Melatonin induces apoptotic death in LNCaP cells via p38 and JNK pathways: therapeutic implications for prostate cancer.

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Apoptosis, a form of cell death, is a fundamental process for the development and maintenance of multicellular organisms that promotes the removal of damaged, senescent or unwanted cells. Induction of cancer cell apoptosis is an important strategy of anticancer therapy. In this study, we examined if melatonin, the main secretory product of the pineal gland, inhibited the growth of prostate cancer cells (LNCaP) and promoted apoptosis via mitogen-activated protein kinases (MAPKs), which are closely associated with apoptosis and survival. Melatonin treatment significantly inhibited the growth of LNCaP cells in a dose- and time-dependent manner.

Melatonin down-regulates HIF-1 alpha expression through inhibition of protein translation in prostate cancer cells.

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Melatonin, the main secretory product of the pineal gland, has been shown to exert an oncostatic activity in cancer cells. Recently, several studies have shown that melatonin has antiangiogenic properties. However, the mechanism by which melatonin exerts antiangiogenic effects is not understood. Hypoxia inducible factor (HIF)-1 is a transcription factor which mediates adaptive response to changes in tissue oxygenation. HIF-1 is a heterodimer formed by the association of a constitutively expressed HIF-1 beta subunit and a HIF-1 alpha subunit, the expression of which is highly regulated. In this study, pharmacologic concentrations of melatonin was found to inhibit expression of HIF-1 alpha protein under both normoxic and hypoxic conditions in DU145, PC-3, and LNCaP prostate cancer cells without affecting HIF-1 mRNA levels. Consistent with the reduction in HIF-1 alpha protein levels, melatonin inhibited HIF-1 transcriptional activity and the release of vascular endothelial growth factor. We found that the suppression of HIF-1 alpha expression by melatonin correlated with dephosphorylation of p70S6K and its direct target RPS6, a pathway known to regulate HIF-1 transcriptional activity and the release of vascular endothelial growth factor. We found that the suppression of HIF-1 alpha expression by melatonin correlated with dephosphorylation of p70S6K and its direct target RPS6, a pathway known to regulate HIF-1 transcriptional activity and the release of vascular endothelial growth factor. Metabolic labeling assays indicated that melatonin inhibits HIF-1 alpha expression at the translational level. Taken together, these results strongly suggest that the pharmacologic concentration of melatonin inhibits HIF-1 alpha expression through the suppression of protein translation in prostate cancer cells.

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Melatonin as a negative mitogenic hormonal regulator of human prostate epithelial cell growth: potential mechanisms and clinical significance.

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Circannual variation in the human serum levels of prostate-specific antigen, a growth marker of the prostate gland, has been reported recently. The present study was conducted to investigate the role of the photoperiodic hormone melatonin (MLT) and its membrane receptors in the modulation of human prostate growth. Expression of MT(1) and MT(2) receptors was detected in benign human prostatic epithelial tissues and RWPE-1 cells. MLT and 2-iodomelatonin inhibited RWPE-1 cell proliferation and up-regulated p27(Kip1) gene and protein expression in the cells. The effects of MLT were blocked by the nonselective MT(1)/MT(2) receptor antagonist luzindole, but were not affected by the selective MT(2) receptor antagonist 4-phenyl-2-propionamidotetraline. Of note, the antiproliferative action of MLT on benign prostate epithelial RWPE-1 cells was effected via increased p27(Kip1) gene transcription through MT(1) receptor-mediated activation of protein kinase A (PKA) and protein kinase C (PKC) in parallel, a signaling process which has previously been demonstrated in 22Rv1 prostate cancer cells. Taken together, the demonstration of the MT(1)/PKA+PKC/p27(Kip1) antiproliferative pathway in benign and malignant prostate epithelial cell lines indicated the potential importance of this MT receptor-mediated signaling mechanism in growth regulation of the human prostate gland in health and disease. Collectively, our data support the hypothesis that MLT may function as a negative mitogenic hormonal regulator of human prostate epithelial cell growth.

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Signaling mechanisms of melatonin in antiproliferation of hormone-refractory 22Rv1 human prostate cancer cells: implications for prostate cancer chemoprevention.

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There is an unmet clinical demand for safe and effective pharmaceuticals/nutraceuticals for prostate cancer prevention and hormone-refractory prostate cancer treatment. Previous laboratory and human studies of our laboratory demonstrated an association between the antiproliferative action of melatonin and melatonin MT(1) receptor expression in prostate cancer. The aim of this study was to determine, using a pharmacological approach, the signaling mechanisms of melatonin in hormone-refractory 22Rv1 human prostate cancer.
Both immunoreactive MT(1) and MT(2) subtypes of G protein-coupled melatonin receptor were expressed in 22Rv1 cells. Melatonin inhibited, concentration dependently, cell proliferation, upregulated p27(Kip1) gene transcription and protein expression, and downregulated activated androgen signaling in 22Rv1 cells. While the effects of melatonin were mimicked by 2-iodomelatonin, a high-affinity nonselective MT(1) and MT(2) receptor agonist, melatonin effects were blocked by luzindole, a nonselective MT(1) and MT(2) receptor antagonist, but were unaffected by 4-phenyl-2-propionamidotetraline, a selective MT(2) receptor antagonist. Importantly, we discovered that the antiproliferative effect of melatonin exerted via MT(1) receptor on p27(Kip1) gene and protein upregulation is mediated by a novel signaling mechanism involving co-activation of protein kinase C (PKC) and PKA in parallel. Moreover, we also showed that a melatonin/MT(1)/PKC mechanism is involved in melatonin-induced downregulation of activated androgen signal transduction in 22Rv1 cells. Taken together with the known molecular mechanisms of prostate cancer progression and transition to androgen independence, our data provide strong support for melatonin to be a promising small-molecule useful for prostate cancer primary prevention and secondary prevention of the development and progression of hormone refractoriness.

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Melatonin and prostate cancer cell proliferation: interplay with castration, epidermal growth factor, and androgen sensitivity.

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BACKGROUND: Potential modulatory effects of melatonin on the proliferation of androgen-sensitive LNCaP and androgen-insensitive PC-3 and DU 145 prostate cancer cells were reported recently. In this study, we investigated the effects of combined melatonin and castration on LNCaP tumor growth in vivo, the interactions between melatonin and epidermal growth factor (EGF) on LNCaP cell proliferation, and melatonin actions on the proliferation of PC-3 and DU 145 cells. METHODS: Tumor development and growth in castrated nude mice inoculated with LNCaP cells or in intact animals inoculated with DU 145 cells, with or without daily melatonin treatment, were monitored by observation and caliper measurement. MT(1) receptor expression in native or transfected prostate cancer cell lines was examined by immunocytochemistry or 2-[125I]iodomelatonin binding. Cyclin D1 expression in LNCaP cells was assessed by Western blotting, and cell proliferation was measured by thymidine incorporation and/or cell count. RESULTS: Melatonin treatment was associated with further decreases in LNCaP tumor incidence and growth rate in castrated nude mice. Melatonin and 2-iodomelatonin (a melatonin receptor agonist) attenuated EGF-stimulated increases in LNCaP cell proliferation and cyclin D1 levels. Melatonin had no effect on the proliferation or growth of MT(1) receptor-expressing DU 145 cells, and of PC-3 cells in which MT(1) receptor protein was undetectable. The proliferation of transfected PC-3 cells expressing MT(1) receptor was unaffected by 2-iodomelatonin. CONCLUSION: Together with previous data, the present results indicate synergistic action of melatonin and castration in inhibiting the growth of androgen-sensitive LNCaP tumor. Androgen-sensitive prostate cancer cell proliferation may be modulated by opposite changes in cyclin D1 levels induced by activated MT(1) and EGF receptors. In androgen-insensitive prostate cancer cells, MT(1) receptor-mediated signal transduction may become defective not only through changes in membrane receptor protein expression and/or functions, but also by means of alterations in downstream postreceptor signaling events. Copyright 2002 Wiley-Liss, Inc.

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