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 disease[1]. Animal studies showed that prenatal androgenisation programmes a polycystic ovary syndrome (PCOS)-like phenotype in adult offspring, including metabolic, reproductive and endocrine abnormalities[2]. 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*[3]. 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 100mgs 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.

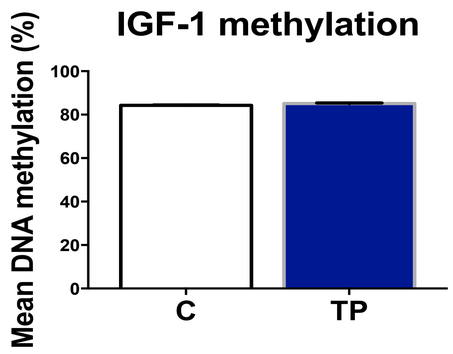
In a separate experiment 3 years old normal female Scottish Greyface ewes were treated biweekly with either 100mgs of testosterone propionate (TP) or vehicle control (C) for two weeks (C=5, TP=5).

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

Results

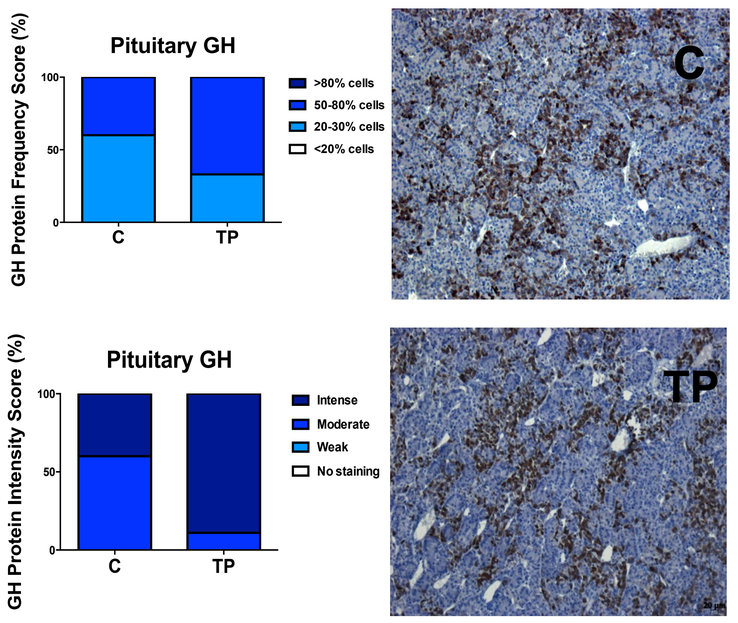
IGF-1 methylation

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

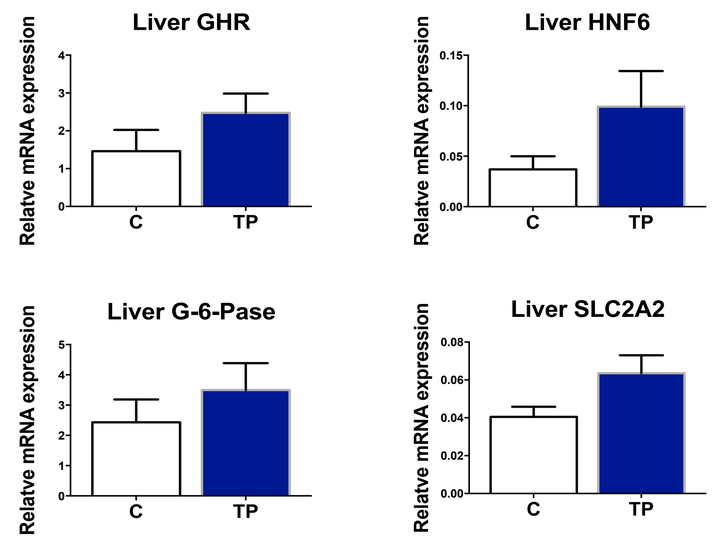


Growth hormone

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.

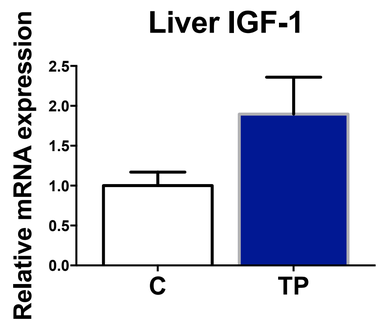


In addition there were no differences in hepatic *GHR* or expression of other GH-regulated genes including *HNF6/ONECUT1*, *G6PC* and *SLC2A2*.



Effect of contemporaneous androgen exposure

Prenatally androgenised sheep express higher hepatic *AR*[3] and have increased capacity for ovarian and adrenal androgen synthesis[4], 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.



The regimen of two week testosterone treatment did not significantly alter hepatic *IGF1* expression.

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:

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3. **Hogg K, Wood C, McNeilly A and Duncan C** (2011) The In Utero Programming of Increased Maternal Androgens and a Direct Fetal Intervention on Liver and Metabolic Function in Adult Sheep. Ploss One. 6: e24877
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