

Consequences of constitutively active Fshr: follicle loss, germ cell tumours, and pituitary, mammary gland and adrenal hyperplasia

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Introduction: In the family of G-protein-coupled receptors, mutations leading to constitutively active receptor forms are common. No human mutations, however, with strong constitutive FSHR activation have yet been detected, despite screening of numerous patients with putative phenotypes. In order to predict the correct human phenotype of such mutations, we have produced several constitutively activated mutants of the *Fshr* and characterised their phenotypes in transgenic mice.

Methodology: Pronuclear injections were used to generate transgenic mice expressing constitutively active Fshr, Fshr-D580H or Fshr-D580Y, under the *AMH* promoter. The corresponding mutations were also introduced into an *Fshr* gene fragment to produce knock in mice via blastocyst injection.

Results and Discussion: All mouse lines created showed several quantitative and qualitative anomalies, but the utmost abnormalities were seen in females expressing the D580H mutant under AMH promoter (*AMH-Fshr-D580H* mice). Typically, hemorrhagic and epidermoid cysts developed in the ovaries, and 30% of them showed germ cell tumours. In addition, constant Fshr action led to elevated E2 and decreased Fsh secretion and accelerated loss of small follicles. Malfunction of ovary furthermore resulted in distorted oestrus cycles, and feedback signals from the ovary to pituitary resulted in enlarged and grossly distorted anterior lobes with multiple neoplastic cells and increased prolactin production. Increased E2 and prolactin secretion also caused extensive development of mammary glands, resembling late pregnancy. Finally, a layer of lipofuscin cells accumulated at the corticomedullary junction of adrenal glands, as is typical of long-term oestrogen induction or occurring in ageing mice. In male mice testis size was slightly but significantly decreased in connection with constitutively active Fshr. In addition, a small fraction of both *AMH-Fshr-D580H* and *-D580Y* mice showed unilateral degeneration and vacuolisation of the seminiferous epithelium with loss of germ cells.

Conclusions: Mice expressing constitutively active Fshr in gonads show severe structural and functional abnormalities in the ovary, leading to infertility of half of the females. They also display several signs typical of extensive estrogen action or ageing. These mice provide a useful model to study several endocrinological disorders such as premature ovarian failure or development of ovarian teratomas.

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