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Review Article

Psycho Neuroendocrino Immune (PNEI) Therapy of Cancer Beyond Melatonin

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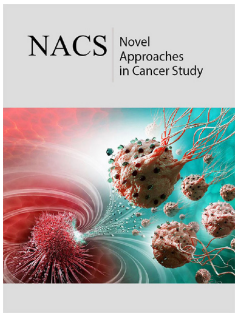

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Abstract

The recent advances in psycho-neuroendocrino-immunology (PNEI) have demonstrated the existence of a natural anticancer neuroendocrine system, mainly expressed by the pineal gland, endocannabinoid system, oxytocin, and Ang 1-7. Moreover, cancer progression has appeared to be associated with a progressive decline in the pineal and cannabinoid system functions. A new approach to cancer therapy according to a PNEI strategy could simply consist of the correction of the main cancer-related neuroimmune and neuroendocrine alterations through the exogenous administration of the same human natural anticancer molecules, whose production declines with cancer progression. PNEI therapy of cancer, because of its complete lack of toxicity, could be applied also to patients, who failed to respond to the conventional anticancer treatments. Most data available up to now regard the treatment with the pineal anticancer hormone melatonin (MLT), whose efficacy has been proven to be a dose-dependent phenomenon. Preliminary results with other human antitumor molecules, mainly the pineal indole 5-MTT, cannabinoids, oxytocin and probably in particular Ang 1-7, could further amplify the already interesting results obtained with high-dose MLT alone in untreatable advanced cancer patients.

Keywords: Angiotensin 17; Cannabinoids; Melatonin; Methoxy tryptamine; Neuroimmunomodulation; Oxytocin, PNEI

Abbreviations: *Ang 1-7: Angiotensin 1-7; CBD: Cannabidiol; 5-MTT: 5-Methoxytryptamine; MLT: Melatonin; OT: Oxytocin

Introduction

Between the two opposite conditions of curative and palliative therapy of cancer, it has been recently demonstrated the possibility of a third way of treatment, consisting of the administration of natural nontoxic anticancer molecules drawn from the vegetal world or human body itself. At present, the main investigated anticancer natural molecule consists of Melatonin (MLT), which is present in both plants and the human body, where it is mainly released from the pineal gland according to a circadian rhythm, with a high production during night and low levels during the day [1]. In fact, it has been known for more than 50 years that the pineal gland MLT plays an anticancer action. Experimental conditions have shown that pinealectomy enhances the frequency of both spontaneous and carcinogen-induced tumor development. MLT exerts an anticancer action through at least three fundamental mechanisms, consisting of direct antiproliferative cytotoxic action, antiangiogenic activity and stimulation of the anticancer immunity [2], which is mainly mediated by IL-2 [3] and IL-12 [4], and suppressed by TGF-beta [5], IL-17 [6] and other inflammatory cytokines [7]. Studies have demonstrated that MLT is not the only anticancer principle of the pineal gland, since MLT alone has appeared to reduce, but not completely abolish the pro-tumoral effect of pinealectomy [8]. In fact, at least another indole hormone, the 5-Metoxytryptamine (5-MTT) [9] and several beta-carbolines, such as 6-methoxy-1,2,3,4-tetra-hydro-beta-carboline, the so-called pinealine [10], have appeared to exert important antitumor activities. However,

the antitumor mechanisms of 5-MTT and pinealine needs to be better investigated and established. While MLT is mainly produced during the night, 5-MTT would represent the main pineal indole hormone released during the day [3]. On the contrary, the circadian secretion of pinealine needs to be better investigated and defined. Further biological studies have documented the existence of other anticancer molecules within the human body, such as neurohypophyseal hormone oxytocin [11], the cardiac hormone Atrial Natriuretic Peptide (ANP) [12], somatostatin for the only neuroendocrine tumours [13], the endocannabinoid agents [14], including cannabinoid agonists and inhibitors of the Fatty Acid Amide Hydrolase (FAAH), the enzyme involved in cannabinoid degradation [14], and more recently Angiotensin 1-7 (Ang 1-7), the peptide produced by ACE2 [15,16]. Unfortunately, despite the evident anticancer role of the pineal gland and MLT, few clinical studies have been performed up to know to evaluate the potential anticancer activity of MLT in human neoplasms, at least in untreatable patients could be considered [17]. In any case, it has appeared that the anticancer action of MLT in humans is a dose-dependent phenomenon [18], since high-dose MLT, such as 100mg/day in the evening, has been proven to exert an anticancer action superior to that obtained at a lower dosage in advanced cancer patients eligible for the only palliative treatment. Then, high-dose MLT at 100mg/day could be considered as the recommended therapy for cancer with natural molecules provided by antitumor and immunomodulating activity. This is the only antitumor complementary treatment with a documented capacity of prolonging the survival time in patients with disseminated cancer, who failed to respond to the standard anticancer therapies and have a life expectancy of less than 6 months [19]. In contrast, most other studies with a complementary approach to cancer therapy with endogenous human molecules or potential anticancer plants, including Aloe, curcumin and mushrooms, have been limited to only the evaluation of some clinical parameters, but not towards survival period [20]. Therefore, from a complementary point of view, the clinical question consists of how to enhance the antitumor efficacy of high-dose MLT by other human natural anticancer molecules according to the principle of MLT by considering all human anticancer molecules, including pineal hormones other than MLT, endogenous cannabinoids, oxytocin, ANP and Ang 1-7. Unfortunately, with respect to the classical medical oncology focalized on the characteristics of each single organ site of tumor, most complementary medicines, despite their apparent revolutionary conceptions, tend to research the reason of cancer within the characteristics of the single cell and its substructures, namely mitochondria, instead of considering the cellular alterations as a consequence of an altered central regulatory control exerted by a cytokine network and its neuroendocrine regulation, which may be piloted into an anti-inflammatory, anti-neoplastic and anti-angiogenic way by the pineal gland, the endocannabinoid system, the endocrine cardiac hormone ANP and Ang 1-7, whose actions are opposite of the endothelin-1 (ET-1-angiotensin II (Ang II) functional axis, which on the contrary exerts inflammatory, pro-tumoral and angiogenic effects [21-23].

Pineal Anticancer Molecules Other than Melatonin

According to the experimental data available up to now, the two main pineal molecules provided by anticancer action other than MLT would be represented by 5-MTT [9] and pinealine [10]. The pineal hypofunction would represent the main cancer progression-related endocrine deficiency [24]. Pineal hypofunction does not only rely on MLT, but rather on the whole endocrine activity of the pineal gland, including the secretion of the two other most known pineal anticancer hormones, 5-MTT and pinealine. *In vitro*, 5-MTT has appeared to have an antitumor cytotoxic action superior to that of MLT [9]. Moreover, preliminary clinical studies seem to suggest that 5-MTT in association with MLT may further enhance the therapeutic antitumor action of MLT and exert an antidepressant activity superior to that of MLT alone [25]. The clinical studies with pinealine are more preliminary than those concerning 5-MTT [10]. In any case, it appears that pinealine, as well as other beta-carbolines, in addition to their anticancer role may also exert important psychic effects in terms of both expansion of consciousness and antidepressant activity, which could further improve a patient's quality of life, even though an anxiogenic effect has been claimed by some patents [10].

The Rationale of Cannabinoids in Cancer Therapy

Cannabinoids have been recently introduced within the palliative therapy of cancer because of their anticachectic, anti-anorexic, anti-emetic, anti-inflammatory and antalgic effects [14,26]. However, several studies have demonstrated that cannabinoids may exert not only palliative effects, but also a direct antitumor cytotoxic effect by inducing apoptosis of cancer cells [14]. Within the cannabinoid group, we may include both cannabinoids' agonists and FAAH inhibitors [15], which may allow an increase in cannabinoid endogenous function by counteracting cannabinoid degradation. The main endogenous cannabinoid agonists consist of arachidonyl-ethanol-amide and 2-arachidonyl-glycerol, while the main exogenous cannabinoid agonist is the Tetra-Hydro-Cannabinol (THC) from Cannabis plant [14]. On the other hand, the main endogenous and exogenous FAAH inhibitors are represented by Palmitoyl-Ethanol-Amide (PEA) [27] and Cannabidiol (CBD) from Cannabis plants [14], respectively. The use of cannabinoids in cancer therapy is justified by at least three reasons, including a direct cytotoxic cytostatic antitumor effect, an anti-angiogenic activity, and a fundamental anti-inflammatory action due to the inhibition of IL-17 secretion [14,28], which would represent the main pro-tumoral inflammatory cytokine effect, due to its direct stimulatory effect on cancer cell proliferation by enhancing their biological malignancy [6]. In fact, IL-17 expression has appeared to predict a worse prognosis in most tumour histotypes, including breast cancer, gastrointestinal neoplasms, and lung cancer [29-34]. Further studies have suggested that cancer progression is associated with a progressive decline in the endocannabinoid function, which could explain cancer-related anhedonia, because of the fundamental role of cannabinoids in the perception of pleasure [35]. This finding is not surprising, since the pineal and brain cannabinoid system would constitute a functional

axis involved in the control of the inflammatory response and cell proliferation [36]. Cancer-related pineal hypofunction would allow a progressive concomitant endocannabinoid deficiency. Therefore, the employment of cannabinoids in cancer would also deserve a substitutive significance to correct cancer-related endocannabinoid deficiency. According to preliminary clinical studies, it has been observed that cannabinoids, including CBD and THC, may be successfully associated with MLT in the treatment of glioblastoma [37].

The Rationale of Oxytocin in Cancer Therapy

The rationale of the neurohypophyseal hormone oxytocin used in cancer therapy is linked to its anti-proliferative and anti-angiogenic actions against several tumour histotypes, mainly brain tumours and gynaecologic neoplasms [11,38]. Oxytocin would also exert anti-inflammatory and immunomodulating effects, whose nature needs to be better investigated. Oxytocin at a dose of 2mg twice/day has appeared to enhance the therapeutic effects of MLT in the treatment of autism [39], while their combination in cancer therapy needs to be better analysed. In addition, oxytocin has also appeared to exert antidepressant effects and to improve the affective relationships [40]. Oxytocin as well as MLT, could be potentially used in the treatment of most tumor histotypes, except prostate carcinoma [41], because of the controversial results reported in the literature about oxytocin action on prostate cancer growth. In contrast, the other neurohypophyseal hormone, vasopressin or Antidiuretic Hormone (ADH) has appeared to exert pro-tumoral angiogenic effects [42].

The Role of Atrial Natriuretic Peptide in Cancer Therapy

In addition to its cardioprotective, hypotensive and natriuretic effects, the cardiac hormone ANP has been proven to play an antineoplastic action, due to its antiproliferative, anti-angiogenic and anti-inflammatory activities [14]. At present, however there is no clinical study involving oncologic patients with ANP, whose use is limited by its too low half-life. Moreover, it is known that the evidence of hyponatremia is a negative prognostic factor in patients with disseminated cancer [43], even though the reason is still unclear. In any case, hyponatremia would be the consequence of an enhanced fluid redemption, probably due to an increased ADH secretion in association with a diminished ANP production, which in contrast stimulates water and sodium elimination [44]. Because of the antitumor activity of ANP and the pro-tumoral by ADH, the negative prognostic significance of hyponatremia could simply depend on an unbalance between ANP and ADH endogenous production. Finally, ANP secretion has been shown to be stimulated by Ang 1-7, as well as by Ang 1-5 [45]. The administration of Ang 1-7 could produce a concomitant increase in ANP blood concentrations. On the contrary, ET-1, which may be released by endothelial and endocardial cells, has appeared to exert pro-tumoral effects, which are due to its stimulatory action on cancer cell proliferation and angiogenesis, as well as to its inflammatory immunosuppressive effects on the anticancer immunity.

The Anticancer Activity of Angiotensin 1-7

Ang 1-7 is a part of the Renin-Angiotensin System (RAS) [46,47]. In more detail, angiotensinogen produced by liver is transformed into angiotensin I (Ang I) by the protease renin produced by the renal juxtaglomerular cells. Ang I may be transformed into Ang II by ACE or into Ang 1-7 by ACE2, which is also able to transform Ang II into Ang 1-7. In addition to its hypotensive and cardioprotective activity, ANG 1-7 has been proven to exert anticancer, anti-inflammatory, anti-fibrotic and immunostimulatory effects on the anticancer immunity [16,48]. As far as its anticancer role, preliminary clinical studies would suggest that Ang 1-7 may be potentially active against most tumor histotypes, including sarcomas and the most aggressive malignancies, such as glioblastoma and triple negative breast cancer [48,49]. In addition, Ang 1-7 may improve the anticancer immunity by stimulating lymphocyte production and inhibiting the monocyte-macrophage system [48]. Ang 1-7 could enhance MLT-induced stimulation of lymphocyte functions. Ang 1-7 could be also useful in the palliative therapy of cancer because of its anti-asthenic, anti-cachectic and antinociceptive effects [49]. The antitumor action of Ang 1-7 is due to an antitumor mechanism, including direct antiproliferative cytotoxic action, anti-angiogenic activity, and anti-inflammatory immunostimulatory effect, which is due to the inhibition of inflammatory cytokine secretion, including that of IL-17, and to a stimulation of lymphocyte proliferation [47]. Even though at present there is no study carried out to evaluate Ang 1-7 secretion in early or advanced cancer patients, it is probable that cancer progression may be characterized by a progressive decline in Ang 1-7 blood concentrations, as already demonstrated for pineal and endocannabinoid system functions [24,35], IL-17, whose secretion is often abnormally high in advanced cancer patients [29-34], may inhibit ACE2 expression and Ang 1-7 production [50]. The antifibrotic action of Ang 1-7 [16,47,51], which is due to the inhibition of TGF-beta-induced fibrosis, may also contribute to its anticancer activity, since tumor-related fibrosis due to TGF-beta [5] would inhibit the cell-cell contact between cancer cells and cytotoxic lymphocytes. Finally, because of the immunosuppressive activity of TGF-beta due to inhibition of the secretion and activity of the two main antitumor cytokines in humans, including IL-2 and IL-12 [5], may explain the anticancer activity of Ang 1-7.

Preliminary Guidelines of Melatonin and Other Neuroimmune Regimens in Cancer Therapy

MLT still remains the main natural anticancer agent in the PNEI therapy of cancer, being the most investigated molecule in both experimental and clinical conditions, as well as because of its complete lack of toxicity and its low social medical cost. Other studies in the area of the complementary therapy of cancer would have to be performed in an attempt to improve the already interesting results achieved by high-dose MLT alone, 100mg/day in the dark period, also in patients for whom no other conventional antitumor treatment may be available [19]. The first improvement may be achieved by the association of the other fundamental anticancer pineal hormone, the 5-MTT [9,25], generally at a dose ranging from 10 to 50 mg/day and constantly during the dark

period of the day, since the dark period-induces activation of the N-acetyltransferase and would transform 5-MTT into MLT itself. A second fundamental improvement may be obtained through the association with cannabinoid agents, including CBD or PEA [26-28], because of its cancer-related endocannabinoid deficiency and the physiological connections occurring between the pineal gland and cannabinoid system in the brain level. CBD and PEA may be administered at a dose of 10 mg and 600mg/twice day, respectively either alone or in combination. After progression under MLT alone at 100mg/day or in association with 5-MTT and cannabinoids in patients, who were already untreatable and suitable for the only palliative therapy prior to MLT therapy. Further neuroimmune regimens may be proposed in relation to tumour histotype by increasing MLT dose until 1,000mg/day or more, and 5-MTT until 100mg/day or through the combination with one of the other endogenous anticancer molecules, including oxytocin [11] or Ang 1-7 [16], at a dose of at least 2mg twice/day for oxytocin and at least 0.5mg twice/day for Ang 1-7. Oxytocin would be particularly indicated for gynaecologic breast and brain tumours, while Ang 1-7 would seem to be effective in most tumour histotypes. Moreover, even though most clinical studies involving MLT therapy in the treatment of metastatic advanced cancer patients, some preliminary suggestions may be proposed also in less advanced patients, either as an adjuvant therapy or in association with chemotherapy to improve its efficacy and reduce its toxicity. In more detail, MLT could be given at a dose of 10-20mg/day in the evening as an adjuvant therapy in cancer patients treated by radical surgery, and at a dose of 20-50mg/day in association with chemotherapy to enhance its efficacy in particular by counteracting chemotherapy-induced suppression of lymphocyte function [52-54]. The algo-rhythm of PNEI approach to a potential cancer cure in advanced cancer patients, who failed to respond to conventional therapies starting from MLT administration, is illustrated in Figure 1.

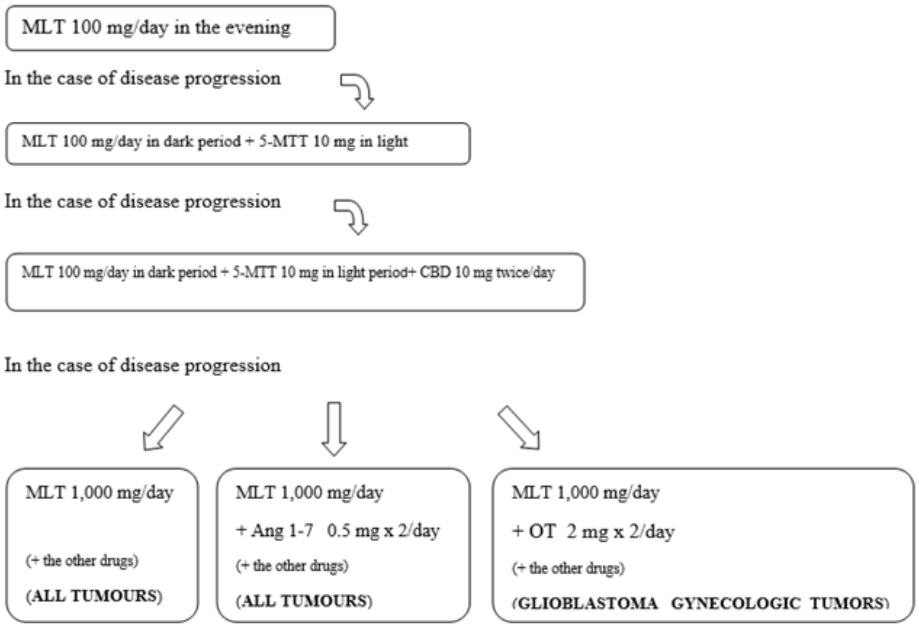

Figure 1: Proposal of an algo-rhythm with Melatonin (MLT) and MLT- containing neuroimmune regimens in the treatment of advanced cancer patients, who failed to respond to the conventional anticancer therapies.

*Ang 1-7: Angiotensin 1-7; CBD: Cannabidiol; 5-MTT: 5-methoxytryptamine; MLT: Melatonin; OT: Oxytocin

Conclusion

Because of the possibility to control cancer growth by a neuroimmune approach with natural human anticancer molecules, such as the pineal hormone, oxytocin, cannabinoids and Ang 1-7. The separation between curative and palliative of cancer would have to be abrogated. In any case, the role of chemotherapy remains fundamental in destroying the major number of cancer cells, since the efficacy of every kind of neuroimmune anticancer approach is greater in the presence of a low tumour burden.

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