Cardiovascular β-adrenergic signaling

Maturation and programming effects of hypoxia in a chicken model

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Linköping 2010
Desensitization/downregulation of cardiovascular β-adrenergic receptors (βARs) blunts the cardiovascular response to catecholamines. The responsible mechanisms are closely linked to cardiovascular disease and are of immense therapeutic importance. Despite the known key role of βARs in cardiovascular disease, not much is known about how βAR signaling develops and how it is affected by the prenatal environment. Thus, the aim of this thesis was to characterize the pre- and postnatal maturation of βAR signaling in the cardiovascular system and the effects of chronic prenatal hypoxia in the embryo and adult animal using the chicken as experimental model.

Hypoxic stress releases catecholamines and thereby triggers βAR activation and desensitization/downregulation mechanisms. Hypoxia quite commonly occurs in utero and it is well known that prenatal insults, like malnutrition or hypoxia, are coupled to an increased risk of developing adult cardiovascular disease. This is referred to as developmental programming and constitutes an important and modern field of research.

In this thesis, I show that; 1) the developmental trajectory for organ, especially cardiac, growth is affected by hypoxia, 2) chronic prenatal hypoxia causes cardiac embryonic βAR sensitization, but causes postnatal desensitization, suggesting that there is a hypoxia-induced “programming” effect on adult β-adrenoceptor function, 3) the adult βAR desensitization following prenatal hypoxia is linked to a decrease in β_1/β_2 ratio, a decrease in cAMP following βAR stimulation with isoproterenol and an increase in Gαs, 4) the chorioallantoic (CA) membrane arteries displays hypoxic vasoconstriction, βAR-mediated relaxation and a lack of α-adrenergic reactivity and 5) hypotension of the chronically hypoxic chicken embryo is linked to a potent βAR relaxation of the CA vasculature and an increased βAR sensitivity of the systemic arteries with no changes in heart rate.

In conclusion, chronic prenatal hypoxia causes growth restriction, re-allocation and has programming effects on the βAR system in the adult. The latter indicates that the βAR system is an important factor in studying hypoxic developmental programming of adult cardiovascular disease.