ARTHRITIS & RHEUMATISM Volume 37
Number 10, October 1994, pp 1521–1527

SOMATOSTATIN RECEPTOR IMAGING

The Presence of Somatostatin Receptors in Rheumatoid Arthritis

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Objective. **To investigate the in vivo and in vitro expression of somatostatin receptors (SS-R) on synovial membranes of patients with rheumatoid arthritis (RA).**

Methods. **The joints of 14 consecutive patients with active RA, 4 patients with severe osteoarthritis (OA), and 30 control patients were studied. The somatostatin analog [^{111}In-DTPA-D-Phe^1]-octreotide was used for in vivo SS-R scintigraphy, and the somatostatin analog [^{125}I-Tyr^3]-octreotide for in vitro SS-R autoradiography.**

Results. **Seventy-six percent (220 of 290) of the painful joints and 76% (207 of 274) of the swollen joints of the patients with RA were visualized by SS-R scintigraphy. The degree of pain and swelling correlated well with positive scintigraphy findings in the joints ($P < 0.0001$). In 2 of the RA patients who underwent scintigraphy, as well as in 4 of 5 other patients, in vitro studies of the synovial membranes showed the presence of specific SS-R. In patients with OA, uptake of radioactivity in the affected joints was significantly lower than that in patients with RA. None of the joints of the control patients demonstrated uptake of radioactivity.**

Conclusion. **SS-R are present in the synovial tissue of patients with active RA, as demonstrated by both in vivo and in vitro techniques. The potential value of SS-R scintigraphy in the clinical evaluation of patients with active RA is presently unknown.**

Somatostatin is a small peptide, known to be a potent inhibitor of growth hormone release (1,2). It has recently been suggested that this neuropeptide is also involved in hematologic and granulomatous diseases such as malignant lymphoma, sarcoidosis, and tuberculosis (3,4). Specific receptors for somatostatin (SS-R) have been found in activated lymphocytes, monocytes, and malignant lymphoid cells, by classic ligand-binding techniques as well as by in vitro autoradiography (4–8).

The somatostatin analog, [^{111}In-DTPA-D-Phe^1]-octreotide, has been used successfully for in vivo visualization of a variety of neuroendocrine tumors, as well as malignant lymphomas and granulomas (3,4,9,10). In 1 patient with sarcoidosis and arthralgia, we observed a high uptake of [^{111}In-DTPA-D-Phe^1]-octreotide in the affected joints. This observation led us to investigate the possible use of SS-R scintigraphy of affected joints in rheumatoid arthritis (RA).

RA is characterized by synovitis. The histopathologic features lack uniformity, especially in more established disease, but diffuse lymphocytic infiltration (predominantly CD4+ lymphocytes) and/or lymphocytic aggregates positioned around postcapillary venules are present in most cases. We postulated that these activated lymphocytes and monocytes in synovial membranes express SS-R in sufficient numbers to allow in vivo visualization, as was the case in the disorders mentioned above. Herein we report our first results of SS-R scintigraphy of the joints in 14 consecutive patients with active RA and 4 selected patients with severe osteoarthritis (OA) resembling RA. The synovial tissues of 2 of these patients with RA, as well

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Submitted for publication October 12, 1993; accepted in revised form May 5, 1994.

Table 1. Characteristics of the rheumatoid arthritis (RA) and osteoarthritis (OA) patients studied*

Patient	Age/sex	RF	ESR (mm/hour)	Treatment	No. of swollen joints	No. of painful joints	No. of SS-R–positive joints
RA							
1	72/F	+	59	Corticosteroids, chloroquine, NSAID	17	12	24
2	73/M	+	28	Corticosteroids, chloroquine, NSAID	7	15	14
3	67/F	+	69	Corticosteroids, chloroquine, MTX, NSAID	34	23	34
4	38/F	–	30	Gold	34	34	27
5	74/F	–	·	Corticosteroids, sulfasalazine	10	16	14
6	66/F	+	39	NSAID	21	21	8
7	55/F	+	79	NSAID	6	6	8
8	80/F	+	66	NSAID	24	38	35
9	52/M	+	56	Azathioprine, NSAID	14	19	31
10	77/M	+	94	NSAID	14	0	22
11	65/F	+	58	Corticosteroids, NSAID	10	14	33
12	59/F	–	48	D-penicillamine, corticosteroids, NSAID	20	29	36
13	68/M	+	87	NSAID	30	28	20
14	32/F	+	80	Gold, NSAID	33	35	40
OA							
15	68/F	–	24	NSAID	12	1	6
16	84/F	–	18	Acetaminophen	1	7	6
17	65/F	–	12	None	12	17	6
18	77/F	–	10	NSAID	4	5	8

* RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; SS-R = somatostatin receptor; NSAID = nonsteroidal antiinflammatory drug; MTX = methotrexate.

as of 5 other patients, were investigated for the presence of specific SS-R in vitro, using binding assays.

PATIENTS AND METHODS

Patients. Fourteen consecutive patients with RA that fulfilled the criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (11) and 4 selected patients with severe OA, all from the rheumatology department at Dr. Daniel den Hoed Clinic, were enrolled in the study after giving informed consent. Demographic and clinical characteristics of the patients are shown in Table 1. Clinical evaluation of the joints was performed by a rheumatologist. The joints were scored for pain and swelling on a 0–3 scale, with 0 representing no swelling or pain and 3 representing extensive pain and swelling. Twenty patients with ophthalmic Graves' disease (OGD), 5 with neuroendocrine tumors, and 5 with malignant lymphomas were used as control patients. None of these patients had signs of arthritis, except for 1 patient with OGD who had severe generalized joint pains but no objective abnormalities found on physical examination. The joints of these control patients were scored according to their uptake of radioactivity, similar to the procedure in the patients with RA and OA.

Scintigraphy. The somatostatin analog [DTPA-D-Phe^1]-octreotide was obtained from Mallinckrodt (Petten, The Netherlands). [DTPA-D-Phe^1]-octreotide was coupled to ^{111}In as described previously (12). [^{111}In-DTPA-D-Phe^1]-octreotide is excreted mainly through the kidneys, 90% of the dose being present in the urine 24 hours after injection. Because of its relatively long effective half-life, [^{111}In-DTPA-D-Phe^1]-octreotide can be used to efficiently visualize SS-R–bearing lymphomas, granulomas, and neuroendocrine tumors after 24 hours when interfering background radioactivity is minimized by renal clearance (13,14).

[^{111}In-DTPA-D-Phe^1]-octreotide (248–360 MBq) was injected, and planar images were obtained with a large-field-of-view gamma camera (Counterbalance 3700 and ROTA II; Siemens Gammasonics, Erlangen, Germany) equipped with a medium-energy collimator. Scanning was done for a preset time of 15 minutes, 24 hours after injection of the ^{111}In-coupled somatostatin analog (14). To define the localizations of SS-R as visualized during this scanning procedure, the joints were scored on a 0–3 scale, where 0 = no uptake, 1 = low uptake, 2 = moderate uptake, and 3 = high uptake. The scintigrams of all patients were analyzed by 2 examiners who were not aware of the patient's identity, medical history, or outcomes of other investigations. In order to compare the number of lesions found by physical examination with those visualized during octreotide scintigraphy, the images were divided into easily recognizable parts. At physical examination a total of 42 joints per patient had been evaluated: the shoulders, elbows, wrists, metacarpophalangeal (MCP)

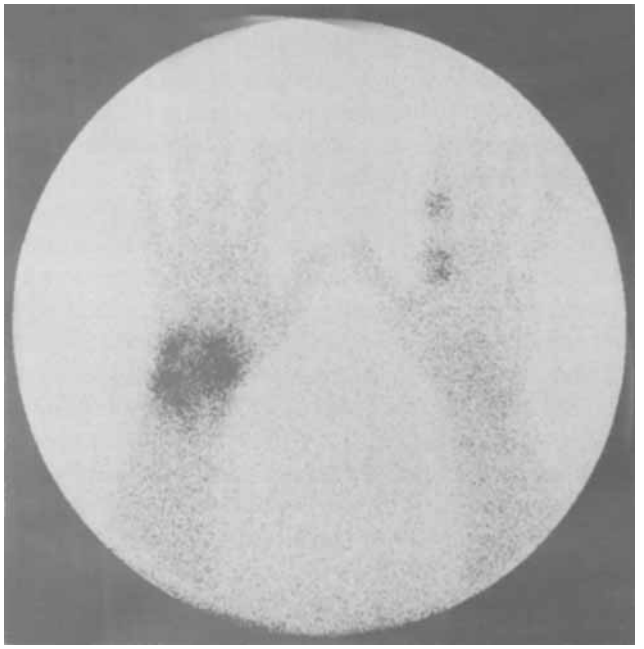

Figure 1. Scintigraphy of the affected right wrist and the left second metacarpophalangeal and proximal interphalangeal joints of patient 8 (anterior view, scanned 24 hours after administration of somatostatin analog).

joints, distal interphalangeal joints, hips, knees, ankles, and metatarsophalangeal (MTP) joints. All of these joints were also evaluated and scored on the scintigrams.

In vitro SS-R binding. The presence of SS-R in synovial tissue was investigated by autoradiography on 10μ thick frozen sections using an iodinated somatostatin octapeptide analog, [^{125}I-Tyr^3]-octreotide. Tissue sections were mounted on precleaned microscope slides and stored at −20°C for at least 3 days to improve adhesion of tissue to the slide. Sections were then incubated for 2 hours at room temperature in the presence of the iodinated ligand (0.15–0.30 × 10^6 disintegrations per minute/ml, or ~80–160 p*M*). The incubation solution was 170 m*M* Tris HCl buffer, pH 7.4, containing 1% bovine serum albumin (BSA), bacitracin (40 μg/ml), and $MgCl_2$ (5 m*M*).

Nonspecific binding was determined by adding a 1 μM solution of unlabeled octreotide. Incubated sections were washed twice for 5 minutes in cold incubation buffer containing 0,25% BSA and then in buffer alone, and dried quickly. The sections were exposed to ^{3}H-labeled ultrafilms (Cambridge Research, Nussdorf, Germany) and maintained for 1 week in x-ray cassettes. Displacement experiments were done on successive sections of synovial membranes. In addition, saturation experiments using increasing concentrations of octreotide were performed on tissue sections incubated with 30,000 counts per minute/100 μl radioligand. The autoradiograms were quantified using a computer-assisted image processing system. Tissue standards for iodinated

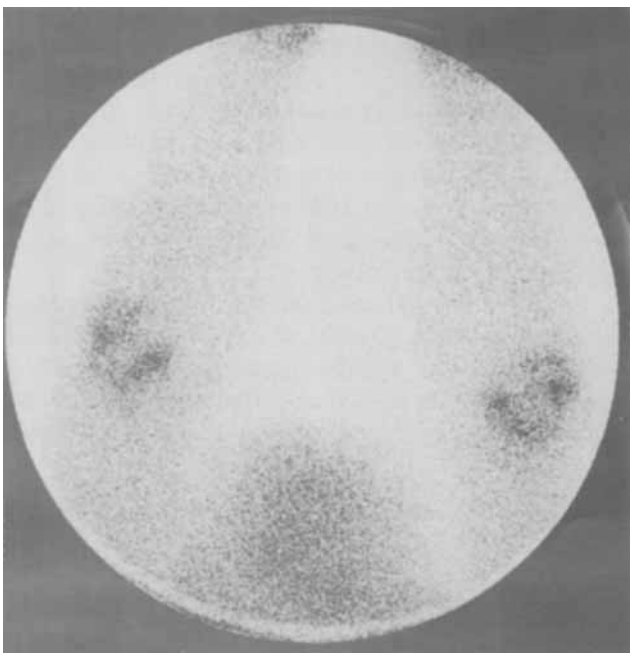

Figure 2. Scintigraphy of both affected elbows of patient 8 (scanned 24 hours after administration of somatostatin analog).

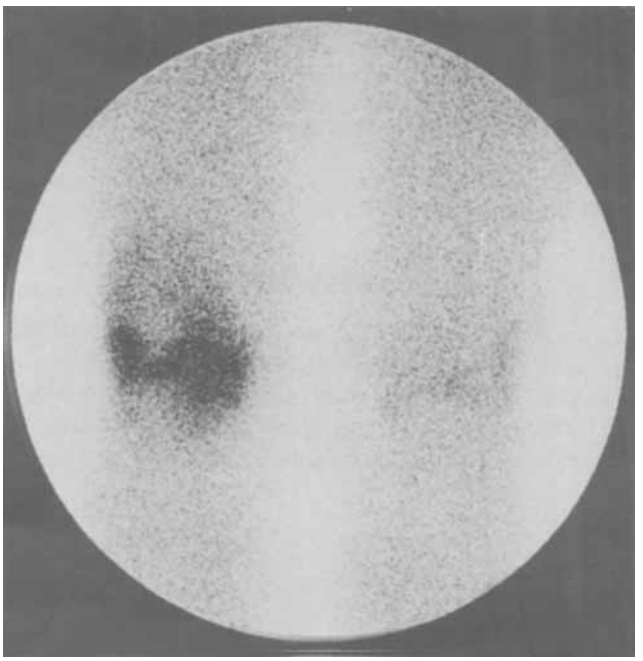

Figure 3. Scintigraphy of the moderately painful and swollen right knee of patient 1 (anterior view, scanned 24 hours after administration of somatostatin analog).

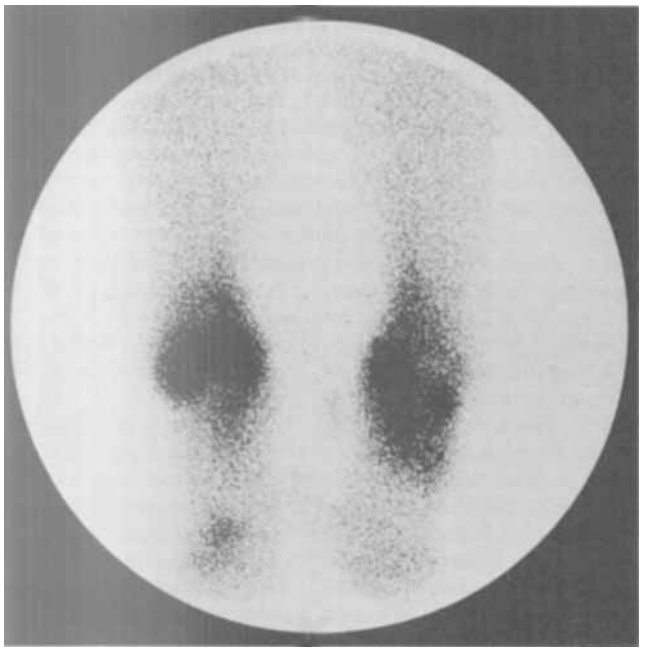

Figure 4. Scintigraphy of the affected ankles and right forefoot of patient 7 (anterior view, scanned 24 hours after administration of somatostatin analog).

compounds (Amersham, Aylesburg, England) were used for this purpose.

Synovial tissue was designated SS-R positive when the optical density of the total-binding section was at least twice the optical density of the nonspecific-binding section. These techniques have been previously described in detail for various types of tumoral and nontumoral tissues (15–18). Autoradiography was performed on synovial biopsy specimens from 2 patients who underwent scintigraphy and 5 other patients who did not undergo scintigraphy, from whom synovial membrane tissue was obtained in the course of a surgical procedure.

RESULTS

In normal individuals, physiologic accumulation of radioactivity is seen 24 hours after administration of [^{111}In-DTPA-D-Phe^1]-octreotide in the pituitary and thyroid glands, the liver, the spleen, and the kidneys, as well as the bladder. Radioactivity at other sites is considered to be abnormal and indicates the presence of abnormal SS-R–positive tissue. Data on the 14 patients with RA and the 4 patients with OA are listed in Table 1. We observed uptake of [^{111}In-DTPA-D-Phe^1]-octreotide in a number of joints of all of the patients with RA (Figures 1–4).

Table 2 illustrates the relationships between SS-R scintigraphy findings and pain and swelling in the RA patients. Five hundred seventy-six joints were scored on the scintigrams. In 2 patients a total of 12 joints (all MTP joints in patient 1 and both shoulders in patient 11) could not be scored due to technical reasons. Two hundred twenty of the 290 painful joints in the 14 patients with RA (76%) were SS-R positive, whereas 125 of the remaining 286 nonpainful joints were also positive. Of the remaining 70 painful joints that were negative on the SS-R scan, 32 were in 2 patients (patients 6 and 11). They did not differ from the other 12 patients with regard to either treatment or clinical symptoms. The median pain score was higher in the patients whose joints were positive by scintigraphy ($P < 0.0001$, Wilcoxon rank sum test). The sensitivity of scintigraphy for swollen joints was also 76% (207 of 274). Thirty-six of the 67 swollen joints that were negative by scintigraphy were also found in patients 6 and 11. Of 302 joints that were not swollen, 138 were SS-R positive. The median degree of swelling correlated well with positivity by scintigraphy ($P < 0.0001$, Wilcoxon rank sum test). The sensitivity of scintigraphy for painful and/or swollen joints was 74% (252 of 340) (Table 2). Ninety-three of 236 joints without clinical involvement (39%) were visualized. When the combination "pain and swelling" was scored, 80% of the joints (175 of 220) were positive by scintigraphy (Table 2). Uptake of radioactivity in the pericardium and pleurae of patient 13 was related to extraarticular RA involvement.

In the OA patients, the sensitivity of scintigraphy for joint swelling and joint pain was only 20% and 14%, respectively, and the frequency of positive findings did not differ significantly between affected and clinically unaffected joints ($P > 0.05$, chi-square test).

Table 2. Relationship between joint pain/swelling and somatostatin receptor scintigraphy results, in 14 patients with rheumatoid arthritis

	Pain		Swelling		Pain and/or swelling		Pain and swelling	
Scintigraphy	No	Yes	No	Yes	No	Yes	No	Yes
Negative	161 (56)	70 (24)	164 (54)	67 (24)	143 (61)	88 (26)	186 (52)	45 (20)
Positive	125 (44)	220 (76)	138 (46)	207 (76)	93 (39)	252 (74)	170 (48)	175 (80)
Total	286 (100)	290 (100)	302 (100)	274 (100)	236 (100)	340 (100)	356 (100)	220 (100)

The median uptake of radioactivity in the OA patients was lower than that in the RA patients (85% of the OA group had a scintigraphy score of 1, versus 36% of the RA group). In none of the control patients with OGD, neuroendocrine tumors, or malignant lymphomas was uptake of radioactivity observed in the joints.

The presence of specific SS-R in surgically excised synovial tissue was confirmed by in vitro autoradiography in 2 patients with RA. Both joints had also been visualized in vivo by scintigraphy. The displacement curve shown in Figure 5 illustrates the high affinity and specificity of the [^{125}I-Tyr^3]-octreotide binding in studies with these synovial tissue sections. This suggests the presence of SS-R in the tissue. However, we were unable to identify by autoradiographic studies which cell type(s) expressed SS-R in this tissue. The presence of specific SS-R was confirmed in 4 of 5 other patients with active RA who did not undergo scanning, from whom MCP, knee, and ankle synovial membrane tissue samples were obtained.

DISCUSSION

SS-R scintigraphy has been used successfully in the visualization of neuroendocrine tumors as well as granulomatous diseases and malignant lymphomas (3,4,9,10). This is, to our knowledge, the first report of the use of this technique in the visualization of clinically affected joints in RA. RA is a chronic inflammatory disorder involving the synovial membranes of multiple joints. There is no "gold standard" for the assessment of the clinical activity of the disease. Subjective parameters are mainly used to quantify arthritis activity (19). Pain and swelling of the joints are the main clinical indicators of inflammatory activity in RA. In the 14 patients with active RA examined in this study, clinical activity correlated well with the results of SS-R scintigraphy. However, in 2 patients, a number of painful and swollen joints were negative by scintigraphy. The reason for this discrepancy in these 2 patients is not clear. The number of false-positive scintigraphy results is unknown, because we did not perform synovial biopsies to exclude subclinical synovitis in these patients. Pleural and pericardial involvement of RA were visualized as well in 1 patient, suggesting that SS-R scintigraphy is also useful in the visualization of extraarticular involvement.

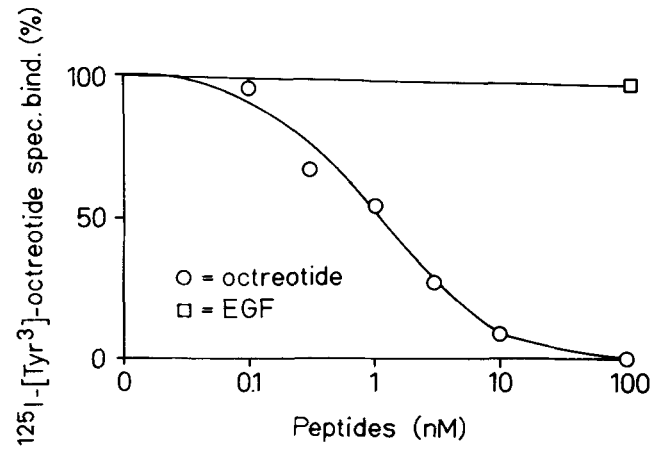

Figure 5. In vitro detection of somatostatin receptors in a synovial tissue sample from a rheumatoid arthritis patient. Tissue sections were incubated with 30,000 counts per minute/100 μl radioligand and increasing concentrations of unlabeled octreotide or 100 μM epidermal growth factor (EGF). The displacement curve of ^{125}I-[Tyr^3]-octreotide is shown. spec. bind. = specific binding.

In the selected patients with severe OA, no significant correlation between pain/swelling and uptake of radioactivity by the affected joints at scintigraphy was demonstrated. However, the osteoarthritic joints demonstrated a lower uptake of [^{111}In-DTPA-D-Phe^1]-octreotide in comparison with the joints of the patients with RA. We cannot rule out the presence of an inflammatory component in the affected joints of these selected OA patients; this is substantiated by the finding of negative scan results in all of the control patients.

Different scintigraphic techniques have been used over the years for the visualization of affected joints in RA (20–25). The markers used can be classified according to the compartment involved. The vascular compartment reflects increased blood flow and interstitial extravasation, the bone compartment reflects normal response to bone destruction, and the inflammatory compartment reflects infiltration of leukocytes. To our knowledge, no scintigraphic technique related to specific receptors in the affected synovial membranes in RA has been described previously. In vitro binding assays showed the presence of specific SS-R in synovial biopsy specimens from our patients, but autoradiography did not enable recognition of which cells expressed these SS-R. [^{111}In-DTPA-D-Phe^1]-octreotide may bind to SS-R on lymphocytes and monocytes that have infiltrated into the affected synovial membranes. The low-grade uptake of radioactivity in OA, which has only a minor inflammatory component, supports this hypothesis.

The specificity of this in vivo method of SS-R visualization might be substantiated by investigation

of the effect of simultaneous administration of high-dose "cold" octreotide. However, our in vitro studies already demonstrated specific binding of octreotide, which could be completely prevented by the addition of excess "cold" octreotide, in the synovial membranes studied.

The relationship to and possible role of SS-R expression in disorders of the immune system have been described previously (3–8,26–35). T and B lymphocytes and monocytes express SS-R, and somatostatin has been shown to modulate the activity of the immune system (5–7,26–28). At low concentrations, somatostatin caused inhibition of the lectin-induced proliferation response of lymphocytes (26–28). Inhibition of cytotoxicity and of the release of cytokines by lymphocytes has also been described (29,30). Somatostatin suppresses immunoglobulin synthesis in Peyer's patches as well as by a myeloma cell line (31,32). Lymphoid cell lines of T cell origin have been shown to express SS-R (33). Somatostatin and SS-R have also been detected in schistosomiasis-induced murine granulomas (34,35). Treatment with the long-acting SS analog octreotide decreased the granulomatous response in this model by ~45% (36). In 10 patients with active RA, a transient beneficial effect was observed after direct intraarticular administration of somatostatin (37). This may be related to the inhibition of the release of substance P by nerve endings within these joints or by modulation of the activity of infiltrating immune cells. Thus, the potential value of somatostatin in the treatment of RA, as well as in monitoring of disease activity, merits further exploration.

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