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Review

Neuroendocrine aspects of immunolymphoproliferative diseases

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Summary

Exchange of information occurs between cells of neuroendocrine and immune systems. Neuroendocrine hormones may modulate lymphoid cell activities, including proliferation and mitogenesis, and immune cells may produce neuropeptides as well. Neuropetide Y is synthesized in B-cell leukaemia lymphoblasts, while substance P immunoreactivity has been detected in neoplastic haematological samples of different types of leukaemias. The presence of receptors for neuropeptides on different animal and human lymphoid cell lines, as well as in several types of animal and human lymphoproliferative diseases has been demonstrated. Species variability in receptor distribution has been shown as well. Receptor expression in immune cells may be regulated by changes in microenvironmental conditions; it may also be related to the activation and/or proliferation state of cells. Vasoactive intestinal peptides receptors have been detected in myeloma cells, while somatostatin receptors have been first detected *in vitro* on resting lymphocytes and cells of the monocyte/macrophage lineage, and later on human activated lymphocytes and on lymphoblastic leukaemia cells. Somatostatin receptors have been found in biopsies from patients with malignant lymphomas. Tumor localization in non-Hodgkin lymphomas and Hodgkin's disease can be visualized by *in vivo* somatostatin receptor scintigraphy, contributing to establish the diagnosis and the stage of the disease. Recently, somatostatin receptors have been *in vivo* and *in vitro* detected in human thymic tumors. Although treatment of lymphoproliferative diseases with somatostatin analogs is a little explored field, partial remission was found in patients with low-grade non-Hodgkin lymphoma and cutaneous T-cell lymphoma, and a successful treatment with octreotide has been reported in patients with thymoma. Specific somatostatin receptors present in progenitors of immune cells are not expressed in the mature phenotype, while they can be detected in transformed cell lines. The possibility that this phenomenon is caused by oncogene expression cannot be ruled out. Moreover, preliminary data showed a developmental expression of somatostatin receptors in lymphoid cells, suggesting a potential role for neuropeptide receptors as differentiation markers. Although controlled studies are warranted to investigate the efficacy of the currently available analogs, somatostatinergic compounds may be of interest in the treatment of lymphoproliferative malignancies. A promising approach in refractory patients with somatostatin receptor positive malignant lymphomas may be radionuclide-targeted and cytotoxic analog therapy. These concepts increase the possibility of a wider antitumor treatment with ligands for neuroepeptide receptors than in established 'classic' neuroendocrine tumors.

Key words: immune system, lymphoma, leukaemia, neuroendocrine differentiation, octreotide, somatostatin receptors

Introduction

Neuropeptides are classically produced and secreted by neuroendocrine cells and neurons, and act as neurotransmitters and/or mediators of well-defined hormonal activities in specific tissues and cells. Communication through soluble effector molecules is not confined to the endocrine and nervous systems, but it is very important in the immune system as well. The immune and the neuroendocrine systems affect each other *via* signalling molecules and receptors shared by both systems. Neuroendocrine hormones may, in an autocrine or paracrine way, modulate lymphoid cell activities, including proliferation and mitogenesis. Alterations in this pathway may lead to the occurrence of diseases. Several neuropeptides and their respective receptors have been detected on cells of the immune system. Many studies described their potential role in regulating immune functions and the reciprocal immuno-neuro-endocrine interactions. This paper gives a brief overview of the potential significance of the neuroendocrine phenotype in lymphoproliferative diseases, a finding that has opened a new stimulating area of research.

Significance of neuropeptide expression in lymphoid cells

In their physiological environment, lymphoid cells are exposed to agents, such as hormones and neuropeptides, that do not strictly belong to the immune system. Moreover, immune cells can produce hormones and neuro-

Table 1. Hormone and neuropeptide sources among lymphoid cells.

Source	Peptides or proteins
T lymphocytes	ACTH, TSH, GH, PRL, HCG, Endorphins, Metenkephalin, PTH related protein, IGF-I
B lymphocytes	ACTH, GH, Endorphins, IGF-I, NPY
Macrophages	ACTH, GH, Endorphins, IGF-I, SP, SS, ANP
Splenocytes	LH, FSH, CRH, α-MSH
Thymocytes	LHRH, CRH, AVP, OXT, GH
Mast cells/PBMC	VIP, SS
Megakaryocytes	NPY

Abbreviations: ACTH – adrenocorticotrophin; TSH – thyreotropin; GH – growth hormone; PRL – prolactin; PTH – parathyroid hormone; IGF-I – insulin-like growth factor 1; NPY – neuropeptide Y; SP – substance P; SS – somatostatin; ANP – atrial natriuretic peptide; LH – luteinizing hormone; FSH – follicle-stimulating hormone; AVP – arginin vasopressin; OXT – oxytocin; VIP – vasoactive intestinal polypeptide; PBMC – peripheral blood mononuclear cells.

peptides themselves (Table 1). The first evidence was that of propiomelanocortin (POMC)-derived peptides, such as adrenocorticotrophic hormone (ACTH) and β-endorphins. ACTH-like immunoreactivity was demonstrated in leukocytes [1]. It is intriguing that corticotrophin releasing factor (CRF), which is the natural stimulator of pituitary ACTH secretion, is also produced by immune cells [2]. Moreover, POMC-derived α-melanocyte-stimulating hormone (α-MSH) has been localized in the spleen [3]. Growth hormone (GH) and prolactin (PRL) are produced by distinct population of immune cells and may play a role in immunoregulation by exerting paracrine and autocrine actions [4–6]. The production and paracrine action of both insulin and insulin-like growth factor 1 (IGF-I) in the immune system has also been described [7]. The presence of neuropeptides, such as vasoactive intestinal peptide (VIP), substance P (SP) and somatostatin (SS), has been demonstrated at either protein or messenger ribonucleic acid (mRNA) levels in immune tissues and cells [8–10]. SP belongs to a family of tachykinin peptides that share a common C terminal amino acid sequence [11]. The mammalian tachykinins include SP, neurokinin A, neurokinin B, and two N-terminally extended forms of neurokinin A, i.e. neuropeptide K and neuropeptide Y (NPY). SP has been found in a subset of lymphocytes and monocytes/macrophages at mRNA and protein levels [12–14]. An autocrine/paracrine loop has been hypothesized for this family of neuropeptides among cells of the immune system (Figure 1). Moreover, SP has been detected in the outer cortex of the thymus [15]. A number of other mediators, including vasopressin, oxytocin, bombesin, enkephalin neurophysin are shared between the neuroendocrine and immune systems [7]. Neuropeptides and hormones involved in controlling the immune system may modulate immune/inflammatory responses, depending on the dose and the timing of their administration. However, their significance in lymphoproliferative diseases is still

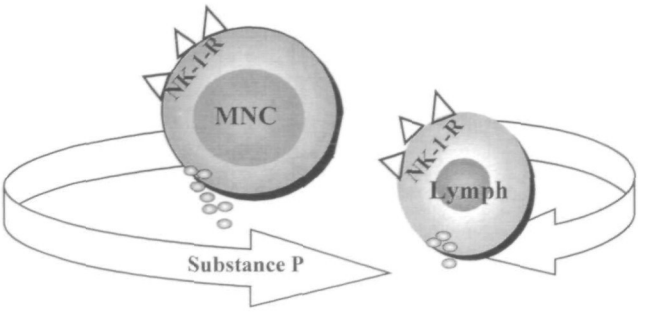

Figure 1 Substance P (SP) immunoreactivity and SP mRNA, as well as SP receptors (NK-1-R) have been detected in granulocytes, monocyte (MNC) and lymphocytes (lymph). This finding suggests the possibility of the existence of autocrine and paracrine activities of this neuropetide in the immune system.

debated. NPY is synthesized in malignant B-cell precursor lymphoblasts either in bone marrow or in peripheral cells from children with acute leukaemia [16]. Plasma NPY immunoreactivity has been found to be higher in children with leukaemia than in age-matched controls, and interestingly, NPY immunoreactivity was significantly higher in those children with favourable clinical risk classification and better outcomes, when compared with those with normal plasma NPY levels [16]. An additional important finding from this latter study is that the elevated plasma NPY immunoreactivity was detected only in patients with B-cell precursor leukaemia, whereas patients with B-, T-cell and myeloid leukaemia had normal NPY levels [16]. SP has been found in activated T lymphocytes, as well as in neoplastic haematological samples from different types of human leukaemia [17]. Conversely, SP was generally undetectable in the majority of non-active normal lymphocytes, while it was found in normal granulocytes and monocytes [17]. SS was also found to be endogenously synthesized in rat basophilic leukaemia [18]. This evidence supports a potential role for NPY, SP and SS both in normal and pathological conditions. Another attractive role for hormones and neuropeptides is the possibility that these agents may function as autocrine regulators of lymphoid cell mitogensis. In fact, the growth of the Burkitt tumor cell line sfRamos has been found to be stimulated in the autocrine pathway by either GH and PRL, indicating that autocrine mitogenesis of tumor B cells may involve neuroendocrine-like secretion [19, 20]. Thus, lymphoid tumor cells seem to produce specific mitogens, which represent potential target for antitumor chemotherapeutic agents.

Significance of neuropeptide receptor expression in lymphoid cells

First observations showed a variable presence of receptors for neuropeptides on different animal and human lymphoid cell lines. However, caution should be taken with the extrapolation of data derived from immortalized cell lines, which may have characteristics different

Table 2. Species-variability of somatostatin receptor mRNA expression in immune tissues and cells.

Tissues and cells	Mouse	Rat	Human
Lymphocytes	sst_2	–	$sst_{3,5}$
Monocytes	sst_4	–	sst_2
Macrophages	sst_4	–	sst_2
PBMC	sst_4	$sst_{3,4}$	sst_2
Limph nodes	sst_1	sst_3	sst_2
Thymus	$sst_{1,2}$	sst_3	$sst_{1,2,3}$
Spleen	$sst_{1,4}$	sst_3	$sst_{2,3}$

Abbreviations: PBMC – peripheral blood mononuclear cells; sst_{1-5} – somatostatin receptor subtypes 1–5.
Data derived from references [30, 38, 39, 41, 73, 74].

from primary lymphoid cells. Moreover, the existence of species variability in the distribution of neuropeptide receptors on immune cells has been demonstrated, suggesting that animal models might be not suitable to study the role of given neuropeptides in humans. This aspect has been particularly shown for SS receptor (SSR) subtypes (Table 2). Generally, neuropeptide receptor expression on endocrine cells is actively regulated by endogenous and exogenous factors, as well as by changes in microenvironmental conditions. This phenomenon becomes even more evident in immune cells, where receptor expression might be related to the activation and/or proliferation state of the cells (see below). Thus, the number or the activity of neuropeptide receptors on immunocytes may change during the specific and aspecific activation of these cells, suggesting that signals mediated by one of these effectors could be predominantly perceived by antigen-activated cells [21].

Receptors for regulatory products of the hypothalamus-pituitary-adrenal axis are widely represented along the immune system. CRF, ACTH and POMC-related peptides, as well as glucocorticoid receptors have been described in lymphoid and accessory cells [2, 22–24]. Receptors for estrogen and testosterone have been found on immune cells. Special emphasis for their role in the thymus derives from the evidence of these hormone receptors on developing immune cells within this organ [25, 26]. GH and PRL receptors have common features with some cytokine receptors and their distribution on immune cells received particular attention because of the well-established actions of both these latter pituitary hormones within the immune systems, as well as for their local production in immune organs [5, 27]. Receptor expression for VIP, SP and SS has been found in different organs of the human immune system, such as lymph nodes, tonsils, Peyer's patches, spleen and thymus [28–30]. VIP_1 and VIP_2 receptors have been recently cloned, and VIP receptor distribution on immune cells has been extensively investigated [31], particularly in the thymus, where both receptor isoforms are expressed on developing thymocytes [32]. These cells, as well as T and B lymphocytes and macrophages express specific receptors for SP [12, 13]. The distribution of SP receptors in immune tissues allowed their visualization after labelling of SP with radioactive Indium. This radiopharmaceutical, [^{111}In-DTPA-Arg^1]-SP, has been used to visualize the thymus and inflammatory sites of disease in patients with autoimmune diseases during *in vivo* SP receptor scintigraphy [33].

In the early eighties, SS-binding sites were found on animal and human circulating B and T cells as well as in spleen-, lymph node- and thymus-derived cells [34, 35]. More recently, different SSR subtype mRNAs have been identified in immune cells with relevant species variability (Table 2) [36, 37]. On peripheral human lymphocytes, sst_3 mRNA was found constitutively expressed, whereas sst_5 mRNA was up-regulated after the activation of these cells [38, 39]. Interestingly, overall SSR number was decreased with the increasing age in the normal human thymus, while the expression of SSR mRNA seems to be developmentally regulated in different subsets of thymocytes [40, 41].

Different neuropeptide receptors have been found in cells from lymphoproliferative diseases. High affinity VIP receptors have been detected on human myeloma cells of the U-266 line and on leukemic T cells of the Jurkat line, suggesting that VIP might influence both antibody-producing cells and T cells [42]. However, a paradigmatic example is offered by the expression of SSR in both immune and haematological cells. As a first piece of evidence, two classes, one of low affinity and a second with higher affinity of SS-binding sites were detected on lymphoblastic leukaemia cells [43]. A Jurkat line of human leukaemic T cells and U-266 IgE producing myeloma cells showed high and low affinity binding sites for fluorescent and radiolabelled SS [44]. In contrast, Nakamura and co-workers did not find SSR on the Jurkat cell line, whereas they detected a large number of SSR on the human adult T leukaemic cell line MT-2 and on the human T-cell line Molt-4F, and a lower number on the Epstein–Barr virus transformed B-cell line Isk [45]. By RT-PCR, a number of lymphoid cell lines of different origin (T cell, B cell, myeloma- and leukemic cells) were shown to express a variable amount of sst_2, sst_3 sst_4 and sst_5 mRNAs, while sst_1 was absent [46]. Moreover, sst_2 mRNA expression in normal human peripheral blood mononuclear cells (PBMC) was very low, compared with the expression of this SSR subtype in cell lines and in PBMC from leukemic patients. In addition, sst_2 mRNA expression in normal PBMC increased after activation with phytohemagglutinin, supporting once more the concept that the receptor expression pattern in human lymphoid cells may be dependent upon their state of activation [46]). Furthermore, it has been demonstrated that the Jurkat T-cell line selectively expresses sst_3 mRNA, suggesting the involvement of this SSR subtype in the regulation of T-cell function [47]. Finally, sst_2 mRNA expression in a number of cell lines of the human T- and B-cell lineage has also been found [48]. An important recent study showed that the SS analog octreotide inhibited growth of different interleukin-6 (IL6)-dependent and IL6-independent human

multiple myeloma cell lines [49]. The effect of octreotide on these cell lines, expressing sst_2, sst_3, and sst_5 receptors, was mainly cytostatic, however, in three out of eight cell lines a weak octreotide-induced apoptosis was detected. Moreover, these authors showed that octreotide induced apoptosis in B-B4$^+$ plasma cells could be isolated from bone marrow of patients with multiple myeloma [49]. Since the growth of these cell lines is promoted by an autocrine IGF-I production, the mechanisms of octreotide-induced growth inhibition might involve this autocrine loop. In fact, octreotide may downregulate IGF-I expression or upregulate the production of inhibitory IGF-I binding proteins, interfering with the IGF receptor signalling. These mechanisms do not exclude the possibility that octreotide-induced apoptosis may play a role as well. In fact, these cell lines express sst_3 receptor, which has been demonstrated involved in this pathway [50].

Additional information on SSR expression on human immune cells derives from *in vivo* SSR scintigraphy studies. This technique is routinely used in the localization of neuroendocrine tumors and their metastasis. However, SSR scintigraphy has been employed in visualizing other non-neuroendocrine tumors expressing SSR [51–53]. Moreover, SSR has been found by autoradiography in the biopsies of patients with both T and B non-Hodgkin's lymphoma and Hodgkin's disease and their metastasis [54–56]. While the *in vivo* imaging technique using [^{111}In-DTPA-D-Phe^1]-octreotide has contributed to optimize the staging procedures in patients with malignant lymphomas, *in vitro* autoradiography demonstrated the presence of SSR predominantly in the lymphoblastic areas of lymphomas, which represents the active part of these tumors. Moreover, the expression of sst_2 and sst_3 mRNA in non-Hodgkin's lymphomas and sst_2 mRNA in Hodgkin's disease has been found [58]. SS-binding sites have been detected *in vitro* using [^{125}I-Tyr^3]-octreotide on cells from patients with acute lymphoblastic leukaemia and acute myeloid leukaemia and SS and octreotide inhibited spontaneous leukaemic cell growth in approximately 33% of cases [59]. Preliminary data demonstrated a partial remission in 36% of patients with low-grade non-Hodgkin's lymphomas treated with octreotide [60]. These studies demonstrated that the presence of SSR in lymphoproliferative diseases is proving useful for their localization and allowing the development of novel receptor-mediated antitumor treatments. Moreover, the accurate evaluation of SSR subtype pattern in lymphoproliferative diseases might become more important when new subtype selective analogs will be available for medical treatment and/or for radiotherapy using high doses of β-emitting coupled somatostatin analogs. Another opportunity is the coupling of stable SS analogs with cytotoxic agents as a form of anticancer therapy [61].

More recently, a high *in vivo* uptake of [^{111}In-DTPA-D-Phe^1]-octreotide has been detected in patients bearing thymoma or thymic carcinoid [62–64]. Moreover, a successful treatment with octreotide has been reported in two patients with thymoma [64, 65]. Although the role and mechanisms of the *in vivo* uptake of the radiolabelled SS analog in these tumors is unclear so far, sst_3 receptor might be involved since a predominant expression of this SSR subtypes was found in a cortical thymoma displaying a high *in vivo* uptake of the analog [66]. SS is present in the thymus, and it may play an autocrine/paracrine regulatory role in this organ [67–69]. In fact, it has been shown that SS can inhibit normal and neoplastic thymic epithelial cells proliferation [30, 66]. Although the significance of specific SSR expression in human thymus remains still unclear, a disturbance in the pathway between SS and its receptors might be involved in the pathogenesis of autoimmune diseases often associated with pathological conditions of this primary lymphoid organ [68]. In line with this hypothesis, SS mRNA was undetectable in the tissue and cells of an epithelial thymic tumor associated with myasthenia gravis [66].

Conclusions

Summarizing, tumor localization in lymphoproliferative disease could be visualized by *in vivo* SSR scintigraphy, a finding that may contribute to the establisment of a diagnosis and a staging of the disease. Treatment of lymphoproliferative diseases with SS analogs is a little explored field. In haematological malignancies, partial remission was found in patients with low-grade non-Hodgkin lymphoma and cutaneous T-cell lymphoma, and a successful treatment with octreotide has been reported in patients with thymoma. Since the expression of SSR in some neuroedocrine tumors [70] may have a prognostic value, it would be interesting to investigate this possibility in lymphoproliferative diseases as well. In fact, specific SSR, expressed in progenitors of immune cells, is not present in the mature phenotype, while its expression can be detected in transformed cell lines. The possibility of such marker expression being caused by oncogene can not be ruled out. However, preliminary data in human lymphoid cells showed a developmental expression of SSR, a fact that supports further research on their potential role as differentiation markers. SS analogs may be of interest in the treatment of lymphoproliferative malignancies, although controlled studies are warranted to investigate the efficacy of the current available SS analogs. A promising approach in refractory patients with SSR positive malignant lymphomas may be radionuclide-targeted therapy. Finally, the development of receptor-based localization and antitumor strategies may be extended to other G protein-coupled receptors. The imaging of tumor using receptors for bombesin, VIP, SP, gastrin has been already employed for the visualization of many neoplasms and cytotoxic analogs of ligands, as these receptors have been developed and display an antiproliferative effects in experimental conditions [71, 72]. Whether these compounds can be of clinical value in lymphoproliferative diseases is

still unknown; however, their development represents an interesting and promising novel approach.

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