Neuropeptides in the Arthritic TMJ and Symptoms and Signs From the Stomatognathic System With Special Consideration to Rheumatoid Arthritis

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The contribution of the nervous system to the pathophysiology of rheumatoid arthritis has been proposed to be mediated by certain neuropeptides. Neuropeptide Y, calcitonin gene–related peptide, substance P, and neurokinin A are considered modulators of inflammatory joint disease. Parameters of pain, as well as occlusal signs of tissue destruction from the arthritic TMJ and the corresponding neuropeptide concentrations in TMJ synovial fluid, were investigated in patients with various inflammatory joint diseases. The patients with rheumatoid arthritis were also examined in a separate diagnostic group. Visual analog scale, palpatory tenderness, maximal voluntary mouth opening, and anterior open bite were correlated to neuropeptide-like immunoreactivities of the above four neuropeptides. It was found that high concentrations of calcitonin gene–related peptide and neuropeptide Y in TMJ fluid are associated with pain, impairment of mandibular mobility, and occlusal signs of TMJ destruction in patients with rheumatoid arthritis. The results indicated neuropeptide involvement in rheumatoid arthritis, proposing a potentiation of the symptoms and signs by the inflammatory action of calcitonin gene–related peptide and neuropeptide Y.

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Since the classic axon-reflex experiments performed by Lewis in 1936, indicating release of proinflammatory substances from peripheral terminals of primary afferents, the concept of neurogenic inflammation has been the focus of intense research. Dysregulation of the immune system has been considered responsible for the pathogenesis of inflammation. The immune system, supposedly the driving force of the pathogenesis of inflammation, cannot be isolated from the influence of other body components in an inflammatory process such as rheumatoid arthritis (RA). Studies during the last decade have implicated the role of the central and peripheral nervous system in the development of RA.[1] The contribution of the nervous system to the pathophysiology of RA has been proposed to be mediated by certain neuropeptides.[2] The present study deals with the neuropeptides substance P (SP), calcitonin gene–related peptide (CGRP), neurokinin A (NKA), and neuropeptide Y (NPY).

Substance P is found in small-diameter, unmyelinated sensory neurons and has been shown to amplify experimental adjuvant arthritis in rats,[3] to activate macrophages in the pannus to secrete prostaglandins,[4] and to activate synoviocytes to secrete prostaglandin E_2 (PGE_2) and collagenase.[5] Substance P also has local effects such as vasodilatation, increased capillary permeability, and release of histamine from mast cells.[6,7] Like SP, CGRP is found in C fibers,[8] and CGRP may cooperate with SP in mediating local reflex reactions due to activation of sensory nerves. In addition, CGRP has a strong vasodilatory effect in joints and muscles and is several times more potent as a vasodilator than is SP.[9] Sensory nerve endings of several organs contain NKA, which is known to be released into the spinal cords of cats on induction of experimental knee joint arthritis.[10] However, the involvement of NKA in the local development of arthritis is unknown and warrants further investigation. Neuropeptide Y is produced with norepinephrine in certain efferent sympathetic nerve fibers[11] and has a strong and long-standing vasoconstrictive effect on both the arterial and venous side of vessels such as those of skeletal muscles. Increased activity in efferent nerves of the sympathetic system has been associated with an increase in joint inflammation and destruction.[12] Sympathetic vasoconstriction, in the acutely inflamed rat knee joints, has been replaced by a neuropeptide-mediated vasodilator response, enhancing responsiveness to SP. In this case, it has been proposed that CGRP contributes to the hyperemia of inflamed joints.[13] Thus, neuropeptides have been suggested as neurogenic mediators in the local neural mechanisms involved in the inflammatory process.

The neuropeptides SP, CGRP, NPY, and NKA are present in nerves of human synovium.[14] Decreased peptidergic innervation in the synovial tissue of patients with RA has raised the question whether reduced neuropeptide immunoreactivity in rheumatoid synovium is a result of an increased release into the synovial fluid or of the destruction of nerve fibers.[14,15] High concentrations of SP were found in the synovial fluid from knee joints of patients with RA compared to that of patients with osteoarthritis, who had higher level of SP-like immunoreactivities in the synovial tissue.[16] Both CGRP and NPY have been found in higher concentrations in the knee joint of arthritic patients than in control subjects with degenerative or traumatic joint disease.[17,18] In fluid from human arthritic temporomandibular joints (TMJs), the levels of SP, CGRP, NKA, and NPY exceeded those in plasma, and CGRP and NPY were correlated to the intra-articular temperature, stipulating neuropeptide-mediated microcirculatory changes.[19-21]

The documentation of the pathophysiology of RA in the TMJ is scarce, although the TMJ, when exposed to inflammation, has characteristics similar to other arthritic joints. Pain, reduced mobility, and tissue destruction are also main features of TMJ arthritis. Formation of a rheumatoid pannus of vascular granulation tissue,[22] which destroys articular cartilage and bone, is a severe consequence of chronic RA in the TMJ. Immunoreactive fibers for SP, CGRP, and NPY have been found in the TMJ capsule of the monkey and rat.[23,24] The most prominent clinical signs of arthritis in the stomatognathic system are an anterior open bite, reduced mandibular mobility, and tenderness of the TMJ laterally and posteriorly.[25] Sources and effects of neuronal mediators in the pathogenesis of inflammation and pain present a complexity that must be understood to improve diagnostics and treatment of the acute and chronic phases of the inflammatory process.

The relation between the severity of the clinical signs of arthritis in the TMJ and the presence of neuropeptides in the synovial fluid has not yet been established. The aim of this study was therefore to investigate whether the levels of SP, CGRP, NPY, and NKA in the synovial fluid of the arthritic TMJ were correlated to pain, decreased mandibular mobility, and occlusal signs of joint destruction in the stomatognathic system.

Materials and Methods

Patients

This study comprised 46 TMJs of 23 patients (19 women and 4 men) with signs and symptoms of TMJ arthritis and with a median age of 50 years (mean = 46.9). The patients with RA were of special interest and were allocated into a separate group, the RA group, while the rest of the patients, having inflammatory joint diseases other than RA, formed the non–rheumatoid arthritis (NRA) group. The RA group comprised 14 patients: nine with positive rheumatoid factors and five with negative rheumatoid factors. The NRA group comprised nine patients: two with ankylosing spondylitis (AS); one with psoriatic arthropathy (PA); two with systemic lupus erythematosus (SLE); two with chronic unspecific polyarthritis (CUPA); and two with chronic unspecific monoarthritis (CUMA). The two groups were examined

together as an inflammatory entity (RA + NRA group), and as two separate subgroups. The mean age was 46.9 years for the RA + NRA group, 48.6 years ± 2.9 for the RA group, and 44.3 years ± 3.0 for the NRA group. The mean duration of the general disease was 11.9 years for the RA + NRA group, 11.0 years ± 3.2 for the RA group, and 14.9 years ± 3.9 for the NRA group. The mean duration of symptoms in the TMJ was 4.0 years for the RA + NRA group, 4.9 years ± 2.1 for the RA group, and 2.6 years ± 0.7 for the NRA group.

Procedure

This study was approved by the Ethical Committee of the Huddinge Hospital, No. 176/91. All patients were examined at their first and second visits. Both these sessions included blood plasma sampling, clinical examination, arthrocentesis, and intra-articular methylprednisolone administration. Each session started with collection of venous blood samples, clinical examination, and arthrocentesis of the symptomatic TMJs, unilaterally or bilaterally. Before the arthrocentesis, local anesthesia of the auriculotemporal nerve was performed with 20 mg of lidocaine (1 mL of Xylocaine, Astra Pharmaceuticals, Södertälje, Sweden, 20 mg/mL), followed by intra-articular infusion of 1 mL of isotonic saline into the upper joint compartment. After 20 seconds, the saline was aspirated. The samples were mixed with 0.1 mL of aprotinin (Trasylol, Bayer, Leverkusen, Germany) and 0.1 mL of heparin, cold-centrifuged (800 G), and immediately frozen at –70°C. Both sessions ended with intra-articular injections of 28 mg of methylprednisolone (0.7 mL of Depo-Medrol, Upjohn, Kalamazoo, Michigan, 40 mg/mL) with a mean of 47.3 days ± 3 between the visits. All patients were referred for radiologic examination of the TMJ including tomography at the first visit.

Blood

Ten mL of venous blood samples were collected and mixed with 0.25 mL of heparin (5,000 IU/mL) and 0.25 mL of aprotinin (Trasylol), immediately cooled to 0°C, and centrifuged at 3,000 rpm for 10 minutes. The plasma was then frozen at –70°C.

Blood samples were also taken for determination of the acute phase reactants: erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); rheumatoid factor (RF); and antinuclear antibody rate (ANA).

Clinical Parameters

The patients were questioned about their TMJ pain with reference to a visual analog scale (VAS) from 0 to 10 (0 = no pain, 10 = worst pain ever experienced). The patients were examined for tenderness on palpation of the TMJ (on both sides):

0 = no tenderness
1 = tenderness lateral or posterior to the TMJ without palpebral pain reflex
2 = tenderness either lateral or posterior to the TMJ with palpebral pain reflex or tenderness both lateral and posterior without palpebral reflex
3 = tenderness lateral and posterior to TMJ with palpebral reflex at one site
4 = tenderness lateral and posterior to TMJ and palpebral reflexes at both sites

The degree of anterior open bite (AOB) was examined:

0 = occlusal contacts of canines, premolars, and molars
1 = occlusal contacts posterior to the canine
2 = occlusal contacts posterior to the first premolar
3 = occlusal contacts posterior to the second premolar
4 = occlusal contacts posterior to the first molar
5 = occlusal contacts solely on the third molar

The maximal voluntary movement (MVM) was measured as the distance in millimeters between the maxillary and mandibular right medial incisors with the addition of the vertical overbite.

Neuropeptides

The joint fluid aspirates and blood plasma were analyzed for concentrations of neuropeptide-like immunoreactivities (Np-LI), ie, SP-LI, CGRP-LI, NKA-LI, and NPY-LI. Technical difficulties with the radioimmunoassay limited the number of concentrations from the SP assay. Therefore, SP-LI could not be correlated to the clinical parameters in the separate RA group; the correlations represent the inflammatory entity of the RA + NRA group. Samples were purified and concentrated using reverse-phase C18 cartridges (Sep Pak, Waters, Milford, MA) and analyzed using competitive radioimmunoassays.[26]

The SP-LI was analyzed using antiserum S2, and intra-assay and interassay coefficients of variation were 7% and 11%, respectively. Samples with concentrations of SP-LI below the formal detection limit of the assay were concentrated in the car-

Table 1 Correlation Coefficients Between the Neuropeptide-like Immunoreactivities in TMJ Fluid and the Clinical Parameters

		Overall†						RA group			
		SP-LI	n	CGRP-LI	n	NPY-LI	n	CGRP-LI	n	NPY-LI	n
Palpatory tenderness	S1	−0.58**	14	NS	32	NS	35	NS	18	NS	20
	S2	NS	14	NS	26	NS	28	NS	13	NS	13
AOB	S1	NS	14	NS	32	NS	35	NS	18	0.45*	20
	S2	NS	14	NS	26	NS	28	0.87***	12	0.56*	15
VAS	S1	NS	14	NS	31	NS	35	NS	18	NS	20
	S2	−0.56*	12	0.42**	26	NS	28	0.78***	13	0.76***	15
MVM	S1	−0.66**	14	−0.71***	32	−0.35*	35	−0.51*	18	NS	20
	S2	NS	14	NS	26	−0.42*	28–	0.71**	13	−0.75***	15

†Data from the RA group and the NRA group. S1 = first session; S2 = second session; NS = not significant.
*P < .05.
**P < .01.
***P < .001.

tridges to detect the minute concentrations. The reported concentrations of SP-LI thus reflect that the samples have been concentrated and express the estimated concentrations in the original samples before extraction. The NKA-LI was analyzed using antiserum K12, and intra-assay and interassay coefficients of variation were 7% and 12%, respectively.[27] The CGRP-LI was analyzed using antiserum CGRPR8, and intra-assay and interassay coefficients of variation were 8% and 14%, respectively. The NPY-LI was analyzed using antiserum N1, and intra-assay and interassay coefficients of variation were 7% and 12%, respectively.[28] Normal reference ranges for blood plasma in healthy individuals obtained with the radioimmunoassays used in this study areas follows: SP-LI < 15 pmol/L, CGRP-LI < 96 pmol/L, NKA-LI < 12 pmol/L, and NPY < 50 pmol/L.[26,28,29]

Statistics

The correlation between the clinical variables AOB, MVM, and the neuropeptides was tested by Pearson's product-moment correlation coefficient. The correlation between the data from the clinical variables VAS, palpatory tenderness, and the neuropeptides was tested by Kendall's rank correlation coefficient. The tests were performed two-tailed, and $P < .05$ was considered statistically significant.

Results

All neuropeptide concentrations in the TMJ fluid exceeded those in plasma. The RA + NRA group exposed correlations between SP-LI, CGRP-LI, and NPY-LI in the TMJ fluid and VAS as well as MVM. The VAS was positively correlated to CGRP-LI and NPY-LI but negatively to SP-LI. The MVM was negatively correlated to all three peptides. The RA group demonstrated the most and the strongest correlations between CGRP-LI, NPY-LI, and the clinical parameters. The VAS and AOB were positively correlated to CGRP-LI and NPY-LI, and the MVM was negatively correlated to the same neuropeptides. Neurokinin A was not related to any of the investigated parameters. The joint aspirate volumes ranged between 0.2 and 1.3 mL, with an average of 0.53 mL. Arthritic radiologic changes supported the inflammatory origin of the development of an anterior open bite. Tomography of the TMJ revealed loss of condylar bone and erosions on either the condylar or temporal components of the TMJ in patients with an AOB of greater than three.

The correlation coefficients between the investigated neuropeptides and the clinical variables and the number of observations in the RA + NRA group, as well as in the RA group, are shown in Table 1. Means and standard errors of the mean (SEM) of SP-LI, CGRP-LI, and NPY-LI in the RA + NRA group and in the RA group are shown in Table 2.

Blood

The neuropeptide concentrations and acute-phase reactants in blood plasma refer to the samples from session 1. The means of acute-phase reactants for the RA + NRA group were 30.7 mm/h for ESR and 25.4 mg/L for CRP. The mean ANA titer was 1:94.6, and the mean RF titer was 1:138.6. The mean neuropeptide concentrations in blood plasma of the same group were (in pmol/L):

SP-LI, 3.8; CGRP-LI, 5.1; and NPY-LI, 36.2. The means in the RA group were the following: ESR, 41.5 mm/h; RF titer, 1:120; ANA titer, 1:137.5; CRP, 33.0 mg/L; and (in pmol/L): SP-LI, 5.3; CGRP-LI, 8.2; and NPY-LI, 47.0. No association was found between the investigated acute-phase reactants and the neuropeptide concentrations in TMJ fluid.

Neuropeptides and Clinical Parameters

SP-LI. Because of SP-LI concentrations below the formal detection limit of the assay, the analysis of the correlations between SP-LI levels and clinical parameters was restricted to the RA + NRA group. In session 1, SP-LI showed a negative correlation with palpatory tenderness ($r = -.58$, $P < .01$, n = 14) and MVM ($r = -.66$, $P < .01$, n = 14). In session 2, a negative correlation between SP-LI and VAS ($r = -.56$, $P < .05$, n = 12) was found.

CGRP-LI. In session 1, CGRP-LI showed a negative correlation with MVM in the RA + NRA group ($r = -.71$, $P < .01$, n = 32) as well as separately in the RA group ($r = -.51$. $P < .05$, n = 18; Fig 1a) and the NRA group ($r = -.73$, $P < .03$, n = 14).

In session 2, the RA + NRA group showed a positive correlation between CGRP-LI and VAS ($r = .42$, $P < .01$, n = 26), but no statistically significant correlation was found with the other clinical variables. The RA group, however, showed a negative correlation between CGRP-LI and MVM ($r = -.71$, $P < .01$, n = 13; Fig 1b) and a strong positive correlation between CGRP-LI and AOB on the contralateral side ($r = .87$, $P < .001$; n = 12; Fig 1c) and with VAS ($r = .78$, $P < .001$, n = 13; Fig 1d).

NPY-LI. In session 1, the only statistically significant correlation in the RA + NRA group was found between NPY-LI and MVM ($r = -.35$, $P < .05$, n = 35). The RA group exposed a weak, but statistically significant, positive correlation between NPY-LI and AOB on the contralateral side ($r = .45$, $P < .05$, n = 20; Fig 2a). The NRA group exposed a weak negative correlation between NPY-LI and palpatory tenderness ($r = -.44$, $P < .03$, n = 15).

In session 2, in the RA + NRA group, there was a negative correlation between MVM and NPY-LI ($r = -.42$, $P < .05$, n = 28). In the RA group, NPY-LI was correlated to all clinical parameters except to palpatory tenderness. The NPY-LI was positively correlated to AOB on the contralateral side ($r = .56$, $P < .05$, n = 15; Fig 2b); showed a positive correlation with VAS ($r = .76$, $P < .001$, n = 15; Fig 2c); and was negatively correlated with MVM ($r = -.75$, $P < .001$, n = 15; Fig 2d).

Table 2 Mean Neuropeptide Concentrations of Neuropeptide-like Immunoreactivities in TMJ Fluid

		Overall†		RA group	
		Np (pmol/L)	SEM	Np (pmol/L)	SEM
SP-LI	S1	95	22.3	—	—
	S2	102	23.2	—	—
CGRP-LI	S1	93	13.9	66	11.1
	S2	70	9.5	58	8.7
NPY-LI	S1	771	121	649	94.9
	S2	654	111	697	166

†Data from the RA group and the NRA group. NP = neuropeptide concentration; S1 = first session; S2 = second session.

Discussion

This study presents relationships between concentrations of SP-LI, CGRP-LI, and NPY-LI in TMJ fluid and clinical parameters related to pain, mobility, and destruction of the TMJ. Although all patients, on their first visit, were given one intra-articular methylprednisolone injection, the corticosteroid effect was not evaluated in this study. The effect of methylprednisolone on inflammatory reactions is well documented, and consequently an improvement of symptoms is to be expected. Correlations between the neuropeptide concentrations and the clinical variables from visit one and visit two are presented separately, with visit one occurring prior to steroid administration and visit two after steroid administration. A relationship between the symptoms and signs from the arthritic TMJ and the neuropeptide content in the joint fluid is demonstrated irrelevant of the methylprednisolone effect. The neuropeptide concentrations in the TMJ fluid, well exceeding those in plasma,[26,28,29] indicate a local release of neuropeptides. Although elevated acute-phase reactants were not associated with high neuropeptide concentrations locally in the arthritic TMJ fluid, they supported other clinical manifestations of an ongoing inflammatory process. Anesthesia of the auriculotemporal nerve, possibly reducing the afferent activity and thereby the neuropeptide release, may have influenced the Np-LI in the TMJ aspirates. It is therefore important to point out that all patients received similar anesthesia, and the presumably decreased peptidergic activity was, nevertheless, significant enough to disclose neuropeptide concentrations above the plasma level. The occurrence of a rheumatoid pannus in the arthritic TMJ does sometimes complicate the arthrocentesis, and by consequence, the aspiration

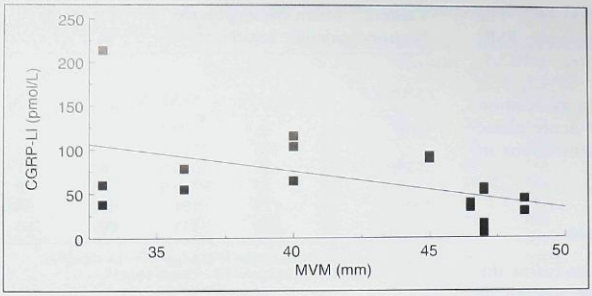


Fig 1a Relation between CGRP-LI in the TMJ fluid and maximal voluntary mouth opening (MVM) in the RA group at session 1 ($r = -.51$, $P < .05$, n = 18).

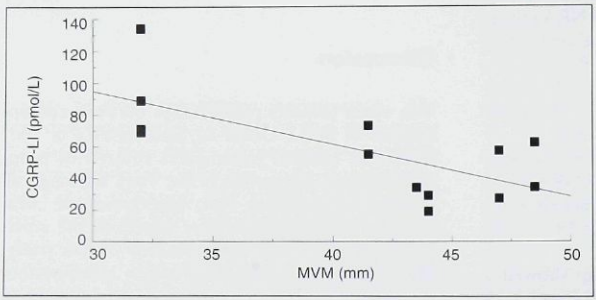


Fig 1b Relation between CGRP-LI in the TMJ fluid and maximal voluntary mouth opening (MVM) in the RA group at session 2 ($r = -.71$, $P < .01$, n = 13).

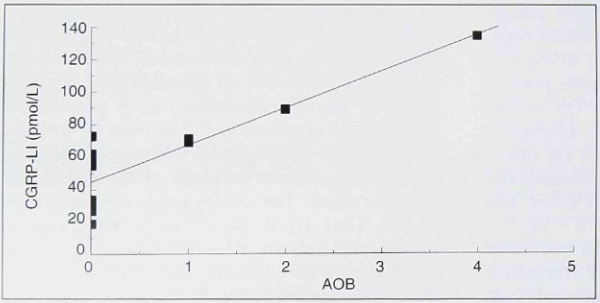


Fig 1c Relation between CGRP-LI in the TMJ fluid and anterior open bite (AOB) in the RA group at session 2 ($r = .87$, $P < .001$, n = 12).

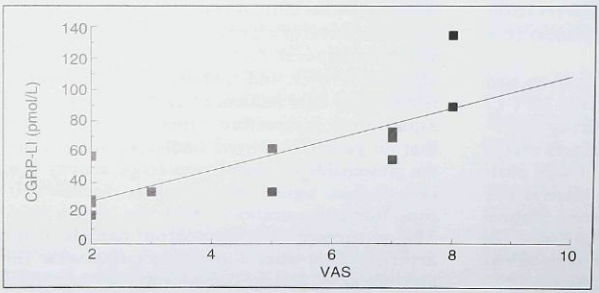


Fig 1d Relation between CGRP-LI in the TMJ fluid and TMJ pain (VAS) in the RA group at session 2 ($r = .78$, $P < .001$, n = 13).

Fig 2a Relation between NPY-LI in the TMJ fluid and anterior open bite (AOB) in the RA group at session 1 ($r = .45$, $P < .05$, n = 20).

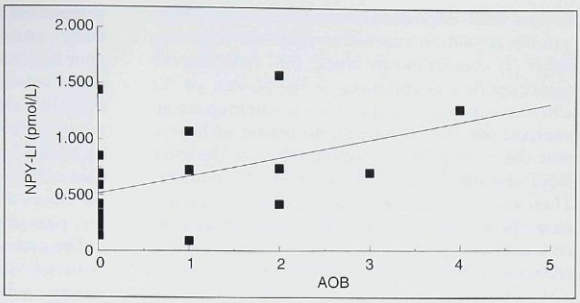


Fig 2b Relation between NPY-LI in the TMJ fluid and anterior open bite (AOB) in the RA group at session 2 ($r = .56$, $P < .05$, n = 15).

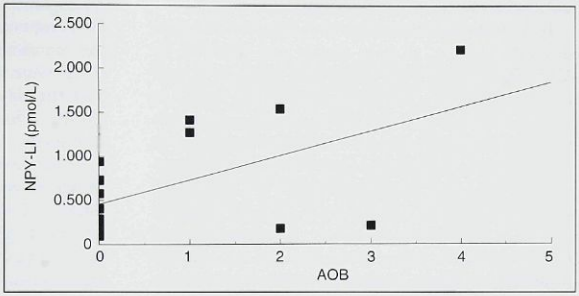


Fig 2c Relation between NPY-LI in the TMJ fluid and TMJ pain (VAS) in the RA group at session 2 ($r = .76$, $P < .001$, n = 15).

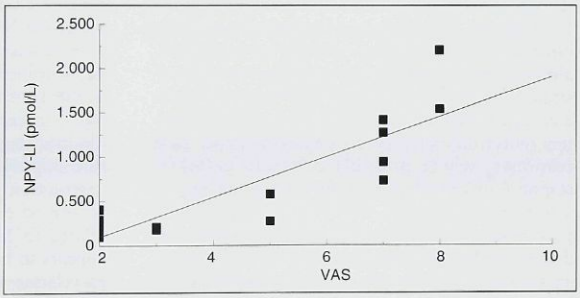
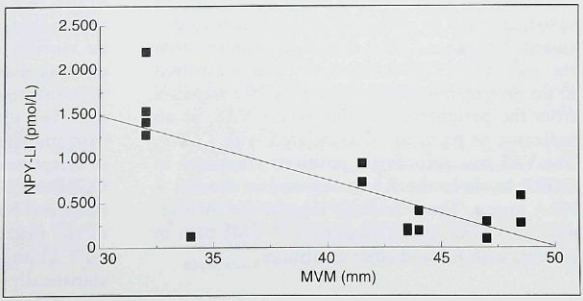


Fig 2d Relation between NPY-LI in the TMJ fluid and maximal voluntary mouth opening (MVM) in the RA group at session 2 ($r = -.75$, $P < .001$, n = 15).



of joint fluid. Aspiration from the soft tissue of the pannus is seldom successful since the aspirates either *(1)* contain mostly blood, thus reflecting the neuropeptide concentrations in the plasma, or *(2)* allow insufficient volumes for radioimmunoassay analysis. We have, however, no reason to believe that the neuropeptide concentrations in the joint fluid should differ from those in the pannus. Therefore, when successfully performed, aspirates from the pannus do reflect the neuropeptide concentrations in the joint fluid. Our results indicate a relationship between neuropeptides in the arthritic TMJ fluid and joint pain, reduced mandibular mobility, and occlusal signs of tissue destruction in patients with rheumatoid arthritis.

In this study, assessed pain is expressed in two different aspects, as pain at rest and function by VAS and as a response to external pressure by palpatory tenderness. Substance-P fibers are found in the synovial lining of the TMJ and adjacent periosteum,[23,30] and both SP and CGRP are proposed to be involved in the propagation of noxious nociceptive impulses.[31] In addition, SP and NPY have been shown to amplify experimental adjuvant arthritis and joint destruction in rats.[3,12] We therefore had reason to expect palpatory tenderness to correlate positively to these peptides. At session 1, palpatory tenderness correlated negatively both to SP-LI in the RA + NRA group and to NPY-LI levels in the NRA group. The VAS was also negatively correlated to SP-LI. Palpatory tenderness and VAS, although both tools for pain assessment, demonstrated different relationships with the pain-associated neuropeptides. It appears that these parameters reflect different aspects of inflammatory pain response, where possibly different cellular-response mechanisms account for the mediation. The negative relation between SP-LI and both pain-related parameters is contradictory to the documented nociceptive properties of SP; however, an anti-inflammatory role of sensory nerves cannot be disregarded.[32]

Calcitonin gene–related peptide is a potent vasodilator and its inflammatory role has been discussed.[13,32–34] Since CGRP is released directly from the nociceptive C-fiber terminals[35] and is involved in the propagation of noxious nociceptive impulses from the periphery,[31] we did expect VAS, as an indicator of pain, to be associated with CGRP. The VAS was accordingly positively correlated to CGRP levels in the RA group and in the RA + NRA group. These findings suggest the involvement of CGRP in the mediation of TMJ pain in patients with RA and other arthritides.

Increased activity in efferent nerves of the sympathetic system has been associated with increases in joint inflammation and destruction.[12] As a regulator of the severity of joint inflammation, it is plausible that NPY also is involved in the pain response from the arthritic TMJ. In this study, high concentrations of NPY-LI were associated with increased joint pain in the RA group only. It is therefore likely that NPY does contribute to the mediation of inflammatory pain of rheumatoid arthritis.

The pathology of the TMJ is a frequent cause of reduced voluntary mouth opening (MVM) in arthritic patients. Tissue destruction as well as subsequent healing in the arthritic TMJ are able to create adhesions between the temporal and condylar components of the TMJ, reducing mobility of the mandible. Destruction of TMJ cartilage and bone tissue is clinically reflected by reduced MVM and the development of an anterior open bite (AOB). It has been suggested that microcirculatory dysfunction in RA may act as a pathogenic factor in joint destruction.[36] Neuropeptides have been shown to contribute to the hyperemia of inflamed joints.[13] Neuropeptide Y, SP, and CGRP have been proposed to be involved in not only vascular regulation, but also immunoregulation and bone metabolism.[37] Substance P stimulates pannus formation,[38] and its inflammatory action is potentiated by CGRP.[39] We have previously shown that increased NPY levels in the TMJ are associated with reduced intra-articular temperature, suggesting neuropeptide-mediated microcirculatory failure in the arthritic TMJ.[20] Synovial fluid acidosis was found in knees with destructive arthritis,[40] and the observed hypoxia of the joint tissues could therefore implicate NPY involvement in the arthritic destruction of the joints. Consequently, we had reason to expect that SP, CGRP, and NPY are related to MVM and AOB. In this study, MVM appears to be the clinical variable with the strongest relation to the neuropeptide content in the synovial fluid of the arthritic TMJ, and it is demonstrated that increased levels of these neuropeptides are associated with an impairment of the mandibular mobility in patients with RA. An anterior bite opening indicates tissue destruction of the joint with subsequent deterioration of the dental occlusion. This process is irreversible and adds muscular pain and tension to the patient's clinical panorama of symptoms. Our findings indicate that release of CGRP and NPY promotes destruction of joint cartilage and bone tissues, which in turn explains part of the negative relation between CGRP-LI and NPY-LI and MVM. The NRA group showed no statistically significant correlation between these

neuropeptides and AOB. Therefore, we believe that action of CGRP and NPY in arthritic joint destruction may be particularly pronounced in rheumatoid arthritis.

We had expected NKA to be related to some of the clinical parameters, but no correlations were found in any of the groups. The reason is unclear, and further studies are needed to elucidate the role of NKA in TMJ arthritis.

It can be concluded that high concentrations of CGRP and NPY in the TMJ fluid are associated with pain, impairment of mandibular mobility, and occlusal signs of TMJ destruction in patients with rheumatoid arthritis. The results of this study indicate neuropeptide involvement in rheumatoid arthritis in particular, proposing a potentiation of the symptoms and signs of TMJ arthritis by the inflammatory action of CGRP and NPY.

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Resumen

El Papel de los Neuropéptidos en la Articulación Temporomandibular Artrítica y los Síntomas y Signos del Sistema Estomatognático con Consideración Especial a la Artritis Reumatoidea

Se ha planteado que la contribución del sistema nervioso a la patofisiología de la artritis reumatoidea es mediada por ciertos neuropéptidos. El neuropéptido Y, el péptido relacionado al gen de la calcitonina, la substancia P y la neurocinina A son considerados moduladores de la enfermedad inflamatoria de la articulación. En este estudio se investigaron los parámetros del dolor, así como los signos oclusales de destrucción tisular de la articulación temporomandibular (ATM) artrítica y las concentraciones de neuropéptidos correspondientes al fluido sinovial de la ATM, en pacientes con varias enfermedades inflamatorias de la articulación. Los pacientes con artritis reumatoidea también fueron examinados en un grupo de diagnóstico separado. Se correlacionó la escala análoga visual, la sensibilidad a la palpación, la apertura bucal voluntaria máxima, y la mordida abierta anterior a las inmunoreactividades de los cuatro neuropéptidos mencionados anteriormente. Se encontró que las concentraciones altas del péptido relacionado al gen de la calcitonina y del neuropéptido Y en el fluido temporomandibular están asociadas al dolor, al deterioro de la movilidad mandibular, y a los signos oclusales de destrucción de la ATM en pacientes con artritis reumatoidea. Los resultados indicaron que los neuropéptidos estaban envueltos en la artritis reumatoidea, y se plantea que la potencia de los síntomas y signos puede elevarse debido a la acción inflamatoria del péptido relacionado al gen de la calcitonina y del neuropéptido Y.

Zusammenfassung

Neuropeptide im arthritischen Kiefergelenk und Symptome und Zeichen des stomatognathen Systems mit spezieller Beachtung der rheumatoiden Arthritis

Der Beitrag des Nervensystems zur Pathophysiologie der rheumatoiden Arthritis wird—so wird angenommen—durch gewisse Neuropeptide vermittelt. Das Neuropeptid Y, "calcitonin gene-related peptide," Substantz P und Neurokinin A sind vermutete Modulatoren der entzündlichen Gelenkerkrankung. Bei Patienten mit verschiedenen Gelenkerkrankungen wurden Schmerzparameter, okklusale Zeichen der Gewebszerstörung im arthritischen Kiefergelenk und Neuropeptidkonzentrationen in der Synovialflüssigkeit der entsprechenden Kiefergelenke gemessen. Die Patienten mit rheumatoider Arthritis wurden in einer separaten diagnostischen Gruppe zusammengefasst. Visual analog scale, Palpationsempfindlichkeit, maximale Mundöffnung und frontoffener Biss wurden mit der neuropeptidähnlichen Immunoreaktivität der obengenannten vier Substanzen in Zusammenhang gebracht. Man fand, dass bei patienten mit rheumatoider Arthritis hohe Konzentrationen von "calcitonin gene-related peptide" und Neuropeptid Y im Kiefergelenk vergesellschaftet sind mit Schmerzen, Einschränkung der Unterkieferbeweglichkeit und okklusalen Zeichen von Kiefergelenkzerstörung. Die Resultate weisen auf eine Beteiligung der Neuropeptide an der rheumatoiden Arthritis hin; die entzündliche Wirkung von "calcitonin gene-related peptide" und Neuropeptid Y scheint eine Verstärkung der Symptome und Zeichen herbeizuführen.