressure, atherogenic lipid profile or impaired glucose tolerance. However, exposed offspring showed evidence of endothelial dysfunction and raised von Willebrand factor [23]. These variations in outcomes could be attributed to the fact that individuals from the Dutch Hunger Winter were well nourished prior to and after the famine, therefore helping to drive catch-up growth, which is associated with an increased propensity for both metabolic and CVD [22]. In contrast, following the end of the Leningrad famine, food still remained scarce and therefore offspring exposed to the famine were born into a nutritionally deprived environment that matched their experiences *in utero*. Thereby supporting the role of the Predictive Adaptive Response [22].

The Dutch Hunger Winter was based on a population not previously malnourished prior to the famine. Consequently, this data cannot be generalized to individuals from nations who live on a malnourished background. Therefore, the Biafran and Chinese famines have proved critical in our understanding of the long-term impact to these individuals. The Biafran famine occurred as a result of the start of the Nigerian Civil War that broke out in July 1967 and ended in January 1970. Offspring exposed to the Biafran famine in early life (fetal-infant exposure) had elevated SBP, DBP and impaired glucose tolerance measured at approximately 40 years of age [24]. The Chinese famine affected the whole country following a decline in grain production. Unlike famines that had a more defined period, the Chinese famine was prolonged with debate as to its beginning and end, making it more difficult to distinguish individuals' true famine exposure. The famine significantly affected rural but not urban populations. Exposure to the famine in early postnatal life led to the development of hypertension in rural populations only [25].

1.2.2. Animal models

Whilst human studies provide us with information on the associations between the early life environment and later disease risk in the offspring, they are unable to address causality. Animal models have proved to be an invaluable resource for evaluating the underlying mechanisms. The power of these models stems from the opportunity for direct manipulation of exposure variables whilst controlling for confounders. Moreover, due to the short lifespan of many laboratory animals, in particular rodents, long-term effects on the cardiovascular system spanning from markers of CVD risk to clinical cardiovascular conditions can be addressed in the same animal longitudinally, using invasive and non-invasive techniques. Such experiments would be difficult to perform in a human setting due to a significantly longer lifespan.

The importance of nutrient access prior to conception has been highlighted by a number of studies that have addressed the impact of periconceptional undernutrition on fetal and adult phenotypes. In an ovine model of preconceptional undernutrition 60 days prior to

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