TMJ Pain in Relation to Circulating Neuropeptide Y, Serotonin, and Interleukin-1β in Rheumatoid Arthritis

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Aims: *The aim of this study was to test the hypothesis that temporomandibular joint (TMJ) pain is influenced by circulating levels of neuropeptide Y, serotonin, and interleukin-1ß in rheumatoid arthritis.* **Methods:** *Forty-three seropositive (RF+) or seronegative (RF–) rheumatoid arthritis patients and 24 healthy individuals were included in the study.* **Results:** *High serum concentrations of serotonin were associated with low TMJ pressure pain thresholds and pain during mandibular movement in the RF+ patients. The results of this study do not support a relationship between circulating neuropeptide Y or interleukin-1ß and TMJ pain. The RF+ patients had higher C-reactive protein levels and erythrocyte sedimentation rates than the RF– patients. There were also higher plasma levels of interleukin-1ß in the RF+ patients than in the healthy individuals. Plasma levels of neuropeptide Y in the RF– patients were higher than in the healthy individuals.* **Conclusion:** *This study indicates that the serum concentration of serotonin is associated with TMJ allodynia in seropositive rheumatoid arthritis.*
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Key words: pain, serotonin, interleukin-1ß, rheumatoid arthritis, temporomandibular joint

Inflammatory joint diseases can affect the temporomandibular joint (TMJ), causing disorders and pain. Common subjective and clinical signs in these patients include hyperalgesia or allodynia of the TMJ, but the mediators of pain in the TMJ and other joints have been largely undetermined. The inflammatory process in the TMJ can be suspected to differ from that in other synovial joints because the articular surfaces in the TMJ are composed of fibrous cartilage, not hyaline cartilage as in most other synovial joints.

There is considerable evidence that neuropeptides, including neuropeptide Y (NPY), take part in the modulation of arthritis and pain.[1] Neuropeptide Y is mainly produced in efferent sympathetic nerve fibers, and it is released from them along with norepinephrine.[2] It has been found in significantly higher concentrations in the knee synovial fluid of patients with arthritis than in control subjects with degenerative knee joint disorders.[3,4] Neuropeptide Y has also been found in concentrations that are high above plasma

Table 1 Age Distribution and Duration of General and TMJ Symptoms

	Age (y)	Duration (y)	
		General	TMJ
RF+ patients (17 female, 7 male)			
Mean	56	16	7
SD	11	13	4
n	24	24	24
RF– patients (14 female, 5 male)			
Mean	55	16	9
SD	18	12	8
n	19	19	19
Healthy individuals (14 female, 10 male)			
Mean	43		
SD	9		
n	24		

n = no. of subjects.

levels in TMJ synovial fluid from patients with rheumatoid arthritis (RA); NPY has also been associated with spontaneous TMJ pain.[5] There are, however, no published reports of a relationship between circulating NPY and joint pain.

Serotonin (5-hydroxytryptamine [5-HT]) has long been known to be an important endogenous mediator of inflammation in peripheral tissues, and to sensitize or excite peripheral sensory nerve endings.[6–9] Serotonin has been found to mediate spontaneous pain from inflamed peripheral tissues by exciting or sensitizing fine afferent units by means of the 5-HT_3 receptor,[10] which has been suggested to play a role in chemical, but not thermal or mechanical, nociceptive mechanisms.[11] Platelets are likely to be the major source of 5-HT in serum as well as in synovial fluid, and they have been found in synovial fluid from the knees of patients with several rheumatic diseases, including RA.[12–14] When compared to platelets from healthy individuals, these platelets were found to be activated, ie, 5-HT had been liberated from them.[12,14] When released locally from activated platelets, 5-HT and other substances have been suggested to contribute to the inflammatory response of RA in several ways,[12] and the platelet content of 5-HT has been found to be decreased during inflammatory episodes of RA.[14] In TMJ synovial fluid, the 5-HT level has been positively correlated to pain that is provoked by joint movement.[15] Several studies have indicated a relationship between the serum level of 5-HT (S-5-HT) and pain as assessed by tenderness to digital palpation or pressure pain threshold[16–18] in patients with RA or fibromyalgia. These studies have not, however, focused on the TMJ, and they have shown divergent results that must be considered inconclusive.

Cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor, play important pathologic roles in RA by taking part in the mediation of acute and chronic inflammation with associated connective tissue destruction.[19] Interleukin-1, which is mainly derived from tissue macrophages, induces several inflammatory events by activating lymphocytes, by stimulating prostaglandin and collagenase production in connective tissue cells, and by stimulating cartilage proteoglycan breakdown. It also has systemic effects by stimulating the acute phase response, ie, by inducing the production and release of C-reactive protein (CRP), eliciting fever, and enhancing muscle protein catabolism.[20] To date, 2 subtypes of IL-1 have been identified (IL-1α and IL-1β), and both have been shown to be involved in inflammatory processes.[21] However, only IL-1β has been found in synovial fluid from patients with RA[22]; the synovial fluid level of IL-1β in human knees has been found to correlate with local disease activity as measured by the Ritchie score and the joint circumference.[23] High levels of plasma in IL-1β (P-IL-1β) have been associated with general disease activity, as measured by Ritchie score, pain, erythrocyte sedimentation rate (ESR), and hemoglobin level in patients with RA.[24] No studies on the influence of P-IL-1β levels on TMJ pain or allodynia have been performed. In rats, intraplantar and intraperitoneal injections of IL-1β sensitize peripheral nociceptors in chronic inflammation and enhance general pain response via actions on either the hepatic vagus nerve or at sites within the central nervous system.[25,26]

The aim of this study was to investigate the hypothesis that TMJ pain or allodynia are influenced by circulating levels of NPY, 5-HT, and IL-1β in patients with seropositive (RF+) or seronegative (RF–) RA.

Methods and Materials

Subjects

This study included 12 male and 31 female patients (86 TMJs) with RF+ or RF– RA. The gender and age distribution and the duration of general and TMJ symptoms are shown in Table 1. The patients were referred to the Department of Clinical Oral Physiology by rheumatologists or general practitioners because of TMJ involvement

in RA. The inclusion criterion was diagnosis of RA according to the 1987 classification criteria of the American College of Rheumatology,[27] including pain localized to the TMJ region for a period of at least 6 weeks or tenderness to lateral or posterior palpation of the joint. The patients had not received any recent treatment of the TMJ symptoms other than analgesics. Patients whose symptoms (eg, toothache, myalgia, or neuralgia) could be referred to disease in other components of the temporomandibular system or to local infection of the skin over the TMJ were excluded.

For comparison with the patients, a healthy group of 14 females and 10 males was included in the study (Table 1). The healthy individuals had no history of temporomandibular disorders or pain.

Assessment of Subjective Symptoms and Clinical Signs

The patients were asked about the number of symptomatic joint regions besides the TMJ at the time of examination (feet, hands, knees, hips, elbows, shoulders, lower back, upper back, and neck; maximum score = 9). A 10-cm visual analogue scale (VAS) with the endpoints modified to "No pain" (0) and "Worst pain ever experienced" (10) was used to assess the highest degree of pain experienced in the TMJ area during the last week. A score of tenderness to digital palpation of the TMJ indicated tenderness of the lateral and posterior aspects of the joint on each side. At each side and location (lateral and posterior), 1 unit was scored if the patient reported tenderness, and 2 units were scored if the palpation caused a pain reflex (maximum score per joint = 4). The pressure pain threshold to linearly increasing pressure over the lateral aspect of the TMJ was assessed with an algometer (Pain Diagnostics and Thermography) with a 1-cm^2 blunt rubber tip and a pressure of 50 kPa/s. The number of mandibular movements—including maximum mouth opening, laterotrusion to both sides, and protrusion—that provoked TMJ pain was counted on each side (maximum score = 4).

Blood Sampling

Venous blood was collected in a sodium citrate tube (0.105 mol/L) for measurement of the ESR. Additional blood was collected in an ethylenediaminetetraacetic acid (EDTA) tube, and immediately cooled, centrifuged (1,500 G for 10 min), and frozen (–70°C); it was later examined for level of immunoreactivity regarding NPY (plasma level of NPY [P-NPY]) and IL-1β (plasma level of IL-1β [P-IL-1β]). In addition, venous blood was collected without additives for analysis of the serum levels of 5-HT (S-5-HT), rheumatoid factor (S-RF), and CRP (S-CRP). These tubes were left at room temperature for 60 min of coagulation and then centrifuged (1,500 G for 10 min at 4°C). The serum was then removed and frozen (–20°C) until analysis. All S-CRP values below 10 mg/L and S-RF titers below 1/20 were considered 0 values.

Analyses of the Mediators

The P-NPY was analyzed by means of a competitive radioimmunoassay. Intraassay and interassay coefficients of variation were 7% and 14%, respectively, and the detection limit of NPY was 8 pmol/L.[28] The S-5-HT was analyzed by means of a commercially available enzyme immunoassay (EIA) kit (Nr 0642, Immunotech International) with a detection limit of 0.5 nmol/L. According to the manufacturer, the intraassay coefficient of variation is less than 9.4% and the interassay coefficient of variation is less than 9.9%. The P-IL-1β was determined with an enzyme-linked immunosorbent assay (ELISA) kit (Cayman Chemical) with a detection limit of 1.5 pg/mL. Performance characteristics for the analysis were: intraassay and interassay coefficient of variation < 10%, specificity of IL-1β 100%, specificity of IL-1α < 0.01%, specificity of IL-2 < 0.01%, and sensitivity > 1.0 pg/mL.

Statistical Analysis

The Komolgorov-Smirnov test for continuous variables was used to test the normality of the variables. To correlate the joint-related variables to the variables related to the individual, the sum of the joint-related variables (right side + left side) was used (VAS_{sum} and $[\text{pressure pain threshold}]_{sum}$). One-way analysis of variance (ANOVA) with Dunnett's multiple comparison test was used to test the significance of the differences between the 3 subject groups for normally distributed variables that were measured on at least an interval scale, and Kruskal-Wallis 1-way ANOVA on ranks with Dunn's multiple comparison test was used for the other variables. The Student's *t* test was used to test the significance of the differences between the 2 patient groups for normally distributed variables that were measured on at least an interval scale, and the Mann-Whitney *U* test was used for the other variables. Pearson's product moment correlation test was used to test the significance of

Table 2 Pain and Blood Variables in 43 RA Patients and 24 Healthy Individuals

		RF+			RF–			Healthy individuals		
	P/NP	Central tendency*	Variability†	n	Central tendency*	Variability†	n	Central tendency*	Variability†	n
Blood variable										
P-NPY (pmol/L)	P	23	4	13	34	5	15	18	3	11
S-5-HT (nmol/L)	P	1027	80	10	909	113	8	944	108	16
P-IL-1β (pg/mL)	NP	2.8	6.5	14	0.0	3.1	9	0.0	0.0	18
B-ESR (mm/h)	NP	34	21	17	11	17	17			
S-CRP (mg/L)	NP	15	33	21	0	0	18			
S-RF	NP	160	240	18						
Pain variable										
NSJ	P	6.4	0.5	24	6.4	0.4	18			
VAS_{sum}	NP	7	7	17	5	10	10			
TDP_{sum}	NP	2	4	17	2	6	10			
PPT_{sum} (kPa)	P	324	39	23	284	29	19			
PM_{sum}	P	3.1	0.5	22	3.4	0.6	18			

*Mean for parametric variables, median for nonparametric variables.
†Standard error of the mean for parametric variables, intraquartile range for nonparametric variables.
P = parametric, normally distributed variable; NP = nonparametric variable; n = no. of observations; P-NPY = plasma concentration of neuropeptide Y; S-5-HT = serum concentration of serotonin; P-IL-1β = plasma concentration of interleukin-1β; B-ESR = erythrocyte sedimentation rate; S-CRP = serum level of C-reactive protein; S-RF = serum level of rheumatoid factor (1/dilutions); NSJ = no. of symptomatic joint regions besides the TMJ; VAS = visual analogue scale; TDP = tenderness to digital palpation of the TMJ; PPT = pressure pain threshold on linearly increasing pressure (kPa) over the TMJ; PM = no. of painful mandibular movements; sum = sum of the right side and left side.

the correlations between normally distributed parameters that were measured with at least an interval scale, and Spearman's ranked correlation test was used when at least one of the parameters was measured with an ordinal scale. A P value of less than 0.05 was considered significant.

Results

Table 2 shows the investigated pain and blood variables in the patients and the healthy individuals. Table 3 shows the correlation between P-NPY, S-5-HT, and P-IL-1β and the pain variables.

Inflammatory Activity

There were significantly higher levels of ESR (P = 0.001) and S-CRP (P = 0.001) in the RF+ patients than in the RF– patients. In the RF+ patients, P-IL-1β and S-RF were significantly correlated (r_s = 0.72, n = 11, P = 0.009).

TMJ Pain and Allodynia

There was no significant difference in the number of symptomatic joint regions or in the TMJ VAS scores between the RF+ and RF– patients. Neither the number of symptomatic joint regions nor the VAS scores were correlated to P-NPY, S-5-HT, or P-IL-1β in any of the patient groups.

There were no significant differences between the RF+ and RF– patients concerning tenderness to palpation, pressure pain threshold, or number of painful TMJ movements. In the RF+ patients, there was a significant correlation between S-5-HT and pressure pain threshold (r = –0.66, n = 10, P = 0.039) (Fig 1), as well as between S-5-HT and the number of painful movements (r_s = 0.93, n = 10, P < 0.001) (Fig 2).

Group and Gender Differences

Compared to the healthy individuals, there were significantly higher levels of P-NPY in the RF– group of patients (P = 0.017), and significantly higher levels of P-IL-1β in the RF+ patients (P = 0.005). No significant differences were found in S-5-HT among the 3 groups. There was no significant difference between the genders within any group in P-NPY, S-5-HT, P-IL-1β, or the pain variables.

Table 3 Correlation Between P-NPY, S-5-HT, P-IL-1β, and Investigated Pain Variables in RA Patients

Variable	Pearson's product moment correlation coefficient/ Spearman's ranked correlation coefficient	RF+ r/r_s	RF+ n	RF+ P^*	RF– r/r_s	RF– n	RF– P^*
P-NPY							
VAS_{sum}	Spearman's	–0.02	7	0.905	0.60	5	0.285
TDP_{sum}	Spearman's	0.20	7	0.602	–0.16	5	0.799
PPT_{sum}	Pearson's	0.16	13	0.600	–0.14	15	0.610
PM_{sum}	Pearson's	–0.40	12	0.093	–0.45	15	0.120
S-5-HT							
VAS_{sum}	Spearman's	0.60	10	0.060	0.01	8	0.976
TDP_{sum}	Spearman's	0.44	10	0.185	0.18	8	0.678
PPT_{sum}	Pearson's	–0.66	10	0.039	0.54	7	0.208
PM_{sum}	Pearson's	0.93	10	< 0.001	–0.06	8	0.886
P-IL-1β							
VAS_{sum}	Spearman's	–0.10	12	0.749	0.07	9	0.858
TDP_{sum}	Spearman's	–0.26	12	0.402	0.02	9	0.952
PPT_{sum}	Spearman's	0.47	13	0.102	0.14	10	0.695
PM_{sum}	Spearman's	–0.05	13	0.863	–0.40	9	0.284

*A value of $P < 0.05$ was considered significant.
n = no. of patients; P-NPY = plasma concentration of neuropeptide Y; S-5-HT = serum concentration of serotonin; P-IL-1β = plasma concentration of interleukin-1β; VAS = visual analogue scale; TDP = tenderness to digital palpation of the TMJ; PPT = pressure pain threshold on linearly increasing pressure (kPa) over the TMJ; PM = sum of no. of painful mandibular movements; sum = sum of the right side and left side.

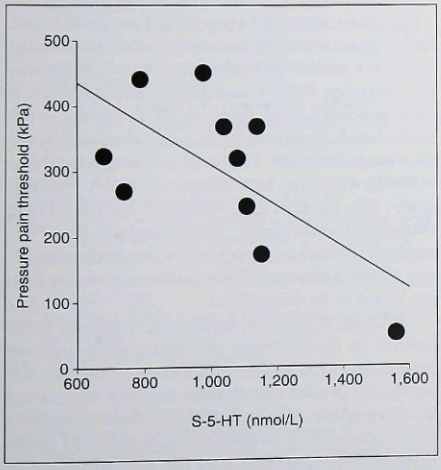

Fig 1 Relation between serum level of serotonin (S-5-HT) and sum (right side + left side) of pressure pain threshold in 10 RF+ patients ($r = –0.66$, $P = 0.039$).

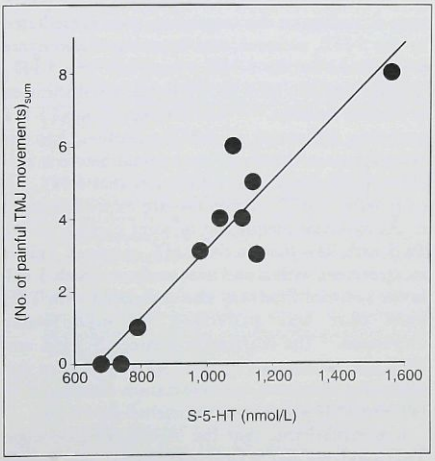

Fig 2 Relation between S-5-HT and sum (right side + left side) of painful TMJ movements in 10 RF+ patients ($r = 0.93$, $P < 0.001$).

Discussion

In this study S-5-HT was found to be correlated with a decrease in the pain threshold to linearly increasing pressure over the lateral aspect of the TMJ, as well as to TMJ pain that is provoked by mandibular movement in RF+ patients. These findings indicate a relationship between S-5-HT and TMJ allodynia in RF+ patients. There was no significant difference in S-5-HT among any of the groups, but the highest S-5-HT levels were found in the RF+ group. The serum levels of 5-HT in this study were comparable with the levels in a study by Ernberg et al[18] in our clinic, where no difference was found between patients with fibromyalgia or local masticatory myalgia or healthy individuals. In that study, low serum levels of 5-HT were associated with allodynia of orofacial muscles in patients with localized myalgia.

Localized TMJ pain that is provoked by mandibular movement is probably a manifestation of local allodynia, and is a result of mechanical stimulation of sensitized nociceptors in the synovial membrane and joint capsule by normally nonpainful joint movements. Taiwo and Levine[9] suggested that spontaneous pain and decreased nociceptive thresholds, which cause hyperalgesia or allodynia, might be 2 separate pain entities that are peripherally mediated via different 5-HT receptors; according to this suggestion, pain is mediated by the 5-HT_3 receptor, and hyperalgesia/allodynia is mediated by the 5-HT_{1A} receptor. The 5-HT_2 receptor has also been shown to cause sensitization of sensory neurons.[10,29] Circulating unbound 5-HT probably influences all 5-HT receptors, but the associations in this study were found between S-5-HT and allodynia, which indicates that 5-HT_{1A}—or possibly 5-HT_2 receptors—are expressed more in the synovial membrane or joint capsule of the TMJ with RF+ than in the 5-HT_3 receptor. This is in agreement with a previous study in which 5-HT in the synovial fluid was also associated with TMJ pain that was provoked by mandibular movement.[15] The correlation between S-5-HT and TMJ pain as assessed by the VAS was close to significance; therefore, an association between S-5-HT and TMJ pain cannot be excluded.

It is remarkable that the associations between TMJ allodynia and S-5-HT were found only in RF+ patients, and not in the RF– patients. This could be a result of the high level of P-IL-1β in RF+ patients, or perhaps of a high synovial fluid level of IL-1β that could sensitize peripheral nociceptors; these nociceptors might be further sensitized by 5-HT. Compared to the healthy individuals in this study, the RF+ patients had a higher level of P-IL-1β, which is consistent with findings in other studies.[24] The P-IL-1β induces the production of acute phase reactants such as CRP and serum amyloid A.[19] According to their significantly higher B-ESR and S-CRP levels—2 widely used parameters of inflammatory disease activity—the RF+ patients had a higher degree of disease activity than the RF– patients. High levels of S-RF have been associated with high disease activity and poor prognosis for the TMJ in patients with RA.[30] In this study we found a direct association between S-RF and P-IL-1β that supports the view that P-IL-1β is related to disease activity.[23]

Interleukin-1β has also been shown to produce a general decrease of nociceptive thresholds in rats,[25,31] or to produce decreased nociceptive thresholds peripherally through the sensitization of peripheral nociceptors. However, we did not find any direct association between P-IL-1β and allodynia. Synovial fluid levels of IL-1β in the TMJ, however, have been associated with allodynia of the TMJ in patients with both systemic and local arthritis,[32] while its correlation with P-IL-1β was poor in that study. It therefore cannot be excluded that S-5-HT acts in concert with locally released IL-1β. The presence of IL-1β within the joint, with an associated high disease activity, could thus, in combination with 5-HT, cause allodynia in RF+ patients.

No associations between P-NPY and TMJ pain, hyperalgesia, or allodynia were found in our study, and there are no published reports of an association between P-NPY and these pain variables. A high synovial fluid level of NPY, on the other hand, has been found to be associated with spontaneous pain of the TMJ and reduced mandibular opening capacity in patients with RA.[5] In this study, RF– patients had a higher P-NPY level than the healthy individuals, which suggests that NPY might be somehow involved in the pathophysiology of this subgroup. The significance of this finding is still to be determined.

Although it was not significant, there was a difference in age between the rheumatoid arthritis patients and the healthy individuals, while the difference in gender distribution between the groups was negligible. The influence of these deviations can be considered minimal because the level of the investigated substances was not related to age or gender. This study indicates that the serum concentration of serotonin is positively related to TMJ allodynia in patients with seropositive rheumatoid arthritis.

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