Somatostatin Receptor Expression in Clinical Immunology

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Specific somatostatin receptors (ssts) have been described in normal and tumor tissues and identified on more than 95% of normal mitogen-activated human peripheral lymphocytes. Somatostatin may modulate the immune response by a variety of mechanisms, most of which are inhibitory, sst scintigraphy in patients with immune-mediated diseases revealed sst expression in 97% of patients with sarcoidosis, 100% of patients with tuberculosis or Wegener's granulomatosis, 75% of patients with Sjögren's syndrome, and 50% of patients with systemic lupus erythematosus or uveitis. sst expression appeared to be related to progression or remission of disease. Patients who responded poorly to therapy remained positive at scintigraphy. Investigation of 10 human B-cell lines and eight human T-cell lines, using a polymerase chain reaction, revealed the presence of sst_2-mRNA in two of the B-cell and two of the T-cell lines. Visualization of ssts on activated mononuclear leukocytes by sst scintigraphy may prove useful in evaluating the spread of immune-mediated diseases and their responses to therapy. The efficacy of octreotide should be studied in patients with these diseases.

SPECIFIC RECEPTORS for somatostatin (ssts), mediating the various actions of this peptide, have been described in normal, as well as tumor tissues.[1] Bhathena et al first identified receptors on human mononuclear leukocytes.[2] Specific, low-affinity receptors were found on resting monocytes and lymphocytes. Subsequently, ssts were identified on more than 95% of normal mitogen-activated human peripheral lymphocytes.[3] Resting peripheral blood lymphocytes, granulocytes, and red blood cells did not present sst.[3] Somatostatin might modulate the immune response by a variety of mechanisms. These include modification of immunoglobulin secretion by plasma cells; suppression or enhancement of lymphocyte proliferation, cytotoxicity, and changes in cytokine production; release of mediators by basophils, recruitment of eosinophils; and changes in macrophage function.[4] Activated lymphocytes and monocytes are involved in various inflammatory diseases.

Recently, we investigated sst expression in patients with immune-mediated diseases using sst scintigraphy.[4-6] The results of these studies are summarized in Table 1. The active infectious and autoimmune diseases described in Table 1 showed a high sensitivity with regard to the results of scintigraphy, suggesting high sst expression in the affected organs. In almost all patients with sarcoidosis, sst expression was found in the affected organs (predominantly the lung). Progression or remission of disease activity seemed to be related to sst expression. The inflammation sites in five patients with sarcoidosis who did not respond well to glucocorticosteroid therapy remained positive at scintigraphy. In contrast, repeated scintigraphy in four sarcoidosis patients who responded well to therapy showed a decrease in or absence of previously present radioactivity. In all patients with tuberculosis, inflammation sites were found to be positive at scintigraphy, while in three patients, additional extrapulmonary sites were found. Affected lungs and nose regions were visualized in all four patients with Wegener's granulomatosis. In Sjögren's syndrome, salivary gland inflammation, lymphadenopathy, lung involvement, and even myocarditis were visualized. In several articular disorders, we could visualize the affected joints; in rheumatoid arthritis, the uptake of radioactivity was related to the degree of inflammation (Wilcoxon test, $P < .001$). Alveolar and interstitial inflammatory lung involvement in sarcoidosis, Sjögren's syndrome, and systemic lupus erythematosus were visualized and seemed to be related to therapeutic response in the four patients investigated. Single-photon emission computed tomography (SPECT) images were made in four patients with uveitis, and in two of these patients with severe posterior uveitis, orbital uptake of radioactivity was found. In vitro investigations have shown specific binding of somatostatin in human granulomatous diseases and rheumatoid arthritis.[5,6] In granulomas, receptors have been found in the epithelioid cell regions and, in rheumatoid arthritis, in the high endothelial venules.[7] To investigate which sst subtype (sst) is expressed by lymphoid cells, we investigated 10 human B-cell lines and eight human T-cell lines by polymerase chain reaction.[8] In two T-cell lines and two B-cell lines, sst_2 mRNA was found. The T-cell lines were in an early differentiation state (CD3-negative), and the B-cell lines were positive in the mature differentiation range. Only sst_2-mRNA was expressed.

Somatostatin and ssts have been demonstrated in nonpathological and pathological lymphoid tissue and may play a regulatory, mostly inhibitory, role in the immune response.[4,9] Somatostatin is produced by lymphocytes and

Table 1. ssts in Patients With Immune-Mediated Diseases and Tuberculosis

Disease	No. of Patients	sst Scintigraphy-Positive	%
Sarcoidosis	30	29	97
Tuberculosis	14	14	100
Wegener's granulomatosis	4	4	100
Sjögren's syndrome	12	9	75
Morbus Reiter	1	1	—
Henoch-Schönlein	1	1	—
Rheumatoid arthritis	16	16	100
Systemic lupus erythematosus	6	3	50
Uveitis	4	2	50

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monocytes, which suggests an autocrine or paracrine regulatory role, but somatostatin may also be released by nerve endings.[10] It can therefore be hypothesized that, as well as a role for somatostatin in the local immunomodulation of cells belonging to the immune system, a second pathway exists in which this peptide exerts its effects via neuroendocrine modulation of the immune response, which might represent a direct regulatory relationship between the nervous and the immune systems. The presence of ssts on activated mononuclear leukocytes allows visualization by sst scintigraphy of diseases in which these cells are involved. This technique may be used in the evaluation of the spread of such diseases and to monitor patient response to therapy. Moreover, the presence of ssts in immune diseases warrants studies on the efficacy of treatment with octreotide in patients suffering from these diseases.

REFERENCES

1. Reubi JC, Kvols LK, Krenning EP, et al: Distribution of somatostatin receptors in normal and tumor tissue. Metabolism 39:78-81, 1990

2. Bhatena SJ, Louie J, Schechter GP, et al: Identification of human mononuclear leucocytes bearing receptors for somatostatin and glucagon. Diabetes 30:127-131, 1981

3. Hiruma K, Koike T, Nakamura H, et al: Somatostatin receptors on human lymphocytes and leukaemia cells. Immunology 71:480-485, 1990

4. Van Hagen PM, Krenning EP, Kwekkeboom DJ, et al: Somatostatin in the immune and haematopoietic system; a review. Eur J Clin Invest 241:91-99, 1994

5. Van Hagen PM, Krenning EP, Reubi JC, et al: Somatostatin analogue scintigraphy in granulomatous diseases. Eur J Nucl Med 21:497-502, 1994

6. Van Hagen PM, Markusse HM, Lamberts SWJ, et al: Somatostatin receptor imaging. The presence of somatostatin receptors in rheumatoid arthritis. Arthritis Rheum 37:1521-1527, 1994

7. Reubi JC, Waser B, Markusse HM, et al: Vascular somatostatin receptors in synovium from patients with rheumatoid arthritis. Eur J Pharmacol 271:371-378, 1994

8. Van Hagen PM, Lichtenauer-Kaligis EGR, Bokum ten AMC, et al: Somatostatin receptor expression in human lymphoid cell lines. (submitted)

9. Reubi JC, Horisberger U, Waser B, et al: Preferential location of somatostatin receptors in germinal centres of human gut lymphoid tissue. Gastroenterology 103:1207-1214, 1992

10. Weinstock JV: Neuropeptides and the regulation of granulomatous inflammation. Clin Immunol Immunopathol 64:17-22, 1992