Leptin and ghrelin are the two major hormones which regulate food intake and energy balance. They have also been reported to have pleiotropic functions, including the modulation of ovarian function via the hypothalamic-pituitary-ovarian system or in a direct manner to the ovaries. Blood leptin levels increase over the menstrual cycle and peak at the time of the luteinizing hormone (LH) surge. Leptin secreted from adipocytes acts on the hypothalamus and pituitary gland to stimulate the secretion of GnRH and gonadotropins. In the ovaries, high levels of leptin inhibit follicle-stimulating hormone (FSH)-induced steroid secretion and follicular development. Ghrelin, secreted by the stomach, has been reported to modulate GnRH secretion in the hypothalamus and to affect FSH and LH secretion, as well as steroidogenesis in the ovaries. Knockout of these hormones leads to impaired fertility. However, the mechanism of the direct effects of leptin and ghrelin on the ovaries has not been well elucidated. In the present study, we investigated the effects of leptin and ghrelin on the ovarian steroidogenesis using primary culture of rat granulosa cells, by focusing on the ovarian bone morphogenetic protein (BMP) system, which plays an important role in follicular development and steroidogenesis and acts as a luteinizing inhibitor. The results showed that treatment with leptin (1 to 300 ng/mL) did not affect either estradiol (E2) or progesterone (P4) production, but enhanced FSH-induced P4 production at low concentrations (10 ng/mL). On the other hand, treatment with ghrelin (1 to 300 nM) did not affect E2 and P4 production, but enhanced FSH-induced P4 production in a concentration-responsive manner. The mRNA levels of the follicular steroid synthases (StAR, P450scc, 3βHSD, 20αHSD) were examined. Leptin treatment enhanced 3βHSD mRNA levels. Both leptin treatment and ghrelin treatment decreased FSH-induced 20αHSD mRNA levels. However, both treatments decreased FSH-induced cAMP production. In addition, leptin treatment tended to suppress the transcriptional activity of Id-1 induced by BMP-6. Collectively, these results indicate that both leptin and ghrelin enhance FSH-induced P4 production by suppressing BMP signaling in rat granulosa cells. It was thus suggested that leptin and ghrelin which regulate food intake and energy balance can also act as endogenous regulators for the modulation of P4 synthesis and luteinizing process by ovarian follicles.

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