The pathophysiology of increased hepatic IGF-1 expression in an ovine model of polycystic ovary syndrome (PCOS)

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Introduction

An adverse fetal environment can result in epigenetic programming events that predispose to adult disease1. Animal studies showed that prenatal androgenisation programs a polycystic ovary syndrome (PCOS)-like phenotype in adult offspring, including metabolic, reproductive and endocrine abnormalities2. Recently we reported that exposure of pregnant sheep to increased concentrations of testosterone during midgestation results in metabolic changes in adult offspring, including increased insulin secretion to glucose load and increased hepatic IGF1. Here, we focus on investigating the molecular pathophysiology of the IGF1 increase.

Aims

- To determine if altered IGF1 is a consequence of prenatally programmed differential gene methylation.
- To determine if IGF1 increase is a consequence of altered growth hormone (GH) secretion or action.
- To determine if contemporaneous androgen exposure is involved in the IGF1 increase.

Methods

Pregnant Scottish Greyface ewes were treated biweekly with either 100mg of testosterone propionate (TP) or vehicle control (C) from d62-102 of gestation (C=5, TP=9). Females offspring were assessed at 11 months of age.

In a separate experiment 3 years old normal female Scottish Greyface ewes were treated biweekly with either 100mg of testosterone propionate (TP) or vehicle control (C) for two weeks (C=5, TP=5).

Livers and pituitaries of experimental animals were snap frozen for qRT-PCR analysis and also fixed in buns for subsequent paraffin wax embedding and immunohistochemistry. Serum GH was measured by ELISA. Gene methylation was measured by pyrosequencing.

Results

IGF-1 methylation

Increased hepatic IGF1 is not a consequence of prenatally programmed hypomethylation as assessed by IGF1 CpG methylation using pyrosequencing.

Growth hormone

The prenatally programmed primary hyperinsulinaemia and subsequently augmented IGF1 is not a consequence of altered growth hormone (GH) secretion or action. There was no difference in pituitary GH mRNA expression, number of somatotrophs assessed by immunohistochemistry or serum GH concentrations.

Effect of contemporaneous androgen exposure

Prenatally androgenised sheep express higher hepatic AR and have increased capacity for ovarian and adrenal androgen synthesis4, therefore to determine if observed increase of hepatic IGF1 was a result of prenatal androgenisation or contemporaneous androgen exposure a separate cohort of adult sheep was utilised.

Conclusion

- Prenatal androgenisation of female fetuses but not a contemporaneous testosterone exposure of adult female sheep increases hepatic IGF1 in adult ovine females.

- The increase is not a consequence of altered growth hormone (GH) secretion or action nor hypomethylation of hepatic IGF1 gene.

- To date the pathophysiology of increased hepatic IGF1 in the ovine model of PCOS is unclear.

References: