The highs and lows of programmed cardiovascular disease by developmental hypoxia

Summary

The present thesis is a collection of studies designed to isolate the effects of chronic fetal hypoxia on fetal growth, fetal cardiovascular and endocrine development and programming of future cardiovascular dysfunction in the adult offspring, using the chicken as an animal model. The combination of high altitude exposure with the use of the chicken embryo model is ideal as it permits investigation of the direct effects of high altitude hypoxia on growth and on cardiovascular development completely independent of alterations in placental function, independent of changes in the maternal physiology and independent of any effects of socioeconomic factors.

In **chapter II** (The role of oxygen in prenatal growth: studies in the chick embryo. *J Physiol*. 2007; 585:911-7), **chapter III** (Cardiac and vascular disease prior to hatching in chick embryos incubated at high altitude. *J Dev Orig Health Dis*. 2010; 1:60-6), and **chapter IV** (Adrenocortical suppression in highland chick embryos is restored during incubation at sea level. *High Alt Med Biol.* 2011; 12:79-87), we investigated the effects of high altitude hypoxia on chicken embryo growth and *in ovo* cardiovascular and endocrine development. For this purpose, we adopted an experimental design based on a three-prong approach using: (1) incubation at high altitude of fertilized eggs laid by sea-level hens; (2) incubation at sea level of fertilized eggs laid by high-altitude hens; and (3) incubation at high altitude of sea-level eggs with oxygen supplementation to equate sea level oxygen partial pressure. The data show that: (1) high-altitude hypoxia promotes embryonic cardiac and vascular disease already evident prior to hatching and that this is associated with growth restriction; (2) the effects can be prevented by increased oxygenation; and (3) the effects are different in embryos from sea-level or high-altitude hens. We conclude that fetal oxygenation, independent of maternal nutrition during development, has a predominant role in the control of fetal growth and cardiovascular development. Further, prolonged high altitude residence confers protection against the deleterious effects of hypoxia.

In **chapter V** (High altitude hypoxia and blood pressure dysregulation in adult chickens. J Dev Orig Health Dis. 2013; 4:69-76) and **chapter VI** (High-altitude hypoxia and echocardiographic indices of pulmonary hypertension in male and female chickens at adulthood. *Circ J.* 2014;78:1459-64), we isolated the long-term consequences of chronic hypoxic incubation of chick embryos on the systemic and pulmonary circulations of the adult bird. This was achieved using noninvasive

echocardiography as well as testing basal and stimulated cardiovascular function in the chronically instrumented adult bird. Additional specific points of interest were to determine whether there were any sex differences and whether any adverse effects of chronic hypoxia during the embryonic period could be ameliorated by generational exposure to hypobaric hypoxia in highland adapted chickens. We show that development at high altitude hypoxia lowers basal arterial blood pressure, alters baroreflex sensitivity, and induces pulmonary hypertension in a sex-dependent manner at adulthood.

Finally, in **chapter VII** (The highs and lows of programmed cardiovascular disease by developmental hypoxia: Studies in the chicken embryo. *J Physiol 2017*), we discuss and put into perspective the findings of this thesis. We summarise studies that have exploited the chicken embryo model to isolate the direct effects of chronic hypoxia on prenatal growth, cardiovascular and endocrine development and in triggering an increased risk of cardiovascular dysfunction and pathology at adulthood.