ADRENOMEDULLARY REGULATION DURING INTRAUTERINE STRESS IN THE FETAL SHEEP

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ABSTRACT

Whilst the mechanisms mediating catecholamine secretion from the fetal adrenal medulla in response to physiological stress are relatively well characterised, the regulation of catecholamine synthesis in the fetal adrenal has yet to be investigated. The primary aims of this thesis were therefore to examine the impacts of development and acute and chronic stress upon the gene expression of two of the key catecholamine synthetic enzymes, tyrosine hydroxylase (TH) and phenylethanolamine *N*-methyltransferase (PNMT), in the adrenal medulla of the fetal sheep.

Adrenal TH mRNA expression was found to be maximal coincident with the establishment of functional splanchnic innervation of the adrenal whilst PNMT mRNA expression peaked in late gestation coincident with the prepartum surge in adrenal glucocorticoid output. Acute fetal hypoxia resulted in a decrease in the expression of adrenal TH mRNA and an increase in PNMT mRNA expression, both before and after development of functional adrenal innervation. These changes were related to the degree of change in fetal arterial PO_2. The changes in adrenal TH and PNMT mRNA expression with hypoxia after the development of adrenal innervation were attenuated by the nicotinic receptor antagonist, hexamethonium, indicating that they were neurally mediated.

There is an increase in cortisol secretion from the fetal sheep adrenal in response to stress and before delivery. Intrafetal infusion of cortisol to mimic the prepartum cortisol rise, at a stage in gestation when fetal cortisol levels are low, resulted in a significant and specific decline in PNMT mRNA and protein expression in the fetal adrenal.

Placental restriction of fetal growth also resulted in a specific decrease in adrenal PNMT mRNA expression in late gestation and there was a direct correlation between PNMT mRNA expression and mean gestational arterial PO_2.

In summary, there is differential regulation of adrenal catecholamine synthetic enzyme gene expression during development and in response to neurogenic and hormonal stimulation. Catecholamine synthetic enzyme gene expression is also differentially regulated by hypoxia prior to adrenal innervation. Intrauterine growth

retardation and inappropriate fetal exposure to excess glucocorticoids exert specific suppressive effects upon adrenal PNMT mRNA expression which may manifest themselves as impaired responses to physiological stress in the fetus and neonate.