Orexins are neuropeptides that express primarily in the hypothalamus and are produced in two isoforms, orexin A and orexin B. There are two kinds of G protein coupled receptors, orexin type 1 (OX1R) and type 2 (OX2R) receptors. Orexin has been reported to have key roles on sleep-wake regulation and feeding behavior in the central nervous system, whereas its receptors are also expressed in peripheral tissues including the endocrine organs, and orexin affects the regulation of the endocrine system. In our previous experiments, we have revealed the impact of orexins on anterior pituitary functions. For instance, we reported that orexin A plays an inhibitory role in prolactin production through the suppression of endogenous bone morphogenetic protein (BMP) activity in rat pituitary lactotrope GH3 cells. It was also reported that orexin A enhances pro-opiomelanocortin (POMC) transcription by upregulating corticotropin-releasing hormone (CRH) receptor signaling and by downregulating BMP-Smad signaling in mouse corticotope AtT20 cells. However, the effects of orexin on the endocrine function regarding gonadotrope cells remain unclear. We have recently uncovered that core clock genes and BMPs have mutual effects on luteinizing hormone (LH) expression in a phase-dependent manner by mouse gonadotrope LβT2 cells. In the present study, we investigated the effect of orexin on pituitary gonadotropin expression using LβT2 cells, which express OX1R and OX2R, by focusing on the functional involvement of BMP system and clock genes. It was revealed that orexin A stimulation increased LHβ and FSHβ mRNA expression in a concentration-responsive manner in the absence of GnRH, and interestingly, GnRH co-treatment further upregulated LHβ mRNA expression in LβT2 cells. Regarding the interrelationships between the signalings of orexin and BMPs, it was also revealed that orexin A pretreatment enhanced the BMP receptor signaling detected as the Smad1/5/9 phosphorylation, indicating that orexin enables to upregulate the BMP actions in LβT2 cells. In our previous studies, we reported that several BMP ligands such as BMP-6, -7 and 15 expressed in LβT2 cells can promote gonadotropin transcription, in which BMP-6 regulates GnRH-stimulated LH expression by modulating the sensitivity to somatostatin analogs. Based on the present results, it was implied that endogenous orexin can be functionally involved in the underlying mechanisms of gonadotropin expression. Collectively, orexin enhances gonadotropin expression by regulating BMP signaling in gonadotrope cells. Here, we will also discuss functional involvement of clock genes in the regulatory system of gonadotropin secretion induced by orexin and BMPs.

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Mutual Effects of Orexin and BMPs on Gonadotropin Expression by Mouse Gonadotrope LβT2 Cells

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