CHAPTER 10

Developmental Programming of Cardiovascular Dysfunction

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Abstract

Population based studies of developmental programming of adulthood cardiovascular disease have implied associations between intrauterine growth restriction and a range of adulthood indices of cardiovascular dysfunction and risk. Whilst the emphasis has been on the programming of hypertension, there is also evidence for an impact of the early life environment on later development of vascular endothelial dilator dysfunction and associated risk factors including inflammatory and thrombogenic bio-markers, dyslipidaemia and vascular compliance. In animal models, researchers have been more circumspect in the cardiovascular parameters studied and it is not always possible to draw parallels with the human situation. There is, nonetheless, strong evidence for developmental programming of reduced endothelium dependent dilatation in a variety of models of maternal nutritional imbalance which share similarity with the human data and may imply an important role in the aetiology of developmentally induced cardiovascular risk. Studies of inflammatory bio-markers, lipid profiles and compliance in animal models are too few to allow comparison. Increasing evidence for altered sympathetic activity in man and animals provides an important channel for future research effort.

Introduction

Investigations in man and in animal models have frequently reported associations between perturbations of the in utero and early life environment and elevation of adulthood blood pressure. These have been reviewed in Chapters 2, 8, 9, and 11 in this volume. The elevation of blood pressure documented in population based studies in man appears to be one of a constellation of disorders centred on insulin resistance which together contribute to the metabolic syndrome. In animal studies there has been considerable emphasis on the measurement of blood pressure whilst other aspects of cardiovascular function, including those which may provide mechanistic insight into hypertension and insulin resistance, have been less extensively studied. This chapter briefly reviews those studies which investigate the relationship between perturbations of the early life environment and adulthood disturbances of cardiovascular function other than hypertension.

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Endothelial Function

The pivotal role of the endothelial cell layer in cardiovascular homeostasis has provided the impetus to determine whether in utero growth restriction or adverse nutritional influences during pregnancy and early postnatal life may have permanent and adverse influences on endothelial function in later life. The endothelium, which forms a lining to all blood vessels was once considered to be a passive barrier which limited transport of water and molecules to the extravascular compartment. Whilst undoubtedly playing a crucial role in vascular permeability, endothelial cells are now recognised to be a major determinant of cardiovascular function and haemostasis. The endothelium, which shows clear heterogeneity between vascular beds, express a wide range of vasoactive factors which influence the tone of the underlying vascular smooth muscle, control platelet and leucocyte adhesion and function and directly affect the thrombogenic potential of the blood. These endothelial factors perform an essential physiological role and contribute to the inflammatory response. Endothelial dysfunction involving abnormal expression of these proteins has been directly implicated in the aetiology of disease, particularly atherosclerosis and insulin resistance.

Endothelium Dependent Dilatation

The endothelium provides local control of underlying vascular smooth muscle tone through synthesis and release of vasoactive agents, most notably the nitrogen radical, nitric oxide (NO) which leads to reduction of vascular smooth muscle calcium, and thus tone, through elevation of cyclic GMP. Other endothelial derived dilators include prostacyclin, evoking vasodilatation through elevation of cyclic AMP, and endothelial derived hyperpolarising factor (EDHF, which is likely to be several different molecules) achieving vasodilatation through hyperpolarization of the vascular smooth muscle membrane and reduction of cell calcium entry through voltage gated calcium channels. The endothelium also synthesises vasoconstrictor factors including endothelin and thromboxane. Synthesis and release of these vasoactive agents is under control of local humoral and mechanical influences. Thus NO synthesis and release may occur through stimulation by vasodilatory agents such as histamine or Calcitonin Gene Related Peptide (CGRP), but is also tonically simulated by the shear stress created as the blood flows past the vessel wall. Blunted endothelium dependent dilatation in man is an important risk factor for subsequent cardiovascular disease, particularly atherosclerosis.

Developmental Programming of Endothelial Function

Studies in Human Populations

Relatively few studies have probed the relationship between birth weight or early catch up growth and endothelial function in later life. Endothelial dilator function may be evaluated noninvasively in man by estimation of flow mediated dilation in the brachial artery. A rapid increment in flow is achieved by application of a cuff on the lower arm. Inflation and subsequent deflation leads to a hyperaemic response and increased flow in the brachial artery. This evokes a shear mediated dilator response which is assessed by measurement of the diameter of the vessel by high resolution ultrasound. Impairment of endothelial function in the brachial artery correlates with that in the carotid artery, a vessel prone to development of atherosclerotic plaques. Leson et al were the first to suggest that low birth weight could herald the later development of blunted endothelial dependent dilatation. In a study of 333, 9-11 year old British children these authors found a significant, graded and positive association of flow-mediated dilation with birth weight which was unaffected by adjustment for potential