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## The Role of Cortistatin in the Human Immune System

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**Abstract**

Cortistatin (CST) is a recently described neuropeptide that shares high homology with somatostatin (somatotropin release-inhibiting factor, SRIF) and binds with high affinity to all somatostatin receptor (sst) subtypes. CST is currently known to have a widespread distribution in many human organs including the immune system. The activities specific to CST may be partially attributable to its binding to the growth hormone secretagogue (GHS) receptor (GHS-R) and the orphan G-protein-coupled receptor MrgX2. Human immune cells produce CST, whereas macrophage lineage and activated endothelium express sst<sub>2</sub>, and human lymphocytes express sst<sub>3</sub>. The human thymus expresses sst<sub>1,2,3</sub>, MrgX2 and almost all immune cells express GHS-R. Moreover, at this very moment promising research with CST in experimental animal models is being performed. On the basis of these promising results, studies aiming to further evaluate the possibilities of CST as a therapeutic agent in human immune mediated inflammatory diseases are warranted.

## Introduction

CST is a neuropeptide that is widely distributed throughout the body (de Lecea et al., 1996; Dalm et al., 2004a). It was first discovered in brain as a neuropeptide with chemical structural and functional similarities with SRIF (de Lecea et al., 1996). In humans, CST is produced as a 17 or 29 amino acid peptide, while SRIF is secreted in two biologically active forms: a 14 amino acid form (SRIF-14) and an amino-terminally extended 28 amino acid form (SRIF-28). Structure-function analysis of native SRIF and CST has shown that the amino acid residues Phe7, Trp8, Lys9 and Thr10 are necessary for receptor binding. The differences are in both the N and C terminal amino regions of the peptide.

Structurally, sst are so-called 7 transmembrane domain (TMD) glycoproteins, comprised of 7 membrane-spanning alpha-helical domains connected by short loops, a N-terminal extracellular domain and a C-terminal intracellular domain. The genes for a family of 5 SRIF receptors have been cloned in recent years. The SRIF receptor genes are all located on different chromosomes, but have a high degree of sequence homology (Patel et al., 1996). CST binds with high affinity to all 5 sst subtypes (Criado et al., 1999; Fukusumi et al., 1997; Siehler et al., 1998). The function of SRIF has been studied far more in depth: it can act as a neurotransmitter and neurohormone and in peripheral tissues it regulates endocrine and exocrine secretion and acts as a modulator of motor activity in the gastrointestinal tract (Reichlin, 1983a; Reichlin, 1983b).

Differential actions have been described for CST and SRIF, for example intracerebral injection of CST causes an increase while SRIF decreases slow wave sleep (de Lecea et al., 1996). Outside the central nervous system (CNS), both CST and SRIF are present in a variety of neural and non-neural tissues such as pancreas, endocrine tissues and the immune system (Dalm et al., 2004a; de Lecea and Sutcliffe, 1996; de Lecea et al., 1996; Reichlin, 1983a; Reichlin, 1983b). The clinically used SRIF analogues octreotide and lanreotide bind with high and moderate affinity to sst<sub>2</sub> and sst<sub>5</sub> whereas the recently developed synthetic SRIF analog SOM-230 (pasireotide) binds with high affinity to sst<sub>1,2,3</sub> and sst<sub>5</sub> (Bruns et al., 2002; Weckbecker et al., 2002). SOM-230 is currently under clinical investigation.

Many cellular effector proteins like adenylate cyclase (AC), phospholipase C, calcium channels, potassium channels, Na<sup>+</sup>/H<sup>+</sup> exchanger, protein tyrosine phosphatases, phospholipase A<sub>2</sub>, mitogen-activated protein kinase (MAPK) and p53 were reported to be modulated by sst subtypes. The antiproliferative effects of SRIF are thought to be due to activation of a subclass of protein tyrosine phosphatase enzymes. SRIF receptors are coupled to intracellular signal transduction cascades via various pertussis toxin-sensitive (Gi/ Go) and -insensitive G-proteins (e.g. Gq, G14,

G16). Depending on the cell type, the various sst subtypes have been shown to couple to a diversity of transduction systems (Patel, 1999; Delesque et al., 1995; Ferjoux et al., 2003; Lopez et al., 1996; ten Bokum et al., 2000; Weckbecker et al., 2003). Cortistatin has been shown to diminish cAMP levels through activation of each individual sst subtype (Fukusumi et al., 1997).

### **Cortistatin, somatostatin and their receptors in the human immune system**

More than 20 years ago Bhathena et al. already demonstrated the presence of SRIF binding sites on human peripheral blood mononuclear cells (PBMC)(Bhathena et al., 1981). Since then, SRIF binding sites have been demonstrated on several immune and haematopoietic cells and tissues using different techniques. Radioligand binding studies demonstrated sst subtypes to be present on various human lymphoid cell lines (Lichtenauer-Kaligis et al., 2004; ten Bokum et al., 2000; van Hagen et al., 1994). Using radioligand binding, as well as fluorescence-labelled SRIF analogues and FACS analysis, SRIF binding sites were detected on mitogen-activated human peripheral lymphocytes (Hiruma et al., 1990). On resting PBMCs, red blood cells and granulocytes no binding sites were detectable by the radioligand assay. We demonstrated unequivocally that human peripheral blood B- and T-lymphocytes selectively express sst<sub>3</sub>, whereas monocytes do not express sst. However, upon activation, monocytes are induced to express sst<sub>2</sub> (table 1) (Lichtenauer-Kaligis et al., 2004).

The thymus is a central lymphoid organ in mammals, which plays a pivotal role in the control of the immune system. The presence of the thymus and its functionality are required for a full establishment of immunocompetence. The thymus involutes with a constant velocity during the first decade of life. Thereafter, the involution process decreases progressively. Binding studies and reverse transcriptase polymerase chain reaction (RT-PCR) analysis have been used to characterize SRIF and sst subtype expression in the normal human thymus SRIF and sst<sub>1,2,3</sub> have been found in thymic tissue (Ferone et al., 1999). The expression of these different subtypes appears heterogeneous within the thymic tissue and on different cell subsets. A selective expression of sst<sub>1</sub> and sst<sub>2</sub> has been found on cultured thymic epithelial cells (TEC) (Ferone et al., 2002). TEC are thought to be a potential source of SRIF and CST production within the thymus, since their mRNA has been detected in these cells (Ferone et al., 1999; Ferone et al., 2002). Conversely, CST is synthesized in thymocytes while no SRIF can be found (Dalm et al., 2003b). Freshly isolated immature thymocytes express sst<sub>2</sub> while more mature thymocytes express sst<sub>3</sub>. The sst<sub>2</sub>/sst<sub>3</sub> switch suggests a role during thymocyte differentiation (Ferone et al., 2002). The spleen has not been studied in depth but, PCR studies show that the spleen expresses both sst<sub>2</sub> and sst<sub>3</sub>, whereas the human bone marrow expresses only sst<sub>2</sub> (Oomen et al., 2000).

Striking differences between human and rodent species have been found with respect to the expression of sst subtype expression in immune cells. In the murine immune system predominantly sst<sub>2</sub> and sst<sub>4</sub> are expressed, while in human immune cells predominantly sst<sub>2</sub> and sst<sub>3</sub> are expressed in distinct cell subsets (Lichtenauer-Kaligis et al., 2004; ten Bokum et al., 2002). Because of this species dependent sst subtype expression in the immune system of animal models, it can be difficult to translate study results directly into the human situation.

CST has been identified previously as a high potency ligand of MrgX2, a human orphan G-coupled receptor (Robas et al., 2003). MrgX2 does not display significant binding affinity to somatostatin. It is mainly expressed in dorsal root ganglions. Notably, however, MrgX2 is not expressed in the cerebral cortex in which CST is most abundant (de Lecea et al., 1996). The biological role of CST binding to MrgX2 is still incompletely characterized, although it probably has a role in the modulatory effect of CST on pain perception (Robas et al., 2003). MrgX2, which also binds to proadrenomedullin N-terminal peptide (PAMP; an endogenous peptide with powerful hypotensive actions), is widely expressed in several human organs (Kamohara et al., 2005; Nothacker et al., 2005). In our studies with human immune cells, MrgX2 mRNA expression is not found in cells of the monocyte-lineage (unpublished results). So monocytes, macrophages and dendritic cells that are known to produce CST and express sst<sub>2</sub> do not express MrgX2. This suggests that the autocrine loop in this lineage is maintained by the CST-sst<sub>2</sub> loop.

Whole thymus preparations and thymocytes express MrgX2, while all human immune cells have the capacity of synthesizing CST. Early thymocytes express sst<sub>2</sub> but switch to sst<sub>3</sub> in the double positive (CD4+CD8+) positive state (Ferone et al., 2002; Lichtenauer-Kaligis et al., 2004). Gene expression profiles (Affymetrix) during human thymocyte development shows MrgX2 expression in single positive T cells but this has not been confirmed yet by Q-PCR (unpublished results). The synthesis of both CST and SRIF and the expression of sst<sub>1,2,3</sub> and MrgX2 in the thymic microenvironment during lymphocyte development may have a regulatory effect on T cell differentiation.

Further research has shown that both CST-14 and CST-17, but not SRIF, bind to the growth hormone (GH)-secretagogue receptor (GHSR-1a), with an affinity comparable to that of ghrelin (Deghenghi et al., 2001). GHS-R is a G-protein-coupled receptor with 7 transmembrane domains, the endogenous ligand of this receptor is acylated ghrelin (Smith et al., 2001). GHS-R is expressed in the anterior pituitary gland and hypothalamus, various extrahypothalamic regions of the central nervous system, multiple peripheral organs (e.g. the stomach, intestine, pancreas, kidney, heart and aorta) and in various human pituitary adenomas and endocrine neoplasms of the lung, stomach and pancreas (van der Lely et al., 2004). Human ghrelin as well as GHS-R mRNA expression has been detected with real time-PCR and confirmed by DNA-sequencing in human T

lymphocytes, B lymphocytes, and neutrophils from venous blood of healthy volunteers. Large interindividual differences in ghrelin mRNA expression levels have been described, however, cell type and maturity of the cells do not seem to have an influence on ghrelin production in immune cells (Dixit et al., 2004; Hattori et al., 2001; Koo et al., 2001). These findings suggest that CST-specific actions could be mediated by the GHSR-1a and CST might thus represent a link between the ghrelin and the SRIF systems (Broglia et al., 2007).

### **Somatostatin receptor activation and immune cell functions**

Numerous effects of SRIF on immune cell function have been demonstrated *in vitro*, as well as *in vivo*. We suppose that the effects of SRIF on immune cell function are a consequence of sst activation and assume that CST activate these receptors in a similar way. It is difficult to compare the reported studies as the experiments have been carried out with cells from different animal species and under different experimental conditions (ten Bokum et al., 2000). As mentioned above, significant species differences are described with regard to sst subtype expression. Predominantly, inhibitory actions on the immune system have been reported. Often a so-called biphasic response has been observed, i.e. inhibition of a certain response at low SRIF concentrations (nM range) and stimulation of that same response at higher concentrations ( $\mu$ M range). This biphasic response appears to be characteristic for the interaction of neuropeptides with immune cells, and may have a physiological correlation: the lower nanomolar concentrations are characteristic levels of neuropeptides found in blood, whereas the higher concentrations may be found at nerve endings (Stanisz et al., 1986). The differential effects may be due to activation of different receptor classes with high and low affinities for the ligand or to modulation of receptor number or activity (ten Bokum et al., 2000).

#### ***Effect of SRIF on the T cell lineage***

Inhibition of lymphoid cell proliferation is the best-documented effect of SRIF on immune function. Previously we summarized the results of *in vitro* studies on the effect of SRIF on the spontaneous or mitogen-induced proliferation of lymphoid cell lines and on cells isolated from lymphoid tissues of several animal species (van Hagen et al., 1994). Most of these studies involved mixed cell populations under T cell-stimulating conditions. The most significant inhibitory effects of SRIF are observed when purified T lymphocytes or T cell lines are used under suboptimal stimulation conditions (Casnici et al., 1997; Krco et al., 1986; Payan et al., 1984). The use of strong activating lectins or cytokines may overrule the effect of a sst agonist or antagonist. Most of the studies have been carried out using native SRIF, octreotide or lanreotide. Murine lymphocyte proliferation is inhibited in the same extent by lanreotide as native SRIF, indicating that the effect is mediated by sst<sub>2</sub> or possibly sst<sub>3</sub> (Agro et al., 1991). Ferone et al. have showed clearly that immature

thymocytes expressing  $sst_2$  can be inhibited by octreotide whereas more differentiated thymocytes expressing  $sst_3$  can be inhibited by SRIF and not by octreotide which has only a low affinity for  $sst_3$  (Ferone et al., 2002).

$Sst_2$  is the  $sst$  subtype which is most often implicated in inhibition of cell proliferation by SRIF, although inhibition of proliferation of human Jurkat T lymphocytes has been shown to be mediated by  $sst_3$  (Cardoso et al., 1998). Induction of SRIF mRNA by proinflammatory stimuli has been demonstrated in murine splenocytes (Blum et al., 1998). Taken together, these studies indicate that SRIF plays an important role in maintaining T cell immune homeostasis.

Besides the inhibitory effect on proliferation, SRIF is able to affect the production of cytokines by T cells. SRIF reduces the secretion of interferon- $\gamma$  (IFN- $\gamma$ ) from human PBMCs (Muscettola and Grasso, 1990). Production of IFN- $\gamma$  by splenocytes and T lymphocytes isolated from murine schistosome granulomas is decreased by SRIF and octreotide *in vivo* and *in vitro* (Blum et al., 1992). This effect is probably mediated by  $sst_2$  as mRNA for this receptor subtype has been shown to be expressed by granuloma T cells and the effect can be blocked by an antiserum directed against  $sst_2$  (Elliott and Weinstock, 1996; Elliott et al., 1994). Controversial reports have been published concerning both IL-2 production and the activation of lymphocyte cytotoxicity by SRIF (ten Bokum et al., 2000). SRIF stimulates also adhesion of resting human T cells to fibronectin which may indicate a role for neuropeptides in the regulation of lymphocyte migration and recirculation (Levite et al., 1998). At physiological concentrations SRIF inhibits T cell proliferation but, it nevertheless may enhance a number of effector functions such as cytokine secretion and receptor expression.

### ***Effects of SRIF on the B cell lineage***

SRIF can inhibit the production of immunoglobulins (Igs) by B cells in a number of experimental settings. SRIF dose-dependently reduces the secretion of IgA from a murine plasmacytoma cell line and from murine Con A-stimulated lymphocytes from spleen, Peyer's patches and mesenteric lymph nodes (Scicchitano et al., 1988). The secretion of IgM and IgG is less affected (Stanisz et al., 1986). The secretion of IgG2, but not IgG1 or IgM by splenocytes from *Schistosoma mansoni*-infected mice can also be inhibited *in vitro* by SRIF. *In vivo* treatment with octreotide completely abrogates IgG2 but not IgG1 or IgM secretion from granuloma cells (Blum et al., 1993). *In vivo* treatment of rats with somatostatin diminishes the number of antigen-specific plasma cells formed during a primary immune response, pointing to an effect on B cell activation, proliferation and/or differentiation (Eglezos et al., 1993). *In vitro* differentiation of human peripheral blood B lymphocytes into plasma cells is shown to be reduced by octreotide, indicating the involvement of  $sst_2$  and/or  $sst_5$ . These findings correlate with the presence of binding sites for octreotide in the

germinal centres of secondary lymphoid follicles (Reubi et al., 1998; Reubi et al., 1992). These are sites of the generation of B memory cells and somatic hypermutation, a process to generate B cells with a high affinity B cell receptor.

### ***Effects of SRIF on the functions of monocytes and macrophages***

SRIF can influence a number of activities of cells of the monocyte-macrophage lineage. Chemotaxis of human peripheral blood monocytes and of a murine macrophage cell line can be blocked by SRIF, although a strong dose-dependency of the effect has not been observed. However, enhancement of chemotaxis by the SRIF analogue octreotide has been described as well (Ahmed et al., 2001; Ahmed et al., 1998; Wiedermann et al., 1993).

There are also contradictory data on the modulation by SRIF of cytokine release from monocytes and macrophages. Komorowski and Stepień have shown that LPS-induced secretion of IL-1 $\alpha$  and IL-6 from human peripheral blood monocytes is potentiated by SRIF in nM concentrations, whereas others have shown that SRIF decreases LPS-induced secretion of IL-1, IL-6 and TNF- $\alpha$  from human monocytes (Komorowski and Stepień, 1995; Peluso et al., 1996). Despite some contradictory results, SRIF in general appears to suppress monocyte and macrophage effector functions (ten Bokum et al., 2000).

### **Cortistatin and SRIF in clinical immunology**

Recently we studied the expression of SRIF, as well as that of CST in human lymphoid tissues, immune cells and lymphoid cell lines (Dalm et al., 2003b). SRIF mRNA can be detected in the human thymus only, while not in thymocytes. Moreover, we have not been able to demonstrate the presence of SRIF in human immune cell types at all (summarized in table 1). On the other hand, CST mRNA is clearly expressed in all immune cells and immune tissues studied. Two CST isoforms have been found and both forms are expressed in the majority of the cells and tissues. Whereas both fragments are detected in nearly all T cell lines (7 out of 8), most of the B cell lines express the short fragment only (8/10) (Dalm et al., 2003b). Autoradiographic studies show that CST is able to displace [125I-Tyr3]octreotide binding on cryostat sections of human thymic tissue and of sst<sub>2</sub> expressing cells with a high affinity. On the basis of these observations, a role for CST as an endogenous ligand of sst in the human immune system, rather than SRIF itself is suggested. Compared to SRIF and octreotide, CST has a slightly lower affinity for sst<sub>2</sub> in human thymic tissue (approximately 20-fold). The inhibition of human thymocyte proliferation by cortistatin is comparable to SRIF (Dalm et al., 2003a; Dalm et al., 2003b).

As indicated above, previous studies show that CST has a high affinity for the different human sst subtypes in stably transfected cell lines (Criado et al., 1999). The expression of two other known receptors capable of binding CST, MrgX2 and GHS-R, in the immune system is a less explored field. Quantitative PCR was used to determine the distribution of MrgX2 in human tissues. The highest levels of MrgX2 are observed in dorsal root ganglions and moderate levels have been detected in thymus (Robas et al., 2003). On the other hand, macrophages and dendritic cells express both CST and sst<sub>2</sub> but do not to express MrgX2 (unpublished results). There are no data reported on the functional relation CST-MrgX2 in the human immune system.

Ghrelin, a recently described endogenous ligand for the GHS-R, is produced by stomach cells and is a potent circulating orexigen, controlling energy expenditure, adiposity, and growth hormone (GH) secretion (van der Lely et al., 2004). Both, GHS-R and ghrelin are expressed in human B- and T cells and monocytes (Dixit et al., 2004; Hattori et al., 2001). Ghrelin acts via GHS-R to specifically inhibit the expression of proinflammatory anorectic cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (Dixit et al., 2004).

Small-molecule GHS has a considerable immune-enhancing effect. GHS may exerts its immune enhancing effect by promoting cell division in lymphoid cells as they exhibit a significant increase in thymic cellularity and differentiation (Koo et al., 2001). Expression of GHS-R and ghrelin is detectable in all immune cells regardless of the maturity and cell types with great individual variations (Hattori et al., 2001). Widespread distribution of GHS-R in human immune cells may indicate unknown biological functions in the immune system. The expression of the GHS-R receptor in immune cells and the functional role of ghrelin as a modulator of lymphocyte function suggest a potential role for CST via the same receptor (Xia et al., 2004).

Many of the studies regarding sst subtype expression described above have been performed *in vitro* using isolated cell populations. Therefore, it is difficult to judge the relevance of these findings for the *in vivo* modulation of an inflammatory response. Various experimental studies have described the *in vivo* effects of SRIF and CST in modulating autoimmune disease and chronic inflammation.

The effect of SRIF on local inflammatory processes has been studied in a subcutaneous air pouch in experimental animals (Karalis et al., 1994). Aseptic inflammation in a rat air pouch reduces, after local or systemic administration of octreotide and lanreotide in a dose-dependent manner. Both SRIF analogues diminish the number of leukocytes and the levels of inflammatory mediators such as TNF- $\alpha$ . Murine schistosomiasis has been used as a model to study the role of SRIF in the regulation of granulomatous inflammation (Elliott et al., 1994). Murine granuloma CD4<sup>+</sup> T lymphocytes express sst<sub>2</sub> (in contrast to human lymphocytes). Both SRIF and octreotide markedly

reduce the production of IFN- $\gamma$  by granuloma T lymphocytes resulting in a decreased granuloma response (Elliott and Weinstock, 1996; Elliott et al., 1999; Weinstock and Elliott, 2000).

The role of SRIF as an anti-inflammatory agent in rheumatoid arthritis has been studied extensively. SRIF receptor expression can be detected by *in vivo* sst-scintigraphy after injection of  $^{111}\text{In}$ -labelled octreotide. This technique is used for the localization and staging of neuroendocrine tumors and other malignancies that express high levels of sst (de Herder et al., 2006; Krenning et al., 2004; Krenning et al., 1992; van der Lely et al., 2003). Among the non-neuroendocrine tumors that can be visualized by sst-scintigraphy are malignant lymphomas: both T and B non-Hodgkin lymphomas and Hodgkin disease lymphomas (Vanhagen et al., 1993). In a number of infectious diseases (e.g. tuberculosis), autoimmune diseases (e.g. Graves' ophthalmopathy) and other immune-mediated diseases (e.g. sarcoidosis and rheumatoid arthritis), the sites of inflammation can also be visualized (Vanhagen et al., 1994a; Vanhagen et al., 1994b). In patients with rheumatoid arthritis (RA) the uptake of radioactivity in the affected joints shows a high correlation with clinical activity. Immunohistochemical and RT-PCR studies confirm the presence of sst<sub>2</sub> receptors. In biopsies of rheumatoid synovium sst<sub>2</sub> expression has been detected on macrophages, as well as on endothelial cells of venules (especially high endothelial venules)(Takeba et al., 1997; ten Bokum et al., 1999a; Vanhagen et al., 1994a).

SRIF can be produced by synovial cells or secreted by sensory nerve endings into the joint capsule (Takeba et al., 1997). These data point towards the existence of a SRIF immunoregulatory circuit within the rheumatoid synovium. Intra-articular injection of SRIF in patients with RA can reduce pain and synovial swelling (Coari et al., 1995; Matucci-Cerinic and Marabini, 1988). The analgesic effect of SRIF may be mediated by reduction of the hypersensitivity of afferent sensory nerves in the joint (Heppelmann and Pawlak, 1997). Sst expression is associated with blood vessels in human rheumatoid synovium (Reubi et al., 1994). SRIF decreases the extravasation of plasma and leukocytes and may reduce synovial swelling through this mechanism (Karalis et al., 1994). Reduction of joint swelling by intra-articular injection of SRIF is also observed in a rabbit model of chronic arthritis (Matucci-Cerinic et al., 1995). In addition, histological studies in this model have revealed reduction of lymphocyte infiltration in the synovium and reduced vasculitis in SRIF-treated animals. In our studies we did not observe a reduction in the severity of rat adjuvant arthritis using the SRIF analogue octreotide (ten Bokum et al., 1999b). Takeba et al. has shown that SRIF at physiological concentrations inhibits the *in vitro* proliferation of fibroblast-like synovial cells from RA patients (Takeba et al., 1997). Cultured fibroblast-like synovial cells express mRNA for both sst<sub>1</sub> and sst<sub>2</sub>, while sst<sub>2</sub> mRNA is sensitive to upregulation by proinflammatory stimuli. The stimulation-induced production of IL-6, IL-8 and matrix metalloproteinases by these cells is also reduced by SRIF treatment *in vitro*. An uncontrolled study shows positive effect of octreotide in the

treatment of RA (Paran et al., 2001). Based on subtype receptor expression in rheumatoid synovium (sst<sub>1-3</sub>), the recently developed long-acting SRIF analogue SOM-230 which binds to all subtype receptors except sst<sub>4</sub>, may be a promising candidate for therapy in RA. Moreover, Gonzalez-Rey et al. show that CST treatment significantly reduces the severity of established collagen-induced arthritis, completely abrogating joint swelling and destruction of cartilage and bone (Gonzalez-Rey et al., 2007). The therapeutic effect of CST is associated with a striking reduction in the two components of disease that are Th1-driven autoimmune and inflammatory responses. Cortistatin downregulates the production of various inflammatory cytokines and chemokines, decreases the antigen-specific Th1-cell expansion, and induces the production of regulatory cytokines, such as interleukin-10 and transforming growth factor beta-1. Interestingly, CST exerts its effects on synovial cells through both SRIF and ghrelin receptors (Gonzalez-Rey et al., 2007). SRIF binds only to sst, while CST can also bind to the ghrelin receptor and MrgX2. In the same model ghrelin shows also anti-inflammatory effects. CST is exerting its therapeutic effect on collagen induced arthritis partially through the ghrelin receptor, which can be partially reversed by a ghrelin-receptor antagonist (Gonzalez-Rey et al., 2007). In two other models studied by the group of Delgado, an experimental inflammatory bowel disease model and a sepsis model, treatment with CST demonstrates clinical and pathological amelioration of disease (Gonzalez-Rey et al., 2006a; Gonzalez-Rey et al., 2006b). These models show the downregulation of the Th1 response and the increase of regulatory T cells that are responsible for the recovery of the immune tolerance. SRIF receptor expression has been shown in colon biopsies of patients with Crohn's disease (unpublished results). Fistulas are a part of Crohn's disease, and although there are many therapeutic modalities used in treating these fistulas, they are only partially successful. SRIF may have a role in treating enterocutaneous fistulas in Crohn's disease and may prevent surgery or prolonged immunosuppressive therapy (Lavy and Yasin, 2003). However, based on the previous animal data, CST seems a more promising candidate in the treatment inflammatory bowel disease than SRIF.

To our knowledge no human data concerning CST in these diseases have been reported yet. However we have found CST expression in malignancies of the immune system, i.e. malignant lymphomas and lymphocytic leukemias (nonpublished results).

In biopsies from patients suffering from other granulomatous diseases such as sarcoidosis and Wegener's granulomatosis, sst<sub>2</sub> expression is also associated with cells of the mononuclear phagocyte lineage, including epithelioid cells and multinucleated giant cells within the granulomas (ten Bokum et al., 1999c). In none of the biopsies sst<sub>2</sub> expression is observed in the lymphocytic areas, which is related to the sst<sub>3</sub> expression pattern in humans as shown in table 1. Previously we

have treated a patient suffering from sarcoidosis with octreotide, which suppressed the granulomatous response (ten Bokum et al., 1999c).

Based on the following observations: a) human immune cells produce CST but no somatostatin, b)  $sst_2$  is expressed by the macrophage lineage and activated endothelium, c) human lymphocytes express  $sst_3$  and GHS-R, d) the thymus expresses  $sst_{1,2,3}$  and MrgX2, e) the human spleen and bone marrow both express at least  $sst_2$ , and f) promising data on CST-treatment in experimental animal models of immune disease, clinical studies evaluating the potential role of CST in human immune mediated inflammatory diseases are warranted. However, we have to take into account that results obtained from animal models cannot be directly translated to human diseases because of the different sst subtype expression in the murine immune system.

Table 1. Expression of SRIF and cortistatin (CST) and their receptors in the human immune system and malignancies of the immune system (Dalm et al., 2003b; Dalm et al., 2004a; Dalm et al., 2003c; Dalm et al., 2004b; Ferone et al., 2004; Ferone et al., 2002; Lichtenauer-Kaligis et al., 2004; Oomen et al., 2000; ten Bokum et al., 2000; ten Bokum et al., 1999a; ten Bokum et al., 1999c; van Hagen et al., 1999).

Cell	SRIF	CST	sst <sub>1</sub>	sst <sub>2a</sub>	sst <sub>3</sub>	sst <sub>4</sub>	sst <sub>5</sub>	MrgX2	GHS-R
CD 34+ stem cells	-	nd	-	+	-	-	-	nd	nd
Thymocytes	-	+	-	-	+	-	-	+	nd
T lymphocytes	-	+	-	-	+	-	-	+	+
B lymphocytes	-	+	-	-	+	-	-	nd	+
T lymphoid cell lines	-	+	-	+	+	-	-	nd	+
B lymphoid cell lines	-	+	-	+	+	-	-	nd	+
Monocytes	-	+	-	-	-	-	-	-	+
Macrophages	-	+	-	+	-	-	-	-	nd
Dendritic cells	-	+	-	+	-	-	-	-	nd
Myeloid leukemia	-	+	-	+	-	-	-	nd	nd
NonHodgkin's lymphoma	-	+	-	+	-	-	-	nd	nd
Hodgkin's lymphoma	-	+	-	+	-	-	-	nd	nd

\* Micro-array data, not confirmed by real time PCR; nd=not determined

## References

- Agro, A., I. Padol, and A.M. Stanisiz. 1991. Immunomodulatory activities of the somatostatin analogue BIM 23014c: effects on murine lymphocyte proliferation and natural killer activity. *Regul Pept* 32:129-39.
- Ahmed, A.A., A.H. Wahbi, and K. Nordlin. 2001. Neuropeptides modulate a murine monocyte/macrophage cell line capacity for phagocytosis and killing of *Leishmania major* parasites. *Immunopharmacol Immunotoxicol* 23:397-409.
- Ahmed, A.A., A. Wahbi, K. Nordlin, A. Kharazmi, K.G. Sundqvist, V. Mutt, and S. Liden. 1998. In vitro *Leishmania major* promastigote-induced macrophage migration is modulated by sensory and autonomic neuropeptides. *Scand J Immunol* 48:79-85.
- Bhathena, S.J., J. Louie, G.P. Schechter, R.S. Redman, L. Wahl, and L. Recant. 1981. Identification of human mononuclear leukocytes bearing receptors for somatostatin and glucagon. *Diabetes* 30:127-31.
- Blum, A.M., A. Metwali, R.C. Mathew, D. Elliott, and J.V. Weinstock. 1993. Substance P and somatostatin can modulate the amount of IgG2a secreted in response to schistosome egg antigens in murine schistosomiasis mansoni. *J Immunol* 151:6994-7004.
- Blum, A.M., A. Metwali, R.C. Mathew, G. Cook, D. Elliott, and J.V. Weinstock. 1992. Granuloma T lymphocytes in murine schistosomiasis mansoni have somatostatin receptors and respond to somatostatin with decreased IFN-gamma secretion. *J Immunol* 149:3621-6.
- Blum, A.M., D.E. Elliott, A. Metwali, J. Li, K. Qadir, and J.V. Weinstock. 1998. Substance P regulates somatostatin expression in inflammation. *J Immunol* 161:6316-22.
- Broglio, F., M. Papotti, G. Muccioli, and E. Ghigo. 2007. Brain-gut communication: cortistatin, somatostatin and ghrelin. *Trends Endocrinol Metab* 18:246-51.
- Bruns, C., I. Lewis, U. Briner, G. Meno-Tetang, and G. Weckbecker. 2002. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antiseecretory profile. *Eur J Endocrinol* 146:707-16.
- Cardoso, A., C. el Ghamrawy, J.P. Gautron, B. Horvat, N. Gautier, A. Enjalbert, and S. Krantic. 1998. Somatostatin increases mitogen-induced IL-2 secretion and proliferation of human Jurkat T cells via sst3 receptor isotype. *J Cell Biochem* 68:62-73.
- Casnici, C., D. Lattuada, C. Perego, P. Franco, and O. Marelli. 1997. Inhibitory effect of somatostatin on human T lymphocytes proliferation. *Int J Immunopharmacol* 19:721-7.
- Coari, G., M. Di Franco, A. Iagnocco, M.R. Di Novi, M.T. Mauceri, and A. Ciocchi. 1995. Intra-articular somatostatin 14 reduces synovial thickness in rheumatoid arthritis: an ultrasonographic study. *Int J Clin Pharmacol Res* 15:27-32.

- Criado, J.R., H. Li, X. Jiang, M. Spina, S. Huitron-Resendiz, G. Liapakis, M. Calbet, S. Siehler, S.J. Henriksen, G. Koob, D. Hoyer, J.G. Sutcliffe, M. Goodman, and L. de Lecea. 1999. Structural and compositional determinants of cortistatin activity. *J Neurosci Res* 56:611-9.
- Dalm, V.A., L.J. Hofland, D. Ferone, R. Croxen, S.W. Lamberts, and P.M. van Hagen. 2003a. The role of somatostatin and somatostatin analogs in the pathophysiology of the human immune system. *J Endocrinol Invest* 26:94-102.
- Dalm, V.A., P.M. van Hagen, P.M. van Koetsveld, A.W. Langerak, A.J. van der Lely, S.W. Lamberts, and L.J. Hofland. 2003b. Cortistatin rather than somatostatin as a potential endogenous ligand for somatostatin receptors in the human immune system. *J Clin Endocrinol Metab* 88:270-6.
- Dalm, V.A., P.M. Van Hagen, R.R. de Krijger, J.M. Kros, P.M. Van Koetsveld, A.J. Van Der Lely, S.W. Lamberts, and L.J. Hofland. 2004a. Distribution pattern of somatostatin and cortistatin mRNA in human central and peripheral tissues. *Clin Endocrinol (Oxf)* 60:625-9.
- Dalm, V.A., P.M. van Hagen, P.M. van Koetsveld, S. Achilefu, A.B. Houtsmuller, D.H. Pols, A.J. van der Lely, S.W. Lamberts, and L.J. Hofland. 2003c. Expression of somatostatin, cortistatin, and somatostatin receptors in human monocytes, macrophages, and dendritic cells. *Am J Physiol Endocrinol Metab* 285:E344-53.
- Dalm, V.A., L.J. Hofland, C.M. Mooy, M.A. Waaijers, P.M. van Koetsveld, A.W. Langerak, F.T. Staal, A.J. van der Lely, S.W. Lamberts, and M.P. van Hagen. 2004b. Somatostatin receptors in malignant lymphomas: targets for radiotherapy? *J Nucl Med* 45:8-16.
- de Herder, W.W., D.J. Kwekkeboom, R.A. Feelders, M.O. van Aken, S.W. Lamberts, A.J. van der Lely, and E.P. Krenning. 2006. Somatostatin receptor imaging for neuroendocrine tumors. *Pituitary* 9:243-8.
- de Lecea, L., and J.G. Sutcliffe. 1996. Peptides, sleep and cortistatin. *Mol Psychiatry* 1:349-51.
- de Lecea, L., J.R. Criado, O. Prospero-Garcia, K.M. Gautvik, P. Schweitzer, P.E. Danielson, C.L. Dunlop, G.R. Siggins, S.J. Henriksen, and J.G. Sutcliffe. 1996. A cortical neuropeptide with neuronal depressant and sleep-modulating properties. *Nature* 381:242-5.
- Deghenghi, R., M. Papotti, E. Ghigo, and G. Muccioli. 2001. Cortistatin, but not somatostatin, binds to growth hormone secretagogue (GHS) receptors of human pituitary gland. *J Endocrinol Invest* 24:RC1-3.
- Delesque, N., L. Buscail, J.P. Esteve, I. Raully, M. Zeggari, N. Saint-Laurent, G.I. Bell, A.V. Schally, N. Vaysse, and C. Susini. 1995. A tyrosine phosphatase is associated with the somatostatin receptor. *Ciba Found Symp* 190:187-96; discussion 196-203.
- Dixit, V.D., E.M. Schaffer, R.S. Pyle, G.D. Collins, S.K. Sakthivel, R. Palaniappan, J.W. Lillard, Jr., and D.D. Taub. 2004. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *J Clin Invest* 114:57-66.

- Eglezos, A., P.V. Andrews, and R.D. Helme. 1993. In vivo inhibition of the rat primary antibody response to antigenic stimulation by somatostatin. *Immunol Cell Biol* 71 ( Pt 2):125-9.
- Elliott, D.E., and J.V. Weinstock. 1996. Granulomas in murine schistosomiasis mansoni have a somatostatin immunoregulatory circuit. *Metabolism* 45:88-90.
- Elliott, D.E., A. Metwali, A.M. Blum, M. Sandor, R. Lynch, and J.V. Weinstock. 1994. T lymphocytes isolated from the hepatic granulomas of schistosome-infected mice express somatostatin receptor subtype II (SSTR2) messenger RNA. *J Immunol* 153:1180-6.
- Elliott, D.E., J. Li, A.M. Blum, A. Metwali, Y.C. Patel, and J.V. Weinstock. 1999. SSTR2A is the dominant somatostatin receptor subtype expressed by inflammatory cells, is widely expressed and directly regulates T cell IFN-gamma release. *Eur J Immunol* 29:2454-63.
- Ferjoux, G., F. Lopez, J.P. Esteve, A. Ferrand, E. Vivier, F. Vely, N. Saint-Laurent, L. Pradayrol, L. Buscail, and C. Susini. 2003. Critical role of Src and SHP-2 in sst2 somatostatin receptor-mediated activation of SHP-1 and inhibition of cell proliferation. *Mol Biol Cell* 14:3911-28.
- Ferone, D., P.M. van Hagen, A. Colao, L. Annunziato, S.W. Lamberts, and L.J. Hofland. 1999. Somatostatin receptors in the thymus. *Ann Med* 31 Suppl 2:28-33.
- Ferone, D., P.M. van Hagen, C. Semino, V.A. Dalm, A. Barreca, A. Colao, S.W. Lamberts, F. Minuto, and L.J. Hofland. 2004. Somatostatin receptor distribution and function in immune system. *Dig Liver Dis* 36 Suppl 1:S68-77.
- Ferone, D., R. Pivonello, P.M. Van Hagen, V.A. Dalm, E.G. Lichtenauer-Kaligis, M. Waaijers, P.M. Van Koetsveld, D.M. Mooy, A. Colao, F. Minuto, S.W. Lamberts, and L.J. Hofland. 2002. Quantitative and functional expression of somatostatin receptor subtypes in human thymocytes. *Am J Physiol Endocrinol Metab* 283:E1056-66.
- Fukusumi, S., C. Kitada, S. Takekawa, H. Kizawa, J. Sakamoto, M. Miyamoto, S. Hinuma, K. Kitano, and M. Fujino. 1997. Identification and characterization of a novel human cortistatin-like peptide. *Biochem Biophys Res Commun* 232:157-63.
- Gonzalez-Rey, E., A. Chorny, G. Robledo, and M. Delgado. 2006a. Cortistatin, a new antiinflammatory peptide with therapeutic effect on lethal endotoxemia. *J Exp Med* 203:563-71.
- Gonzalez-Rey, E., A. Chorny, R.G. Del Moral, N. Varela, and M. Delgado. 2007. Therapeutic effect of cortistatin on experimental arthritis by downregulating inflammatory and Th1 responses. *Ann Rheum Dis* 66:582-8.
- Gonzalez-Rey, E., N. Varela, A.F. Sheibanie, A. Chorny, D. Ganea, and M. Delgado. 2006b. Cortistatin, an antiinflammatory peptide with therapeutic action in inflammatory bowel disease. *Proc Natl Acad Sci U S A* 103:4228-33.
- Hattori, N., T. Saito, T. Yagyu, B.H. Jiang, K. Kitagawa, and C. Inagaki. 2001. GH, GH receptor, GH secretagogue receptor, and ghrelin expression in human T cells, B cells, and neutrophils. *J Clin Endocrinol Metab* 86:4284-91.

- Heppelmann, B., and M. Pawlak. 1997. Inhibitory effect of somatostatin on the mechanosensitivity of articular afferents in normal and inflamed knee joints of the rat. *Pain* 73:377-82.
- Hiruma, K., T. Koike, H. Nakamura, T. Sumida, T. Maeda, H. Tomioka, S. Yoshida, and T. Fujita. 1990. Somatostatin receptors on human lymphocytes and leukaemia cells. *Immunology* 71:480-5.
- Kamohara, M., A. Matsuo, J. Takasaki, M. Kohda, M. Matsumoto, S. Matsumoto, T. Soga, H. Hiyama, M. Kobori, and M. Katou. 2005. Identification of MrgX2 as a human G-protein-coupled receptor for proadrenomedullin N-terminal peptides. *Biochem Biophys Res Commun* 330:1146-52.
- Karalis, K., G. Mastorakos, G.P. Chrousos, and G. Tolis. 1994. Somatostatin analogues suppress the inflammatory reaction in vivo. *J Clin Invest* 93:2000-6.
- Komorowski, J., and H. Stepien. 1995. Somatostatin (SRIF) stimulates the release of interleukin-6 (IL-6) from human peripheral blood monocytes (PBM) in vitro. *Neuropeptides* 29:77-81.
- Koo, G.C., C. Huang, R. Camacho, C. Trainor, J.T. Blake, A. Sirotina-Meisher, K.D. Schleim, T.J. Wu, K. Cheng, R. Nargund, and G. McKissick. 2001. Immune enhancing effect of a growth hormone secretagogue. *J Immunol* 166:4195-201.
- Krco, C.J., A. Gores, and V.L. Go. 1986. Gastrointestinal regulatory peptides modulate in vitro immune reactions of mouse lymphoid cells. *Clin Immunol Immunopathol* 39:308-18.
- Krenning, E.P., D.J. Kwekkeboom, R. Valkema, S. Pauwels, L.K. Kvols, and M. De Jong. 2004. Peptide receptor radionuclide therapy. *Ann N Y Acad Sci* 1014:234-45.
- Krenning, E.P., D.J. Kwekkeboom, J.C. Reubi, P.M. Van Hagen, C.H. van Eijck, H.Y. Oei, and S.W. Lamberts. 1992. <sup>111</sup>In-octreotide scintigraphy in oncology. *Metabolism* 41:83-6.
- Lavy, A., and K. Yasin. 2003. Octreotide for enterocutaneous fistulas of Crohn's disease. *Can J Gastroenterol* 17:555-8.
- Levite, M., L. Cahalon, R. HersHKoviz, L. Steinman, and O. Lider. 1998. Neuropeptides, via specific receptors, regulate T cell adhesion to fibronectin. *J Immunol* 160:993-1000.
- Lichtenauer-Kaligis, E.G., V.A. Dalm, S.P. Oomen, D.M. Mooij, P.M. van Hagen, S.W. Lamberts, and L.J. Hofland. 2004. Differential expression of somatostatin receptor subtypes in human peripheral blood mononuclear cell subsets. *Eur J Endocrinol* 150:565-77.
- Lopez, F., J.P. Esteve, L. Buscail, N. Delesque, N. Saint-Laurent, N. Vaysse, and C. Susini. 1996. Molecular mechanisms of antiproliferative effect of somatostatin: involvement of a tyrosine phosphatase. *Metabolism* 45:14-6.
- Matucci-Cerinic, M., and S. Marabini. 1988. Somatostatin treatment for pain in rheumatoid arthritis: a double blind versus placebo study in knee involvement. *Med. Sci. Res.*:233.
- Matucci-Cerinic, M., F. Borrelli, S. Generini, A. Cantelmo, I. Marcucci, F. Martelli, P. Romagnoli, S. Bacci, A. Conz, P. Marinelli, and et al. 1995. Somatostatin-induced modulation of inflammation in experimental arthritis. *Arthritis Rheum* 38:1687-93.

- Muscettola, M., and G. Grasso. 1990. Somatostatin and vasoactive intestinal peptide reduce interferon gamma production by human peripheral blood mononuclear cells. *Immunobiology* 180:419-30.
- Nothacker, H.P., Z. Wang, H. Zeng, S.K. Mahata, D.T. O'Connor, and O. Civelli. 2005. Proadrenomedullin N-terminal peptide and cortistatin activation of MrgX2 receptor is based on a common structural motif. *Eur J Pharmacol* 519:191-3.
- Oomen, S.P., L.J. Hofland, P.M. van Hagen, S.W. Lamberts, and I.P. Touw. 2000. Somatostatin receptors in the haematopoietic system. *Eur J Endocrinol* 143 Suppl 1:S9-14.
- Paran, D., O. Elkayam, A. Mayo, H. Paran, M. Amit, M. Yaron, and D. Caspi. 2001. A pilot study of a long acting somatostatin analogue for the treatment of refractory rheumatoid arthritis. *Ann Rheum Dis* 60:888-91.
- Patel, Y.C. 1999. Somatostatin and its receptor family. *Front Neuroendocrinol* 20:157-98.
- Patel, Y.C., M. Greenwood, R. Panetta, N. Hukovic, S. Grigorakis, L.A. Robertson, and C.B. Srikant. 1996. Molecular biology of somatostatin receptor subtypes. *Metabolism* 45:31-8.
- Payan, D.G., C.A. Hess, and E.J. Goetzel. 1984. Inhibition by somatostatin of the proliferation of T-lymphocytes and Molt-4 lymphoblasts. *Cell Immunol* 84:433-8.
- Peluso, G., O. Petillo, M.A. Melone, G. Mazzarella, M. Ranieri, and G.F. Tajana. 1996. Modulation of cytokine production in activated human monocytes by somatostatin. *Neuropeptides* 30:443-51.
- Reichlin, S. 1983a. Somatostatin. *N Engl J Med* 309:1495-501.
- Reichlin, S. 1983b. Somatostatin (second of two parts). *N Engl J Med* 309:1556-63.
- Reubi, J.C., U. Horisberger, A. Kappeler, and J.A. Laissue. 1998. Localization of receptors for vasoactive intestinal peptide, somatostatin, and substance P in distinct compartments of human lymphoid organs. *Blood* 92:191-7.
- Reubi, J.C., U. Horisberger, B. Waser, J.O. Gebbers, and J. Laissue. 1992. Preferential location of somatostatin receptors in germinal centers of human gut lymphoid tissue. *Gastroenterology* 103:1207-14.
- Reubi, J.C., B. Waser, H.M. Markusse, E.P. Krenning, M. VanHagen, and J.A. Laissue. 1994. Vascular somatostatin receptors in synovium from patients with rheumatoid arthritis. *Eur J Pharmacol* 271:371-8.
- Robas, N., E. Mead, and M. Fidock. 2003. MrgX2 is a high potency cortistatin receptor expressed in dorsal root ganglion. *J Biol Chem* 278:44400-4.
- Scicchitano, R., P. Dazin, J. Bienenstock, D.G. Payan, and A.M. Stanisiz. 1988. The murine IgA-secreting plasmacytoma MOPC-315 expresses somatostatin receptors. *J Immunol* 141:937-41.
- Siehl, S., K. Seuwen, and D. Hoyer. 1998. [125I]Tyr10-cortistatin14 labels all five somatostatin receptors. *Naunyn Schmiedebergs Arch Pharmacol* 357:483-9.

- Smith, R.G., R. Leonard, A.R. Bailey, O. Palyha, S. Feighner, C. Tan, K.K. McKee, S.S. Pong, P. Griffin, and A. Howard. 2001. Growth hormone secretagogue receptor family members and ligands. *Endocrine* 14:9-14.
- Stanisz, A.M., D. Befus, and J. Bienenstock. 1986. Differential effects of vasoactive intestinal peptide, substance P, and somatostatin on immunoglobulin synthesis and proliferations by lymphocytes from Peyer's patches, mesenteric lymph nodes, and spleen. *J Immunol* 136:152-6.
- Takeba, Y., N. Suzuki, M. Takeno, T. Asai, S. Tsuboi, T. Hoshino, and T. Sakane. 1997. Modulation of synovial cell function by somatostatin in patients with rheumatoid arthritis. *Arthritis Rheum* 40:2128-38.
- ten Bokum, A.M., L.J. Hofland, and P.M. van Hagen. 2000. Somatostatin and somatostatin receptors in the immune system: a review. *Eur Cytokine Netw* 11:161-76.
- Ten Bokum, A.M., J.G. Rosmalen, L.J. Hofland, E.P. Krenning, P.M. Van Hagen, and W.A. Breeman. 2002. Tissue distribution of octreotide binding receptors in normal mice and strains prone to autoimmunity. *Nucl Med Commun* 23:1009-17.
- ten Bokum, A.M., M.J. Melief, A. Schonbrunn, F. van der Ham, J. Lindeman, L.J. Hofland, S.W. Lamberts, and P.M. van Hagen. 1999a. Immunohistochemical localization of somatostatin receptor sst2A in human rheumatoid synovium. *J Rheumatol* 26:532-5.
- ten Bokum, A.M., E.G. Lichtenauer-Kaligis, M.J. Melief, P.M. van Koetsveld, C. Bruns, P.M. van Hagen, L.J. Hofland, S.W. Lamberts, and M.P. Hazenberg. 1999b. Somatostatin receptor subtype expression in cells of the rat immune system during adjuvant arthritis. *J Endocrinol* 161:167-75.
- ten Bokum, A.M., L.J. Hofland, G. de Jong, J. Bouma, M.J. Melief, D.J. Kwekkeboom, A. Schonbrunn, C.M. Mooy, J.D. Laman, S.W. Lamberts, and P.M. van Hagen. 1999c. Immunohistochemical localization of somatostatin receptor sst2A in sarcoid granulomas. *Eur J Clin Invest* 29:630-6.
- van der Lely, A.J., W.W. de Herder, E.P. Krenning, and D.J. Kwekkeboom. 2003. Octreoscan radioreceptor imaging. *Endocrine* 20:307-11.
- van der Lely, A.J., M. Tschop, M.L. Heiman, and E. Ghigo. 2004. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. *Endocr Rev* 25:426-57.
- van Hagen, P.M., E.P. Krenning, D.J. Kwekkeboom, J.C. Reubi, P.J. Anker-Lugtenburg, B. Lowenberg, and S.W. Lamberts. 1994. Somatostatin and the immune and haematopoietic system; a review. *Eur J Clin Invest* 24:91-9.
- van Hagen, P.M., L.J. Hofland, A.M. ten Bokum, E.G. Lichtenauer-Kaligis, D.J. Kwekkeboom, D. Ferone, and S.W. Lamberts. 1999. Neuropeptides and their receptors in the immune system. *Ann Med* 31 Suppl 2:15-22.

- Vanhagen, P.M., H.M. Markusse, S.W. Lamberts, D.J. Kwekkeboom, J.C. Reubi, and E.P. Krenning. 1994a. Somatostatin receptor imaging. The presence of somatostatin receptors in rheumatoid arthritis. *Arthritis Rheum* 37:1521-7.
- Vanhagen, P.M., E.P. Krenning, J.C. Reubi, A.H. Mulder, W.H. Bakker, H.Y. Oei, B. Lowenberg, and S.W. Lamberts. 1993. Somatostatin analogue scintigraphy of malignant lymphomas. *Br J Haematol* 83:75-9.
- Vanhagen, P.M., E.P. Krenning, J.C. Reubi, D.J. Kwekkeboom, W.H. Bakker, A.H. Mulder, I. Laissue, H.C. Hoogstede, and S.W. Lamberts. 1994b. Somatostatin analogue scintigraphy in granulomatous diseases. *Eur J Nucl Med* 21:497-502.
- Weckbecker, G., U. Briner, I. Lewis, and C. Bruns. 2002. SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. *Endocrinology* 143:4123-30.
- Weckbecker, G., I. Lewis, R. Albert, H.A. Schmid, D. Hoyer, and C. Bruns. 2003. Opportunities in somatostatin research: biological, chemical and therapeutic aspects. *Nat Rev Drug Discov* 2:999-1017.
- Weinstock, J.V., and D. Elliott. 2000. The somatostatin immunoregulatory circuit present at sites of chronic inflammation. *Eur J Endocrinol* 143 Suppl 1:S15-9.
- Wiedermann, C.J., N. Reinisch, and H. Braunsteiner. 1993. Stimulation of monocyte chemotaxis by human growth hormone and its deactivation by somatostatin. *Blood* 82:954-60.
- Xia, Q., W. Pang, H. Pan, Y. Zheng, J.S. Kang, and S.G. Zhu. 2004. Effects of ghrelin on the proliferation and secretion of splenic T lymphocytes in mice. *Regul Pept* 122:173-8.