CHAPTER 9


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Abstract

Hypertension can be programmed by experimental manipulation of the intrauterine environment. Studies to date suggest that, at least in some models, common pathways such as glucocorticoids or the renin-angiotensin system cause programming of arterial pressure. How mechanisms involved in controlling “normal” arterial pressure have been altered, remains a largely unanswered question, though the process may include the programming of the major organs and endocrine/neural systems involved in long-term blood pressure regulation. Clear evidence demonstrates a prominent role for the programming of the kidney in the development of hypertension. The major mechanisms examined to date include a reduced nephron endowment and alterations to the function of renal renin-angiotensin system. These studies do not preclude a role for other major cardiovascular organ systems (brain, vasculature, heart) in the programming of hypertension. Several studies have identified sex-specific differences in the programming of hypertension, which may relate to fetal sex-specific rates of placental gene expression and/or sex-specific timing of fetal development. Future studies should be directed towards examining the integrative control of blood pressure in prehypertensive animals to differentiate between the primary initiating programming events and events secondary to the development of hypertension. Understanding the mechanisms involved will be essential for devising preventative and/or treatment strategies.

Introduction

High blood pressure affects 20% of adults and is a major risk factor for cardiovascular diseases such as stroke, myocardial infarction, peripheral vascular disease and chronic renal failure.1,2 In the majority of cases, the cause of the hypertension is unknown, with less than 10% of cases accounted for by secondary (i.e., renal artery stenosis, adrenal tumour) or genetic factors. Recently, attention has shifted to the idea that adult hypertension can be programmed in utero.3 It is hypothesised that an adverse intrauterine environment during critical stages of development permanently alters, or ‘programmes’ the development of fetal tissues, which enables the fetus to survive, but with adverse consequences in postnatal life.3 The mechanisms by which an altered intrauterine environment might exert these effects may involve epigenetic effects in the embryo/fetus (discussed elsewhere in this book, Chs. 6, 7).

Here we will briefly outline animal models of adverse intrauterine environments that have been demonstrated to lead to adult hypertension. However, our primary focus will be to explore, where evidence is available, the organs and physiological systems that may be affected and thus underlie the development of hypertension (Fig. 1). A clearer understanding of these

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mechanisms and the delineation of possible common pathways, such as glucocorticoids for which there is strong evidence, may ultimately lead to potential treatments or strategies for prevention of programmed hypertension.

**Models of Arterial Pressure Programming**

There is now compelling evidence to support the hypothesis that events occurring during fetal life can have life-long consequences for the health of the adult. The first models centred on producing low birth weight via maternal nutrient restriction, in line with the original hypothesis that low birth weight was associated with high blood pressure. With an increasing understanding of the mechanisms of fetal programming, models have become more specific, examining the impact of micro-nutrient deficiencies, hormones, and conditions that are common in human pregnancy, such as anaemia and hypertension. Attention has also begun to focus on critical windows during development when different organs have a greater susceptibility to programming.

**Arterial Blood Pressure**

In considering the topic of programming of blood pressure, it is timely to evaluate the methodologies associated with its measurement. The most significant factor is whether blood pressure is measured directly, that is via an indwelling arterial catheter, or indirectly via tail-cuff. This is an important consideration for two reasons: (1) the degree of stress associated with each method and (2) the length of time over which the measurement is made varies considerably. Thus, whilst the tail-cuff method can provide reliable measurements and is the most frequently used method in rats (see Table 1), for reasons that will be discussed, direct measurement of blood pressure, preferably by telemetry, is the gold standard.