Light during darkness, melatonin suppression and cancer progression

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It is well known that light of sufficient intensity, wavelength and duration present during the dark phase of an alternating light/dark cycle rapidly suppresses the pineal gland production of melatonin. Many studies now support a direct inhibitory role for physiological nocturnal concentrations of melatonin in cancer development and growth, particularly estrogen receptor positive (ER+) breast cancer. Recent epidemiological studies support the Stevens’ melatonin hypothesis that the increased risk of breast cancer in the industrialized world may be due, in part, to the suppression of the oncostatic melatonin signal by light-at-night. The reported increase in the incidence of carcinogen-induced mammary cancers in constant light-exposed rats provided some initial support for the Stevens’ postulate. However, more definitive experimental evidence for this hypothesis was lacking until recently. During the past few years, we have shown that the surge of melatonin in the circulation during darkness represents a potent oncostatic signal to tissue-isolated rat hepatoma 7288CTC, which is an ER+ adenocarcinoma of the liver. This oncostatic effect occurs via a melatonin receptor-mediated suppression of tumor cAMP production which leads to a suppression of the tumor uptake of linoleic acid (LA), an essential fatty acid with substantial oncogenic properties. The ability of LA to promote cancer progression is accomplished by its intracellular metabolism to 13-hydroxyoctadecadienoic acid (13-HODE) which amplifies the activity of the epidermal growth factor receptor/mitogen-activated protein kinase pathway leading to cell proliferation. By blocking tumor LA uptake, melatonin effectively blocks the production of 13-HODE and thus, markedly attenuates tumor growth. A similar effect of melatonin is observed in tissue-isolated, ER+ MCF-7 human breast cancer xenografts and nitrosomethylurea (NMU)-induced rat mammary cancers. When male rats bearing tissue-isolated hepatomas are exposed either to constant bright light (300 lux) or dim light (0.25 lux) during the dark phase of a 12L:12D photoperiod, the latency to onset was significantly reduced while the growth of tumors was markedly increased over a 4 wk period as compared with control tumors in 12L:12D-exposed rats. In constant light- and dim light during darkness-exposed rats, melatonin levels were completely suppressed while tumor growth, LA uptake and 13-HODE production were markedly increased. Similar results were obtained in constant bright light-exposed female rats bearing tissue-isolated NMU-induced mammary cancers or MCF-7 human breast cancer xenografts. These findings provide the first definitive experimental evidence that light exposure during darkness increases the risk of cancer progression via elimination of the nocturnal melatonin signal and its suppression of tumor LA uptake and metabolism to 13-HODE.