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INVITED NEL REVIEW

The pineal gland as a central regulator of cytokine network

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Abstract

Even though cytokines may fundamentally act as local factors, the recent advances in the knowledge of neuroimmunomodulation (NIM) would suggest the existence of a central regulation of their secretion and activity. Several neuroactive substances have appeared to influence cytokine secretion, and on the other hand cytokines may modulate the neuroendocrine functions. However, at present only for the pineal gland, whose fundamental NIM role is well known, it is possible to recognize reciprocal influences between cytokine action and pineal endocrine activity, suggesting the existence of feedback mechanisms responsible for a central regulation of cytokine network. Melatonin (MLT), which is the most investigated pineal immunomodulating hormone, may stimulate IL-2 release by T helper-1 (TH-1) lymphocytes and that of IL-12 by dendritic cells (DC), whereas both IL-2 and IL-12 would inhibit MLT release. The physiological significance of IL-2—IL-12—MLT interactions would be the maintenance of an effective TH-1-dependent cellular immunity, including the anticancer immune response. A third possible pineal-cytokine feedback mechanism involves tumor necrosis factor-alpha (TNF-alpha) secretion, with a stimulatory effect of TNF-alpha on MLT release and an inhibitory one of MLT on TNF-alpha production. This finding would explain the anticachectic property of MLT itself. A further knowledge of pineal-cytokine interactions, as well as of other endocrine-immune circuits, will allow a better definition of the physiopathology of human chronic immunoinflammatory diseases, whose clinical course has appeared to be influenced by psychoemotional factors.

1. Introduction

Cytokines may be either detrimental or therapeutic for the living organisms [1]. They may either destroy or repaire the structure of the organs. Generally, it is a common opinion that cytokines may substantially act as local factors, only active where locally produced. However, because of their fundamental role in human physiopathology, it is probable that the local production and activity of cytokines may be under a central regulatory control, capable of piloting their functions on the basis of the general status of the various biological systems. In fact, several neuroactive substances, produced by both central nervous systems (CNS) and peripheral nervous systems (PNS), may influence cytokine secretion and amplify or reduce their biological activity [2]. Both positive and negative feedback mechanisms have been described within the cytokine network [1]. Obviously, the evidence of several positive feedback mechanisms makes the cytokine system as more difficult to be investigated with respect to the endocrine system, which is mainly characterized by negative feedback circuits.

Within the neuroimmunomodulation (NIM), a fundamental immunoregulatory role has been proven to be exerted by the pineal gland, through the circadian release of melatonin (MLT) and other less investigated indoles and neuropeptides [3]. The importance of the pineal gland in the regulation of cytokine production and activity is confirmed by the fact that pharmacological or surgical pinealectomy produces evident changes in cytokine secretion, namely in the release of IL-2 [4], with a following generation of an immunosuppressive status. On the other hand, several experimental studies have suggested that cytokines may modulate the pineal function [5, 6]. In more detail, MLT release from the pineal has been shown to be influenced by IL-2 [5], IL-12 [7], tumor necrosis factor-alpha [8] and granulocyte-macrophage colony stimulating factor (GM-CSF) [9].

It is known that the pineal gland contains two major cell populations, consisting of pinealocytes and glial cells [3]. A present, it is still unknown whether pinealocytes may express cytokine receptors. In contrast, it has been well demonstrated that glial cells, which originate from the monocyte-macrophage cell line, may express receptors for several cytokines [2]. Since pineal glial cells modulate the metabolic functions of pinealocytes [3], it is not necessary that pinealocytes may express cytokine receptors to explain their response to the action of cyto-kines, which could influence them indirectly by acting on the glial cells of the pineal gland. In any case, further studies will be necessary to establish whether pinealocytes may indirectly express cytokine receptors.

2. Physiology of Neuroimmunomodulation

Lymphocytes are one of the most important target cells for NIM. As far as lymphocyte physiology is concerned, until few years ago a great value was clinically assigned to T helper/T suppressor lymphocyte ratio (CD4/CD8), and a decrease in its value was considered as an expression of immunosuppression [10]. In the last years, the fundamental advances in the knowledge of the immune system have allowed us to identify more physiopathologically and clinically significant immune parameters, consisting of T helper-1 (TH-1)/T helper-2 (TH-2) ratio (TH-1/TH-2) [11, 12], TH-1 and TH-2 being the main cells responsible for the activation of cellular or humoral immune response, respectively. TH-1 hypofunction and TH-2 hyperfunction would represent the main immune alteration occurring in human diseases. TH-1 hypofunction may predispose to cancer, whereas TH-2 hyperfunction may predispose to allergic and autoimmune diseases [11, 12]. In addition, it may be suggested that TH-1/TH-2 ratio constitues a useful immune parameter to explain the great variety of immunomodulating effects induced by hormones and neuroactive substances, as well as those of psychoemotional factors [13, 14].

According to NIM knowledge, both stress and pleasure conditions may influence the neuroendocrinoimmune interactions [15, 16]. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis [17]. Infections and inflammations also activate the HPA axis through cytokines released from the activated immune cells [18]. HPA axis-stimulating activity is exerted by most cytokines, including IL-1, IL-2, IL-6, IL-12 and TNF-alpha [17]. At present, cytokine-HPA axis is the most investigated neuroimmunomodulatory feedback mechanism. The aim of cytokine-HPA axis is the protection against the risk of an exaggerated immune response, which could predispose to autoimmune or allergic disease [12]. However, on the other hand the existence of concomitant endocrine-cytokine feedback circuits, must be considered, mainly involving the pineal gland, whose aim is the protection against the risk of an immune hyporesponse to infectious agents and eventual transformed cells [7]. A typical deficiency of cytokine-HPA axis has been described in autoimmune disease [1]. All hormones and neuroactive agents released during stress, including corticosteroids, catecholamines and opi-oids, are characterized by a common mechanism of action, consisting of the stimulation of T helper-0

(TH-0) differentiation into TH-2 cells and of the inhibition of TH-1 differentiation [19, 20]. This finding would be at least in part mediated by the inhibition of the dendritic cell (DC) induced release of IL-12 [19, 21], which is the main factor responsible for TH-1 differentiation. Therefore, IL-12 deficiency would allow a preferential differentiation of TH-0 into TH-2 cells, a consequent release of IL-4 and a following further enhanced TH-2 differentiation. On the other hand, neurohormones and neuroactive agents related to psychic and spiritual pleasure conditions and to expansion of consciousness, such as pineal hormones, GABA-A agonists and cannabinoid substances, would mainly activate TH-1 differentiation, even though there are still controversial results, particularly those concerning the action of endogenous cannabinergic agonists, namely arachidonyl-ethanolamide, the so-called anandamide [22]. Therefore, stress and pleasure would mainly activate TH-2 and TH-1 lymphocyte functions respectively [19]. Then, stress—by activating TH-2 dependent immune function—would predispose to autoimmune and allergic diseases, whereas the concomitant TH-1 hypofunction may be a risk factor for cancer. On the other hand, relaxation, spiritual experiences and sexual pleasure would activate TH-1 pineal axis, with a following reduced risk of autoimmune diseases and an increased resistance against cell proliferation. According to the knowledge available up to now, the pineal hormone MLT would be the main endogenous anti-stress substance, capable of counteracting stress-related chemical and psychic conditions [3].

3. Anticancer Cytokine Network

At present, we may substantially recognize two fundamental antitumor cytotoxic systems in humans, involved in immunity-mediated cancer cell destruction [23]. The first system consists of an IL-2-dependent phenomenon, which mediates an antigen-independent tumor cell destruction, and it is characterized by Natural Killer (NK)/Lymphokine-Activated Killer (LAK) cell system and TH-1 lymphocytes. IL-2 released by TH-1 cells activates the evolution of PBMC into LAK cells [24], which are able to destroy fresh human cancer cell lines irrespective of their antigenic properties. The second antitumor circuit, which is an IL-12-dependent system, realizes an antigen-dependent cytotoxicity, mediating a specific tumor cell lysis, and it consists of Dendritic Cells (DC), which produce IL-12 itself, and T cytotoxic lymphocytes (CD8+ cells) involved in cancer cell destruction [21, 25]. The two cytotoxic antitumor systems would be reciprocally linked by IL-12 itself, which may also activate the first system by promoting TH-1 differentiation and a following increased production of IL-2 and an enhanced LAK cell generation induced by IL-2 itself. In the same way, we may identify two major systems suppressing the anticancer immunity [26, 10]. The first system is that of macrophages, which may release several immunosuppressive substances, such as IL-6 and soluble IL-2 receptor (sIL-2R), which may inhibit IL-2 induced NK activation [27] and LAK cell gen-

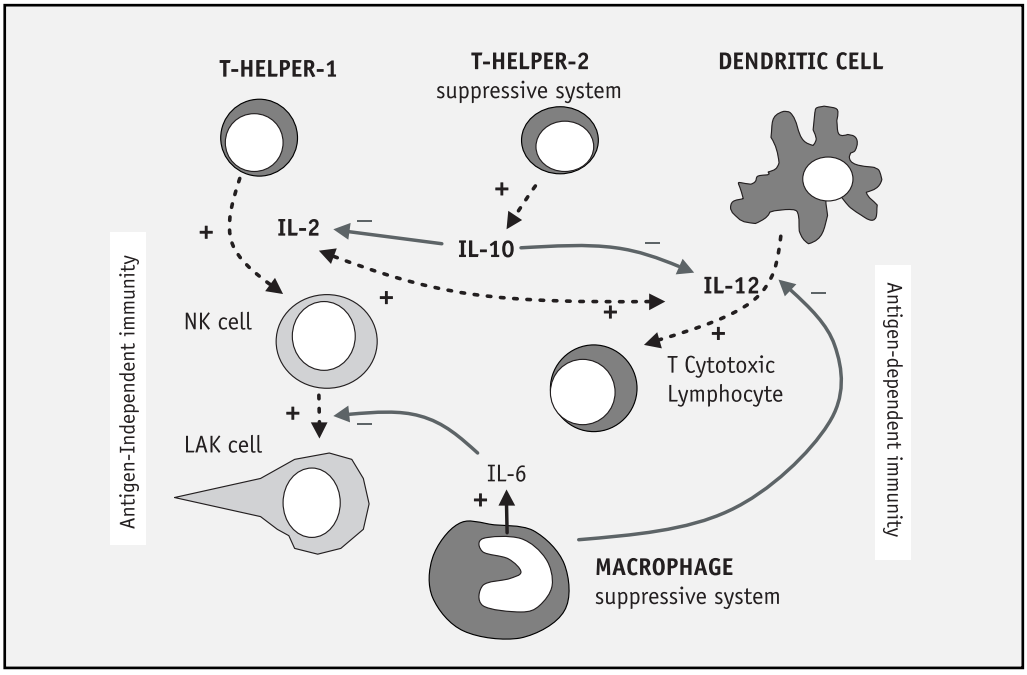

Fig. 1. Main antitumor cytotoxic and immunosuppressive systems.

eration [28]. The second system is represented by TH-2 lymphocytes, which produce IL-10–capable of inhibiting the activity of both IL-2 and IL-12– and IL-4, which further promote TH-2 differentiation itself, with a consequent worsening of the already altered TH-1/TH-2 ratio occurring in the advanced neoplasms [11]. Anticancer cytotoxic, suppressive system and their relations are illustrated in Fig. 1. From a clinical point of view, the main cytokines to monitor the biological response during IL-2 cancer immunotherapy, the most promising tumor biotherapy available up to now would have to be at least IL-2, IL-12, IL-10, IL-4 and IL-6 [23, 10]. Lower levels of IL-2 or IL-12 and abnormally high levels of IL-6 and IL-10 have been proven to be associated with a poor prognosis in metastatic cancer patients [10].

4. Pineal gland and Immunity

Several biological regulatory functions may be assigned to the pineal gland and to its main hormone MLT, including the modulation of neuroendocrine, immune, hemopietic and cardiovascular systems [3]. The first evidence suggesting a pineal modulation of the immunity was proposed about 30 years ago by Jankcovic et al. [29]. Then, several immunostimulating effects were attributed to the pin-eal and its most investigated hormone MLT, namely stimulation of T lymphocyte functions in a TH-1 way, stimulation of NK cell activity and of their evolution into LAK cells, inhibition of macrophage-mediated immunosuppressive effects on the anticancer reaction and of TH-2–mediated immunosuppression [30]. Therefore, the pineal would preferentially activate the cellular immunity, whereas the humoral immunity is not amplified by MLT. Both lymphocytes, namely TH-1 cells, and macrophages may express MLT receptors and—in addition—MLT may be directly released from both T lymphocytes and macrophages [30, 31]. The activation of TH-1 functions would have to be considered as the main effect to explain the well documented pineal stimulation of the anticancer immunity. However, it has to be considered that MLT is not the only potentially active hormone produced by the pineal gland. In fact, preliminary results seem to suggest that at least two other pineal indoles, 5-methoxytryptophol and 5-methoxytryptamine, may play immunomodulating effects [32, 33].

5. Pineal-Cytokine feed-back mechanisms

The basis-mechanism capable of explaining the great variety of immunomodulatory effects of the pineal gland may be identified in the regulation of the cytokine network. The pineal may influence the release of cytokines, which in turn influences the pineal endocrine activity. The pineal would modulate the cytokine network in relation to both environmental and psychoemotional conditions. It is known that cytokines may influence the whole neuroendocrine system, including CNS and PNS, not only the pineal gland, and—on the other hand—the pineal is not the only neuroendocrine organ capable of influencing cytokine secretions [2, 6]. At present, however, it is possible only for the pineal to identify not only reciprocal neuroimmune influences, but clinically evident cytokine-pineal feedback mechanisms, involved in maintaining an effective TH-1–dependent immune response. At present, at least three pineal cytokine feedback mechanisms may be recognized in humans according to preliminary clinical investigations [5, 8, 30, 34]. MLT has been proven to stimulate IL-2 secretion [30], which in turn tends to inhibit MLT release, even though the effects of IL-2 on MLT production would depend on IL-2 dose and way of administration [5] . MLT stimulates IL-12 and enhances IL-2-induced secretion of IL-12 [7, 34] which in contrast may inhibit MLT release [7]. The aim of these two pineal-cytokine feedback circuits is to induce an effective TH-1-dependent immunity, including the anticancer reaction. Therefore, whereas the biological significance of cytokine-HPA axis circuit is the prevention of an exaggerated immune response, the aim of pineal/IL-2/IL-12 neuroimmune network is to guarantee an adequate immune response against the various pathological agents. In more detail, the activation of HPA-axis induces a preferential TH-2 response, whereas IL-2 -IL-12 -pineal axis would generate a TH-1-dependent immunity. In other words, the cellular immunity, which is a TH-1 dependent phenomenon, is influenced by the pineal-neuroimmune circuit, whereas the humoral one, which is a TH-2-dependent phenomenon, is controlled by HPA-axis cytokine interactions. The third possible pineal-cytokine feedback mechanism involves TNF-alpha secretion. TNF-alpha stimulates MLT release [8], whereas MLT suppresses TNF-alpha secretion [35], and MLT-induced inhibition of TNF-alpha release would be one of the main mechanisms responsible for the well documented anti-cachectic property of MLT [35]. Therefore, the physiopathological significance of pineal-TNF-alpha interactions would be the prevention of cancer or infection induced weight loss. Pineal and HPA-cytokine feedback mechanisms are illustrated in Fig. 2.

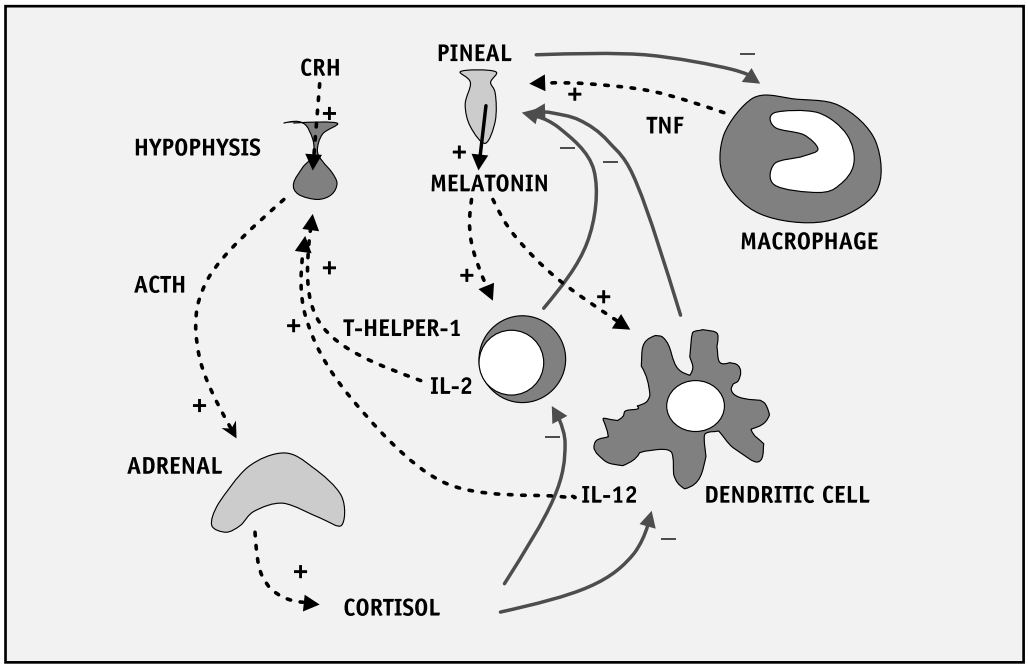

Fig. 2. Hypothalamic-pituitary-adrenal axis and pineal-cytokine feed-back mechanisms.

6. Pineal modulation of the anticancer cytokine network

Because of the preferential effect of MLT on TH-1 rather than TH-2 cell differentiation [6, 30] and of its inhibitory activity on macrophage-mediated suppression of the anticancer immunity [36], an effective pineal endocrine function could reverse the major immune alterations occurring in human neoplasms, including the hyperfunction of macrophage and TH-2 system and the hypofunction of TH-1–Dendritic Cells–NK cell system. Unfortunately, it has been proven that cancer progression is associated with a progressive pineal hypofunction, with a consequently diminshed production of MLT during the dark period of the day [37, 38]. At present, it is still unknown whether which may be the primum movens between pineal damage and cancer-related immune alterations. In experimental conditions, it has been observed that pharmacological corrections of the neurochemical alterations occurring during the carcinogenetic process may counteract the onset of tumor itself [39]. Therefore, it is probable that a pre-existing pineal hypofunction may be at least in part involved and predisposed to cancer development or cancer recurrence for patients radically operated for a primary tumor. This statement may be justified by the fact that all conditions characterized by a pineal hypofunction or dysfunction, including depression, stress and exposition to magnetic fields, may predispose to cancer, whereas the evidence of a pineal hyperfunction, such as blindness, is associated with a diminished risk of cancer [40, 41]. Moreover, in experimental conditions it has been shown that pinealectomy reduces IL-2 anticancer activity [4]. Since cancer progression is associated with a progressive pineal hypofunction [37, 38], its pharmacological correction by the exogenous administration of MLT could improve the efficacy of IL-2 itself. In fact, our previous clinical studies had already demonstrated better therapeutic results with IL-2 plus MLT than with IL-2 alone in patients with disseminated cancer [36]. In any case, further studies will be required to better define which relation may exist between IL-2, as well IL-12, antitumor efficacy and changes in pineal endocrine function. Preliminary clinical studies have shown that a chronic injection of IL-2 may normalize MLT secretion in advanced cancer patients with a pretreatment abnormal light/dark rhythm of the pineal hormone, consisting of a lack of its physiological nocturnal increase [42].

7. Heart-Pineal interaction and Neuroimmuno-modulation

It is a common opinion that the brain is the most important organ of NIM. However, recent studies suggest that also the heart may play evident NIM effects through the release of immunomodulating substances, namely Atrial Natriuretic Peptide (ANP) and Endothelin-1 (ET-1) [43, 44]. They are provided by opposite cardiovascular effects, since ANP induces vasodilation and activation of the parasympathetic system, whereas ET-1 is the most potent endogenous vasoconstrictive agent, capable of activating the

adrenergic system. In addition, ANP may be effective in the treatment of heart failure, whereas ET-1 is the main molecule capable of inducing heart failure-related cardiac hypertrophy [43]. Moreover, recent data would suggest that ANP and ET-1 may play opposite effects also on other biological functions, including immune response, cell proliferation and angiogenesis [43, 44]. ANP would play immunostimulatory effects by directly activating T-lymphocytes functions [45], whereas ET-1 would immunosuppress by enhancing the inhibitory effect of Vascular Endothelial Growth Factor (VEGF) on Dendritic cell (DC) maturation [46], with a following diminished availability of IL-12. Finally, ET-1 stimulates cancer cell proliferation by acting as a tumor growth factor per se and enhancing the activity of other tumor growth factors and angiogenic molecules, such as VEGF [43, 47]. In contrast, ANP would play an anti-tumor role by stimulating T-lymphocyte activation [45] and counteracting the pro-angiogenic effect of ET-1 [44]. Then, the heart may either stimulate or inhibit the immunity, with important consequences on tumor growth. In addition, myocardiocytes have been proven to release antiproliferative substances, whose nature, however, is still unknown [48]. According to preliminary data, there would be a feedback mechanism between cardiac endocrine activity and pineal gland, which may explain the environmental influence on the cardiac functions [49]. In more detail, ANP stimulates MLT secretion [50], whereas MLT would inhibit ET-1 production, and this fact could explain the preferential hypotensive effect of MLT itself [3]. The activation of ANP-pineal axis would protect against the risk of an exaggerated adrenergic stimulation of the heart, and a possible alteration of this axis would be involved in the pathogenesis of sudden infant death syndrome [51]. Therefore, ANP-pineal axis could be considered as another anti-stress circuit, capable of enhancing the immune response and protecting against the negative influence of stress on cardiac function and immunity. Then, the pineal gland would represent

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