that binds Creb in vitro, and mutation of this half-CRE results in loss of preferential GnRH stimulation of Fshb at low pulse frequencies in immortalized gonadotrope LβT2 cells. Therefore, the purpose of this study was to identify the direct role of Creb on gonadotropin regulation in vivo. We hypothesized that gonadotrope-specific deletion of Creb would influence pubertal timing and/or fertility due to reduced Fshb expression. **Methods and Results:** Gonadotrope-specific Creb knockout (Creb1 fx/fx / Gnrhr GRIC/+; Creb KO) and control (Creb1 fx/fx) mice were generated by Cre-Lox recombination and markers for pubertal onset were evaluated. We observed no differences in body weights of Creb KO and littermate control mice in either females or males from postnatal day (PND) 21 to 3 months of age (n=9/genotype/sex). The age of vaginal opening, a marker of puberty onset in female mice, was not significantly different between female Creb KO (PND 28.4±0.5; n=21) and littermate control (PND 29.5±0.6; n=17) mice. Similarly, the age of first estrus, determined by vaginal lavage and cytology, was not significantly different between Creb KO mice (PND 37.6±1.9; n=9) and littermate controls (PND 36.6±2.2; n=8). Estrous cyclicity was normal over a three-week period in Creb KO and control mice, which spent similar amounts of time in diestrus/metestrus, proestrus, or estrus. Male Creb KO mice tended to show preputial separation at a younger age (PND 28.8±0.3; n=19) compared to littermate control (PND 29.6±0.3; n=22) mice, but the difference did not reach statistical significance (p=0. 06). **Conclusions:** Deletion of Creb from pituitary gonadotropes did not affect the timing of pubertal onset in female mice, but we did observe a trend for male Creb KO mice to have advanced puberty, as measured by preputial separation. Normal pubertal timing does not preclude potential effects of Creb-mediated gonadotropin regulation on folliculogenesis, spermatogenesis, or fertility (including litter size), for which studies are ongoing.

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Effects of Gonadotrope-Specific Knockout of Creb on HPG Axis Function in Mice

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Background and Objective: Reproduction is regulated by FSH and LH, which are synthesized and secreted by pituitary gonadotropes in response to pulsatile hypothalamic GnRH in a frequency dependent manner. Low and high GnRH pulse frequencies preferentially increase Fshb and Lhb expression, respectively, mediated by preferential coupling to Gαs-PKA-Creb and Gαq-PKC-MAPK-AP1 signaling cascades in vitro. The mouse Fshb proximal promoter contains a half-AP1/half-CRE recognition motif