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# FGF21 contributes to neuroendocrine control of female reproduction

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**Preventing reproduction during nutritional deprivation is an adaptive process that is conserved and essential for the survival of species. In mammals, the mechanisms that inhibit fertility during starvation are complex and incompletely understood[1–7]. Here we show that exposure of female mice to fibroblast growth factor 21 (FGF21), a fasting-induced hepatokine, mimics infertility secondary to starvation. Mechanistically, FGF21 acts on the suprachiasmatic nucleus (SCN) in the hypothalamus to suppress the vasopressin-kisspeptin signaling cascade, thereby inhibiting the proestrus surge in luteinizing hormone. Mice lacking the FGF21 co-receptor, β-Klotho, in the SCN are refractory to the inhibitory effect of FGF21 on female fertility. Thus, FGF21 defines an important liver-neuroendocrine axis that modulates female reproduction in response to nutritional challenge.**

FGF21 is an atypical member of the FGF superfamily that can enter the circulation and function as a hormone[8]. Physiologically, plasma FGF21 levels are increased during starvation as a result of hepatic PPARα-mediated gene transcription[9,10]. FGF21 coordinates a systemic response to fasting by increasing ketogenesis, suppressing growth and promoting torpor[9,11–13]. Pharmacologically, FGF21 has beneficial metabolic effects in obese and diabetic animal models as an insulin sensitizer[12], and therefore considerable effort is being devoted to understanding its mechanism of action[14].

We previously reported that female, but not male, mice engineered to transgenically overexpress FGF21 (TgFgf21)) are infertile[9]. Although the female Tg(Fgf21) mice are smaller and have higher insulin sensitivity, their body fat percentage and plasma adiponectin and leptin concentrations do not differ from their wild-type counterparts[15]. Initial characterization of the cause of infertility revealed a delay in the onset of puberty (**Fig. 1a**) and a failure to mate with proven stud males (**Fig. 1b**). Vaginal cytology and ovarian histology showed abnormalities consistent with anovulatory hypogonadism. Tg(Fgf21) mice rarely entered the ovulatory estrus phase of the cycle and displayed a prolonged diestrus (**Fig. 1c**). Ovarian histology revealed the presence of mature follicles in Tg(Fgf21) mice, but there were few, if any, postovulation corpora lutea (**Fig. 1d**). The abnormal estrous cycles in female Tg(Fgf21) mice were concordant with altered plasma gonadotropin concentrations: whereas plasma follicle stimulating hormone (FSH) concentrations were normal, concentrations of ovulation-inducing luteinizing hormone were significantly lower than those of wild-type mice (**Fig. 1e**). These analyses demonstrate that female Tg(Fgf21) mice exhibit hypogonadotropic hypogonadism.

To assess the function of the hypothalamic-pituitary-gonadal axis in female Tg(Fgf21) mice, we performed a series of hormone challenge tests. In response to exogenous gonadotropin (PMSG, gonadotropin from pregnant mare serum), plasma estradiol levels increased normally in both wild-type and Tg(Fgf21) mice (**Fig. 2a**). However, ovariectomized Tg(Fgf21) mice had a markedly reduced luteinizing

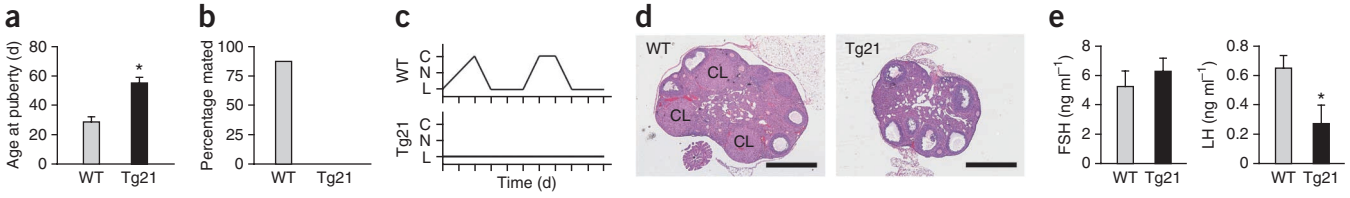


**Figure 1** Female Tg(Fgf21) mice are infertile. (**a**) Age at onset of puberty (vaginal opening) in female wild-type (WT) and Tg(Fgf21) (Tg21) mice ($n = 6$ or 7). (**b**) Proportion of WT and Tg(Fgf21) mice that mated with proven stud males ($n = 8$). (**c**) Representative examples ($n = 18$) of estrus cycles in WT and Tg(Fgf21) mice as determined by vaginal cytology. C, cornified cells (estrus); N, nucleated cells (proestrus); L, leukocytes (diestrus). (**d**) Examples of ovarian histology from WT and Tg(Fgf21) mice. CL, corpora lutea. Scale bars, 500 μm. (**e**) Plasma FSH and luteinizing hormone (LH) concentrations measured in diestrus at zeitgeber time (ZT) 6–7 ($n = 5$). Data are expressed as mean ± s.e.m. $^*P < 0.05$ compared to WT.

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