

Direct action of melatonin in human granulosa-luteal cells

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摘要

Abstract

The direct involvement of melatonin in modulation of ovarian steroidogenesis, the high levels of melatonin found in human follicular fluid, and the presence of melatonin binding sites in the ovary led us to hypothesize that melatonin acts as a modulator of ovarian function. In contrast to the hypothalamus and pituitary, the mechanism of melatonin action at the level of the ovary is still poorly understood. In the present study, we investigated the gene expression of the two different forms of melatonin receptors in human granulosa-luteal cells, using RT-PCR. PCR products corresponding to the expected sizes of the melatonin receptor subtypes, mt1-R and MT2-R, were obtained from granulosa-luteal cells, and the authenticity of the PCR products was confirmed by Southern blot hybridization with cDNA probes. Subsequent cloning and sequence analysis revealed that the ovarian mt1-R and MT2-R cDNAs are identical to their brain counterparts. Because gonadotropins and GnRH acting through specific receptors in the human ovary regulate cellular functions, we investigated the role of melatonin in the regulation of FSH receptor, LH receptor, GnRH, and GnRH receptor levels. Treatment with melatonin (10 pM–100 nM) significantly increased LH receptor mRNA levels without altering the expression of the FSH receptor gene. Both GnRH and GnRH receptor mRNA levels were significantly decreased, to 61% and 45% of control levels, respectively, after melatonin treatment. Melatonin treatment alone had no effect on basal progesterone production but enhanced the effects of human CG-stimulated progesterone production. Because MAPKs are activated in response to a diverse array of extracellular stimuli leading to the regulation of cell growth, division, and differentiation, and because melatonin has been shown to modulate cellular proliferation and differentiation, in this study, we demonstrated that melatonin activated MAPK in a dose- and time-dependent

manner. In summary, our studies demonstrate, for the first time, that melatonin can regulate progesterone production, LH receptor, GnRH, and GnRH receptor gene expression through melatonin receptors in human granulosa-luteal cells, which may be mediated via the MAPK pathway and activation of Elk-1. Our results support the notion that melatonin plays a direct role in regulating ovarian function