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Joni Macdonald, Lee B Smith*, Richard A Anderson, Rod T Mitchell*

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*Contributed equally

University of Edinburgh, Edinburgh, UK
(J Macdonald PhD, Prof L B Smith PhD, Prof R A Anderson PhD, R T Mitchell PhD)

Correspondence to:
Dr Rod T Mitchell, MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh EH16 4TJ, UK
rod.mitchell@ed.ac.uk

Abstract

Background Androgen signalling is essential for masculinisation of the male fetus. Failure of masculinisation during fetal life can result in disorders of sex development. Masculinisation is mediated partly by ligand binding to the luteinising hormone/human choriogonadotropin receptor (LHCGR). In rodents, the initial stages of masculinisation are gonadotropin independent, though whether this also occurs in human beings remains unknown because accurate timing and cell-type localisation of LHCGR protein expression in human fetal testis remains unresolved. We aimed to characterise the spatiotemportal expression of LHCGR in human fetal testis.

Methods Human fetal testis tissue (n=12, 8–20 weeks' gestation) was obtained from elective terminations after informed patient consent. We used a combination of RT-PCR for LHGCR and Leydig cells (marker 3β hydroxysteroid dehydrogenase [3βHSD]) and immunofluorescent co-localisation for LHCGR, Leydig cell steroidogenesis (3βHSD), and endothelial cells (markers CD31 and von Willebrand factor) to determine the exact timing and cellular location of LHCGR mRNA and protein in the human fetal testis. The study received ethics approval.

Findings LHCGR mRNA was detected from 9 weeks' gestation, but protein was not detectable until 12 weeks'. Expression of 3βHSD (indicating active steroidogenesis) was detected in the first trimester (10 weeks') preceding the expression of LHCGR. LHCGR did not co-localise with the Leydig cell marker 3βHSD during the early second trimester and only became consistently co-localised at 20 weeks' gestation. Before expression in fetal Leydig cells, LHCGR was restricted to endothelial cells (demonstrated by co-localisation with CD31 and von Willebrand factor).

Interpretation These results indicate that gonadotropin-mediated signalling through the LHCGR in human fetal Leydig cells is not established until later than previously described, suggesting a period of gonadotropin insensitivity during masculinisation in fetal life. Future functional studies will determine the mechanisms involved in androgen signalling in the human fetal testis. The present findings are important for understanding the pathogenesis of disorders of sex development in man.

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Contributors
JM and LBS performed experiments and analysed the data. RAA analysed the data. RTM designed the study, analysed the data, and wrote the abstract.

Declaration of interests
We declare no competing interests.