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The Psychoneuroimmune Pathogenesis of Cancer: Therapeutic Strategy to Normalize Cancer-Related Brain Unbalance Between Hyperfunction of Opioid System and Hypofunction of Cannabinoid-Pineal Axis by Antitumor Pineal Indoles, and the Mu-Opioid Antagonist Naltrexone in Untreatable Advanced Cancer Patients

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Abstract

Today it is known that *in vivo* the immune reactions cannot be separated from their neuroendocrine regulation, which is mainly mediated by the brain opioid system and by the functional unit constituted by brain cannabinoid system and pineal gland. The opioid system is active in stress and depression conditions, and it mediates the suppression of the anticancer immunity. On the contrary, the pineal-cannabinoid functional system, which is involved in the perception of pleasure and mind spiritual expansion, stimulates the anticancer immunity, by playing a fundamental role in the natural resistance against cancer. Then, cancer progression would be due to an unbalance between hypoactivity of the cannabinoid-pineal system and hyperactivity of the opioid system, which could be corrected by a substitute therapy of the main antitumor pineal hormones, including Melatonin (MLT) and 5-Methoxytryptamine (5-MTT) in association with cannabinoids to normalize the cannabinoid-pineal function, and by the administration of opioid antagonists, such as Naltrexone (NTX) to counteract the opioid hyeractivity. The present study was carried out to evaluate the influence of a concomitant NTX administration in advanced cancer patients, for whom no other conventional anticancer therapy was available, and who had progressed under a complementary therapy with the only pineal hormones. The study included 14 untreatable solid tumor cancer patients. All drugs were given orally every day without interruption according the following schedule: MLT at a dose of 100 mg/day in the dark period of the day, 5-MTT at 10 mg/day in the light period of the day, and NTX at 20 mg in the evening. A control of tumor growth was achieved in 8/14 (57%) patients, and it was associated with an improvement in Lymphocyte-To-Monocyte Ratio (LMR). These preliminary results would suggest that the concomitant block of the opioid system by NTX may allow a control of tumor growth superior to that, which may be obtained with the only pineal antitumor hormones, and this effect would be mediated at least in part by an improvement in the immune status, as suggested by the rise in LMR values. Further promising antitumor results could be achieved with the association of cannabinoid agonists, or with Fatty Acid Amide Hydrolase (FAAH) inhibitors to enhance brain cannabinoid content.

Keywords: Cancer; Cannabinoid system; Melatonin; Naltrexone; Opioid system; Pinealgland

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Introduction

The different hypotheses concerning the possible influence of the psychological and spiritual status on cancer onset and development[1-3], have finally found their confirmation on scientific bases after the discovery of the fundamental role of the immunity in tumorcell growth inhibition[4], and the existence of a psychoneuroendocrine regulation of the immune responses, including the anticancer immunity[5-8]. Then, the main responsible for the natural biological resistance against cancer is the immune system, whose function however, is under a neuroendocrine regulation. Despite the great complexity of the NeuroImmunoModulation (NIM), it is possible to identify two major brain interneuronal immune modulatory systems, consisting of the opioid system[5,6], and the endocannabinoid system[7,8] through its functional connections with the pineal gland[9,10]. The opiod system, namely through a mu-opioid receptor, may inhibit the antitumor immunity[5,6], whereas the pineal-cannabinoid system axis stimulates the antitumor immunity[7,8,11]. The opioid system is active in stress, depression, and anxiety conditions, whereas the pineal-cannabinoid axisis operating in the perception of pleasure and spiritual expansion of mind. This evidence may constitute the explanation of the protumoral influence of stress and depression, and on the other side the preventing antitumor effect of pleasure and spirituality on tumor growth[3]. In more detail, the mu-opioid agonists, such as beta-endorphin and morphine, have been proven to play a pro-tumoral action through several mechanisms, including a direct proliferative activity, an angiogenic action, and a suppression of the antitumor immunity by inhibiting the secretion of IL-2 and IL-12, which represent the main anticancer cytokines in humans, respectively from T Helper-1 (TH1) lymphocytes, and by stimulating that of immunosuppressive cytokines, namely TGF-beta and IL-10, from regulatory T lymphocytes (T reg)[5,6]. On the other hand, both pineal and brain cannabinoid system play a natural anticancer activity[9-11]. The pineal gland has appeared to represent the main immunomodulating organ in the human body by modulating the cytokine network[11-14] through the light/dark circadian release of the indole Melatonin (MLT)[11], other less investigated indole, suchas the 5-Methoxytryptamine (5-MTT)[15], and beta-carbolines, namely the pinealine[16], all provided by anticancer activity, even though the mechanisms of action have been clarified for the only MLT. The pineal is the main anticancer organ in humans, and it counteracts tumor growth through several mechanisms, including a direct antiproliferative cytotoxic action, an anti-angiogenic activity, and an antitumor immunostimulatory effect, namely consisting of a direct stimulation of IL-2 and IL-12 secretions[11-14], while the cannabinoid agents would play an anticancer activity namely by a direct inhibition of cancer cell proliferation, whereas their effects on the antitumor immunity are still controversial[7,8]. The pineal gland may modulate the activity of both brain opioid and cannabinoid systems, but the pineal gland would namely consitute an unique fundamental functional axis with the cannabinoid system in mediating the perception of pleasure and the spiritual expansion of consciousness through a reciprocal stimulatory influence, since CB1 cannabinoid agonists may directly stimulate MLT release from the pineal gand[9], and on the other side MLT has been proven to contribute to the inhibition of Fatty Acid Amide Hydrolase (FAAH)[10], the enzyme responsible for cannabinoid degradation[7,8], with a following increase in brain cannabinoid content. Then, the functionless of cannabinoid-pineal system constitutes a fundamental requirement for the status of health. The recent advances in Psycho Neuro Endocrino Immunology (PNEI) researches have shown than cancer progression is associated with a progressive unbalance between brain opioid and endocannabinoid systems, consisting of the association between hyperfunction of the opioid system and hypofunction of the cannabinoid system[7,8,17]. The cannabinoid hypofunction would be at least in part a consequence of the progressive decline in the pineal function with cancer progression, which constitutes the main cancer-related endocrine deficiency[11,18] because of the interactions occurring between pineal and cannabinoid system[9,10]. This unbalance would already explain cancer progression, because of the protumoral role of the opioid system and the anticancer one of the cannabinoid system. The existence of a cancer-related brain opioid system hyperactivity is documented by the evidence that the concomitant administration of the mu-opioid antagonist Naltrexone (NTX) may abolish the promoting effect of stress on cancer development[17]. On the other side, the occurrence of cancer-related brain cannabinoid system hypofunction would be suggested by the evidence of a progressive decline in pleasure perception, the so-called anaedonia, with tumor progression, because of the fundamental role of the cannabinoid system in the perception of pleasure, including appetite and sexual interest[7,8]. The endogenous cannabinoid system may be clinically investigated by measuring the blood or liquoralconcentrations of the two main endogenous cannabinoids, the Arachidonyl-Ethanol-Amide (AEA), the so-called anandamide because of its psychedelic effects, and the 2-Arachidonyl-Glycerol (2-AG), or in a more synthetic manner by the simple detection of the blood levels of FAAH, the main enzyme involved in cannabinoid metabolism and degradation[7,8,19], since it has been shown that high blood levels of FAAH are associated with abnormally low concentrations of both AEA and 2-AG, by reflecting a condition of cannabinoid hypofunction, whereas low FAAH levels allow increased cannabinoid concentrations[20], as an expression of cannabinoid hyperactivity. Moreover, it has been shown that the evidence of an enhanced FAAH synthesis or activity, which allows an endogenous cannabinoid deficiency, may induce a chronic inflammatory status[21], because of the anti-inflammatory activity of the cannabinoid system, mainly due to an inhibition of IL-17 secretion from TH17 lymphocytes[7,8]. Finally, it has been shown that the inflammatory response induced by the increased levels of FAAH may exert a negative prognostic significance in cancer, cardiovascular diseases, and neurodegenerative pathologies[21]. On the contrary, the inhibition of FAAH synthesis, with a following increase in the endogenous content of cannabinoids, has been proven to exert a therapeutic action in several human diseases by counteracting the inflammatory response[19-21]. Therefore, in addition to its importance in the perception of pleasure and consciousness status,the endocannabinoid system would play a fundamental role in maintaining the status of health, including the cardiovascular function and the immuno-inflammatory response. At present, one of the most simple FAAH inhibitors is represented by the same Cannabidiol (CBD), the non-psychotropic agent of Cannabis[7,8,22]. On the contrary, no study has been performed up to now in an attemp to evaluate the influence of the pineal gland and its main hormone

MLT on FAAH synthesis and activity. On the same way, no study has been carried to investigate the interactions occurring between FAAH activity and heart endocrine function, namely consisting of the secretion of atrial natriuretic peptide [ANP] and endothelin-1 [ET-1]. The anti-inflammatory action of ANP[23] and the pro-inflammatory one played by ET-1[24] could be due at least in part to a possible inhibitory effect of ANP and a possible stimulatory action of ET-1, respectively, on FAAH activity. Cancer-related opioid system hyperfunction may be simply blocked by the administration of the mu-opioid antagonist NTX, while the cannabinoid-pineal hypofunction may be corrected by the exogenous administration of pineal indoles and cannabinoid agonists. Therefore, the use of cannabinoids in cancer therapy could deserve not only palliative benefits, but it could also influence cancer progression itself because of the antitumor role of the cannabinoids agents[7,8]. FAAH inhibitors could be also successfully used to correct cancer-related cannabinoid system deficiency. On the contrary, there are controversial results concerning the use of the opioid antagonists, such as NTX, in Oncology, since either low-dose[25] or high-dose NTX[17,26], have been proposed, respectively in an attempt to modulate opioid receptor sensitivity, or to completely block the functionless of the opioid system and its immunosuppressive and protumoral activity. On the basis of the evidence of cancer-related opioid hyperactivity in association with cannabinoid failure, a study was performed to evaluate the impact of a correction of cannabinoid-pineal axis deficiency by pineal indoles and cannabinoid agents in association with a control of opioid system hyperfunction by the mu-opioid antagonist NTX on tumor growth and survival in advanced cancer patients, for whom no other standard anticancer therapies were available.

Patients and Methods

The phase II study included 14 consecutive untreatable advanced solid tumor patients (M/F: 8/6; median age 62 years, range 54-81), for whom no other effective standard anticancer therapy was available, and who had already been under complementary medicine with the two main pineal antitumor hormones, consisting of Melatonin (MLT) and 5-Methoxytryptamine (5-MTT) [14,15], according to previous clinical experimental studies[27], both orally with MLT at a dose of 100 mg/day in the dark period of the day and 5-MTT at a dose of 10 mg during the light period of the day. Eligibility criteria were, as follows: histologically proven solid tumor, measurable lesions, no double tumor, no chronic therapy with opioids to avoid the possibile NTX-induced withdrawal syndrome, no availability olf other standard anticancer treatments, and progression under a previous therapy with the only pineal hormones. Tumor histotypes were, as follow: Glioblastoma (GBM): 7; malignant astrocytoma: 3; colon cancer: 1; gastric cancer: 1; pancreatic adenocarcinoma: 1; lung adenocarcinoma: 1. The clinical response was assessed by the more appropriate radiological examinations, and according to the WHO criteria. Under the previous therapy with the only pineal indoles, a disease control (DC) was obtained in 9/14 (64%) patients, consisting of partial response (PR) in 1 and stable disease (SD) in 8, whereas the remaining 5 patients had a Progressive Disease (PD). After disease progression, patients received the same doses of pineal indoles with the association of the mu-opioidantagonist NTX at an oral dose of 20 mg/day in the evening, by evaluating the clinical response after 3 months of therapy. The experimental study was explained to each patient, and written consent was obtained. Moreover, on the basis of the well demonstrated negative prognostic significance of low values of lymphocyte-to-monocyte ratio (LMR)[29] because of the antitumor immunostimulatory and immunosuppressive role of lymphocytes and monocytes, respectively[30], LMR wase valuated at weekly intervals. Normal values of LMR obtained in our laboratory (95 % confidence limits) was greaterthan 2.1. Moreover, becuse of the possible hepatotoxicity of NTX, transaminase levels were also particularly monitored. Data were statistically analyzed by the chi-square t, and the Student's t test, as appropriate.

Results

No complete response was observed in patients under therapy with pineal indoles plus NTX. A partial response (PR) was achieved in one patient with GBM. Seven other patients had a SD. Then, a DC (PR + SD) was achieved in 8/14 [57%], whereas the other 6 patients had a PD. The percentage of DC was higher in patients, who had already obtained a DC under the previous therapy with the only pineal indoles than in those who had a PD, event hough the difference was not statistically significant because of the low number of cases[6/9 (67%) VS 2/5 (40%)]. As far as the immune response is concerned, abnormally low pretreatment values of LMR were seen in 6/14 (43%) patients. The percentage of DC achieved in patients with low LMR values prior to therapy was lower than that achieved in patients with normal pretreatment LMR values, without, however, significant differences [5/8 (63%) vs 3/6 (50%)]. Moreover, as illustrated in Figure 1, LMR mean values increased in patients who achieved a DC, and decreased in those with PD with respect to the pretreatment values, even though the differences were not statistically significant. However, LMR mean values observed after 3 months of therapy in patients with DC were statistically significantly higher than those found in patients with PD ($P < 0.05$). No toxicity occurred on treatment, and in particular no important transaminase increase was observed under NTX administration.

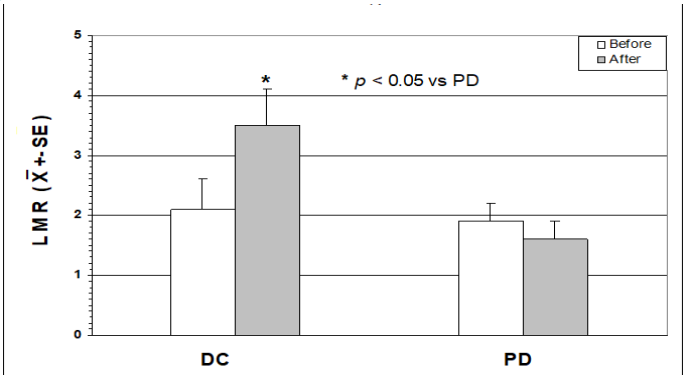

Figure 1: Lymphocyte-to-monocyte (LMR) in patients with disease control (DC) or progressive disease (PD) before and after 3 months of therapy

Discussion

According to a possible psychoneuroendocrine of cancer, which

considers cancer-related immunosuppression of a consequence of an unbalancebe tweenopioid and cannabinoid-pineal systems, which represent the two main brain neuroimmunomodulatory systems, this preliminary phase II study seems to suggest that the association of a block of the opioid system through the administration of a mu-opioidantagonist, suchas NTX, may allow a further control of tumor growth in advanced cancer patients, for whom no other effective standard anticancer therapy was available, and who had already received some benefits from the previous therapy with the only most investigated pineal antitumor hormones, including MLT and 5-MTT, which may reactivate the functionless of cannabinoid-pinealaxis[7-10]. This finding is not surprising, since cancer-related neuroimmune alterations do not consist of the only endogenous cannabinoid system deficiency, but also on a concomitant hyperacitivy of the opioid system[17], which may be counteracted by the administration of the opioid antagonist NTX. This statement is particularly justified in the case of brain tumors, since their expression of opioid receptors has been proven to predict a greater biological malignancy and a worse prognosis[28]. Finally, the improvement in the efficiency of the antitumor immunity, as shown by the increase in LMR, observed in patients, who achieved a DC under NTX therapy, would suggest that NTX may stimulate the anticancer immunity by counteracting opioid system-mediated immunosuppression occurring in cancer. Obvioulsy, further studies will be required to better define the immunomodulating effects of NTX, particularly on regulatory T lymphocytes (T reg), which are the main suppressive regulator of the anticancer immunity, since in experimental conditions it has been shown that NTX may counteract T reg cell generation and activation[29]. However, since LMR represents a synthetic parameter reflecting the relation between antitumor immunostimulatory and protumoral immunosuppresive events, respectively exerted by lymphocyte and macrophage systems[30], LMR increase in patients, who obtained a control of tumor growth on NTX administration, would suggest that NTX-induced block of brain opioid system may contribute to cancer control by also improving the antitumor immunity. Further therapeutic results in terms of control of the clinical course of the neoplastic disease in cancer patients, for whom no other conventional treatment is available, could be achieved by the association with another antitumor pineal hormone of beta-carboline nature, the pinealine[16], as well as by the direct administration of cannabinoid agents, or cannabidiol to inhibit FAAH activity[7,8,22], with a following increase in brain cannabinoid content and function.

References

1. Riley, V. Psychoneuroendocrine influences on immunocompetence and neoplasia. (1981) Science 212(4499): 1100-1109.
Pubmed | Crossref | Others
2. Antoni, M.H. Psychoneuroendocrinology and psychoneuroimmunology of cancer: plausible mechanisms worth pursuing? (2003) Brain Behav Immunol 1(1): 84-91.
Pubmed | Crossref | Others
3. Lissoni, P., Messina, G., Lissoni, A., et al. The psychoneuroendocrine-immunotherapy of cancer: historical evolution and clinical results. (2017) J Res Med Sci 22(1): 45-52.
Pubmed | Crossref | Others
4. Riesco, A. Five-year cancer cure: relation to total amount of peripheral lymphocytes and neutrophils. (1979) Cancer 25(1): 135-140.
Pubmed | Crossref | Others
5. Manfredi, B., Sacerdote, P., Bianchi, M. Evidence for an opioid inhibitory tone on T cell proliferation. (1993) J Neuroimmunol 44(1): 43-46.
Pubmed | Crossref | Others
6. Sacerdote, P., Panerai, A.E. Role of opioids in the modulation of TH1/TH2 responses. (1999) Neuro immunomodulation 6: 422-423.
Pubmed | Crossref | Others
7. Grotehnermen, F. Pharmacology of cannabinoids. (2004) Neuro Endocrinol Lett 25(1-12): 14-23.
Pubmed | Crossref | Others
8. Nagarkatti, P., Pandey, R., Rieder, S.A., et al. Cannabinoids as novel anti-inflammatory drugs. (2009) Future Med Chem 1(7): 1333-1349.
Pubmed | Crossref | Others
9. Lissoni, P., Resentini, M., Mauri, R., et al. Effects of tetrahydrocannabinol on melatonin secretion in man. (1986) Horm Metabol Res 18(1): 77-88.
Pubmed | Crossref | Others
10. Spadoni, G., Bedini, A., Furiassi, L., et al. Identification of bivalent ligands with melatonin receptor agonist and Fatty Acid Amide Hydrolase (FAAH) inhibitory activity that exhibit ocular hypotensive effects in the rabbit. (2018) J Med Chem 61(17): 7902-7916.
Pubmed | Crossref | Others
11. Brzezinski, A. Melatonin in humans. (1997) N Engl J Med 336(3): 186-195.
Pubmed | Crossref | Others
12. Maestroni, G.J. The immunon euroendocrine role of melatonin. (1993) J Pineal Res 14(1): 1-10.
Pubmed | Crossref | Others
13. Conti, A., Maestroni, G.J.M. The clinical immunotherapeutic role of melatonin. (1995) J Pineal Res 19(3): 103-110.
Pubmed | Crossref | Others
14. Lissoni, P. The pineal gland as central regulator of cytokine network. (1999) Neuro Endocrinol Lett 20(6): 343-349.
Pubmed | Crossref | Others
15. Sze, S.F., Ng, B., Liu, W.K. Antiproliferative effect of pineal indoles on cultured tumor cell lines. (1993) J Pineal Res 14(1): 27-33.
Pubmed | Crossref | Others
16. Airaksinen, M.M., Kari, I. Beta-carbolines, psychoactive compounds in the mammalian body. (1981) Med Biol 59(1): 21-34.
Pubmed | Crossref | Others
17. Lewis, J.W., Shavit, Y., Terman, G.V. Apparent involvement of opioid peptides in stress-induced enhancement of tumor growth. (1983) Peptides 4(5): 635-638.
Pubmed | Crossref | Others
18. Bartsch, C., Bartsch, H. Melatonin in cancer patients and in tumor-bearing animals. (1999) Adv Exp Med Biol 467: 247-264.
Pubmed | Crossref | Others
19. Ogawa, S., Kunugi, H. Inhibitors of fatty acid amide hy-

drolase and mono-acyl-glycerol-lipase: new targets for future antidepressant therapy. (2015) Curr Neuro Pharmacol 13(6): 760-775.
Pubmed | Crossref | Others

20. Ahn, K., Johnson, D.C., Cravatt, B.J. Fatty acid amide hydrolase as a potential therapeutic target for the treatment of pain and CNC disorders. (2009) Exp Opin Drugs Disov 4(7): 763-784.
Pubmed | Crossref | Others
21. Godlewski, G., Alapafuja, S.O, Baktai S, et al. Inhibitor of fatty acid amide hydrolase normalizes cardiovascular function in hypertension without adverse metabolic effects. (2010) Cell Chem Biol 17(11): 1256-1266.
Pubmed | Crossref | Others
22. Scharf, E.L. Translating endocannabinoid biology into clinical practice: cannabidiol for stroke prevention. (2017) Cannabis Cannabinoid Res 2(1): 259-264.
Pubmed | Crossref | Others
23. De Vito, P. Atrialnatriuretic peptide: a hold hormone, or a new cytokine? (2014) Peptides 58: 108-116.
Pubmed | Crossref | Others
24. Grant, K., Loizidou, M., Taylor, I. Endothelin-1: a multifunctional molecule in cancer. (2003) Br J Cancer 88(2): 163-166.
Pubmed | Crossref | Others
25. Brown, N., Panksepp, J. Low-dose naltrexone for disease prevention and quality of life. (2009) Med Hypoth 72(3): 333-337.
Pubmed | Crossref | Others
26. Lissoni, P., Messina, G., Porro, G., et al. A psycho-neuroendocrino-immune (PNEI) approach to enhance the efficacy of radiochemotherapy in glioblastoma. (2016) J Radiat Oncol 3: 1-4.
Pubmed | Crossref | Others
27. Lissoni, P., Rovelli, F., Brivio, F., et al. Five-year survival with high-dose melatonin and other antitumor pineal hormones in advanced cancer patients eligible for the only palliative therapy. (2018) Res J Oncol2: 1-7.
Pubmed | Crossref | Others
28. Westphal, M., Li, C.H. Beta-endorphin: characterization of binding sites specific for the human hormone in human glioblastoma SF 126 cells. (1984) Proc Natl Acad Sci USA 81(9): 2921-2923.
Pubmed | Crossref | Others
29. Lissoni, P., Messina, G., Tantarelli, R., et al. The psychoneuroimmunotherapy of humans immune-mediated systemic diseases, including cancer and autoimmune diseases. (2017) J Mol Oncol Res 1(1): 7-13.
Pubmed | Crossref | Others
30. Nishijma, T.F., Muss, H.B., Shachar, S.S., et al. Prognostic-value of lymphocyte-to-monocyte ratio in patients with solid tumors: a systematic review and meta-analysis. (2015) Cancer Treat Rev 41(10): 971-978.
Pubmed | Crossref | Others