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Effect of Intracerebroventricular Administration of an Antisense Oligodeoxynucleotide against Type I Receptor of Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) on the Pituitary Luteinizing hormone β messenger RNA level

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Pituitary adenylate cyclase-activating polypeptide (PACAP) was found to regulate pitutary hormone biosynthesis and secretion through its cognate receptors. The present study aimed at elucidating the regulatory role of PACAP on the gene expression of luteinizing hormone (LH) in the anterior pituitary. We sought to determine the changes in PACAP and PACAP receptor type I (PVR1) mRNA levels during the reproductive cycle of female rat using RNase protection assay. Levels of PACAP and PVR1 mRNA were clearly increased at the diestrus I in the medial basal hypothalamus, while level of PVR1 mRNA in the pituitary was not significantly changed during the estrous cycle. To determine the regulatory effect of PACAP on the LH β mRNA, antisense PVR1 oligodeoxynucleotide (ODN) was intracerebroventricularly injected and LH β mRNA was measured with Northern blot hybridization. The ODN markedly decreased the LH β mRNA level at the proestrous stage of the estrous cycle, while no such an ODN-induced decrease was found at other stages. The effect of ODN on the LH β mRNA level was further analyzed in the ovariectomized (OVX) and estrogen-treated (OVX+E) rats. The ODN clearly suppressed the LH β mRNA as well as the hypothalamic LHRH mRNA level in the OVX+E-treated rats. Therefore, PACAP seems to be involved in the regulation of preovulatory increase in the LH β mRNA level through hypothalamic LHRH neural apparatus.

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A Possible Role of a Homeobox Containing Nkx-2.1 Gene in the Regulation of Diurnal Rhythm in Neu (ErbB-2), a Receptor Tyrosine Kinase, and Cyclooxygenase II Gene Expression in the Rat Hypothalamus

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Nkx-2.1 is a transcription factor of mammalian Nkx family of homeodomain containing genes and a pattern formation gene for the development of the fetal dienchephalon. The present study aimed to elucidate the role of Nkx-2.1 in the regulation of diurnal rhythm in the gene expression of cyclooxygenase II (COXII) and neu in the hypothalamus. We found that COXII and neu are the down-stream target genes of Nkx-2.1, using promoter assay with co-transfection of COXII- and neu-promoter-luciferase fusion genes and Nkx-2.1 expression vector. We determined diurnal rhythm in the gene expression of Nkx-2.1, COXII, and neu using RNase protection assay. Level of Nkx-2.1 mRNA was low during the day and high during the night. The level reached the lowest at 0900 h and the peak at 2100 h during the normal light-dark (LD) cycle (lights on 0600 h and off 2000 h). Changes in the COXII and neu mRNA levels showed nearly the same pattern with Nkx-2.1 in LD. After 2 weeks under the continuous dark (DD) condition, the diurnal rhythm in Nkx-2.1 mRNA level was modified but still maintained. The rhythms in COXII and neu mRNA levels in DD nearly followed that in Nkx-2.1 mRNA level in DD. In summary, we found that Nkx-2.1 play a role in the trans-activation of COXII and neu gene expression, which may be important in the regulation of hypothalamic diurnal rhythm.