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A Review on Cancer Progression - Related Pineal Endocrine Deficiency: Possible Mechanisms and Clinical Implications

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Abstract

Several experimental studies have demonstrated the existence of a natural immunobiological resistance cancer growth, which is mediated by both immune and neuroendocrine mechanism. Moreover, further researches have shown that the pineal gland plays a fundamental role in the natural antitumor resistance, by representing the most important anti-cancer organ in the human body. The anticancer property of the pineal gland is due to the production of several anticancer molecules, including the indole hormone melatonin (MLT), which represent the most investigated pineal hormone, other indoles, such as the 5-methoxytryptamine, and beta-carbolines. MLT has been proven to play anticancer activity through several mechanisms, consisting of cytotoxic antiproliferative action and stimulation of the anticancer immunity, by promoting IL-2 production by T helper lymphocytes and IL-12 secretion by dendritic cells. Cancer-progression has appeared to be associated with a progressive decline in MLT nocturnal production. Then, the pineal failure would constitute the main cancer-related endocrine deficiency. Preliminary clinical studies have demonstrated that MLT therapy at mild pharmacological doses may prolong the survival time of metastatic cancer patients, for whom no other effective standard therapy was available, and improve their clinical status. Therefore, a neuroendocrine therapy with MLT and other pineal hormones could constitute a new strategy in cancer treatment, either as a substitutive therapy of cancer-related MLT diminished endogenous production, or to employ its antitumor pharmacological properties.

Keywords: Melatonin; Methoxytryptamine; Neuroendocrine therapy; Pineal gland

Introduction

It is known since more than 30 years that pinealectomy or pineal damage may predispose to cancer development and stimulate cancer dissemination in the presence of a locally limited tumor [1]. However, it was only with the identification of the hormones produced by the pineal gland that it became possible to investigate the mechanisms responsible for its fundamental anticancer activity, in particular after the experimental demonstration of the antitumor properties of its most investigate hormone, melatonin (MLT) [2]. However, it is known that MLT is only one of at least three other indole hormones released by the pineal gland, one of them, the 5-methoxytryptamine (5-MTT) has appeared to exert an in vitro antitumor activity superior to that of MLT itself [3]. In fact, the exogenous administration of MLT has been proven to only partially abrogate the pro-tumor effect of pineal surgical removal or damage [4]. Several studies have confirmed that the pineal gland plays a fundamental role in the maintenance of the natural biological resistance against cancer development [5], and this evidence justifies the elaboration of clinical studies to investigate the possible therapeutic role of MLT and the other pineal indoles in the treatment of human neoplasms. Unfortunately, even though the pineal is one of the seven major endocrine glands, until now it has not been taken into an adequate consideration by the Endocrinologists. On the same way, despite the well demonstrated anticancer role of the pineal gland and the antitumor properties of its most investigated hormone MLT in several experimental conditions, only very few oncologists are using MLT in the clinical treatment of tumors, at least as a palliative therapy. Then, it is essential that the knowledge of pineal function has to involve both Endocrinologists and Oncologists, on the basis of the evidence that the pineal gland may produce several anticancer immunomodulating endocrine molecules, including MLT itself, the 5-MTT, the peptide epithalamin [1-3], and a great number of beta-carbolines, which are provided by both antitumor action and mind expansion activity, the so-called psychedelic effect, the most active of them is pinoline, corresponding to the 6-methoxy-1,2,3,4-tetrahydro-beta-carboline [6], even though the antitumor mechanisms have been well investigated and established for the only MLT. By summarizing, the pineal gland plays an antitumor activity by exerting both cytotoxic anti-proliferative effects and an immunostimulating activity on the anticancer immunity by acting as a central modulator of the cytokine network [7]. Moreover, because of the anticancer properties of several pineal molecules, as well as their involvement in the chemical mediation of emotions and consciousness states, the pineal gland would constitute the main link between psychospiritual life and cancer onset and progression [8]. The importance of the pineal gland in the natural resistance against cancer is also confirmed by the fact that all conditions, which have been proven to predispose to cancer, including stress, depression and exposure to magnetic fields, are characterized as a common evidence by the occurrence of alteration in the pineal endocrine function [9,10].

The pineal function in human neoplasms

The main cancer progression-related endocrine failure referred in the literature would be represented by the pineal deficiency, which could contribute to cancer dissemination itself because of its physiological anti-cancer role [2]. In fact, cancer progression is associated with a progressive decline in the nocturnal production of MLT, with a following disappearance of the physiological light/dark

circadian rhythm of MLT itself, which is mainly produced by the dark period of the day [11]. However, pineal histological damages have been observed in patients died from cancer [10]. Therefore, MLT reduced production would not be the only pineal endocrine defect, but it could be the simple expression of a general pineal failure involving the all molecules produced by the pineal gland. Moreover, because of its involvement in brain neurochemical processes and in the modulation of the different neurotransmissions and the psychological behaviour [2], at least some cancer-related symptoms, including depression, asthenia, anorexia and anaedonia, would be the consequence of the pineal failure. Finally, MLT deficiency has appeared to be associated with a poor prognosis [11]. On the contrary, tumor cell expression of MLT receptors (MT-R) may predict a more favourable prognosis [12]. On the same way, a progressive reappearance of MLT light/dark rhythm on cancer therapy is associated with a control of cancer growth (13) The light/dark rhythm of MLT may be clinically investigated by collecting blood samples at least at the four main moments of the photoperiod, early in the morning, at noon, in the afternoon and at night [2], or more easily by measuring the diurnal and the nocturnal urinary excretion of its main metabolite, the 6-sulphatoxymelatonin (6-MTS) [14]. The mechanisms responsible for the progressive decline in MLT nocturnal production with cancer dissemination are still to be better investigated and established. However, it could depend at least in part on a direct action of tumor cells themselves through the release of molecules able to inhibit the pineal endocrine functions. In fact, it has been demonstrated that tumor cells may actively produce the enzyme 2,3-indole-dioxygenase (IDO), which allows a depletion of tryptophan content, which is essential for T helper-1 (TH1) lymphocyte activation, and whose deficiency may induce an evolution of TH1 cells into T regulatory lymphocytes (T reg) [15], that represent the main immune cells responsible for the suppression of the anticancer immunity through the activation of immune checkpoints, the most important of them ate the CTLA-4 and PD-1 [16]. Then, the same mechanism might explain the pineal deficiency, since tumor hyper-production of IDO would determine tryptophan deficiency also at pineal sites, with a following potential diminished production of the overall pineal indoles, being tryptophan their precursor. Cancer cell-induced decline in the endocrine function of the pineal gland is also suggested by the evidence of a restablishment of MLT light/dark rhythm after the removal of tumor mass in cancer patients [17].

Cancer-related neuroendocrine alterations

The systemic nature of the neoplastic disease is demonstrated by the occurrence of several endocrine alterations during cancer progression, some of them are characterized by a negative prognostic significance, in particular the evidence of hyper-cortisolemia or an altered cortisol circadian rhythm, which may predict a poor prognosis in several tumor histotypes including lung cancer, breast carcinoma and ovarian cancer [18,19], and that of abnormally high PRL levels in metastatic breast and prostate carcinomas [20,21], which is associated with a worse prognosis and with a lack of efficacy of the different anticancer therapies, being PRL a growth factor for both breast and prostate tumors [22]. GH also would exert a stimulatory action of cancer cell growth, by stimulating both the proliferation of cancer cells expressing GH-receptors, and tumor angiogenesis [23]. At present, however, it is still controversial whether the production of the various tumor growth factors, including EGF, FGF and PDGF, may be or not under a central stimulatory control played by GH itself, as well as demonstrated for IGF-1, whose hepatic production is induced by GH. A paradoxical response to GH to TRH has been described in cancer patients [24], by showing an altered neuroendocrine control of GH release by the pituitary gland in the neoplastic diseases. On the contrary, GH-RH antagonists have appeared to inhibit the angiogenic processes [25], by suggesting a stimulatory role also of GH-RH on tumor neo-angiogenesis. On the other hand, somatostatin, in addition to its inhibitory action on GH secretion, would play a direct inhibitory effect on the proliferation of cancer cells expressing somatostatin receptors, such as the neuroendocrine tumors. The antitumor action of somatostatin as a consequence of its possible inhibitory effect on the production of the various potential tumor growth factors is still controversial and to be demonstrated. Finally, MSH-alpha would act as growth factor for the malignant melanoma [26], and the evidence of abnormally high levels of MSH could negatively influence the prognosis of patients suffering from advanced melanoma.

In conclusion, because of the modulatory effect of the pineal gland on the hypothalamic-pituitary functions, as well as its fundamental role in the synchronization of the biological rhythms [2], the alterations of the endocrine secretions and their circadian rhythm, which may occur during cancer progression, could depend at least in part on an altered pineal function, as confirmed by the fact that MLT therapy in association with chemotherapy may restore a normal circadian rhythm of cortisol in cancer patients, who respond to the treatment [27].

The antitumor mechanisms of melatonin

At present, it is known that the clinical history of the neoplastic diseases may be synthetized into six main sequential phases, even though the recent cancer therapies and the Oncologists tend to consider the only cell proliferation induced by tumor growth factor receptor activation and by the angiogenic processes, as follows: 1) Concomitant existence of an immunosuppressive status [28], probably due to an altered psycho-neuro-endocrine control of the immune system rather than to a primary alterations of immune cell functions, which would be responsible for the evolution from the single transformed cell into a clinically evident tumor as a consequence of a decreased antitumor natural resistance; 2) Spontaneous or carcinogen-induced cancer cell transformation; 3) Alterations of connexines, which are the major components of the intercellular junctions [29], with following changes in the intercellular matrix; 4) Tumor neo-angiogenesis induced by changes in intercellular matrix content; 5) Tumor cell proliferation and production of several immunosuppressive substances, including TGF-beta [30], IL-10, IDO, and VEGF itself, which in addition to its angiogenic properties, may also exert immunosuppressive effects by counteracting dendritic cell maturation [31]; 6) FAS-L tumor expression [32], which induces the apoptosis of FAS-expressing T lymphocytes during tumor cell-lymphocyte contact. MLT is at present the only molecule existing in the nature, which has been proven to be able to counteract the all six major phases of the clinical course of the neoplastic diseases, including stress-related immunosuppression [28], cancer cell proliferation by exerting a direct cytotoxic action through the induction of the apoptotic process or the inhibition of tumor growth factor receptor activation [26], intercellular junction alterations [29], tumor angiogenesis [33], and tumor FAS-L expression. As far as the anticancer immunostimulatory activity of MLT is concerned, its immunomodulating proprieties would essentially consist of stimulation of IL-2 production by TH1 lymphocytes, promoting effect on IL-12 production by dendritic cells, inhibition of macrophage-mediated inflammatory-immunosuppressive events, and blockade of T reg generation and activation [34]. The antitumor antiproliferative action of MLT would

require tumor expression of MT-R, whereas its immunostimulatory activity is due to a direct action of lymphocytes and dendritic cells expressing MT-R. Therefore, MLT-induced objective tumor regressions reported in the literature in humans [26,35,36], event though generally rare, would have not to be considered as surprising events, by depending on well demonstrated biochemical mechanisms.

Pineal endocrine therapy of cancer with melatonin and other pineal molecules

The endocrine therapies of cancer available up to now commonly used in the medical treatment of human neoplasms are limited to the administration of anti-estrogens and aromatase inhibitors in breast cancer, to that of anti-androgens in prostate cancer, to that of LH-RH analogues to block the hypothalamic-pituitary-gonadal axis in both breast and prostate carcinomas, and to that of long.-acting somatostatin analogues in somatostatin receptor-expressing neuroendocrine tumors. Finally, corticosteroids and progestative agents are also employed in the palliative therapy of tumors. Therefore, the aim of the overall most commonly utilized endocrine therapies of cancer available up to now is the block of the action of potentially pro-tumor hormones, such as gonadal steroids. In contrast, the treatment of human neoplasms with the anticancer pineal hormones could constitute a new original kind of cancer endocrine therapy, consisting of the administration of endogenous antitumor hormones, such ads the pineal substances, rather than to act by blocking the action of endogenous hormones, which may potentially stimulate cancer cell growth. At present, however, the treatment of human tumors with pineal hormones provided by anticancer activity is almost limited to the administration of the only MLT, but there are some preliminary data also concerning the effects of pineal indoles other than MLT, such as 5-MTT [37]. In any case, even though very few randomized studies are available up to now, the clinical results on tumor therapy with pineal hormones are already sufficient to conclude that at least MLT is essential for both palliative and curative therapies of cancer [36]. In fact, it is known since many years that in experimental studies MLT may exert anticancer in vivo activity only it is administered during the dark period of the day, corresponding to the time of its maximal production in normal conditions, and at pharmacological doses [38], corresponding to a dosage of at least 20 mg/day in humans [26]. Moreover, preliminary clinical studies would suggest that the anticancer action of MLT is a dose-dependent phenomenon, and no toxicity occurred even at very high doses greater than 500-1000 mg/day [26]. From a clinical point of view, MLT has appeared to enhance the efficacy of several chemotherapeutic regimens and to reduce some their toxicities, in particular the thrombocytopenia [39], to enhance the efficacy of subcutaneous low-dose IL-2 in several tumor histotypes [40], to induce a stabilization of cancer growth and a prolongation of the survival time in untreatable metastatic solids tumor patients, for whom no other standard antitumor therapy may be available and with life expectancy less than 6 months or 1 year, also when it is given as a single agent, with potential tumor regressions at high doses, even though only in a less percent of patients [26,35]. At the other side from a palliative point of view, MLT at a dose of 20 mg/day has appeared to be effective in the treatment of cancer-related symptoms, for whom no other standard therapy may be available [36], including thrombocytopenia, cachexia, asthenia and hepatotoxicity, and in a less manner anemia and anorexia. On the contrary, MLT has no relevant efficacy in the treatment of neutropenia, and chemotherapy-induced alopecia and vomiting , whereas some effect has been described in the treatment of the anticipatory vomiting. On the contrary, at present no clinical study with 5-MTT alone has been performed, despite its in vitro antitumor activity superior to that of MLT itself [3]. However, preliminary clinical studies would suggest that 5-MTT at a dose ranging from 1 to 10 mg/day may amplify both antiproliferative and thrombopoietic activities of MLT [37]. Moreover, 5-MTT seems to exert anti-depressant effects superior to those played by MLT, whereas it has no hypnotic activity. On the contrary, MLT may be effective in the treatment of sleep disorders [2], and about one third of patients on MLT therapy referred a reappearance of the capacity of dreaming, by suggesting an involvement of MLT in the induction of REM phase of sleep. Finally, preliminary results with pinoline (unpublished data) would show a profound effect on mood and consciousness status in terms of antidepressant effect and expansion of mind.

Conclusions

The clinical investigation of the pineal gland could make the Endocrinology as the most olistic medical branch, the only one capable of explaining the interactions among endocrine, nervous and immune systems by representing the main human anatomic structure responsible for the complex processes of the psycho-neuro-endocrino-immune modulation, in an attempt to achieve a more adequate knowledge of the neurochemical mechanisms involved in cancer and in the psychiatric diseases.

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