

A review on cancer-psychospiritual status interactions

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Abstract

With the advances in the knowledge of neuroimmunomodulation, a new era of investigations about the chemical basis of the state of mind has been initiated. Both emotions and states of spiritual consciousness may influence immune functions and cancer growth. Stress, anxiety and depressive states are associated with immunosuppression and enhanced frequency of tumors. On the other hand, the states of sexual pleasure and spiritual joy enhance the immune efficacy, by counteracting tumor onset and dissemination. The biochemistry of pleasure and immunostimulation is mainly mediated by pineal indoles and cannabinergic substances, whereas that of stress, anxiety and depression is associated with enhanced production of adrenal steroids, opioids and catecholamines. The sexual repression would allow a progressive immunosuppression through a profound damage in the biochemistry of pleasure. Therefore, a better definition of psychospiritual status-associated neuroimmunochemistry could allow us to improve the immune dysfunction by acting on the same neuroendocrine secretions which are involved in mediating the psychic influence on the immunity, including that against cancer.

1.0 Introduction

The recent advances in the knowledge of neuroendocrine biochemistry and the chemical basis of emotions and consciousness states allowed us the possibility to better analyze, and verify, some psychic hypotheses proposed several years ago, concerning the possible influence of the psychospiritual status on cancer progression, tumor physiopathology and clinical history of the neoplastic disease [1]. In particular, as observed by Reich more than 50 years ago [2], the repression of sexual pleasure would constitute one of the most common cancer-related psychic disturbances. Obviously, at the time of Reich's experience, because of the availability of very few neuropsychological informations, it was not possible to define the neuroendocrine mechanisms involved in mediating the influence of pleasure repression on the prognosis of cancer patients.

2.0 The pineal physiology

One of the main advances in the knowledge of the chemical mediation of the psychospiritual life was the discovery of the fundamental role of the pineal gland in the regulation of the immune system, namely the anticancer immunity [3, 4], in relation to both psychological status and universal environmental information through the light/dark circadian release of various indole neurohormones. The most well-known of them are melatonin (MLT) and 5-methoxytryptamine (5-MTT) [3, 4], mainly secreted during the dark and the light period of the day, respectively. Therefore, the light/dark ratio, which was considered only by Philosophists and Theologists until few years ago, may constitute a scientific biological parameter based on the studies on the physiology of the pineal gland [3]. In fact, the Theologists, as shown in the biblical book Genesis itself, have always considered the separation between light and dark as the first principle of the universal order. At present, we know that the light/dark ratio is maintained in each single living organism by the pineal function [3]. In particular, it has been shown that the pineal gland may contain various psychoactive indoles, namely tryptamines and beta-carbolines [3, 5].

3.0 The psychedelic biochemistry

The psychoactive indole molecules are interesting not only for their effects on the human emotions and mind, but also for their natural presence and function in humans in both physiological and pathological conditions [5]. Methylated tryptamines have been shown to have more pronounced psychoactive and psyche-

delic effects than the non-methylated ones [6]. Moreover, psychedelic methylated tryptamines, such as dimethyl-tryptamine (DMT), have been detected in normal humans [4, 5], even though their biological significance has still to be better defined.

4.0 Neuroimmunomodulation

In addition to the well-known immunomodulatory role played by the pineal gland [3, 4], two other fundamental systems involved in the Neuroimmunomodulation (NIM) are represented by the brain opioid [7] and cannabinergic pathways [8]. Beta-endorphin [7] and arachidonil-ethanol-ammide [8], the so-called anandamide, are the main substances released from opioid and cannabinoid systems, respectively. Cannabinoid agonists would play a major in vivo immunostimulatory role by stimulating pineal indole secretion [9], namely MLT itself, whose fundamental immunoregulatory activity has been shown to mainly consist of stimulation of IL-2 production and lymphocyte activation [3, 10]. In contrast, the in vitro immune effects of cannabinoids are still controversial. With respect to the pineal, the adrenal gland would constitute its polar endocrine gland, with opposing biological effects. In fact, the pineal may play both immunomodulating and thrombopoietic activities [4], whereas the adrenal steroids induce immunosuppression and thrombocytopenia. The immune system is also modulated by neurotransmitters, and each neurotransmitter may potentially act on the immune functions. However, within the neurotransmitter group, the more active substances in terms of NIM would be represented by catecholamines [7] and GABA-A agonists [3], which are provided by immunosuppressive and immunostimulatory effects, respectively. The mechanisms responsible for catecholamine and opioid-induced immunosuppression have been recently well characterized [7, 11], by consisting of stimulation of IL-4 and IL-10 release and inhibition of the most active antitumour cytokines, IL-2 and IL-12, with a following unbalanced T helper-1 (TH1) – T helper-2 (TH2) ratio. Obviously, the knowledge of explaining the psychic influence on cancer growth through the immune system may be realized on the basis of the recent adequate definition of the mechanisms responsible for the anticancer immunity [12]. At present, it is well known that TH1 cells, dendritic cells (DC) and NK cells are the main cells involved in tumor cell recognition and destruction [3, 4], whereas TH2 cells and macrophages would play a major immunosuppressive activity by inhibiting TH1 and DC activation. In addition, TH1, DC and, NK cells are stimulated by the pineal gland [4, 10], whereas catecholamines, corticosteroids and opioids

play an inhibitory effect [7]. Moreover, it has to be remarked that pineal-cannabinergic and GABA-A systems are linked by reciprocal interactions, by constituting a functional unity, which is activated in dark conditions [10], during spiritual expansion of consciousness [4], the so-called psychedelic state, and during sexual excitation [13]. Therefore, the neurobiochemistry of sexual excitation and spiritual experiences is very similar, despite the behavior of human culture having separated these two aspects of the human identity. On the other hand, noradrenergic pathway, opioid system and adrenal glands may be also considered as a functional unity, which is activated in stress-conditions, chronic pain, anxiety and depression [1, 7].

5.0 Considerations on the psychospiritual states

It is fundamental to understand that neurohormone-psyche interaction is active in a bi-directional way, since each psychic condition is characterized by a secretion of specific neuroactive substances, while on the other hand each neurohormone or psychoactive substance may induce particular immunobiological and psychic effects. In addition, it is essential to understand that the influence of the mind on immune system and cancer growth does not depend entirely on emotions and other psychological events, since consciousness and thoughts may be also active in influencing the immunobiological homeostasis [1, 3]. Therefore, the word psychospiritual state would seem to be more adequate than that of the psychic state alone.

At the time of the beginning of Psychoanalysis, it was not possible to postulate a chemical mediation of emotions and consciousness states, because of the lack of many neurochemical knowledge. In any case, Freud never did exclude a possible biological mediation of the psychological life [14]. Despite the great and complex variety of neurohormones and neuropeptides, from a psychospiritual point of view they may be classified according to archetypic criteria, consisting of Light and Dark ontological aspects, the so-called Hebraic terms of Hahòr and Hahoshék of Biblical memory, respectively. Pain, depression, anxiety, lack of pleasure and absence of joy represent the state of Dark, whereas pleasure and spiritual joy are the effects of the state of Light. According to both Freud's theory [14] and Theological tradition, the maximal pleasure is the sexual one, and sexual energy would constitute the origin of the whole psychological life. By synthesizing, it is possible to affirm that the Dark states of mind (pain, depression, anxiety) induce immunosuppression and stimulate cancer development, whereas the Light states (spiritual joy

and sexual pleasure) determine immunostimulation and inhibition of cancer cell proliferation. In fact, even though controversial data exist, psychological epidemiology has demonstrated an association between depression, chronic stress and cancer frequency and progression [1], whereas spiritual joy and sexual pleasure would prevent cancer onset. Moreover, recent experimental data have shown that the same neurohormones involved in NIM may also regulate oncogene expression [3], by directly influencing the biological grade of malignancy of tumor cells themselves. In more detail, the same neurohormones provided by immunoenhancing effects tend to suppress oncogene expression, by stimulating the cytodifferentiation of cancer cells, whereas the immunosuppressive neuroactive substances may further enhance the grade of tumor malignancy. Therefore, consciousness, mind and emotions may influence cancer growth not only through the immune dysfunction, but also directly by influencing the genetic characteristics of cancer cells. Moreover, since anticancer immunity and angiogenesis have appeared to be connected by an inverse correlation [15], the regulation of angiogenic processes would also constitute one of the possible mechanisms involved in the influence of mind on cancer growth.

6.0 Sexuality and coccygeal gland

Within the psychic conditions, it was shown by Reich [2] that sexual repression is strictly linked to the neoplastic disease. Moreover, recent experimental observations have suggested that the coccygeal gland may play a role in the regulation of sexuality [16]. In addition, it has been shown that the excision of the coccygeal gland may induce lymphocytopenia and immunosuppression [16]. Finally, the coccygeal gland has appeared to influence the myeloproliferative processes, by regulating bone marrow catecholaminergic content [16]. Therefore, in addition to the action of pleasure related brain structures, namely pineal gland and cannabinoid system, sexual repression would induce an immunosuppressive status through a possible functional damage of the coccygeal gland. In any case, it has to be remarked that the history of humans has been characterized by a progressive opposition between the two major pleasures, consisting of spiritual joy and sexual pleasure. The opposition between sexuality and spirituality has depended on an X-event, which was identified as the Origin of Sin by theologians and as a social necessity to control the sexual energy by the Psychoanalysis [14]. In any case, irrespective of the different theories, it is an objective evidence that the psychosexuality of humans is regulated by neither the mind, nor the spiritual consciousness, but it is under an unconscious regulation reflecting the psychoaffective his-

tory of each human, as shown by Freud [14]. Moreover, according to Freud's criteria [14], it should be remarked that the sexual repression may consist of at least two fundamental psychic processes, represented by Removal and Perversion. Removal is characterized by a separation between sexual energy and its natural psychic imagination, whereas the Perversion consists of an arrest of the preliminary states of the psychosexual life maturation, the so-called oral and anal stages of psychosexual development. The existence of a block of the sexual energy would characterize only the removal processes of the sexual repression, whereas there would be no block of sexual energy in the process of perversion. Therefore, within the sexual repression states, only the mechanism of removal would induce immunosuppression and promote cancer onset and development. However, as far as cancer/psyche relation is concerned, it is fundamental to consider that the transformation of the single cell does not correspond to the neoplastic disease. Therefore, the psychospiritual influence on cancer disease would act on the evolution of a single transformed malignant cell, by allowing its immune system-mediated destruction or its evolution into a clinically evident neoplasm, due to a deficiency of the natural immunobiological resistance against cancer onset and development. In other words, if the action of carcinogens may explain the malignant transformation of the single cell, its evolution into a clinical tumor clearly depends on host immuno-psychoneuroendocrine status.

7.0 Psychoimmunobiochemistry of cancer patients

Unfortunately, the neuroimmunobiochemistry of cancer patients is generally not considered by Oncologists, and it has been investigated by only few authors. However, according to preliminary clinical investigations [3, 17, 18], it is possible to affirm that cancer progression is associated with profound neuroendocrine anomalies, and the progressive pineal deficiency would represent the most common cancer progression-associated neuroendocrine dysfunction, which could play a role in the pathogenesis of cancer dissemination itself [3, 17]. In contrast, opioid and adrenergic systems would be hyperactivated in the neoplastic disease [3]. The progressive lack of the physiological nocturnal increased secretion of the pineal hormone MLT [3, 17] would reflect a profound damage in the light/dark rhythm influencing the biological systems, which may either precede or be induced by the neoplastic disease. Moreover, from a psychological point of view, it is a common clinical evidence that the neoplastic disease is constantly

characterized by a progressively diminished capacity of feeling pleasure [1], which would depend on a deficiency of the same brain structures responsible for the NIM [1, 3]. Therefore, if the immunosuppressive status characterizing the cancer patients at the onset of the neoplastic disease would be mainly due to an altered psychoneuroendocrine regulation of immunity, cancer progression itself would allow a progressive deficiency of pleasure-related neurohormones, by justifying an exogenous neuroendocrine replacement therapy. In particular, preliminary clinical results have shown that the exogenous administration of the pineal indole 5-MTT, whose production is diminished in advanced neoplasms [3], may have a dramatic capacity of improving mood and treating asthenia and anorexia [19], by confirming that the psychic and mind states of cancer patients do not depend only on disease-related psychological factors, but also on an objective neuroendocrine deficiency.

8.0 Conclusions

Irrespective of the initial point of view, including psychological, biochemical, philosophical or theological hypotheses, according to the recent advances in the psychoneuroendocrinological knowledge, it is possible at present to reach a final common theoretical proposal, like a Mecca of the unity of all possible theories, showing that the repression of sexual pleasure and of the spiritual life may suppress the natural immunobiological resistance against tumor growth, by piloting the physiology of the human organism in a protumourigenical way, as illustrated in Fig. 1.

In conclusion, the biochemistry related to both spiritual and sexual pleasures may play an immunostimulatory role and protect against cancer onset and dissemination, whereas the biochemistry of pleasure deficiency-related conditions immunosuppresses and promotes tumor growth. In any case, the better definition of cancer-psyche status relation is not only a medical problem, but it would require a cooperation among the entire range of human sciences, including Psychology, Philosophy and Theology. Moreover, more defined neurochemical knowledge is required. In particular, it will be the aim of successive investigations the characterization of the biochemistry of the coccyeal gland and of the pineal gland, respectively related to sexual excitation and consciousness states. The immunoregulatory role of the pineal indole MLT has been well established [3, 10], but it has to be remarked that MLT is only one of several other potentially psychoneuroimmunologically active indoles and neuropeptides released from the pineal gland [3]. On the other hand, the biochemistry of the coccyeal gland is still completely obscure [16].

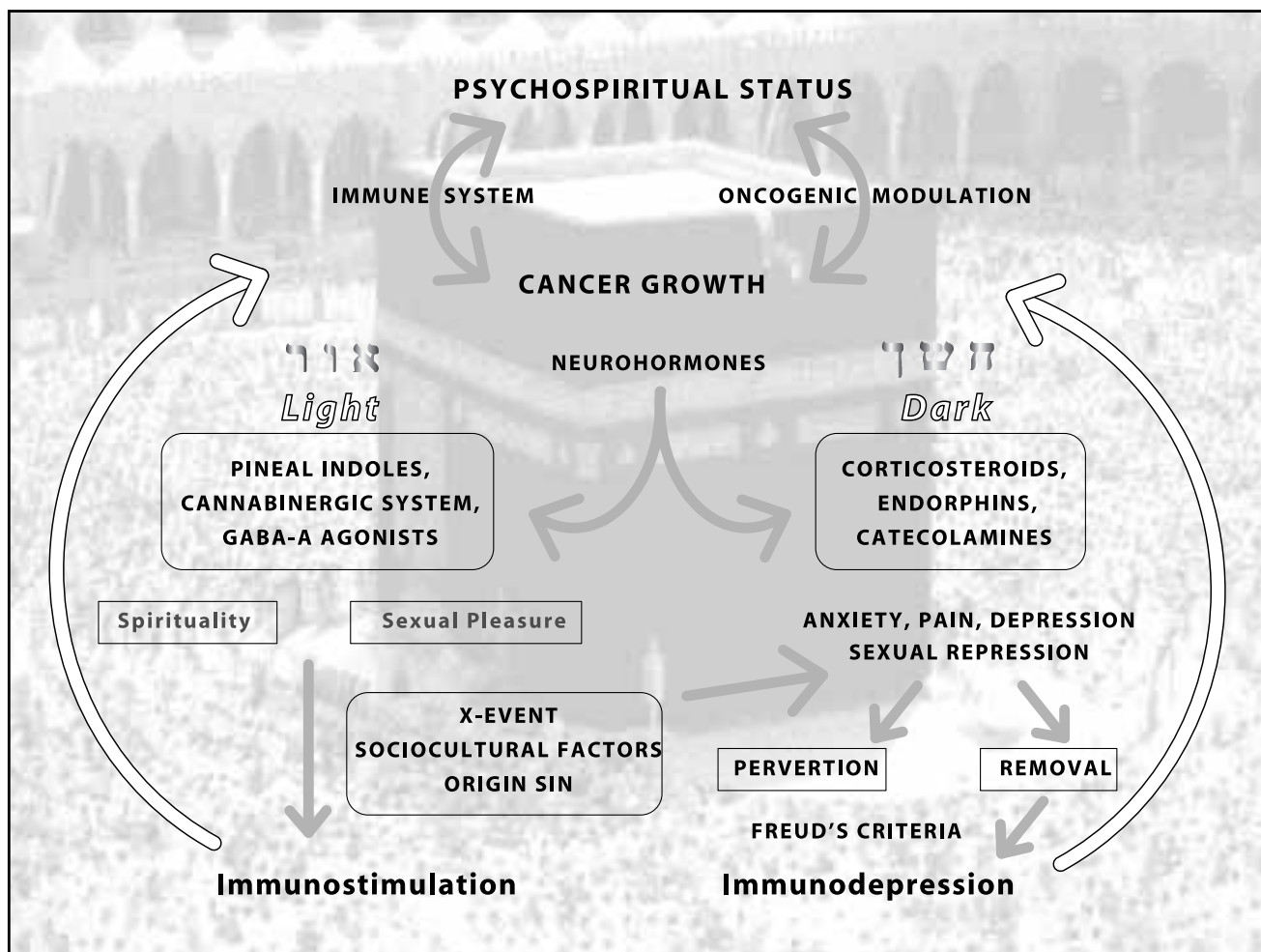


Fig.1. Cancer/Psychospiritual status interactions according to Psychoneuroimmunology, Psychoanalysis experience, Reich's theory and Theology.

Therefore, the discovery of endogenous psychoactive and psychedelic substances [3–6], will allow us in the near future to completely characterize the neurobiochemical basis of the states of mind. Moreover, on the basis of the absolute unity between neurobiochemistry and states of mind, future Medicine will consist of the reconstitution of the perfect neuroimmunobiochemistry of the biopsychic status of health.

REFERENCES

- 1 Rubinow DR. Brain, behavior and immunity: an interactive system. *J Natl Cancer Inst Monogr* 1990; **10**:79–82.
- 2 Reich W. *The sexual revolution*. Feltrinelli, editor. Milan, Italy, 1966.
- 3 Brzezinski A. Melatonin in humans. *N Engl J Med* 1997; **336**:186–195.
- 4 Lissoni P. The pineal gland as a central regulator of cytokine network. *Neuroendocrinol Lett* 1999; **20**:343–349.
- 5 Guichhait RB. Biogenesis of 5-methoxy-N,N-dimethyltryptamine in human pineal gland. *J Neurochem* 1976; **26**:187–190.
- 6 Airaksinen MM, Kari I. Beta-carbolines. Psychoactive compounds in the mammalian body. Occurrence and metabolism. *Med Biol* 1981; **59**:21–34.
- 7 Sacerdote P, Paneirai AE. Role of opioids in the modulation of TH1/TH2 responses. *Neuroimmunomodulation* 1999; **6**: 422–423.
- 8 Klein TW, Newton C, Friedman H. Cannabinoid receptors and immunity. *Immunol Today* 1998; **19**:373–381.
- 9 Lissoni P, Resentini M, Mauri R, et al. Effects of tetrahydrocannabinol on melatonin secretion in man. *Horm Metab Res* 1986; **18**:77–78.

- 10 Maestroni GJM. The immunoneuroendocrine role of melatonin. *J Pineal Res* 1993; **14**:1–10.
- 11 Elenkov IJ, Papanicolaou DA, Wilder RL, Chrousos GP. Modulatory effects of glucocorticoids and interleukin-10 production: clinical implications. *Proc Ass Am Phys* 1996; **108**:374–381.
- 12 Lotze MT, Hellerstedt B, Stolinski L, et al. The role of interleukin-2, interleukin-12, and dendritic cells in cancer therapy. *Cancer J Sci Am* 1997; **3**:S109–S114.
- 13 Grugni G, Granata A, De Medici C, et al. Effects of erotic visual stimulation on melatonin serum levels. *J Endocrinol Metab* 1994; **17**(Suppl 1):36.
- 14 Freud S. *Introduction to Psycho-analysis*. Payot, editor. Paris, France, 1951.
- 15 Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumor inhibits the functional maturation of dendritic cells. *Nat Med* 1996; **2**:1093–1103.
- 16 Conti A, Maestroni GJM, Cosentino M, et al. Evidence for a neuroimmunomodulatory and hematopoietic role of the Luschka's coccygeal body. *Neuroendocrinol Lett* 2000; **21**:391–403.
- 17 Bartsch C, Bartsch H, Lippert TH. The pineal gland and cancer: facts, hypotheses and perspectives. *Cancer J* 1992; **5**:194–199.
- 18 Esposti G, Lissoni P, Tancini G, et al. A study on the relationship between the pineal gland and the opioid system in patients with cancer. *Cancer* 1988; **62**:494–499.
- 19 Lissoni P, Rovelli F, Frassinetti A, et al. Oncostatic activity of pineal neuroendocrine treatment with pineal indoles melatonin, and 5-methoxytryptamine in untreatable metastatic cancer patients progressing on melatonin alone. *Neuroendocrinol Lett* 2000; **21**:319–323.