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Pineal gland, melatonin and cancer

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Abstract Studies on the relationship between the pineal gland, melatonin and neoplastic disease have recently become one of the most fascinating aspects of pineal research. The first data suggesting a link between the pineal and cancer were published 70 years ago. However, the real progress in this area of research has been made in the last two decades. The bulk of the experimental evidence indicates the influence of the pineal gland on the malignant tumor formation and/or growth. The majority of reports point toward the oncostatic action of the pineal, exerted most probably by its hormone, melatonin, via different mechanisms, including modulation of endocrine and immune systems and direct antiproliferative action. The mechanisms of the oncostatic action of the pineal seem to be, however, very complex. There is some indication that the pineal gland may also play a role in human malignancy. Alterations in melatonin concentrations have been demonstrated in various tumor types including breast cancer, prostate cancer, colorectal carcinoma, and uterine cancer. Moreover, melatonin has been reported to be helpful in therapy of advanced cancer of various types. However, detailed 24h melatonin profiles must be studied in large numbers of patients with different types of tumors before determining whether melatonin concentrations have any diagnostic and/or prognostic values in cancer patients. Moreover, well designed clinical trials should be performed on the possible therapeutic significance of melatonin in neoplastic disease.

NEL REVIEW

Introduction

The first data on the possible relationship between the pineal gland and neoplastic growth were published already 70 years ago [1]. Since then numerous reports, both experimental and clinical, have been published suggesting links between the pineal, melatonin and neoplastic disease. The results of these studies are briefly summarized below.

Pineal gland, melatonin and experimentally induced tumors

There is substantial experimental evidence indicating the influence of the pineal gland and its hormone melatonin on the malignant tumor formation and/or growth [see 2–7]. Some data indicate also that the presence of the malignant tumor alters the morphology of the host pineal gland [6, 8].

Effects of pinealectomy as well as melatonin administration (in vivo and in vitro) on tumor initiation, growth or survival time of the animals have been studied in various experimental tumors (transplantable or chemically induced). Generally, pinealectomy exerted stimulatory effect on neoplastic growth, whereas melatonin administration effects were of inhibitory nature. However, different effects of both procedures have been reported in some tumor types and also within the same type of tumor by various authors. The effects of pinealectomy or melatonin administration are listed below [for references concerning the particular tumor type see 2, 3, 6, 8].

Stimulation of tumorigenesis by pinealectomy has been reported in the following tumor types: transplantable Todo sarcoma, transplantable ovarian carcinoma, transplantable Walker 256 carcinoma, transplantable Ehrlich's tumor, transplantable Yoshida's tumor, transplantable Guerin's epithelioma, transplantable MM1 melanoma, dimethylbenzanthracene (DMBA)-induced melanoma, methylcholanthrene (MCA)-induced fibrosarcoma, N-methylonitrosourea (NMU)-induced mammary carcinoma. In dimethylbenzanthracene-induced mammary carcinoma stimulation, lack of effect or even inhibition of tumor growth have been reported, whereas slight inhibition of the growth of DMBA-induced hepatocarcinoma has been found.

Melatonin administration in vivo inhibited initiation and/or growth of the following tumor types: DMBA-induced mammary carcinoma, NMU-induced mammary carcinoma, spontaneous C_3H/Jax mammary carcinoma, spontaneous C_3CF_1 mammary carcinoma, transplantable R3290AC mammary carcinoma, transplantable B16 melanoma, transplantable LSTRA-leukemia, transplantable Kirkmann-Robbins hepatoma, transplantable Guerin epithelioma, transplantable Colon 38 adenocarcinoma. No effect has been found in transplantable Walker's 256 carcinoma, and transplantable Yoshida tumor, whereas in transplantable Lewis's lung carcinoma either stimulatory or inhibitory effect has been observed. It has been demonstrated that the effect of melatonin depends on the time of its administration. In transplantable Ehrlih's tumor, melatonin injected in the evening inhibited tumor growth but after morning injections slight stimulation of tumor growth has been observed. Similarly, in transplantable MtT/F4 pituitary tumor only evening administration of melatonin was effective in tumor growth inhibition, whereas morning administration was ineffective. It has been also shown that in DMBA-induced mammary tumors melatonin inhibited growth of slow-growing early pass-ages, but it was ineffective in advanced fast-growing passages. On the other hand, in Dunning's prostatic adenocarcinoma, melatonin did not influence the growth of slow-growing type (W-2), and stimulated the growth of fast-growing type (R3327HIF).

In vitro effects of melatonin seem to depend on its concentration in the incubation media. Inhibitory influence on growth of tumor cells in vitro (in certain concentrations) has been reported in the following tumor types: MCF-7 breast cancer, EFM-19 mammary carcinoma cells, B7 melanoma, M2R melanoma cell line, diethylstilbestrol-induced prolactinoma, SK-OV-3 and JA-1 ovarian carcinoma cell lines, ME-180 human cervical cancer cells, human choriocarcinoma JAR cell line, S180 sarcoma cell line, Hep-2 larynx carcinoma cells, Jurkat human T lymphoma cells, CCLL mouse cytotoxic T cell line and transplantable Colon 38 adenocarcinoma. Melatonin did not influence (in any used concentrations) the growth of transplantable Kirkman-Robbins's hepatoma, melanoma B16 cell line, DLD-1 colon carcinoma cell line, EFO-27 ovarian carcinoma cells, HSB-2 human T lymphoma cells, P388 leukemia cell line, WIL729-HF-2 human B lymphoblastoid cell line, and K562 erythroleukemia cells. Finally, the effects of melatonin on the growth of melanoma cells from metastatic nodules were different in individual cases (inhibition, stimulation, no effect).

It appears from the presented data that though the majority of the reports point to oncostatic action of melatonin, the results are sometimes contradictory. According to Karasek [6, 8] differences in the results may depend on different factors, such as: (i) various tumor models, (ii) different species used in the experiments, (iii) differences in mode and timing

of melatonin administration, (iv) in vivo or in vitro studies, (v) various photoperiods used in the experiments, and (vi) different methods of tumor growth measurement (i.e. tumor size, tumor volume, tumor diameter, tumor weight, tumor incidence, tumor latency, survival time of the animals, neoplastic cell proliferation). The importance of different experimental paradigms is evident from several papers. The time of melatonin administration seems to be of crucial importance [9, 10]. Different results have been obtained in the same tumor type in in vivo and in vitro studies [11]. Effects of melatonin administration differed depending on whether the lifespan of animals or mitotic activity of the tumor cell was considered as a parameter [12].

Possible mechanisms of action of melatonin on oncogenesis

As it can be concluded from the data presented above, the effects of melatonin are mainly oncostatic. The mechanisms of this oncostatic action are complex and only partially clarified (Fig.1).

Melatonin may exert its oncostatic effect indirectly, via modulation of the endocrine and immune systems. Antigonadotropic effect of melatonin may result in decreased gonadal steroid secretion and, subsequently, may influence the growth of steroid-dependent tumors. Melatonin has been repeatedly shown to exert the immuno-enhancing activity. Melatonin influences several elements of particular importance for the anti-cancer immunity, e.g. it enhances interleukin-2 and interferon-gamma productions [13] as well as increases the anti-tumoral effectiveness of exogenous interleukin-2 [14, 15]. Moreover, melatonin may influence directly all steps of carcinogenesis: i.e. tumor initiation, promotion and progression. Melatonin probably restrains the tumor initiation by acting as a potent antioxidant [for review see 16]. The important role of free radicals in carcinogenesis is now generally accepted.

As it has been mentioned in the preceding paragraph, melatonin exerts the antiproliferative on several non-neoplastic and neoplastic cells. Since these antiproliferative effects have been observed not only in vivo but also in vitro, it seems that they involve directly the melatonin receptors. Very interesting findings which clarify, at least in part, the intracellular mechanism of the antiproliferative action of melatonin have been recently reported by Blask et al. [17]. The quoted authors have studied the inhibitory effect of melatonin on rat hepatoma 7288CTC. They have found that the effect of melatonin is reversed by pertussis toxin, forskolin, cyclic AMP or 13-hydroxy-9,11-octadecadienoic acid (13-HODE). The conclusion is that melatonin exerts its effect via membrane melatonin receptors which are coupled to the adenylate cyclase via pertussis toxin-sensitive G proteins. The inhibition of the adenylate cyclase leads to the drop of the intracellular cAMP levels and, subsequently, to decreased transport of linoleic acid into the cells because of decreased phosphorylation of the fatty acid transporting protein (FATP). The linoleic acid is oxidized intracellularly by lipoxygenase to 13-HODE; the latter molecule promotes the cell growth by up-regulation of the expression of epidermal growth factor (EGF) receptor tyrosine kinases. In our laboratory we have studied the effects of melatonin and of the compound CGP 52608 on the proliferation of murine colonic adenocarcinoma Colon 38 in vitro and in vivo [18]. We have found that both melatonin and CGP 52608 inhibit

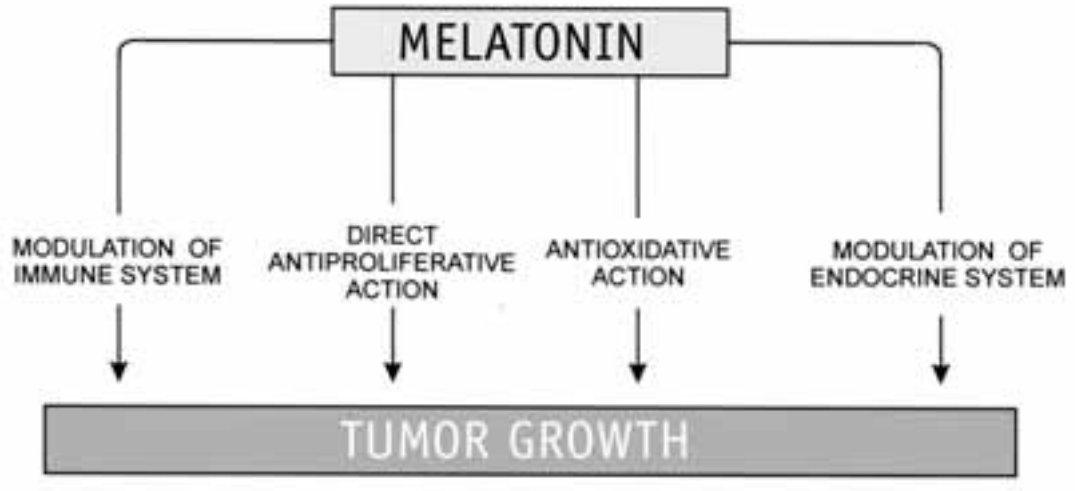

Fig. 1. The pathways of oncostatic action of melatonin.

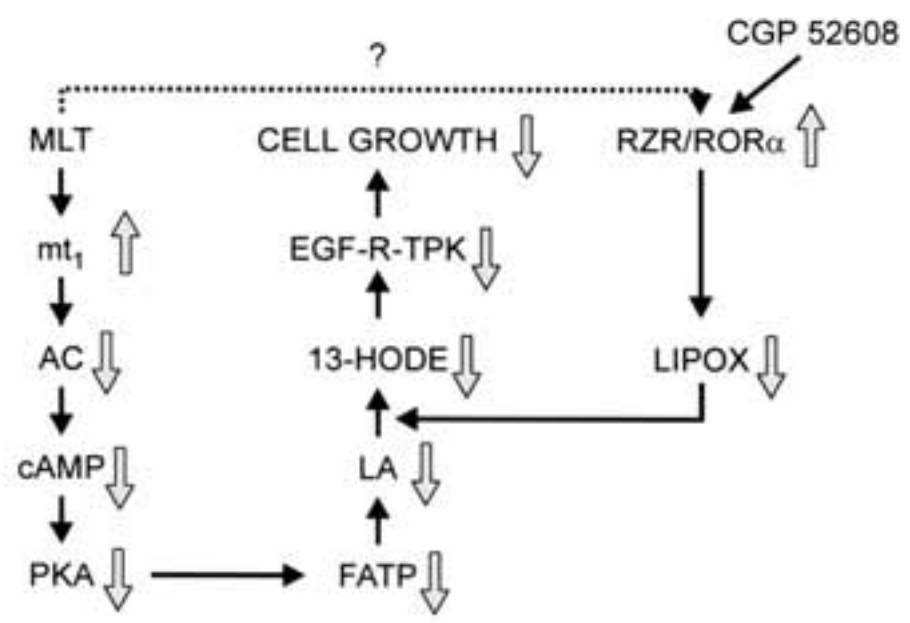

Fig. 2. The putative mechanisms of antiproliferative action of melatonin.

MLT – melatonin; mt_1 – membrane melatonin receptor 1a; AC – adenylate cyclase; cAMP – cyclic adenosine 3'5'-monophosphate; PKA – cAMP-dependent protein kinase;
FATP – fatty acids transporting protein; LA – linoleic acid; 13-HODE – 13-hydroxyoctadecadienoic acid; EGF-R-TPK – epidermal growth factor receptor tyrosine protein kinase; RZR/RORα – nuclear retinoid Z receptor/retinoid acid receptor related orphan receptor α; LIPOX – 5-lipoxygenase; CPG 52608 – RZR/ROR receptors agonist.
––stimulation; ⊥–inhibition.

the cell proliferation of Colon 38 cells in vitro and in vivo with very similar potency. A thiazolidinedione derivative CGP 52608 has been found to specifically activate the nuclear RZR/ROR receptors [19]. It has been suggested that melatonin is an endogenous natural ligand of these nuclear receptors [20]. If the latter is true, the nuclear signalling might constitute an alternative pathway for antiproliferative action of melatonin. However, the interaction of melatonin with RZR/ROR receptors is still controversial [21, 22]. Irrespectively of this controversy, RZR/ROR receptors were found to repress the 5-lipoxygenase gene [23] and in this way to contribute to the drop of the intracellular 13-HODE.

The putative model of the antiproliferative action of melatonin at the cellular level via membrane and nuclear receptors is presented in Fig. 2. Recently, it has been also found in our laboratory that melatonin increases the number of apoptotic nuclei (revealed by means of the so-called TUNEL method) in murine Colon 38 tumors [24]. This finding indicates that melatonin exerts its oncostatic effect not only via inhibition of tumor cell proliferation but also via induction of apoptosis.

Melatonin and human malignancy

Although there is some indication that the pineal gland may also play a role in human malignancy, studies on the relationship between melatonin and neoplastic disease in humans are scarce and contradictory. Serum or urinary melatonin concentrations in neoplastic patients have been reported to be low, high or normal, when compared to healthy subjects [see 6, 25]. It should be emphasized, however, that in many earlier studies melatonin measurements were often performed at one time point only, mostly during the daytime, and therefore these reports are not meaningful. Moreover, the differences could be due to various histological types of tumors, limited sampling approaches, different stages of the neoplastic disease, different states of therapy, and not tightly controlled age-matching. Studies of detailed diurnal rhythm of melatonin secretion should be performed on these types of malignant tumors in which alterations in daytime melatonin levels have been reported.

Some studies on melatonin diurnal profiles revealed alterations in melatonin concentrations during a 24-h cycle. Depression in amplitude of the nocturnal peak of either serum or urinary melatonin concentrations has been demonstrated in patients with primary breast cancer [26–28]. Moreover, stage-dependency in melatonin levels has been found; the peak declined with tumor size (by 23% in T1 stage, 53% in T2 stage, and 73% in T3 stage) [27]. However, in recurrent breast cancer, melatonin concentrations were similar or even higher in comparison to healthy subjects [27, 29, 30]. It has been also shown that melatonin levels were lowered only in patients with estrogen-positive tumors, but not in those with estrogen-negative tumors [28]. The observation of a

negative correlation between the estrogen receptor status of the tumor and melatonin concentrations has not been, however, confirmed by Bartsch et al. [29].

Decreased nocturnal serum melatonin concentrations and urinary 6-sulfatoxymelatonin excretion have been found in patients suffering from prostate cancer in comparison to patients with benign prostate hyperplasia [31, 32]. Lack of nocturnal rise in plasma melatonin levels has been reported also in colorectal carcinoma [33]. Recently, we have found depressed nightime serum melatonin concentrations in women suffering from adenocarcinoma of the uterine corpus [34].

Based on the observation that the percentage of objective responses to chemotherapy was significantly higher in patients with chemotherapy-induced melatonin increase of more than 20 pg/ml, measured at 09:00h than in those with no melatonin increase, Lissoni et al. [35], suggested that measurement of melatonin levels could be considered as a predictor of clinical response to chemotherapy.

Antiproliferative properties of melatonin that have been shown in many experimental studies constituted the rationale for its possible therapeutic use in clinical oncology. Some clinical trials have been performed in treating neoplastic patients who failed to respond to standard anticancer therapy, in patients with untreatable solid neoplasms, and in patients with advanced cancer, eligible for supportive care only [30, 36–38]. Melatonin administration resulted in stabilization of the disease in some cases, and an improvement in performance status. Moreover, it has been shown that melatonin amplifies the therapeutic effect of cytokines, especially interleukin-2 in cancer patients [14, 15]. These preliminary results suggest that, although melatonin can not be recommended as an oncostatic agent, the possibility of its use in the therapy of human neoplastic disease, in order to improve the patients' performance status, should not be ruled out.

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