Substance P–Associated Increase of Intra-articular Temperature and Pain Threshold in the Arthritic TMJ

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Neuropeptides are considered mediators and modulators of inflammatory joint disease. Substance P (SP) has been proposed as a mediator of pain, and its vasoactive properties are well documented. In this study, the presence of SP-like immunoreactivity in the synovial fluid was correlated to intra-articular temperature (IAT) and pain from the arthritic temporomandibular joint (TMJ) 3 to 5 weeks after one intra-articular injection of glucocorticosteroids. Eighteen TMJs were investigated for IAT and the presence of SP-like immunoreactivity in the synovial fluid in 12 patients with systemic inflammatory joint disease. After arthrocentesis, the aspirates were analyzed for SP-like immunoreactivity by means of competitive radio immunoassay. A visual analogue scale and an algometer determining the pressure pain threshold and tolerance level assessed arthritic pain and hyperalgesia in the TMJ. Our results indicate that SP-like immunoreactivity is associated with IAT and that increased concentrations of joint fluid SP-like immunoreactivity correspond to increased pain threshold and tolerance and a concomitantly decreased visual analogue scale. These findings suggest that SP is implicated in the vascular and nociceptive response of the arthritic joint and that SP, possibly assisted by the antinociceptive effect of local corticosteroids, has a modulatory role in arthritic pain and hyperalgesia.
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key words: substance P, pain, pain threshold, hyperalgesia, intra-articular temperature, temporomandibular joint arthritis

Neural involvement in symmetric arthritis has been described.[1] The bioactive undecapeptide substance P (SP) is found in primary afferent nociceptors and localized in human synovium in both perivascular and free nerve fibers.[2,3] Substance P-immunoreactive nerve fibers have been demonstrated in the temporomandibular joint (TMJ) capsule, disc attachment, fascia, and adjacent periosteum in monkeys.[4] Substance P induces plasma extravasation and vasodilation, and is one of the major neurotransmitters of painful stimuli by unmyelinated C-fibers exerting in the acute stage a proinflammatory effect in the joint.[5,6] In acute inflammation, an increase in the rate of blood flow due to vasodilatation results in hyperemia of the synovial membrane and an increased temperature in the joint.[7] In chronic inflammatory arthritis, the intra-articular environment is hypoxic, hypercapnic, and acidotic.[8–10] In chronic rheumatoid knees, the total blood flow correlates directly to synovial fluid pH, glucose, and temperature, and both increased and decreased total perfusion have been reported.[11–13] Reduced temperature suggests a decreased blood flow and metabolism in the TMJ, in turn possibly caused by micro-

circulatory failure, sympathetic vasoconstriction, or atrophy.[14] Proinflammatory effects of SP may cause defective neurovascular regulation in the chronically inflamed synovium.[15] The intra-articular temperature (IAT) has been used to estimate the vascular changes that occur in the TMJ of patients with rheumatoid arthritis.[16] In a previous investigation of the relationship between IAT and the presence of neuropeptide Y–like immunoreactivity (NPY-LI), as well as calcitonin gene related peptide-like immunoreactivity (CGRP-LI) in human arthritic TMJ before intra-articular glucocorticoid (GC) treatment, the present authors reported that IAT was positively correlated to CGRP-LI but negatively correlated to NPY-LI, indicating neuropeptide involvement in microcirculatory changes in the arthritic TMJ.[17,18] The presence of substance P–like immunoreactivity (SP-LI), CGRP-LI, NPY-LI, and neurokinin A–like immunoreactivity (NKA-LI) has also been found in concentrations above the plasma level in the non-GC-treated rheumatoid TMJ, and similar results (with the exception of SP-LI) have been found in the rheumatoid knee joint.[19,20] The relationship between arthritic TMJ pain and joint fluid SP-LI prior to and after intra-articular GC administration has been investigated in an earlier study of clinical signs and symptoms in the arthritic TMJ in relation to joint fluid concentrations of SP-LI, CGRP-LI, and NPY-LI. The results of that study indicated that arthritic pain, assessed by a visual analogue scale (VAS), was positively correlated to CGRP-LI and NPY-LI, while negatively correlated to SP-LI in the GC-treated rheumatoid TMJ; however, no significant correlation was found between VAS and the neuropeptides in the nontreated rheumatoid TMJ.[21] The negative correlation between SP-LI and pain in the GC-treated arthritic TMJ was unexpected.

The aim of the present study was to investigate the relationship between SP-LI, microcirculation, pain, and hyperalgesia in the arthritic TMJ after intra-articular glucocorticoid administration, using the parameters IAT, VAS, pressure pain threshold (PPT), and pressure pain tolerance (PPTL).

Materials and Methods

Patients

This study comprised 12 female patients with a mean age of 41.8 years. All of the patients had been referred to the authors' department with signs and symptoms of TMJ arthritis unilaterally or bilaterally in a total of 18 TMJs. This study was approved by the Ethical Committee of the Huddinge Hospital, #176/91.

Table 1 Specification of the Anti-Inflammatory Drug Regimen of the Patients in the Study Population

Systemic medication	No. of Patients
NSAID	8
Glucocorticoid	3
Sulphasalazine	1
Chloroquine	1
Gold	1

NSAID = nonsteroidal anti-inflammatory drug.

All 18 symptomatic TMJs underwent arthrocentesis (upper joint compartment) followed by an injection of 28 mg methylprednisolone (0.7 mL Depo-Medrol, 40 mg/mL, Upjohn, Kalamazoo, MI) 28 + 7 days prior to the present arthrocentesis. Five of the patients had rheumatoid arthritis (three positive rheumatoid factor), two had ankylosing spondylitis, one had psoriatic arthropathy, one had systemic lupus erythematosus, and three had chronic unspecific polyarthritis.

The mean duration of the TMJ arthritis was 2.9 years, and the mean duration of the systemic joint disease was 9.8 years. Eight of the 11 patients were on an individual and regular systemic anti-inflammatory drug regimen prescribed by their rheumatologist. This regimen was not altered throughout the oral physiologic treatment program; the disease-related drugs and the number of patients who used each one are accounted for in Table 1.

After venous blood samples were collected, patients underwent clinical examination, including pressure algometry and arthrocentesis of the symptomatic TMJs, either unilaterally or bilaterally.

Blood. Venous blood samples of 10 mL were collected and diluted in 0.25 mL heparin sodium and 0.25 mL aprotinin (Trasylol, Bayer, Leverkusen, Germany), which were immediately cooled and centrifuged (3000 rpm for 10 minutes). The plasma was then frozen (–70°C).

Pain Parameters

Pressure Pain Threshold. The PPT was defined as the minimal pressure required to induce pain.

Pressure Pain Tolerance. The PPTL was defined as the maximum pressure the patient was able to tolerate. The PPT and the PPTL were determined by means of a pressure threshold meter (PTM) with a 1-cm-diameter rubber disc and with an 11-kg-

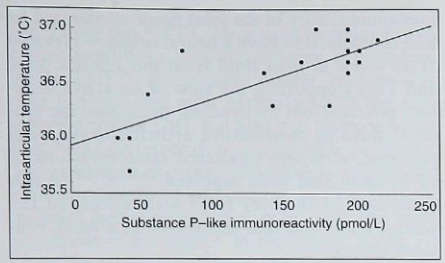

Fig 1 Relationship between joint fluid SP–LI and intra-articular temperature in 18 arthritic TMJs (Spearman's rank correlation coefficient = 0.67; $P < 0.002$).

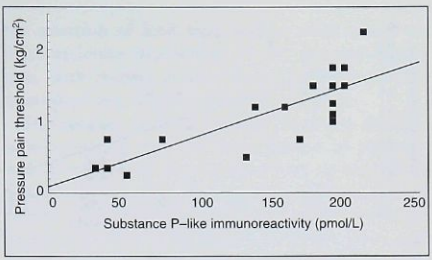

Fig 2 Relationship between joint fluid SP–LI and pressure pain threshold in 18 arthritic TMJs (Spearman's rank correlation coefficient = 0.86; $P < 0.0001$).

gauge range, calibrated in kg/cm^2 (Pain, Diagnostics, and Thermography, Great Neck, NY). The PTM was placed laterally over the condylar head of the arthritic TMJ, and the pressure was smoothly increased at a rate of approximately 0.25 kg/cm^2 per second. The PPT and PPTL were measured separately; patients were instructed to raise their hand when the pain sensation started (PPT) and when the pain could no longer be tolerated (PPTL).[22]

Visual Analogue Scale. Patients were asked to describe the maximum TMJ pain during movement and rest during the last week using a visual analogue scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = worst pain ever experienced).

Arthrocentesis

Temperature Recordings. The IAT was measured to assess vascular changes associated with joint inflammation. The IAT of the TMJs was measured after a 30-minute rest and before saline washing of the joint. Measurement was made with a thermocouple probe (Exacon C-N5, Exacon Scientific, Roskilde, Denmark), put through the same cannula as used for saline washing, and a digital thermometer (Exacon MC 9200) with an accuracy of .1°C.

Joint Fluid. A sample of joint fluid was obtained by intra-articular infusion of 1.0 mL isotonic saline into the upper joint compartment and aspiration after 20 seconds. The samples were diluted in 0.25 mL heparin sodium and 0.25 mL aprotinin and then immediately cold-centrifuged (800 G for 2 minutes). The supernatant was then frozen (–70°C).

Substance P–Like Immunoreactivity. The aspirates were analyzed for SP-like immunoreactivity. Samples were purified and concentrated by means of reverse-phase C18 cartridges (Sep Pak, Waters, Milford, MA) and analyzed by means of competitive radioimmunoassays (RIAs).[23] SP-LI was analyzed using antiserum SP2,[24] which reacts with SP-LI and SP sulfoxide, but not with other tachykinins. 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 cartridges so as to allow detection of the minute concentrations. Thus, the reported concentrations of SP-LI reflect that the samples have been concentrated and represent the estimated concentrations in the original samples before extraction. The normal value for blood plasma obtained with the radioimmunoassay used in this study is less than 15 pmol/L.[22,25,26]

Statistics. The correlation between SP-LI and IAT, PPT, PPTL, and VAS was tested by Spearman's rank correlation coefficient. Analysis of partial correlation was performed for IAT, PPT, and SP-LI. The probability level of $P < 0.05$ was considered significant.

Results

The average volume of aspirated joint fluid after the saline washing was 0.45 mL. All neuropeptide concentrations in the TMJ fluid exceeded those in plasma. The results show that increased levels of SP-LI are significantly correlated to increased IAT (Fig 1) as well as increased PPT (Fig 2) and PPTL. Increased IAT per se was also correlated to increased PPT. A decrease in TMJ pain as measured on a VAS was associated with an increase of

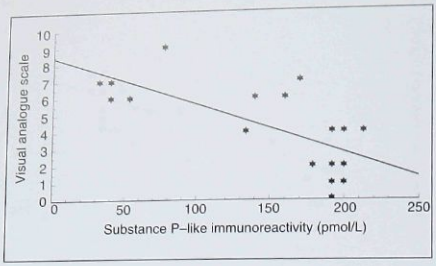

Fig 3 Relationship between joint fluid SP–LI and TMJ pain according to visual analogue scale in 18 arthritic TMJs (Spearman's rank correlation coefficient = 0.72; $P < 0.001$).

intra-articular SP-LI (Fig 3) as well as an increase in PPT and PPTL. IAT varied between 35.7°C and 37.0°C, with a mean temperature of 36.6°C. SP-LI varied between 32 and 213 pmol/L, with a mean of 151.3 pmol/L. The PPT ranged between 0.25 and 2.25 kg/cm^2 with a mean of 1.1 kg/cm^2, and the PPTL ranged between 0.75 and 3.0 kg/cm^2 with a mean of 1.6 kg/cm^2. VAS ranged between 0 and 9 with a mean of 4.4. The mean plasma concentration of SP-LI was 5.8 pmol/L.

There was a significant positive correlation between SP-LI and IAT ($r = 0.67$, $P < 0.001$), SP-LI and PPT ($r = 0.86$, $P < 0.0001$), and SP-LI and PPTL ($r = 0.79$, $P < 0.001$). There were also significant positive, albeit weak, correlations between IAT and PPT ($r = 0.51$, $P < 0.05$) and between IAT and PPTL ($r = 0.41$, $P < 0.05$). VAS exposed significant negative correlations of SP-LI ($r = -0.72$, $P < 0.001$) to PPT ($r = -0.69$, $P < 0.001$) and to PPTL ($r = -0.62$, $P < 0.01$). PPT was significantly and positively correlated to PPTL ($r = 0.84$, $P < 0.0001$).

Partial correlations revealed that, when IAT was selected as the neutral (constant) variable, the correlation between SP and PPT remained essentially the same (SP-PPT: $r = 0.80$, $P < 0.0001$). When SP was selected as the neutral (constant) variable, the significant correlation between IAT and PPT disappeared.

Discussion

Inflammatory joint disease is presumed to entail quantitative alterations of neuropeptides, and, since neuropeptide concentrations in blood are low, the majority of the neuropeptide-like immunoreactivity in the joint tissue as assessed by RIA is assumed to have a neural origin.[27] Elevated SP-LI levels in joint fluid from the arthritic knee and TMJ (supporting the view of an active secretory process from the synovial tissue into the synovial fluid in rheumatoid arthritis) have been reported, although unaltered concentrations of SP-LI have also been reported.[19–21,27–29] In this study, SP-LI in joint fluid well exceeded the plasma levels and was interpreted as a local, neuronal release.

Acutely inflamed joints often exhibit high intra-articular temperatures and increased synovial blood flow, while chronic rheumatoid joints are characterized by synovial hypoperfusion and intra-articular acidosis.[13,30] The reported range for IAT in the healthy TMJ is 35.7 to 36.9°C, while the rheumatoid TMJ, ranging from 33.7 to 37.5°C, is often characterized by either hypothermia or hyperthermia.[16,31] The vasoactive properties of SP, ie, vasodilation and plasma extravasation, may explain increased IAT as a vascular response in the inflamed joint.[32] In a previous investigation of the untreated arthritic TMJ, IAT varied from 35.5 to 37.5°C, with a mean of 36.5°C, and was positively correlated to joint fluid concentrations of CGRP-LI.[18] In the present study, IAT in the GC-treated, arthritic TMJ correlated positively with SP-LI and varied from 35.7 to 37°C, thus reaching the interval of the healthy as well as the untreated arthritic TMJ.

The present results indicate that increased joint fluid SP-LI in the GC-treated TMJ corresponds to increased PPT and reduced VAS. The SP-associated reduced pain response is in conflict with the reported role of SP as a neurochemical mediator of certain kinds of peripheral noxious stimuli.[6] A parallelism between increased vascular permeability and pain response has been considered and, while SP in the periphery acts mostly proinflammatory in acute models, the physiologic release of SP from sensory nerves may also be a protective response to tissue injury and the increased perfusion of hypoxic synovium.[32,33] In an earlier study, no significant correlations were found between pain according to VAS and the neuropeptide-like immunoreactivity of SP, CGRP, and NPY in the untreated arthritic TMJ, whereas VAS in the GC-treated arthritic TMJ exposed significant positive correlations to CGRP-LI and NPY-LI and a significant and negative correlation to SP-LI.[21]

It has been suggested that mechanisms mediating pain can differ from those mediating hyperalgesia.[34] Arthritic TMJ pain in this study is assessed by VAS, describing pain upon movement

and during rest.[35] PPT, often used to define hyperalgesic conditions, assesses arthritic hyperalgesia in the TMJ.[36] The present results indicate that pain is associated with hyperalgesia in the GC-treated arthritic TMJ, but also that increased joint fluid SP-LI corresponds to a reduced hyperalgesia. The generation of arthritic hyperalgesia, involving both the peripheral and central nervous systems, includes inflammatory rest pain and pain upon movement of the joint.[37] In that study, a role for SP in the mediation of pain upon movement was suggested, since peripheral stimulation (joint movement) of the arthritic joint was required to increase SP in the generated arthritic hyperalgesia in the monkey dorsal horn. Central and peripheral involvement of SP in arthritic hyperalgesia, and perhaps also in arthralgia, may also depend on the distinction between rest pain and pain upon movement, thus offering limits in the interpretation PPT and VAS associated with SP-LI. In the periphery, when injected into human temporal muscle, SP produced neither a sensation of pain nor a decrease in the PPT, whereas it produced both a pain sensation and a lower PPT when injected in the skin. This suggests that SP not only requires the presence of other inflammatory mediators, but that it can differentiate between nociceptors in different tissues.[38] Differences in SP release therefore seem to exist between both central and peripheral sites of action and between peripheral sites of inflammation involving different tissues.

It must be considered that the decrease in arthritic pain and hyperalgesia associated with SP-LI occurred 3 to 5 weeks after intra-articular GC injection. GC anti-inflammatory effects include the production of certain neuropeptide-degrading enzymes as well as a direct inhibitory effect on the normal C-fiber excitability.[39–41] This would probably account for reduced SP release in the periphery, and hence a reduction of the ensuing sensitization. In the arthritic TMJ, the GC effect on a short-term basis (2 to 3 weeks) has been shown to reduce both VAS and PPT, and this reduction in arthritic pain and hyperalgesia was associated with a reduction of joint fluid NPY-LI; these parameters had, however, returned to pretreatment levels after 4 to 6 weeks.[42] But it has also been demonstrated that the mean concentrations of SP-LI in the arthritic TMJ were hardly affected by GC treatment and that, after intra-articular GC administration, a decrease in VAS was associated with an increase in SP-LI, whereas no such correlation was found in the untreated TMJ.[21] Hence, the question of how long and to what extent an intra-articular deposition of GC remains bioactive, with respect to the release of SP and other neuropeptides, seems to be of importance.

Differences in time elapsed between the GC administration and the investigation of parameters as well as in the local activity of degrading enzymes may explain the reported differences with regard to GC effect on neuropeptide-like immunoreactivity. The reduction in arthritic pain and hyperalgesia in the GC-treated TMJ could be explained by the vascular response associated with SP-LI, improving the synovial perfusion. However, partial correlation analysis indicates that the positive correlation between the PPT and SP-LI is independent of IAT. Hence, we can hypothesize an alternative explanation, that is, an antinociceptive and pain modulatory role for SP as a protective response from primary afferents of the inflamed joint to hypoxia and tissue damage. Central involvement of SP in dorsal horn antinociception, linking the N-terminal end of the peptide to the antinociceptive effect, has been positively demonstrated in experimental pain models.[43,44] Whether SP in the periphery depends on the antinociceptive effect of the locally administered GC, or whether SP, by its own action, can reduce the pain and hyperalgesia in the inflamed TMJ, cannot be concluded from this study. Further studies are necessary to elucidate the peripheral action of SP in the development and sustenance of arthritic joint pain and hyperalgesia and the impact of intra-articular GC on the petidergic activity in the inflamed joint.

The present results indicate that increased concentrations of joint fluid SP-LI in the GC-treated arthritic TMJ correspond to an increase in intra-articular temperature and pain threshold and tolerance, and to a concomitant decrease in joint pain. These findings suggest that SP is implicated in the vascular and nociceptive response of the arthritic joint, and that, possibly assisted by the antinociceptive effect of local corticosteroids, SP has a modulatory role in arthritic pain and hyperalgesia.

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Resumen

Aumento de la temperatura intra-articular y el umbral del dolor asociado a la sustancia P en la articulación temporomandibular artrítica

Los neuropéptidos son considerados mediadores y moduladores de la enfermedad inflamatoria de la articulación. Se ha propuesto que la sustancia P (SP) es un mediador del dolor, y sus propiedades vasoactivas han sido documentadas apropiadamente. En este estudio se correlacionó, la presencia de una inmunoreactividad parecida a la SP en el fluido sinovial, a la temperatura intra-articular (TIA) y al dolor de la articulación temporomandibular (ATM) artrítica, 3 a 5 semanas después de una inyección intra-articular de glucocorticosteroides. Se investigaron 18 ATM en cuanto a la TIA y la presencia de inmunoreactividad parecida a la SP en el líquido sinovial de 12 pacientes que sufrían de enfermedad inflamatoria sistémica de la articulación. Después de realizar una artrocentesis las aspiraciones fueron analizadas para verificar la inmunoreactividad parecida a la SP por medio de un radioinmunoensayo competitivo. El dolor artrítico y la hiperalgesia de la ATM fueron evaluados con una escala análoga visual y un algómetro que determinaba el umbral de dolor a la presión y el nivel de tolerancia. Nuestros resultados indican que la inmunoreactividad parecida a la SP está asociada con la TIA y que las concentraciones elevadas de inmunoreactividad parecida a la SP en el fluido articular corresponden a un umbral de presión y a una tolerancia elevados, y concomitantemente a una escala análoga visual visual reducida. Estos hallazgos indican que la SP está implicada en la respuesta vascular y nociceptiva de la articulación artrítica y que la SP, posiblemente utilizando la ayuda del efecto antinociceptivo de los corticosteroides locales, tiene un papel modulatorio en el dolor artrítico y la hiperalgesia.

Zusammenfassung

Substanz P-assozierter Anstieg der intraartikulären Temperatur und der Schmerzschwelle im arthritischen Kiefergelenk

Neuropeptide werden als Mediatoren und Modulatoren von entzündlichen Gelenkserkrankungen angesehen. Substanz P (SP) wurde als ein Schmerzmediator vorgeschlagen, und seine vasoaktiven Eigenschaften sind gut dokumentiert. In dieser Studie wurde die Anwesenheit einer Sp-artigen Immunoreaktivität in der Synovialflüssigkeit korreliert mit der intraartikulären Temperatur (IAT) und dem Schmerz aus arthritischen Kiefergelenken 3 und 5 Wochen nach einer intraartikulären Injektion von Glukokortikosteroiden. Achtzehn Kiefergelenke wurden in Bezug auf die IAT und die Anwesenheit einer SP-artigen Immunoreaktivität in der Synovialflüssigkeit bei 12 Patienten mit einer systemischen entzündlichen Gelenksertrankung untersucht. Nach der Arthrozentese wurden die Aspirate bezüglich einer SP-artigen Immunoreaktivität mittels kompetitivem Radio-Immunoassay analysiert. Mit einer visuellen Analogskala und einem Algometer, welches die Druckschmerzschwelle (PPT) und das Toleranzniveau (PPTL) bestimmt, wurden die arthritischen Schmerzen und die Hyperalgesie in den Kiefergelenken beurteilt. Unsere Resultate deuten daraufhin, dass eine SP-artige Immunoreaktivität mit einer erhöhten Schmerzschwelle und Toleranz, sowie mit einer begleitenden Abnahme in der visuellen Analogskala korrespondiert. Diese Befunde lassen vermuten, dass SP in die vaskuläre und nozizeptive Antwort des arthritischen Gelenkes verwickelt ist, und dass SP, möglicherweise unterstützt durch die antinozizeptive Wirkung der lokalen Kortikosteroide, eine modulierende Rolle beim arthritischen Schmerz und der Hyperalgesie besitzt.