



The New Endocrinology as the Study of Endocrine Alterations in Human Diseases Other than the Pathologies of Endocrine Glands

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Abstract

A new Endocrinology requires to consider not only the pathologies of the various endocrine glands, but also the endocrine alterations occurring in human systemic diseases, including cancer and autoimmunity, because of their possible influence on the clinical evolution and prognosis. The most frequent systemic disease-associated endocrine alteration is represented by an increased adrenal activity concomitantly to a decline in the pineal function, with the following evidence of high cortisol levels in association with a diminished secretion of melatonin (MLT), the main pineal hormone. The evidence of an increased cortisol secretion in association with a diminished MLT production has been proven to negatively influence the prognosis of the neoplastic diseases, while its prognostic significance in autoimmune pathologies is still unknown. Moreover, an abnormal PRL secretion may occur in breast and prostate metastatic tumours. On the contrary, the role of GH in the neoplastic diseases is still controversial. Most systemic human disease would be due to immune alterations, which would depend on an anomalous function of the cytokine network. Because of the interactions occurring between endocrine and cytokine secretions, systemic disease-related endocrine alterations would be due at least in part to the abnormal cytokine secretion responsible for systemic diseases themselves. The main cytokines involved in the pathogenesis of the systemic diseases consist of IL-1beta, IL-6, TNF-alpha and IL-17. Then, the treatment of cancer and autoimmunity-associated endocrine and cytokine alterations may contribute to the improvement of the prognosis of systemic diseases themselves.

Keywords: ACE system; Autoimmune diseases; Cancer; Cortisol; Cytokines; Endocrinology; Interleukins; Melatonin; Pineal gland

Introduction

Until few years ago, the only endocrine alterations clinically considered were those directly due to an altered function of some endocrine glands, generally consisting of their hyper- or hypofunction. In contrast, because of the interactions occurring among immune system, immunoinflammatory biological response and endocrine functions [1], several endocrine alterations may be present in human systemic diseases, some of them could contribute to the exacerbation of the symptomatology by influencing their physio-pathological processes. Then, the investigation and therapeutic pharmacological correction of systemic disease-related endocrine alterations could improve the treatment of systemic diseases themselves. Moreover, the recent advances in the Psycho-neuro-endocrine-immunology (PNEI)

have demonstrated that a fundamental role in the regulation of the interactions between endocrine and immune functions is played by the pineal gland [2,3]. Then, the investigation of the pineal function, which has been substantially forget until now by the Endocrinologists, becomes fundamental for generating a new Endocrinology, which may really consider the unity of the human biology and physiology.

The Physiology of the Pineal Gland

The relation between pineal and pituitary glands has appeared to play a fundamental role in the regulation of the whole endocrine system, and to change during the evolution of the living species [3]. The pineal may be considered as a neurochemical transducer, capable of transforming the information coming from the

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environmental conditions, namely the light/dark rhythm, into a different regulation of the biological systems, including nervous, endocrine, cardiovascular, and immune systems [2,3]. Even though most studies are limited to the only indole hormone melatonin (MLT) [3], the pineal gland may produce more than ten endocrine-like molecules, including indoles, peptides, and beta-carbolines, which are generated by the link between an indole-amine and an aldehyde group [4,5]. At present, four main indole hormones have been identified, consisting of MLT, corresponding to the N-acetyl-5-methoxytryptamine, 5-methoxytryptamine (5-MTT), 5-methoxytryptophol (5-MTP), and 5-methoxy-indole acetic acid (5-MIA), which are differently secreted in relation to the various phase of the light/dark period [3]. MLT is mainly produced during the night, with a following light/dark circadian rhythm, 5-MTP during the period of maximal light, 5-MTT during the afternoon, and 5-MIA in the early morning. The main peptides are represented by arginin-vasotocin (AVT) and the tripeptide epithalamin. Finally, more than ten beta-carbolines have been identified, the most known of them is the 6-methoxy-1,2,3,4-tetrahydro-beta-carboline, the so-called pinealine (PNL) [5]. Beta-carbolines are provided by anti-tumor cytotoxic activity and psychedelic effects due to their ability to expand and amplify the status of consciousness. The main stimulus for MLT secretion consists of the noradrenaline released from the post-ganglion fibre coming from the superior cervical ganglion by acting on a beta-adrenergic receptor [3]. The light inhibits noradrenaline release from the post-ganglion fibre, then MLT secretion is low during the light period of the day. Then, the administration of beta-blockers during the evening may inhibit MLT night secretion. However, MLT release is under a complex neuroendocrine and immune regulation, and it is inhibited by the alpha-2 adrenergic agonists, high-dose steroid hormones and inflammatory cytokines [3], whereas it is stimulated by the alpha-1 adrenergic agonists [3] and the cannabinoid agonists [6]. The regulation of the secretion of the other pineal hormones is still unknown. The most important biological effect of MLT is the anticancer activity, which is due to a control of DNA expression with the induction of the apoptotic process, and to a stimulation of the antitumor immunity [2,3]. Moreover, MLT would play a fundamental regulatory role on the interactions occurring between brain opioid and cannabinoid inter-neuronal systems [6,7]. On the contrary, the endocrine effects of MLT on the pituitary function would be minimal in humans with respect to their importance in the animals, in whom it exerts evident anti-gonadotropic and anti-adrenal actions [3]. Finally, MLT has been proven to act on specific MLT receptors (MT-R), consisting of two cell surface receptors, the MT-R1 and MT-R2, and a nuclear receptor [3]. On the contrary, no data are available about the possible receptors for the other pineal indoles, peptides and beta-carbolines. According to the knowledgements available up to now, the pineal alterations would probably

represent the most frequent endocrine disorders occurring during the clinical course of the systemic diseases, including cancer and autoimmunity [2,3,8]. By synthesizing, the pineal gland may be considered as the main connection between endocrine and immune systems, because of its function of central regulator of the cytokine network. Obviously, the inclusion of the pineal gland in the clinical endocrinology requires a reinterpretation of the whole endocrine system as under a double central regulatory control exerted by the adenohypophysis and the pineal, respectively in relation to the endogenous biological status and to the universal environmental conditions.

The Main Endocrine-Cytokine Physiological Circuits

It is known that the immune cells may communicate not only through cell-cell contact, but also by releasing some proteins provided by immunoinflammatory effects, the so-called cytokines. Moreover, it has been demonstrated that most cytokines play not only immunoinflammatory activities, but also systemic biological actions, including endocrine, metabolic, nervous, and cardiovascular effects [2,9]. The main immune-endocrine circuit is the connection between hypothalamic-pituitary-adrenal (HPA) axis and macrophage-related inflammatory cytokines, namely IL-1, IL-6, and TNF-alpha. In fact, the inflammatory cytokines have been proven to stimulate cortisol production by acting either on hypothalamic-pituitary levels, or directly on the adrenal gland [1,10]. Inflammatory cytokine-induced cortisol secretion may counteract the immunoinflammatory response following the enhanced cytokine secretion, by protecting against the risk of an exaggerated immunoinflammatory reaction, with potential aggression also against self-antigens. Another fundamental anti-inflammatory functional system is that realized by the interactions among brain cannabinoid system, pineal gland, and cytokine network [5-7]. The endogenous cannabinoid agonists arachidonyl-ethanol-amide (AEA) and 2-arachidonyl-glycerol (2-AG), as well as the exogenous cannabinoid agonist from Cannabis plant tetrahydrocannabinol (THC), play their anti-inflammatory action by inhibiting both macrophage-related cytokines, including TNF-alpha and IL-6, and IL-17 released from Th17 lymphocytes [7,11]. On the contrary, the non-psychoactive agent from Cannabis cannabidiol (CBD) [7] and its endogenous equivalent palmitoyl-ethanol-amide (PEA) [12] are not cannabinoid agents, but they may allow an increased endogenous cannabinoid content by inhibiting the activity of the enzyme involved in cannabinoid degradation, the fatty acid amide hydrolase (FAAH) [13], with a consequent increase in cannabinoid endogenous content, which allows a decline in IL-17 production. On the same way, MLT, the most investigated pineal hormone [3] may also inhibit

macrophage-related inflammatory cytokine secretion [14] and at least in part that of IL-17 itself [15]. On the other side, cytokines may influence the functional status of cannabinoid-pineal axis, particularly IL-10 and IL-12 [16], which are respectively provided by a major anti-inflammatory and inflammatory activity. In more detail, IL-10 has been proven to activate FAAH with a following decline in cannabinoid endogenous content, whereas FAAH is inhibited by IL-12, with a consequent increase in cannabinoid content [16]. Because of the anti-inflammatory role of the endocannabinoid system [7,11], IL-10-induced decline in cannabinoid content would counteract the anti-inflammatory activity of IL-10 itself. On the same way, IL-12-induced increase in cannabinoid content would balance the inflammatory action of IL-12 itself. Then, both inflammatory cytokine-HPA axis and cytokine-brain cannabinoid system-pineal axis are involved in the control of the inflammatory response, with, however, a great difference concerning their influence on the antitumor immunity, since HPA activation allows a suppression of the antitumor immunity because of the immunosuppressive action of cortisol, while the antitumor immunity is stimulated by the pineal-cannabinoid axis [3,7,11]. A third less investigated immune-endocrine circuit, which is involved in the regulation of the cardiovascular system, is represented by two functional axes with opposite effects, consisting of the relation between the neurohypophyseal hormone vasopressin (ADH) and the cardiovascular hormone endothelin-1 (ET-1) [17], and the connection between the neurohypophyseal hormone oxytocin and the cardiac hormone atrial natriuretic peptide (ANP) [18]. ADH and ET-1 play hypertensive, pro-inflammatory and pro-tumoral effects [19], whereas oxytocin [20] and ANP [21] exert hypotensive, anti-inflammatory, cardioprotective, and anti-tumoral actions. A fourth fundamental immunoendocrine circuit is that occurring among renin-angiotensin I-angiotensin-converting enzyme (ACE) and ACE-2 [22]. In addition to the hypertensive activity of ACE and hypotensive action of ACE-2, ACE and ACE-2 may influence several biological functions, including cell proliferation, inflammatory status, and fibrosis processes, but with opposite effects. In fact, ACE through the production of angiotensin II (AngII) has appeared to activate the inflammatory response and to stimulate both cell proliferation and organ fibrosis, whereas ACE-2 through its product angiotensin-(1-7) (Ang 1-7) has been proven to exert an anti-inflammatory activity and to inhibit both cell proliferation and fibrotic mechanisms. ACE – ACE-2 system has appeared to be under a regulation namely played by IL-17, which has been shown to promote ACE expression and inhibit that of ACE-2 [23]. On the other hand, the pineal hormone MLT has appeared to counteract ACE expression and promote ACE-2 activation [24] by inhibiting IL-17 secretion [15], which in contrast stimulates ACE and reduces ACE-2 expression [23]. Then, the functional axis existing

between IL-17 and ACE - ACE-2 system through their respective products AngII and Ang 1-7 may be considered as the major connection among cardiovascular, endocrine and immune functions, because of Ang II-induced stimulation of inflammatory response, cell proliferation and fibrosis, and Ang 1-7-related inhibition of the inflammatory status, cell proliferation and fibrosis processes.

Finally, a fifth neuroimmune functional axis is determined by the connection among adipocytes, cytokine network, and ACE – ACE-2 system, which is mediated by leptin, a protein released from adipocytes [25]. In fact, leptin has been proven to stimulate the adipocyte production of the inflammatory cytokines IL-6, IL-1 beta, and TNF-alpha, which in contrast is inhibited by another adipocyte protein, the adiponectin. The chronic adipocyte-related enhanced production of inflammatory cytokines allows an increased insulin resistance [26].

The Metabolic Syndrome

The main feature of the metabolic syndrome, which includes obesity, hypertension, and dyslipidaemia, is represented by the progressive increase in insulin resistance [26], which is not only due to endocrine factors, but also to the presence of a persistent inflammatory status. Leptin would be involved in promoting the insulin resistance by stimulating the adipocyte release of inflammatory cytokines. Moreover, leptin has appeared to reduce food intake and appetite by stimulating FAAH activity, with a consequent decline in brain cannabinoid content, which in contrast stimulates the appetite. Obesity is associated with increased blood levels of leptin, whose aim is to reduce food intake, but leptin has been proven to be unable to counteract food intake in obese patients, probably because of a possible obesity-related decreased sensitivity to leptin action [27].

Cancer-Related Endocrine Alterations

Cancer-related endocrine and metabolic alterations are generally defined in a non-specific manner as paraneoplastic syndromes, which, however, would have to be subdivided at least into two different subtypes, which consist of a syndrome directly due to some molecules produced by cancer cells themselves, or indirectly induced by an altered neuroendocrine and immune biological response to cancer growth itself. Moreover, some paraneoplastic syndromes are characterized by biological conditions, which may furtherly contribute to tumor progression, such as cancer-related enhanced cortisol secretion [28], because of the immunosuppressive action of cortisol on the anticancer immunity. The progressive decline in the pineal function would represent the main cancer progression-related endocrine deficiency [3,8], at least in experimental conditions. The pineal deficiency with a decline in MLT secretion may either precede

tumor development [29], such as occurring in stress and depressive conditions, or be induced by cancer cells themselves through the production of specific molecules, such as the enzyme 2,3-indole-dioxygenase (IDO) [30], which induce tryptophan depletion, with a following pineal endocrine deficiency, since the pineal indoles originate from tryptophan itself. Moreover, most advanced neoplasms, mainly lung cancer, may present an enhanced cortisol secretion [31], and this evidence has appeared to predict a worse prognosis and a lower survival. The altered cortisol secretion would be the consequence of the altered pineal function, since MLT therapy has appeared to induce a normal circadian secretion of cortisol [32]. In any case, because of the anticancer action of MLT [3,8], advanced cancer-related progressive decline in MLT secretion may contribute to tumor progression itself. In fact, the correction of MLT deficiency through an exogenous administration of pharmacological doses of MLT has appeared to prolong the survival time in cancer patients, for whom no other standard anticancer therapy was available [33]. Another important cancer-associated endocrine alteration is represented by metastatic breast cancer-related hyperprolactinemia, which has been proven to predict a lower survival [34], because of the stimulatory role of PRL on breast cancer cell proliferation [35]. On the contrary, breast surgery-induced hyperprolactinemia has appeared to be associated with a more favourable prognosis [36], and this finding is not surprising, since each breast manipulation stimulates PRL secretion. Then, the lack of PRL enhanced secretion following breast surgery would already reflect the existence of an altered neuroendocrine central control of breast tissue growth. Moreover, prostate cancer may be also stimulated by PRL [35]. Finally, GH could act as tumor growth factor by stimulating the secretion of IGF-I and other tumor growth factors, but at present the relation between GH secretion and cancer development has still to be better defined [37]. Therefore, at present it is still unclear whether hyperprolactinemia may predispose to breast and prostate cancers, as well as whether the enhanced GH secretion, such as in acromegaly, may allow an enhanced frequency of tumours. In contrast, a clear pro-tumoral activity is played by the protein induced by PTH, the PTH-related protein (PTH-rP), which has appeared to be a growth factor for several tumor histotypes, and whose secretion is often abnormally enhanced in advanced cancer patients [38,39]. PTH-induced hypercalcemia is also mediated by the peripheral secretion of PTH-rP, and this finding may explain the association between hypercalcemia and tumour progression in advanced cancer patients.

Autoimmunity-Related Endocrine Alterations

Because of the stimulatory role of macrophage-related inflammatory cytokines on the adrenal function, including IL-6 and TNF-alpha, the autoimmunity diseases may be characterized

by normal or increased cortisol levels, with a loss of its circadian rhythm [1,10,40]. MLT secretion has also appeared to be altered in autoimmune diseases, and the most frequent alteration would consist of the loss of MLT light/dark circadian rhythm [3,40]. However, the clinical and prognostic significance of autoimmune disease-related alterations of pineal and cortisol rhythms is still unknown. In any case, the possible autoimmune disease-related sterility may be due to the inhibitory effects of the abnormal inflammatory cytokine production on gonadotropin secretion [41]. IL-17 would constitute the main inflammatory cytokine responsible for the onset of autoimmune processes [42]. Unfortunately, at present no study has been performed to evaluate the effects of IL-17 on the endocrine secretions. However, because of its stimulatory role on IL-1beta secretion [43], it is probable that IL-17 also may in vivo enhance cortisol secretion.

Endocrine Functions in the Cardiovascular Pathologies

Both cardiac and brain ischemic diseases are characterized by a decline in MLT, with a consequent loss of its light/dark circadian rhythm [44]. The evidence of abnormally high levels of ET-1 [45] and/or inflammatory cytokines, such as TNF-alpha and IL-18, has appeared to predict a poor prognosis in the myocardial infarction [46]. The prognosis is also worse in the presence of low levels of oxytocin, which has been proven to play a cardioprotective activity [47]. The cardiac hypertrophy is promoted by ET-1 and ADH, whereas it is counteracted by ANP and oxytocin [17,18], and heart failure is characterized by high levels of both ET-1 and ANP, as well as brain natriuretic peptide (BNP), with, however, a different significance, since the increased secretion of ET-1 is responsible of heart hypertrophy and failure, whereas that of ANP and BNP would represent a compensatory mechanism to counteract the progressive heart failure. Then, the evaluation of ANP-to-ET-1 may represent a more appropriate clinical index to evaluate the cardiac functionless rather than the single values of ET-1 and ANP [48]. On the same way, the detection of ADH-to-oxytocin ratio would be more appropriate with respect to their single determinations. Recently, IL-17A has appeared to play an important role in cardiovascular diseases [49], because of its stimulatory action on ACE expression and inhibition of ACE2 activity [23].

Endocrine Disturbances in the Neuropsychiatric Diseases

The psychiatric diseases frequently present endocrine anomalies, which may be due to the pathogenesis of the various diseases, or to the effect of the pharmacological therapies. Even though there are controversial data, the depressive disease would be characterized by an unbalance between adrenal and pineal



functions, with an increased cortisol secretion and a diminished production of MLT during the night, with a following desynchronization of their circadian rhythms [3,50]. Schizophrenia may be also characterized by an altered MLT circadian rhythm in association with an altered function of brain cannabinoid system (50). PRL may be often increased in psychiatric patients, but this evidence is generally due to the treatment with neuroleptics, because of their anti-dopaminergic activity.

The Menopausal Syndrome

In addition to the known oestrogen deficiency, recent studies have demonstrated that the menopause is characterized by a concomitant decline in the pineal function and MLT secretion [51]. Then, because of its antidepressant [3,48] and anti-osteoclast activity [52], the diminished production of MLT could play a role in menopause-associated mood changes and osteoporosis. Moreover, menopause-related increase in FSH secretion in association with a decline in the release of anti-mullerian hormone (AMH) could be involved in the pathogenesis of the ovarian cancer, whose frequency enhances in the postmenopausal status. In fact, FSH has been proven to be a growth factor for ovarian cancer [53], which in contrast is inhibited by AMH [54]. Because of its anticancer activity [3,8,29], the decline in MLT production could also promote the onset of an ovarian carcinoma in the postmenopausal period. Therefore, a substitute therapy with MLT could improve the clinical management of the postmenopausal status, as suggested by preliminary clinical studies [55].

Conclusion

The better definition of the functional circuits occurring between endocrine and immune systems will allow the possibility to control the immune status and the inflammatory response by acting on the neuroendocrine regulation of the immune system rather than directly on immune cells themselves.

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