ROLE OF TGFβ IN ADRENAL STEROIDOGENESIS BEFORE BIRTH

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During mammalian development there are periods when the fetal adrenal is either relatively refractory or increasingly sensitive to trophic stimulation. This pattern of regulation of adrenal growth and function ensures that the fetal lungs, liver, brain and kidney are exposed in a programmed temporal sequence to the genomic actions of circulating glucocorticoids. A range of studies in the rat and sheep have also demonstrated that exposure to excess glucocorticoids at inappropriate times in fetal life inhibits fetal growth and permanently reprograms the development of the cardiovascular and metabolic systems resulting in postnatal hypertension, abnormal hepatic glucose production and poor glucose tolerance In most mammalian species, there are therefore a range of mechanisms that protect the fetus from exposure to glucocorticoids of either maternal or fetal origin at inappropriate times in gestation. The factors that act to maintain periods of adrenal quiescence are not known. There is evidence that intra-adrenal transforming growth factor beta 1 (TGFβ1) is an inhibitor of adrenocortical steroidogenesis in the adult. In recent studies, we have demonstrated that expression of TGFβ1 is high in the fetal sheep adrenal at around 100 days gestation and that adrenal TGFβ1 expression then falls with increasing gestational age and is lowest immediately after birth. Following the activation of adrenal cytochrome P450 C17 (CYP17), there is an inverse relationship between adrenal TGFβ1 and CYP17 expression and TGFβ1 may therefore play a novel inhibitory role in the regulation of adrenal steroidogenesis during mid and late gestation. Whilst functional activation of the fetal adrenal is dependent on the fetal hypothalamo–pituitary axis, adrenal TGFβ1 mRNA expression is not altered by disconnection of the fetal hypothalamus and pituitary in late gestation. It therefore appears unlikely that TGFβ1 mRNA expression is regulated directly by either bioactive ACTH or cortisol in late gestation. The mechanism by which TGFβ1 expression is upregulated in mid gestation remains to be determined.

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