

## Estrogen in Female Reproductive Axis: Positive Estrogen Feedback to Pituitary

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Hypothalamic gonadotropin releasing hormone (GnRH), pituitary gonadotropins, and ovarian steroid hormones are the key components of the regulatory endocrine network that controls both the menstrual and estrous cycles. GnRH controls the release of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. LH and FSH control ovarian functions, such as folliculogenesis, ovulation, corpus luteum formation and synthesis of estrogens, progesterone, and other ovarian hormones. These ovarian hormones, in turn, exert positive and negative feedback effects on the hypothalamic-pituitary-ovary (HPO) axis, which is also under the influence of numerous other inputs, such as environment, nutrition, and stress. While the mechanism of estrogen negative feedback on gonadotropin release has been well established, whether positive estrogen feedback to the pituitary is critical for LH surge induction and the potential mechanism of the estrogen action in the pituitary has yet to be unveiled. Estrogen plays its role by modulating the activity of  $\alpha$  and/or  $\beta$  subtypes of estrogen receptors (ERs) in a tissue type dependent manner. While both ER $\alpha$  and ER $\beta$  are present in the pituitary, ER $\alpha$  has been shown to be the effector of estrogen action in the pituitary as is supported by the finding that ER $\alpha$  knockout (ER $\alpha$ KO) female mice are completely infertile and do not ovulate, but ER $\beta$ KO mice are fertile. Therefore, it has been believed that ER $\alpha$  may mediate the positive feedback effect of estrogen in the pituitary. However, the fact that all of HPO tissues express ER $\alpha$  has made it difficult to isolate its role using either pharmacological as well as traditional gene knockout approach. This impeding difficulty is now being overcome by utilizing a conditional gene knockout approach. This review summarizes on-going efforts to determine the pituitary specific roles of ER $\alpha$  in mediating estrogen positive feedback.